

Search for a Realistic View of Hydrophobic Effects

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Received September 5, 1989 (Revised Manuscript Received November 20, 1989)

Like many other facts of nature, the insolubility of hydrocarbon liquids in water is easy to observe and describe but unexpectedly difficult to explain. An adequate understanding of the molecular behavior underlying this immiscibility is a prerequisite for any satisfactory rationalization of a great variety of phenomena. Examples include the effect of solvent changes on activation parameters of organic reactions,¹ the formation of micelles and biological membranes,² and the stability and thermal denaturation of globular proteins.³ In this Account I should like to review very briefly the progress made in recent years toward such an understanding. I will call attention to some anomalies which imply that even what has been called⁴ “the new view of hydrophobic effects” still stands in need of amendment, and I will describe an approach that may point the way toward achieving the needed modifications. (The phrase “new view” has not been generally adopted to identify this rather complex conceptual edifice, but it will serve here as a needed and very convenient tag.)

Development of the Concept of Hydrophobic Hydration

In thermodynamic terms, the low solubility of hydrocarbons means that transfer of the solute molecule from the pure liquid alkane to a dilute water solution involves a large increase in the standard Gibbs free energy, that is, $\Delta G^\circ_{\text{tr}} > 0$. The value of $\Delta G^\circ_{\text{tr}}$ is related to X_s , the mole fraction of the solute in the saturated solution, by the formula

$$\Delta G^\circ_{\text{tr}} = -RT \ln X_s \quad (1)$$

The large heat of vaporization and surface tension of water imply that it has a high cohesive energy density.⁵ Therefore, creating a cavity to accommodate a solute molecule should require a sizable enthalpy input. Although some of this energy should be recovered when the solute is subsequently placed in the cavity, it may be argued that the overall process involves replacing strong attractive water–water interactions by much weaker water–solute ones. This would account for a net positive $\Delta H^\circ_{\text{tr}}$, which in turn would explain the observed $\Delta G^\circ_{\text{tr}}$.

The need for a more sophisticated analysis of these phenomena became apparent in the 1930s when experimental values of $\Delta H^\circ_{\text{tr}}$ began to be available. The

first evaluations of these enthalpy changes were indirect, based on the thermodynamic relation, at constant pressure,

$$d(\Delta G^\circ_{\text{tr}}/T)/dT = -\Delta H^\circ_{\text{tr}}/T^2 \quad (2)$$

For many nonpolar solutes, the saturation concentration decreases on raising the temperature near 25 °C, and then unexpectedly eqs 1 and 2 imply that $\Delta H^\circ_{\text{tr}}$ is negative. Often the solubility passes through a minimum not far above room temperature. $\Delta H^\circ_{\text{tr}}$ must vanish at the minimum solubility temperature, and it takes on gradually increasing positive values only on further heating.

In light of this situation, the relation

$$\Delta G^\circ_{\text{tr}} = \Delta H^\circ_{\text{tr}} - T\Delta S^\circ_{\text{tr}} \quad (3)$$

shows that at 25 °C transfer of the solute into the solution must involve a large entropy decrease, i.e., $\Delta S^\circ_{\text{tr}} < 0$. Since the transfer free energy would not be positive in the absence of this entropic term, it seems natural to regard the insolubility as being “entropy controlled”. Similar entropy losses do not occur when nonpolar solutes enter other polar media; this behavior is apparently uniquely characteristic of aqueous solutions. These considerations form the background for all subsequent attempts to rationalize the behavior of these solutions by invoking a “hydrophobic”⁶ effect reflecting special structural or thermodynamic features of liquid water.

Statistical mechanics teaches that an increase in entropy for a collection of molecules indicates a transition to a state of greater disorder. Then a negative $\Delta S^\circ_{\text{tr}}$ suggests that when a nonpolar solute dissolves in water, it causes some sort of reorganization of nearby solvent molecules, which leaves them in a more ordered state. A number of conceptual models have been offered that represent attempts to visualize this transformation. Most of these involve formation near the solute of short-lived aggregates of water molecules, having more or less well defined structure. They may be called “icebergs”,⁷ “flickering clusters”,^{8,9} or “clathration shells”, polyhedral cages similar to those found in the crystalline hydrates formed by some small nonpolar molecules.¹⁰ Any of these is consistent with a terminology in which the class of inert, nonpolar solutes is referred to as “structure makers”. Whatever the geo-

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Professor Norbert Muller has long been captivated by the manifold practical and symbolic significance of water. As a child in the great port city of Hamburg, he dreamed of becoming captain of an ocean liner. After student years at Berkeley (B.S. in chemistry, 1949) and Harvard (Ph.D. in chemical physics, 1953; mentor: E. Bright Wilson, Jr.), his continuing fascination with One who claims to be a source of living water led to his being baptized with water. In his professional career, spent mostly at Purdue University, he has focused on teaching physical chemistry and on diverse applications of proton and fluorine nuclear magnetic resonance, often aimed at elucidating special chemical, spectroscopic, or structural properties of water-containing systems.

metric details may be, the concept of structure making has several testable implications, and the results of appropriate experiments were initially very encouraging. As more and more information has been accumulated, some disturbing inconsistencies have emerged. Let us first briefly examine some findings that appear to support the conclusion that "structure making" well describes the changes produced in water by dissolved alkanes or alkyl groups.

First, it is quite plausible to suppose that formation of polymeric aggregates involves increased or strengthened hydrogen bonding. Since this would be expected to produce a negative contribution to ΔH°_{tr} , it neatly solves the puzzle of why very small or even negative values are actually observed, whereas intuition had suggested substantial positive ones. The overall ΔH°_{tr} may then consist of a positive term associated with creation and filling of a cavity, which is largely canceled by the negative one reflecting the enhancement of structure in the surrounding solvent. In part, this is equivalent to saying that the enthalpy demand for cavity creation is unexpectedly low because there is little or no net breaking of hydrogen bonds, just as one may create a rather large hole in a loosely woven fabric by distorting the pattern of the threads without actually needing to break any of them. Actually, it goes farther than this, because the solute may cause a net making of hydrogen bonds.

Secondly, it is reasonable that any structure that may exist around a dissolved particle should be progressively disrupted on raising the temperature. This "melting" involves breaking some of the excess hydrogen bonds presumed to have been formed, and the required energy should be observable as an enhancement of the heat capacity. It has indeed often been noted that the partial molar heat capacity of a nonpolar solute at infinite dilution in water, $\bar{C}^\circ_{p,2}$ is much greater than the molar heat capacity of the pure liquid solute, $C^\circ_{p,2}$. The difference, or excess molar heat capacity,

$$\Delta C^\circ_{p,2} = \bar{C}^\circ_{p,2} - C^\circ_{p,2} \quad (4)$$

is far larger at 25 °C when the solvent is water than for any other solvent, hydrogen bonded or not.⁴ This seems to provide rather convincing confirmation of the structure-making hypothesis.

Third, it is to be expected that for any liquid containing molecules with hydroxyl groups, an increase in the strength of the hydrogen bonds or the concentration of hydrogen-bonded species should result in a shift of the corresponding proton magnetic resonance signal to lower applied field.¹¹ If dissolving a nonpolar solute has a structure-promoting effect, one should then find that the water proton signal moves downfield by an amount proportional to the concentration, and to the number of water molecules that each solute particle is able to affect. Such shifts cannot be observed with hydrocarbons because they are too sparingly soluble, but they are easily detected with solutes having hydrocarbon groups with solubilizing substituents, such as the alcohols.¹² Although there is then some uncertainty as to the best way to allow for the effect of the

polar group,¹³ it has been noted¹⁴ that "all the available evidence supports the picture of the alcohols as 'soluble hydrocarbons' rather than as 'alkylated water.'" Indeed, the dependence of these shifts on the alcohol molecular weight suggests that they do not differ dramatically from those that would be produced by alkanes of similar size. The largest downfield displacements are found near the freezing point. Their rapid falloff on even gentle heating seems to show that whatever excess structure exists in the chilled solutions soon melts out when the temperature is raised.

The "new view" of hydrophobic effects represents a further development of the ideas just presented, including efforts to predict and observe how the thermodynamic and spectroscopic properties of these solutions change when measurements are made at temperatures approaching 100 °C or even exceeding this, by working at pressures above 1 atm. Again, a couple of equations from elementary thermodynamics are of central importance. Since the $\Delta C^\circ_{p,2}$ of eq 4 is just the heat capacity change of transfer of the solute from pure liquid hydrocarbon to the water solution, one may write

$$d(\Delta H^\circ_{tr})/dT = \Delta C^\circ_{p,2} \quad (5)$$

and

$$d(\Delta S^\circ_{tr})/dT = \Delta C^\circ_{p,2}/T \quad (6)$$

Then the negative "structural" contribution to ΔH°_{tr} must become progressively less negative as the temperature rises, and the same applies to ΔS°_{tr} . This is in essence a more sophisticated restatement of the idea that the solute-imposed structure melts away on heating of the solution. It gives rise to the attractive notion that water becomes less and less anomalous as it is heated, and that then one may hope to identify a temperature where all effects of hydrophobic hydration have finally become negligible.

A characteristic tenet of the "new view" is that a temperature indeed exists where water no longer shows the anomalous behavior that distinguishes it so markedly from other polar solvents, especially near the freezing point. This temperature is identified³ with the one at which the value of ΔS°_{tr} has become 0 and is represented by the symbol T_S . Its precise value is not known but is estimated to lie in the range 130–160 °C. Arguments advanced to undergird this belief cannot be presented here because of space limitations but may be found in refs 3, 4, and 15–19. One of several possible weaknesses of these arguments is a failure to recognize that, while $\Delta S^\circ_{tr} = 0$ is almost certainly a *necessary* condition for the absence of hydrophobic hydration, it may not be a *sufficient* condition.

Agreeing for the sake of discussion to overlook these weaknesses for the present, one may note that at $T = T_S$, where $\Delta S^\circ_{tr}(T_S) = 0$ and hence $\Delta G^\circ_{tr}(T_S) = \Delta H^\circ_{tr}(T_S)$, these enthalpy and free energy changes contain, *by assumption*, no hydrophobic hydration contribution. This has surprising further implications. When the temperature is reduced, ΔG°_{tr} changes rather

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slowly and therefore remains nearly equal to $\Delta H^\circ_{tr}(T_S)$, that is, to the enthalpy of transfer into "nonaqueous or inhibited water". Hydrophobic hydration is regarded as the cause of the more negative values attained by both ΔH°_{tr} and ΔS°_{tr} when the temperature is lowered to reach the normal liquid range, but in light of eq 3, these changes have offsetting or compensating effects on ΔG°_{tr} . Then it is concluded that the "real cause" of the insolubility of hydrocarbons at ordinary temperatures is that contribution to the enthalpy of transfer which is equal to $\Delta H^\circ_{tr}(T_S)$. This is similar to transfer enthalpies found when nonpolar solutes enter nonaqueous polar solvents.¹⁸ The effects of hydrophobic hydration are superimposed on this, but because of entropy-enthalpy compensation, they have little net influence on the transfer free energy. Therefore, water structural reorganization, while admittedly real, is nearly irrelevant to the energetics of transfer processes or micellization.¹⁸

The argument may be carried one step farther^{3,15} by noting that measured values of $\Delta G^\circ_{tr}(25^\circ\text{C})$ are somewhat less positive than those of $\Delta G^\circ_{tr}(T_S)$. If this difference is a result of hydrophobic effects which become appreciable only at the lower temperatures, then the net consequence of these effects is actually to enhance the room-temperature solubility of nonpolar species, as suggested earlier by Shinoda and Fujihira.¹⁹

Difficulties with the "New View" of Hydrophobic Effects

When one attempts to use the concept of water structure promotion elaborated as described above to rationalize as many as possible of the reported experimental data, a number of problems emerge. In the limited space available, I must focus on a few of these, which are variations on the following theme: In addition to ΔS°_{tr} , other observable quantities may reasonably be regarded as "effects" having hydrophobic hydration as their "cause". Among these are ΔH°_{tr} , $\Delta C^\circ_{p,2}$, and $\Delta\delta/m$, the downfield displacement of the water proton chemical shift produced by a solute at molality m . These depend on temperature in ways not compatible with the hypothesis that water becomes a "normal" solvent at $T = T_S$ or indeed at any attainable temperature.

It was the anomaly involving $\Delta\delta/m$ that first convinced me that current ideas on hydrophobic hydration needed careful reevaluation, because I had previously carried out studies of hydrogen bonding using proton chemical shifts.²⁰ That there is a difficulty is at once apparent on examining the temperature dependence of $\Delta\delta/m$ for aqueous solutions of alcohols.²¹ In each case, $\Delta\delta/m$ is large and has the expected positive sign near 0°C , then diminishes and passes through 0 at a somewhat solute-dependent temperature in the range $25\text{--}75^\circ\text{C}$, and becomes unmistakably negative at higher temperatures. As mentioned above, it seems unavoidable that structure making should result in a positive $\Delta\delta/m$. Hence the authors state²¹ that "an increase in the temperature changes the alcohol behavior, being a structure former at low temperature and a structure

breaker at high temperature." This is very difficult to accept.

Since these observations are not easy to understand, and because of the possibility that they may arise in some unexpected way from the presence of the hydroxyl groups in the alcohols, no great amount of attention seems to have been paid to them. My own interest in the topic mostly lay dormant until late in 1986, when it was reported²² that at 25°C various alkylammonium chlorides produce negative values of $\Delta\delta/m$, i.e., upfield shifts, which increase in magnitude with increasing size of the alkyl chain, apparently showing that an alkyl group is a structure breaker. These workers cite similar results obtained much earlier for some tetraalkylammonium halides but also refer to evidence from other experiments that tends to confirm that ions with large alkyl groups are structure makers. They therefore suggest that "structure enhancement is not due to enhanced hydrogen bonding" except at temperatures just above the freezing point. Here is another puzzling conclusion that seems to demand an alternative conceptual structure for interpreting these data, and it did much to trigger the development of the approach to be described in the next section. At this point, it may be said that what these results have to teach us is that although it seems attractive to propose a cause-and-effect relationship between hydrophobic hydration and $\Delta\delta/m$, it is dangerous to go on to infer that when the effect is 0, the cause is absent. (As noted above, this kind of reasoning is involved in arguing for the notion that there is no hydrophobic effect when $\Delta S^\circ_{tr} = 0$.)

Of the thermodynamic variables to be considered in this section, the crucial one is $\Delta C^\circ_{p,2}$. Several authors^{4,23} have pointed out that if one were required to select the single variable most directly and unequivocally connected with the unique solvating behavior of water, $\Delta C^\circ_{p,2}$ would almost certainly be the one chosen. Then perhaps the most serious problem with the "new view" is that this excess heat capacity does not vanish at $T = T_S$. Values of $\Delta C^\circ_{p,2}$ at about 160°C from model calculations^{23,24} are approximately 0.3–0.5 times as large as those at 25°C . Experimental determinations for several noble gases and gaseous hydrocarbons give roughly similar results.^{17,25,26} No reason has been proposed for the persistence of such large excess heat capacities if the solvent may legitimately be regarded as "inhibited water".

The high-temperature values of $\Delta C^\circ_{p,2}$ may be used with eqs 5 and 6 to follow the variation of ΔH°_{tr} and ΔS°_{tr} into the domain $T > T_S$. One finds, of course, that ΔS°_{tr} now becomes positive and increases on further heating. If it is agreed that at T_S water has lost the anomalous properties that make $\Delta S^\circ_{tr}(25^\circ\text{C}) < 0$, one now seems forced to conclude that when $T > T_S$, it becomes anomalous in the opposite sense! Similarly, ΔH°_{tr} continues to rise with increasing temperature, and if $\Delta H^\circ_{tr}(25^\circ\text{C})$ is regarded as abnormally small and $\Delta H^\circ_{tr}(T_S)$ as normal, then its values at still higher

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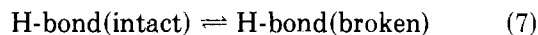
temperatures must be taken as abnormally large, again apparently indicative of "reversed" anomalous behavior.

In the same way, graphs showing the temperature dependence of the enthalpy and entropy of transfer of hydrocarbon chains from water into micelles¹⁸ seem to imply that "reversed" hydrophobic hydration occurs when $T > T_S$. Rather than speculate on the hypothesis that the strongly superheated liquid should now be considered as "antiaqueous water", it is better to take all this as a warning signal indicating that at and above T_S , water retains, albeit to a lesser degree, the same capacity for structural reorganization that makes it a unique solvent at 25 °C.

Modified Hydration-Shell Hydrogen-Bond Model

The state of affairs just described points to a need for an approach that recognizes that the terminology of structure promotion and breaking is probably too limited to provide a good description of the underlying molecular reality. Instead, what appears to happen is a reorganization of molecules or hydrogen bonds that can be *perceived* either as structure making or breaking depending on the experimental probe used to study it. In attempting to see how this might be implemented, I began by focusing on $\Delta\delta/m$ and $\Delta C_{p,2}^\circ$, because obviously these can take on values that suggest opposite conclusions as to whether structure promotion is occurring or not.²⁴

Results of vibrational^{27,28} and NMR^{20b} spectroscopy are consistent with a two-state description of water where every hydrogen atom is assigned to either a broken or intact hydrogen bond. This does not require the now unfashionable assumption that the liquid is a mixture of "dense" and "bulky" domains but can occur even with an essentially uniform local density. The development of the present model starts with the assumption that the progressive breaking of hydrogen bonds on heating accounts for about half of the observed heat capacity of bulk water,²⁹ and that this bond-breaking process is perturbed by introduction of a solute in a way that gives rise to $\Delta C_{p,2}^\circ$. If the process is viewed as a chemical equilibrium,



with

$$K_b = \exp(-\Delta G_b^\circ/RT) = \exp(-\Delta H_b^\circ/RT + \Delta S_b^\circ/R) \quad (8)$$

then the fraction of broken bonds is given by

$$f_b = K_b/(1 + K_b) \quad (9)$$

and the temperature dependence of this quantity generates a heat capacity contribution per mole of hydrogen atoms of

$$C_{p,b}^h = \Delta H_b^\circ(df_b/dT) = (\Delta H_b^\circ)^2 K_b/RT^2(1 + K_b)^2 \quad (10)$$

The superscript h identifies a hydrogen-bond-breaking contribution, and the subscript b refers to bonds in bulk water as opposed to those in the hydration shell, where the corresponding variables will be labeled with a subscript hs.

The values $\Delta H_b^\circ = 9.80 \text{ kJ mol}^{-1}$ and $\Delta S_b^\circ = 21.60 \text{ J mol}^{-1} \text{ K}^{-1}$ were chosen²⁴ because they produce an acceptable value, 40 J K^{-1} per mole of water for the hydrogen-bond contribution to the heat capacity at 0 °C, and they give $f_b(0 \text{ °C}) = 0.1522$, close to the value suggested by Pauling.³⁰

With the help of eq 10, one can soon devise a way to attain positive values of $\Delta C_{p,2}^\circ$ by invoking a change that is not simply described as structure promotion or breaking. It is only necessary to suppose that the behavior of hydrogen bonds in the solvation shell of a nonpolar guest is governed by equations formally like eqs 7–9 but with $\Delta H_{hs}^\circ \neq \Delta H_b^\circ$ and $\Delta S_{hs}^\circ \neq \Delta S_b^\circ$, so that the heat capacity contribution in the shell is

$$C_{p,hs}^h = (\Delta H_{hs}^\circ)^2 K_{hs}/RT^2(1 + K_{hs})^2 \quad (11)$$

Then if n^h is the number of hydrogen bonds in a hydration shell, one would expect

$$\Delta C_{p,2}^\circ = n^h(C_{p,hs}^h - C_{p,b}^h) \quad (12)$$

From calculated values of the surface area of the solute molecules,³¹ one can obtain³² the number, N , of water molecules in the hydration shell. Then a plausible choice²⁴ is $n^h = 3N/2$, because with a given N this is the largest geometrically allowed number of bonds between neighboring molecules both resident in the same shell.

Positive values of $\Delta C_{p,2}^\circ$ could now arise in two ways. If K_{hs} and K_b were equal, this would require $\Delta H_{hs}^\circ > \Delta H_b^\circ$; if instead the two enthalpy changes were equal, it would need $K_{hs} > K_b$. It is somewhat unexpected that enhanced hydration-shell heat capacity could be achieved either by making the bonds enthalpically *stronger* or by reducing the bond-breaking free energy and thus *increasing* the fraction of *broken* bonds. Experimental results are best explained with this model by allowing both factors to operate simultaneously, that is, taking $\Delta H_{hs}^\circ > \Delta H_b^\circ$ and $\Delta S_{hs}^\circ > \Delta S_b^\circ$, with the latter inequality assuring that $K_{hs} > K_b$.

It is consistent with eqs 5, 6, and 12 to propose that these hydrogen-bonding equilibria produce contributions to ΔH_{tr}° and ΔS_{tr}° given by

$$\Delta H^h = n^h[(1 - f_b)\Delta H_b^\circ - (1 - f_{hs})\Delta H_{hs}^\circ] \quad (13)$$

and

$$\Delta S^h = n^h[(1 - f_b)\Delta S_b^\circ - (1 - f_{hs})\Delta S_{hs}^\circ] + Rn^h(F_b - F_{hs}) \quad (14)$$

with

$$F_b = f_b \ln f_b + (1 - f_b) \ln (1 - f_b)$$

$$F_{hs} = f_{hs} \ln f_{hs} + (1 - f_{hs}) \ln (1 - f_{hs}) \quad (15)$$

The term in $(F_b - F_{hs})$, inadvertently omitted in ref 24, arises from the entropy of mixing of broken and intact bonds in each variety of water. To fix ΔH_{hs}° and ΔS_{hs}° then requires two pieces of input data, such as an observed value of $\Delta C_{p,2}^\circ$ and a value of ΔH^h estimated from a measured ΔH_{tr}° with an assumption about the relation between these two enthalpy changes. This involves too much uncertainty to allow one to determine an unequivocally best set of parameters. Hence all

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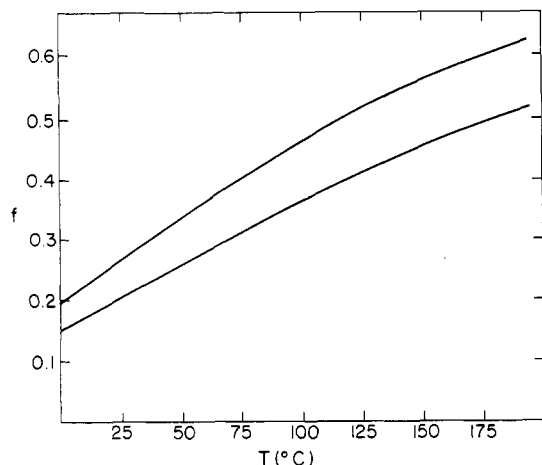


Figure 1. Calculated temperature dependence of the fraction, f , of broken hydrogen bonds: lower curve, bulk water; upper curve, hydration-shell bonds.

numerical results presented here are illustrative rather than definitive.

It was found²⁴ that with $\Delta H_b^\circ = 9.80 \text{ kJ mol}^{-1}$ and $\Delta S_b^\circ = 21.60 \text{ J mol}^{-1} \text{ K}^{-1}$, using $\Delta H_{hs}^\circ = 10.696 \text{ kJ mol}^{-1}$ and $\Delta S_{hs}^\circ = 27.36 \text{ J mol}^{-1} \text{ K}^{-1}$ gives values of $\Delta C_{p,2}^\circ(25^\circ \text{C})$ in good agreement with experimental data³² and allows one to appreciate how the model "works". Figure 1 shows the temperature dependence of f_b and f_{hs} obtained with these parameters. The variation is almost linear below 100°C . The difference, $(f_{hs} - f_b)$, increases steadily from 0.042 at the freezing point to 0.112 at 188°C .

A simple extension of this scheme provides a rationale for the NMR observations described above. The chemical shift displacement produced by the solute at molality m should be given by

$$\Delta\delta/m = (n^h/111.1)[B(1 - f_{hs}) - A(1 - f_b)] \quad (16)$$

where A is the downfield shift arising from formation of a hydrogen bond in bulk water, estimated to be about 5.5 ppm, and B is the corresponding parameter for hydration-shell water. Since ΔH_{hs}° is about 10% larger than ΔH_b° , one would expect B to be somewhat larger than A , and a value of 6.0 was tentatively adopted.²⁴ The surprising temperature dependence of $\Delta\delta/m$ then arises quite automatically. Near the freezing point, both $(1 - f_{hs})$ and $(1 - f_b)$ are relatively large and not very different. Then the shift is controlled by the difference between A and B and is therefore downfield. When the temperature is raised, $(1 - f_{hs})$ falls more rapidly than $(1 - f_b)$. Consequently, the shift is reduced to 0 at about 35°C and becomes a progressively increasing upfield shift thereafter. The predicted behavior is solute independent but somewhat sensitive to changes in the model parameters. Since eq 16 does not allow for possible polar-group effects, it is not rewarding to try to achieve detailed agreement with particular experimental results. What is important is that the model accounts naturally for the possibility that a solution may produce shifts that *seem* to show that a structure-making solute is mysteriously transformed into a structure breaker on heating.

At the temperature where $\Delta\delta/m = 0$, it is obviously untrue that hydrophobic hydration is absent. Instead, a downfield tendency arising from the greater enthalpic strength of the hydration-shell bonds is just balanced

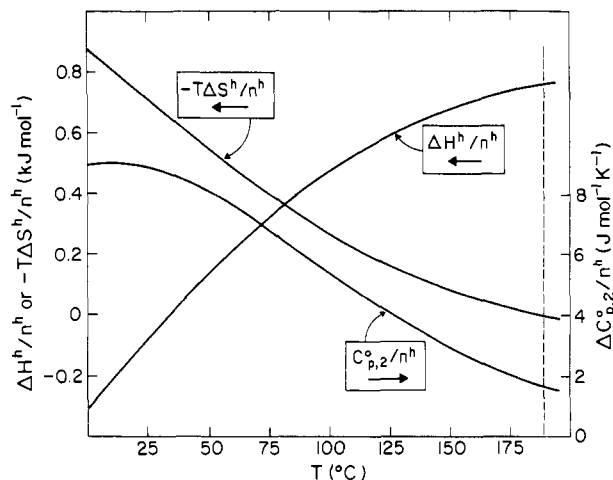


Figure 2. Results of model calculations of $\Delta H^h/n^h$, $-T\Delta S^h/n^h$, and $\Delta C_{p,2}^\circ/n^h$ at various temperatures. The dashed vertical line identifies T_S .

by the effect of having a larger fraction of them broken. These factors have *opposing* effects on $\Delta\delta/m$ but *reinforcing* effects on $\Delta C_{p,2}^\circ$, and the calculated excess heat capacity is quite large at this temperature. Then whether or not one concludes that there is structure promotion will indeed depend on how one looks for the phenomenon. The model thus suggests that there is no clear-cut answer to the question of how much structure there is in the solvent, i.e., that this is "not a good question". Then it seems desirable to avoid terminology implicitly based on the assumption that an answer exists.

Without any further adjustment of parameters, one can use eqs 12–15 to calculate the solute-independent quantities $\Delta C_{p,2}^\circ/n^h$, $\Delta H^h/n^h$, and $\Delta S^h/n^h$ at any desired temperature, though of course it is risky to assume that the parameters remain unchanged even above 100°C . Results of such calculations²⁴ appear in Figure 2. To obtain $\Delta C_{p,2}^\circ$, ΔH^h , or ΔS^h for a particular solute, it is only necessary to put in the appropriate value of n^h . All three quantities are simply proportional to the surface area of the solute. Such a proportionality has been repeatedly noted^{3,15,23} for observed values of $\Delta C_{p,2}^\circ$ and ΔS_{tr}° .

As already stated, the choice of parameters assures that the predicted values of $\Delta C_{p,2}^\circ(25^\circ \text{C})$, given by $n^h(8.92 \text{ J mol}^{-1} \text{ K}^{-1})$, are in good agreement with observed values,³² for hydrocarbon gases. Values of ΔH^h cannot be compared with measured transfer enthalpies because the latter included non-hydrogen bonding contributions. However, values of $\Delta S^h(25^\circ \text{C})$ should be similar to experimental $\Delta S_{tr}^\circ(25^\circ \text{C})$ values. The calculated values of $\Delta S^h(25^\circ \text{C})$ include -88.4 , -101.4 , and $-98.9 \text{ J mol}^{-1} \text{ K}^{-1}$ for propane, butane, and isobutane, and the observed values³ are -75.32 , -93.20 , and $-89.14 \text{ J mol}^{-1} \text{ K}^{-1}$. The ratio $\Delta S^h/\Delta C_{p,2}^\circ$ at 25°C is independent of n^h and equal to -0.266 . Observed values of $\Delta S_{tr}^\circ/\Delta C_{p,2}^\circ$ at 25°C show some variation; they include -0.257 , -0.263 , -0.248 , -0.257 , -0.269 , -0.247 , and -0.227 , for pentane, cyclohexane, hexane, benzene, toluene, ethylbenzene, and propylbenzene.³³

Above the normal boiling point, Figure 2 shows that for all solutes ΔS^h goes to 0 at 188°C and then becomes positive. The *same* behavior that leads to negative

values at ordinary temperatures now requires this. Neither $\Delta C_{p,2}^\circ$ nor ΔH^h vanishes at 188 °C, and nothing in the model implies that the condition $\Delta S_{tr}^\circ = 0$ is sufficient to assure that water will have lost its peculiar properties.

The calculated contribution of hydrogen-bond reorganization to ΔG_{tr}° is given by $\Delta G^h = \Delta H^h - T\Delta S^h$. It is smaller at 25 °C than at $T_S = 188$ °C, but it is always positive. Therefore it is not necessary to accept the paradoxical assertion that hydrophobic hydration increases the solubility of nonpolar species at room temperature.^{3,19}

What Remains To Be Done

The idea of assigning special thermodynamic properties to hydration-shell hydrogen bonds provides a way of thinking about hydrophobic hydration that avoids the problems associated with the treatments in refs 3, 15, and 18. However, in its present form it falls far short of being a theory of the hydrophobic effect. It is vulnerable to two rather obvious criticisms, i.e., that it is simplistic and that it offers no argument to show that the values chosen for ΔH_b° , ΔH_{hs}° , and the corresponding entropy changes are in any fundamental sense the "correct" ones.

To the first charge one can only plead *nolo contendere*; any model containing only a few numerical parameters would be simplistic. In the present instance, it is especially regrettable that there is no way to allow for the fact that the properties of the hydrogen bond connecting any given pair of water molecules should depend on the state of intactness of the six other bonds that the two partners may form with neighboring molecules. Any effort to remedy this would involve the introduction of even more adjustable parameters and hence make the model more cumbersome and less appealing. Perhaps the most encouraging comment that can be made is that the model focuses on *differences* between the properties of two populations, the bulk and hydration-shell bonds, and if the approximations and omissions involved in dealing with both have similar consequences, one may reasonably hope for some beneficial cancellation of errors.

Formidable difficulties stand in the way of attempts to evaluate the thermodynamic parameters of the model from first principles. It is recognized that water molecules form an extended hydrogen-bonded network³⁴ in which the local configuration around each bond is unique, so that each represents a special quantum mechanical problem. It is not even universally agreed that appropriate criteria can be set up to allow making an unequivocal distinction between intact and broken bonds.³⁴ To evaluate quantities like ΔH_b° , one would need to find such criteria and then calculate average properties for the great variety of subspecies belonging in each category.

For the present, it seems possible at least to justify using parameters that are unequal in the sense $\Delta H_{hs}^\circ > \Delta H_b^\circ$ and $\Delta S_{hs}^\circ > \Delta S_b^\circ$. It is rather generally agreed that even partial formation of a hydrogen-bonded clathration shell enhances the favorable interactions between a group of water molecules and a nonpolar guest.^{9,10} The inequality $\Delta H_{hs}^\circ > \Delta H_b^\circ$ may then reflect the fact that this stabilization is reduced when hydration-shell hydrogen bonds are broken. If so, it follows that in analyzing the overall ΔH_{tr}° an absolutely sharp separation *cannot* be made between the contribution associated with reorganizing the water surrounding a cavity and that arising when the solute is placed in the cavity. Formation of a clathration shell should also involve a loss of configurational freedom, larger than that associated with formation of a local network containing the same number of hydrogen bonds but without the geometric constraint imposed by the presence of the solute. In this case, the inequality $\Delta S_{hs}^\circ > \Delta S_b^\circ$ also has the expected sense.

It is my hope that the modified hydration-shell hydrogen-bond model represents a needed step toward a truly satisfying explanation of hydrophobic hydration. Even if this hope is disappointed, the anomalies inherent in the "new view", which motivated me to develop the model, will remain as problems that must be resolved.

Registry No. H₂O, 7732-18-5.

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