
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

A Two-State Model of Hydrophobic Hydration That Produces Compensating Enthalpy and Entropy Changes

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Received November 15, 1995[⊗]

Abstract: Many of the mixture models of water seek to explain the large free energy change associated with hydrophobic hydration by means of changes in the number and character of the hydrogen bonds in water. All of these models, regardless of detail, are in clash with the idea that hydrogen bond rearrangements will produce changes in both enthalpy and entropy, which largely compensate to produce little net free energy change. One of the simplest and most recent of these mixture models is Muller's two-state model, which produces small enthalpy and large negative entropy changes. In this paper, Muller's model is examined in detail. It is found that only slight changes are required in order for the model to produce nearly compensating enthalpy and entropy changes.

Introduction

The hydrophobic effect is generally considered to be one of the most important forces that govern the structure and interaction of all biological molecules.¹⁻³ Although there is as yet no consensus on the physical cause of this effect, a consistent theory is slowly emerging.⁴ An important aspect of this new theory is the recognition that any changes in the hydrogen bonding arrangement of water molecules will produce nearly or exactly compensating changes in both enthalpy and entropy.⁵⁻¹⁰ Such changes, therefore, would not produce a large free energy

change, although they may account for the large heat capacity change associated with the hydrophobic effect. The free energy change, and hence the low solubility, is considered to arise from the small size of water molecules.¹¹⁻¹⁵

This theory is in contrast with a class of theories that attempt to explain hydrophobicity in terms of a change in the hydrogen bonding pattern of water, typically using a mixture model.¹⁶⁻¹⁸ In a simplest model of this type, one imagines that water molecules exist in equilibrium between two hydrogen bonding

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[⊗] Abstract published in *Advance ACS Abstracts*, May 15, 1996.

(1) Kauzmann, W. *Adv. Protein Chem.* **1959**, *14*, 1-63.
 (2) Tanford, C. *The hydrophobic effect: formation of micelles and biological membranes*; Wiley: New York, 1980.
 (3) Dill, K. A. *Biochemistry* **1990**, *29*, 7133-7155.
 (4) Blokzijl, W.; Engberts, J. B. F. N. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1545-1579.
 (5) Ben-Naim, A. *Biopolymers* **1975**, *14*, 1337-1355.
 (6) Lumry, R.; Battistel, E.; Jolicoeur, C. *Faraday Symp. Chem. Soc.* **1982**, *17*, 93-108.

(7) Lee, B. In *An anatomy of hydrophobicity*; Eisenfeld, J., DiLisi, C., Eds.; Elsevier, North-Holland: Amsterdam, 1985; pp 3-11.

(8) Grunwald, E. *J. Am. Chem. Soc.* **1986**, *108*, 5726-5731.

(9) Yu, H.-A.; Karplus, M. *J. Chem. Phys.* **1988**, *89*, 2366-2379.

(10) Lee, B. *Biophys. Chem.* **1994**, *51*, 271-278.

(11) Lucas, M. *J. Phys. Chem.* **1976**, *80*, 359-362.

(12) Lee, B. *Biopolymers* **1985**, *24*, 813-823.

(13) Lee, B. *Biopolymers* **1991**, *31*, 993-1008.

(14) Madan, B.; Lee, B. *Biophys. Chem.* **1994**, *51*, 279-289.

(15) Souza, L. E. S. de; Ben-Amotz, D. *J. Chem. Phys.* **1994**, *101*, 9858-9863.

(16) Némethy, G.; Scheraga, H. A. *J. Chem. Phys.* **1962**, *36*, 3382-3400.

(17) Ben-Naim, A. *Water and aqueous solutions*; Plenum: New York, 1974.

(18) Kauzmann, W. *Coll. Int. C.N.R.S.* **1976**, *246*, 63-71.

states. Gill et al.¹⁹ used such a model to derive a formula for the heat capacity change upon dissolution of small molecules from the gas phase to water. Muller^{20,21} modified this model by assuming that the bulk, as well as the hydration shell, water is in equilibrium between two states. By adjusting the several parameters of this model, Muller found that this model can yield the approximately correct enthalpy and entropy as well as the observed sign reversal of the proton NMR chemical shift as a function of temperature. The interesting point here is that the required large free energy change could be produced from the structural reorganization alone, without invoking the small size of water molecules.

In this paper, we examine this model, which is one of the most recently proposed two-state mixture models of water, and seek to answer the following question: Is it possible to reconcile this mixture model with the idea that purely structural reorganization will produce only compensating enthalpy and entropy changes? Specifically, we ask if it is possible to find a reasonable set of parameters for the model that will produce nearly compensating changes in enthalpy and entropy as well as their known temperature dependence.

Theory and Methods

Description of the Model. The basic elements of Muller's two-state model of water structure are hydrogen bonds, which exist in two states in mutual equilibrium:²²



An equivalent way of describing the same model is to concentrate on the hydrogen atoms of the water molecules and consider that they exist in one of two discrete states, corresponding to the case when the hydrogen atom is or is not involved in a hydrogen bond. These two states will be referred to as "lower" (lower energy, hydrogen bonded) and "upper" (higher energy, broken) states. Each of these states is considered to be a thermodynamic state with definite enthalpy and entropy values. The system is characterized by the enthalpy and entropy differences between the two states, ΔH_b° and ΔS_b° , respectively. The subscript b refers to the bulk phase of water in order to distinguish it from the hydration shell water which will be introduced later. The two states are in equilibrium with the equilibrium constant K_b , which is given by

$$K_b = f_b/(1 - f_b) = \exp(-\Delta G_b^\circ/RT) \quad (2)$$

where f_b is the fraction of broken hydrogen bonds (fraction of hydrogen atoms that are not in a hydrogen bond), $\Delta G_b^\circ \equiv \Delta H_b^\circ - T\Delta S_b^\circ$, and R and T are the gas constant and the absolute temperature, respectively. Assuming that ΔH_b° and ΔS_b° are independent of temperature, the contribution to the heat capacity per each hydrogen atom of the system by this two-state equilibrium is given by

$$C_{p,b}^h = (\Delta H_b^\circ)^2 f_b(1 - f_b)/RT^2 \quad (3)$$

where the superscript h indicates that this is the hydrogen bonding contribution to the total.

If the values of $C_{p,b}^h$ and f_b are known, eqs 2 and 3 can be solved for ΔH_b° and ΔS_b° . The difference in heat capacity between steam and liquid water is about 40 J/K per mole of water. Assuming that this difference arises mainly from the hydrogen bond breakage, $C_{p,b}^h$, which is per hydrogen atom, can be expected to be close to half of this value. Pauling²³ estimated f_b to be about 0.15, which is the ratio between the heat of fusion of ice and the heat of vaporization of water

at 0 °C. Using these estimates, Muller obtains 9.80 kJ/mol and 21.6 (J/K)/mol for ΔH_b° and ΔS_b° , respectively.^{20,21}

Water in the hydration shell around a nonpolar solute molecule is also considered to be in a similar two-state equilibrium, again characterized by the two temperature-independent parameters ΔH_{hs}° and ΔS_{hs}° . The thermodynamics for the hydration shell water is then exactly analogous to that for the bulk, and we have

$$K_{hs} = f_{hs}/(1 - f_{hs}) = \exp(-\Delta G_{hs}^\circ/RT) \quad (4)$$

and

$$C_{p,hs}^h = (\Delta H_{hs}^\circ)^2 f_{hs}(1 - f_{hs})/RT^2 \quad (5)$$

where the subscript hs stands for the hydration shell. However, the values for ΔH_{hs}° and ΔS_{hs}° cannot be determined from these equations because the values for $C_{p,hs}^h$ and f_{hs} are unknown. Instead, Muller uses values for the hydration enthalpy, entropy, and heat capacity changes to estimate the values for these parameters.

The differences in the hydrogen bonding states between the bulk and the hydration shell water will contribute to the enthalpy, entropy, and heat capacity changes upon hydration, which are experimentally measurable. In order to compute this contribution, however, one needs three additional parameters, two to measure the relative enthalpy and entropy levels of the hydration shell with respect to those in the bulk and the third to measure the size of the hydration shell.

For example, one can use n^h , ΔH_U , and ΔS_U as the three parameters. n^h is the number of hydrogen atoms in the hydration shell. ΔH_U and ΔS_U are the enthalpy and entropy, respectively, of the upper state in the hydration shell relative to that in the bulk. In terms of these parameters, the hydrogen bonding contributions to the changes in thermodynamic quantities upon hydration are given by

$$\Delta H^h = n^h[\Delta H_U - (1 - f_{hs})\Delta H_{hs}^\circ + (1 - f_b)\Delta H_b^\circ] \quad (6)$$

$$\Delta S^h = n^h[\Delta S_U - (1 - f_{hs})\Delta S_{hs}^\circ + (1 - f_b)\Delta S_b^\circ - R\Delta F] \quad (7)$$

and

$$\Delta C_p^h = n^h[C_{p,hs}^h - C_{p,b}^h] \quad (8)$$

where the superscript h again indicates the hydrogen bonding contribution. In eq 7,

$$\Delta F \equiv F_{hs} - F_b$$

with

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

and F_{hs} similarly defined for the hydration shell. These are the "mixing" entropies characteristic of all mixture models.

In order to estimate n^h , Muller assumes that each of the two hydrogen atoms of each water molecule in the hydration shell points to the bulk, and should be counted as bulk, in one out of four times on average. It then follows that $n^h = 3N/2$, where N is the hydration number, or the number of water molecules in the hydration shell. The hydration number can be estimated from the size of a water molecule and the accessible surface area of the solute molecule.¹⁹

Muller further assumed that ΔH_U and ΔS_U are both zero. In other words, he assumed that the enthalpy and entropy of the upper state do not change upon hydration and that all changes are associated with the bonded-state. As will be seen later, one of the main features of our modification of Muller's two-state model is to let both states change upon hydration.

With n^h estimated and ΔH_U and ΔS_U set to zero, there are three equations, eqs 6–8, and two unknowns, ΔH_{hs}° and ΔS_{hs}° . Muller used two equations, eqs 6 and 8, to solve for the two unknowns and used the entropy as an independent check of the calculated parameter values. In order to follow this procedure, one obviously needs estimates of the quantities on the left-hand side of eqs 6–8. These are the changes due to alterations in the hydrogen bonding states only and not

(19) Gill, S. J.; Dec, S. F.; Olofsson, G.; Wadsö, I. *J. Phys. Chem.* **1985**, *89*, 3758–3761.

(20) Muller, N. *J. Solution Chem.* **1988**, *17*, 661–672.

(21) Muller, N. *Acc. Chem. Res.* **1990**, *23*, 23–28.

(22) Angell, C. A. *J. Phys. Chem.* **1971**, *75*, 3698–3705.

(23) Pauling, L. *The nature of chemical bonds*, 3rd ed.; Cornell University Press: Ithaca, NY, 1960.

necessarily the same as the total, experimentally measurable hydration quantities.²⁴ Muller arbitrarily assumed that $\Delta H_h = 0.125\Delta H^*$ and $\Delta C_p^h = \Delta C_p^*$ at 25 °C, where the quantities with the superscript \bullet indicate the total change upon hydration, and obtained 10.696 kJ/mol and 27.36 (J/K)/mol for ΔH_{hs}° and ΔS_{hs}° , respectively. With these parameter values, he calculates ΔS^h values of -88.4 , -101.4 , and -98.9 (J/K)/mol, respectively, for propane, butane, and isobutane at 25 °C. These compare favorably with the experimental total hydration entropy, ΔS^* , values at the same temperature, which are -75.32 , -93.20 , and -89.14 (J/K)/mol. However, the relation between the hydrogen bonding contribution and the total hydration quantities is nontrivial, especially in the case of entropy, and will be discussed later.

The NMR chemical shift for protons changes depending on their hydrogen bonding state, and the observed chemical shift upon insertion of nonpolar molecules in water is an indication that hydrogen bonding states change upon hydration. Curiously, the chemical shift is downfield at low temperature, which normally indicates an enhanced hydrogen bonding, but becomes zero as temperature is raised and eventually becomes upfield at higher temperatures.²⁵ In order to explain this feature, Muller writes the downfield chemical shift as

$$\Delta\delta/m = (n^h/111.1)[B(1 - f_{hs}) - A(1 - f_b)] \quad (9)$$

where m is the molality of the solution and A and B are the downfield shifts arising from a hydrogen bond in the bulk and in the hydration shell, respectively. If the values of A and B are known, the chemical shift data provide an additional means of verifying the calculated f_{hs} and f_b values. Muller estimates the value of A to be 5.5 ppm from the literature. The value for B was set to 6.0 ppm partly from the fact that ΔH_{hs}° is about 10% higher than ΔH_b° and partly because this value will reproduce the value of $\Delta\delta/m$ for propane at 0 °C, which he estimates to be 0.06 ppm/m from data on dilute alcohol solutions.²⁵ With these parameter values, $\Delta\delta/m$ can be calculated at each temperature. It turns out that $\Delta\delta/m$ is positive at low temperature because B is larger than A , but that it decreases as the temperature is raised because $1 - f_{hs}$ decreases faster than $1 - f_b$, and eventually becomes negative. Thus, Muller's model reproduces the upfield shift at high temperatures despite the fact that each hydrogen bond is stronger in the hydration shell ($\Delta H_{hs}^\circ > \Delta H_b^\circ$), and therefore produces a downfield shift ($B > A$), at all temperatures.

Relation to Solvent Reorganization and Enthalpy–Entropy Compensation. As seen above, the model requires a relation between the hydrogen bonding contribution and the total hydration. Muller concentrated on the changes due to the hydrogen bonding and used rather arbitrary relations between the two. However, the relation between the hydrogen bonding contribution and the total hydration quantities is nontrivial, especially in the case of entropy. Therefore, we begin modifying the model by first putting it in the proper context of the whole hydration process.

The hydration shell water not only is internally in an equilibrium state, but must of course be in equilibrium with the bulk water as well. If the hydrogen bonding states of the hydration shell water are different from those in the bulk, it is because of the presence of the solute molecule nearby, which can be considered as a perturbing potential. Thus, the total change in a thermodynamic quantity upon transfer of a molecule into water is made of two terms: the primary effect representing direct perturbation and the secondary effect that arises from an alteration of the hydrogen bonding state of water molecules as a result of the perturbation.

The total enthalpy change upon hydration is generally given by¹³

$$\Delta H^* = E_a + \Delta H_r \quad (10)$$

where E_a is the solute–solvent interaction energy and represents the direct enthalpic perturbation and ΔH_r is the enthalpy change due to the solvent reorganization that happens as a result of the perturbation. According to the two-state hydrogen bonding model, one then has ΔH_r

$= \Delta H^h$. Thus, one of the modifications is to use the estimated values of ΔH_r for ΔH^h , rather than the arbitrary value of $0.125 \Delta H^*$.

The situation with entropy is trickier. If Ben-Naim's standard state is used, the solute molecule can be considered fixed in space and all entropy change upon hydration is due to the solvent reorganization.¹³ However, some of this change is direct outside perturbation rather than a response to the perturbation; from an entropic point of view, introduction of a solute molecule is little more than a process of excluding the solvent molecules from the space occupied by the solute molecule. This is the excluded volume effect, which is independent of the hydrogen bonds.¹⁴ An alteration in the hydrogen bonding states arises as a response to this volume exclusion. Thus, the total hydration entropy change is given by

$$\Delta S^* = \Delta S_r = \Delta S_x + \Delta S^h \quad (11)$$

where ΔS_r is the total entropy change upon all solvent reorganizations and ΔS_x is the entropy change due to the excluded volume effect representing the direct perturbation. The entropy change upon the alteration of the hydrogen bonding, ΔS^h , represents entropic response to the direct perturbation and is only a part of the total change. Unlike the enthalpy case, however, no quantitatively rigorous scheme has yet been proposed for dividing the total ΔS_r into ΔS_x and ΔS^h components. (ΔS_x is not necessarily equal to the entropy change upon cavity formation because the latter involves hydrogen bond reorganization also.) Since the purpose of this study is to test the compatibility of the two-state model with compensation, we deliberately assume that the hydrogen bonding contribution compensates, i.e.

$$\Delta S^h = \Delta H^h/T \quad (12)$$

at one particular temperature, which we choose to be 25 °C. Since ΔH^h is nearly zero at 25 °C, this assumption makes ΔS^h small at room temperature and represents a major modification of the original model, which produces a large negative ΔS^h at room temperature.

The division of ΔH^* and ΔS^* into their respective direct and response components need be defined at only one temperature. The temperature dependence of the response components is defined by eqs 6 and 7 in terms of that of f_b and f_{hs} . The temperature dependence of f_b and f_{hs} is of course given by the chemical equilibrium condition, eqs 2 and 4. (We are indebted to one of the reviewers for pointing out that the compensation relation (eq 12) cannot be maintained at all temperatures unless some model parameters are made to depend on temperature. Although it is probably more realistic to assume that some of the parameters, especially n^h , ΔH_U , and ΔS_U , do depend on temperature, we assume in this paper that all model parameters are independent of temperature. This means that perfect compensation is possible at most at only one temperature. Approximate compensation is, however, maintained at all temperatures (see Tables 7 and 8), a consequence of the fact that the heat capacity change is much larger than the entropy change.¹⁰)

The Gibbs free energy change is also given by the sum of two terms:

$$\Delta G^* = \psi + \Delta G^h \quad (13)$$

where $\psi = E_a - T\Delta S_x$ is the perturbing potential and $\Delta G^h \equiv \Delta H^h - T\Delta S^h$. This latter quantity is the change in the free energy due to the solvent's response to the perturbation and measures the degree of incompleteness of the compensation.

Finally, the heat capacity change is also given by the sum of two terms:

$$\Delta C_p^* = \partial\Delta H^h/\partial T + \partial E_a/\partial T \quad (14)$$

However, $\partial E_a/\partial T$ is expected to be small in the aqueous phase,¹³ and ΔC_p^* is dominated by the temperature dependence of the response function.

Modified Two-State Model. There are seven parameters in the model. Two of these, ΔH_b° and ΔS_b° , are the bulk water properties; three, n^h , ΔH_{hs}° , and ΔS_{hs}° , are the hydration shell water properties; and two others, ΔH_U and ΔS_U , are the properties that connect the bulk and hydration shell properties. The values for ΔH_b° , ΔS_b° , and n^h need

(24) Dec, S. F.; Gill, S. J. *J. Solution Chem.* **1985**, *14*, 827.

(25) Marciacq-Rousselot, M.-M.; Lucas, M. *J. Phys. Chem.* **1973**, *77*, 1056–1060.

(26) Lee, B. *Methods in Enzymol.*; 1995, Vol. 259, Chapter 25, pp 555–576.

Table 1. Input Data Used for Determination of the Parameters of the Model

	N^a	ΔH_r^b (kJ/mol)	ΔS_r^c (J/K)/mol)	ΔC_p^{*d} (J/K)/mol)
CH ₄	16.9	1.2	4.03	217.5
C ₂ H ₆	21.3	2.9	9.73	284.0
C ₃ H ₈	24.8	6.6	22.14	332.0
iC ₄ H ₁₀	27.7	10.8	36.22	377.0
C(CH ₃) ₄	30.0	13.2	44.27	486.0

^a Number of water molecules in the first hydration shell.²⁰ ^b Solvent reorganization enthalpy change at 25 °C.¹³ ^c Solvent reorganization entropy change at 25 °C. Calculated by $\Delta S_r = \Delta H_r/T$. ^d Heat capacity change upon hydration at 25 °C.²⁰

Table 2. Model Parameter Values When $\Delta H_U = \Delta S_U = 0$

	f_{hs} at 25 °C (%)	ΔH_{hs}° (kJ/mol)	ΔS_{hs}° (J/K)/mol)	ΔS^h at 25 °C (J/K)/mol)
CH ₄	26.8	10.58	27.16	-52.71
C ₂ H ₆	27.3	10.59	27.34	-65.98
C ₃ H ₈	27.7	10.54	27.37	-71.35
iC ₄ H ₁₀	28.3	10.50	27.48	-74.80
C(CH ₃) ₄	29.6	10.65	28.51	-93.15

not be changed from those in the original Muller's model. The remaining four parameters are related to each other by three equations, eqs 6–8. The model is therefore underdetermined, and we will generate a set of models, each corresponding to a particular value of one selected parameter, which we choose to be ΔH_U . As will be seen later, a fairly narrow range of values for ΔH_U can be established by examining the NMR chemical shifts and other features that the models predict.

Solving eqs 5 and 6 for f_{hs} and ΔH_{hs}° , one obtains

$$\Delta H_{hs}^\circ = (L^2 + RT^2 C_{p,hs}^h)/L \quad (15)$$

and

$$f_{hs} = RT^2 C_{p,hs}^h / (L^2 + RT^2 C_{p,hs}^h) \quad (16)$$

where

$$L = (1 - f_{hs})\Delta H_{hs}^\circ = (1 - f_b)\Delta H_b^\circ - \Delta H^h/n^h + \Delta H_U \quad (17)$$

The value of $C_{p,hs}^h$ can be determined from the relation $C_{p,hs}^h = C_{p,b}^h + \Delta C_p^h/n^h$, and using the heat capacity of water for $C_{p,b}^h$ and the experimental ΔC_p^* values for ΔC_p^h . For ΔH^h we use the ΔH_r values reported earlier.¹³ The values for f_{hs} and ΔH_{hs}° can then be determined from these equations for each assumed value of ΔH_U . Once the f_{hs} and ΔH_{hs}° values are at hand, ΔS_{hs}° can be obtained from eq 4. Finally, ΔS_U is obtained from eq 7 and using $\Delta S^h = \Delta H^h/T$, which we assume to be valid at 25 °C. Once the seven parameter values are determined at 25 °C in this way, the values for ΔH^h and ΔS^h at any other temperature can be obtained from the temperature dependence of f_b and f_{hs} according to eqs 2, 4, 6, and 7.

Results

The molecules used for this study were simple hydrocarbons for which the solvent reorganization contributions to the hydration enthalpy change are known. The compounds and the input data used are listed in Table 1.

Using these data, we first computed the parameter values for the case when ΔH_U and ΔS_U were both set to zero. We will refer to this model as the five-parameter model. This is the same as Muller's original model except that ΔH^h values were set equal to ΔH_r rather than to 1/8 of ΔH^* . The results, given in Table 2, are similar to those from Muller's original model.^{20,21} For example, for propane at 25 °C, Muller's values for f_{hs} , ΔH_{hs}° , ΔS_{hs}° , and ΔS^h are, respectively, 26.4, 10.70, 27.36, and -88.4 in the same units as used in Table 2.

Table 3. Fraction (%) of Broken Hydrogen Bonds in the Bulk and in the Hydration Shell of Propane

T (°C)	bulk	ΔH_U (kJ/mol) =					
		-0.5	0	0.3	0.5	1	5
0	15.2	23.1	20.6	19.3	18.5	16.6	7.6
25	20.5	30.5	27.7	26.2	25.3	23.1	12.3
50	25.9	37.7	34.8	33.2	32.2	29.8	18.0
75	31.3	44.3	41.4	39.8	38.8	36.5	24.3
100	36.3	50.2	47.4	45.9	44.9	42.6	31.0

Table 4. NMR Downfield Chemical Shifts, $\Delta\delta/m$, in Parts per Million per Molal Concentration of Propane

T (°C)	ΔH_U (kJ/mol) =					
	-0.5	0	0.3	0.5	1	5
0	-0.017	0.033	0.060	0.077	0.115	0.295
25	-0.069	-0.012	0.018	0.037	0.081	0.299
50	-0.112	-0.054	-0.022	-0.001	0.045	0.284
75	-0.147	-0.088	-0.057	-0.036	0.011	0.255
100	-0.172	-0.116	-0.085	-0.066	-0.020	0.215

In order to determine the range of reasonable ΔH_U values to use for the full seven-parameter models, f_{hs} and $\Delta\delta/m$ values were calculated for a number of solute species at different temperatures and using various values of ΔH_U . Some of the calculated f_{hs} values for propane are given in Table 3, which also includes the f_b values for comparison. As can be expected, f_{hs} increases with temperature and decreases as ΔH_U is increased. At all temperatures, f_{hs} starts out greater than f_b when ΔH_U is zero, but quickly becomes less than f_b before ΔH_U reaches 5.0 kJ/mol.

The calculated NMR chemical shift values for propane are given in Table 4. For models with small ΔH_U values, the chemical shift changes its sign as the temperature is raised, as in Muller's original five-parameter model. However, when ΔH_U is greater than 1 kJ/mol, f_{hs} values become sufficiently small at all temperatures that the NMR chemical shift no longer changes its sign. Muller's estimated value of $\Delta\delta/m$ for propane is about 0.06 ppm/m at 0 °C.²⁰ With the current set of parameters, this value is obtained when the ΔH_U value is 0.3 kJ/mol.

The dependence of the enthalpy and entropy of the two states on ΔH_U is shown in Figure 1 for propane. The enthalpy and entropy of both the upper and the lower states of the hydration shell increase with ΔH_U , but the two states do not behave symmetrically; the enthalpy and entropy values for the lower state in the hydration shell change only modestly from those in the bulk. For the upper state, however, the change is large unless ΔH_U is small.

Numerical values for some of the parameters are given in Tables 5 and 6 for $\Delta H_U = 0.3$ and 5.0 kJ/mol, respectively. The model with $\Delta H_U = 0.3$ kJ/mol is the most reasonable from considerations of the heat capacity (see below) and the NMR chemical shift characteristics. The model with $\Delta H_U = 5.0$ kJ/mol is presented for contrast. It can be seen that both models produce ΔH_{hs}° and ΔS_{hs}° values that are essentially independent of the solute species, as was the case for the original five-parameter model. For the model with $\Delta H_U = 0.3$ kJ/mol, ΔS_U values are small and the ΔH_{hs}° and ΔS_{hs}° values are little different from those of the five-parameter model given in Table 2. Both are larger than the corresponding ΔH_b° and ΔS_b° values for the bulk, 9.80 kJ/mol and 21.60 (J/K)/mol, respectively. For the models with small ΔH_U , changes in both the lower and the upper states contribute to these increases (Figure 1). The f_{hs} values are slightly smaller than those for the five-parameter model (compare with Table 2.)

With the parameter values determined, one can calculate the hydrogen bonding contributions to the hydration quantities at

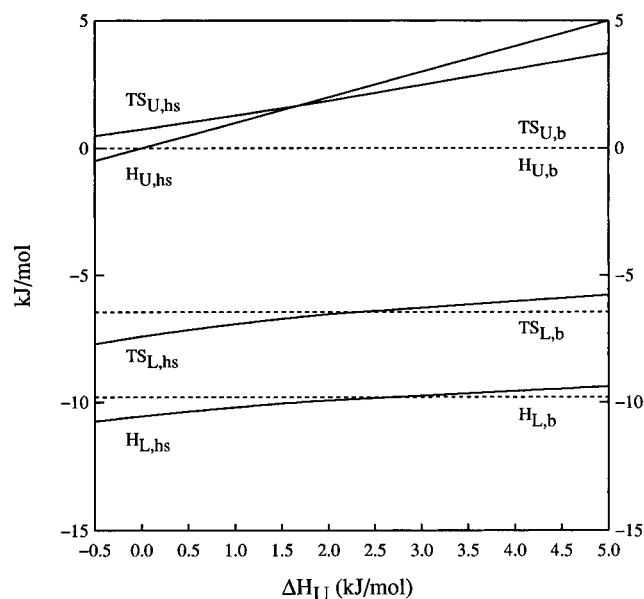


Figure 1. Enthalpy ($H_{U,hs}$) and entropy ($S_{U,hs}$) of the upper state in the hydration shell and similar quantities for the lower state (subscript L), all plotted against ΔH_U . The entropy values have been multiplied by $T = 298.15$ for scale. Thus, all values are in kJ/mol units. The dotted lines are for the corresponding quantities for the bulk (subscript b), which are independent of ΔH_U . The enthalpy and entropy of the upper state in the bulk have been arbitrarily set to zero.

Table 5. Model Parameter Values When $\Delta H_U = 0.3$

	f_{hs} at 25 °C (%)	ΔH_{hs}° (kJ/mol)	ΔS_{hs}° ((J/K)/mol)	ΔS_U ((J/K)/mol)
CH ₄	25.4	10.78	27.18	2.78
C ₂ H ₆	25.8	10.78	27.35	2.91
C ₃ H ₈	26.2	10.73	27.37	3.05
iC ₄ H ₁₀	26.7	10.69	27.45	3.21
C(CH ₃) ₄	28.0	10.83	28.46	3.60

Table 6. Model Parameter Values When $\Delta H_U = 5.0$

	f_{hs} at 25 °C (%)	ΔH_{hs}° (kJ/mol)	ΔS_{hs}° ((J/K)/mol)	ΔS_U ((J/K)/mol)
CH ₄	11.9	14.47	31.91	12.27
C ₂ H ₆	12.1	14.45	31.98	12.39
C ₃ H ₈	12.3	14.38	31.86	12.50
iC ₄ H ₁₀	12.5	14.32	31.81	12.63
C(CH ₃) ₄	13.1	14.39	32.56	13.07

Table 7. Hydrogen Bonding Contribution to the Hydration and the NMR Downfield Chemical Shift for Neopentane, with $\Delta H_U = 0.3$ kJ/mol^a

T	propane				neopentane				
	ΔH^h	ΔS^h	ΔG^h	ΔC_p^h	ΔH^h	ΔS^h	ΔG^h	ΔC_p^h	$\Delta\delta/m$
0	-1.7	-7.1	0.2	330.8	0.8	1.0	0.5	495.7	0.039
25	6.6	22.2	0	331.9	13.2	44.4	0	485.9	-0.021
50	14.6	47.9	-0.9	302.1	24.8	81.5	-1.6	431.4	-0.077
75	21.6	68.8	-2.3	255.3	34.6	110.9	-4.0	354.8	-0.125
100	27.3	84.7	-4.3	203.7	42.5	132.8	-7.0	274.5	-0.162

^a The units used are °C for T , kJ/mol for ΔH^h and ΔG^h , (J/K)/mol for ΔS^h and ΔC_p^h , and ppm/m for $\Delta\delta/m$.

any temperature. The temperature dependencies are given for two solutes, propane and neopentane, for the models with $\Delta H_U = 0.3$ kJ/mol in Table 7 and for $\Delta H_U = 5.0$ kJ/mol in Table 8. As with the five-parameter model, both the enthalpy and the entropy changes increase rapidly with temperature. The striking difference from the five-parameter model (Table 2) is the large positive contribution to the entropy change at 25 °C and above. The enthalpy and entropy changes were forced to compensate

Table 8. Hydrogen Bonding Contribution to the Hydration and the NMR Downfield Chemical Shift for Neopentane, with $\Delta H_U = 5.0$ kJ/mol^a

T	propane				neopentane				
	ΔH^h	ΔS^h	ΔG^h	ΔC_p^h	ΔH^h	ΔS^h	ΔG^h	ΔC_p^h	$\Delta\delta/m$
0	0.9	2.2	0.3	126.7	4.3	13.0	0.8	227.7	0.343
25	6.6	22.2	0	331.5	13.3	44.2	0	486.3	0.340
50	17.3	56.4	-0.9	514.5	28.3	92.5	-1.6	706.5	0.314
75	31.9	99.9	-2.9	642.7	47.9	150.9	-4.7	849.7	0.271
100	48.8	147.0	-6.0	705.8	70.1	212.3	-9.1	907.5	0.217

^a The units used are °C for T , kJ/mol for ΔH^h and ΔG^h , (J/K)/mol for ΔS^h and ΔC_p^h , and ppm/m for $\Delta\delta/m$.

at 25 °C, but they remain nearly compensating at all other temperatures as indicated by the small values for the noncompensating remainder, ΔG^h . For models with small ΔH_U , the heat capacity change decreases with temperature in the high-temperature range. This is in accord with experimental data.²⁷ On the other hand, the model with large ΔH_U gives ΔC_p^h values that keep increasing even at 100 °C. The NMR chemical shift values for neopentane are roughly similar to those for propane (Table 4).

Discussion

Muller's two-state model is attractive because of its simplicity. However, it is a pure solvent reorganization model which, according to many authors,⁵⁻¹⁰ should produce only compensating enthalpy and entropy changes. Instead, the model produces a small enthalpy change and a large entropy change at room temperature. (For example, ΔH^h and $T\Delta S^h$ are -2.94 and -26.4 kJ/mol, respectively, for propane at 25 °C.) The fact that the entropy change produced is approximately equal to the full hydration entropy change was considered by Muller to be one of the merits of the model.²¹ However, the hydrogen bonding contribution, ΔS^h , is only a part of the total hydration entropy change, ΔS^* . It has been argued^{11,12,14} that the excluded volume effect produces a large, negative entropy change. If the solvent reorganization also produced such a large, negative entropy change at room temperature, the total entropy change would be too large in magnitude.

It is instructive to see qualitatively how Muller's model produces the large negative entropy change. The function $f(1-f)$ that appears in eqs 3 and 5 has a maximum at $f = 0.5$. Since f_{hs} and f_b are less than 0.5, this means that the heat capacity increases when either ΔH° or f increases, as noted by Muller.²¹ On the other hand, when ΔH_U is set to zero, an increase in f alone will produce a positive ΔH^h while an increase in ΔH° alone will produce a negative ΔH^h . As Muller points out, this means that both ΔH° and f must increase at least at the temperature at which $\Delta H^h = 0$. In other words, the hydrogen bonds are stronger ($\Delta H_{hs}^\circ > \Delta H_b^\circ$) but also more broken ($f_{hs} > f_b$) in the hydration shell. Since ΔS_U is also assumed to be zero, this can happen only if the entropy of the lower state decreased so much as to overwhelm the enthalpy decrease.

Thus, the assumption that ΔH_U and ΔS_U are both zero is an essential ingredient for the production of the large negative entropy change. Muller assumed $\Delta H_U = \Delta S_U = 0$, presumably in order to reduce the number of parameters. However, there is no a priori reason to expect that the enthalpy and entropy changes should be restricted to the lower state only. The two states of the model are merely two discrete representatives of an ensemble of microstates over which the energy would vary continuously. The effective dielectric constant and volume

(27) Naghibi, H.; Dec, S. F.; Gill, S. J. *J. Phys. Chem.* **1987**, *91*, 245-248.

packing density near a hydrophobic atom will be different from those in the bulk, and these differences will influence the enthalpy and entropy when the hydrogen atom is in the non-hydrogen-bonded state as well as in the bonded state. Indeed Figure 1 shows that, when both states are allowed to change, the magnitude of the changes in the upper state is comparable to or larger than that of the lower state.

By abandoning the assumption of $\Delta H_U = \Delta S_U = 0$, we generated a whole set of models with different values of ΔH_U , all of which are required to produce compensating enthalpy and entropy changes at 25 °C. When ΔH_U is large, hydrogen bonds in the hydration shell have higher enthalpy than in the bulk at room temperature ($H_{L,hs} > H_{L,b}$, Figure 1), but can be said to be stronger than those in the bulk since more energy is required to break them than in the bulk ($\Delta H_{hs}^\circ > \Delta H_b^\circ$). In this regime of ΔH_U values and temperature, less hydrogen bonds are broken in the hydration shell than in the bulk ($f_{hs} < f_b$, Tables 3 and 6) and the hydration shell is akin to the "iceberg". When ΔH_U is small, on the other hand, the hydrogen bonds are still stronger in the hydration-shell at room temperature ($\Delta H_{hs}^\circ > \Delta H_b^\circ$, Figure 1), but now more hydrogen bonds are broken in the hydration shell than in the bulk ($f_{hs} > f_b$, Tables 3 and 5). The small ΔH_U models are therefore qualitatively similar to Muller's original model. This similarity can also be discerned from the similarity of the model parameter values given in Tables 2 and 5. Thus, it is possible to move continuously from the iceberg-like model for the hydration shell water to Muller's new model, with stronger but more broken hydrogen bonds, by varying one single parameter, in a rather narrow range of only about 5 kJ/mol.

As mentioned before in the Results, there are a number of reasons why models with small ΔH_U values are likely to be closer to reality than those with larger ΔH_U . Firstly, Muller's estimated value of about 0.06 ppm/m for $\Delta\delta/m$ for propane at 0 °C occurs when ΔH_U is 0.3 kJ/mol (Table 4). Also only models with small ΔH_U (Tables 4 and 7) reproduce the experimentally observed sign reversal of $\Delta\delta/m$ with temperature.²⁵ Finally, the heat capacity change decreases with temperature in the high temperature range only when ΔH_U is small (Tables 7 and 8). These observations in favor of a non-iceberg-like model are consistent with the results of numerous computer simulation studies,^{28–34} which failed to detect an iceberg-like structure around a nonpolar solute molecule at room temperature, with thermodynamic and other theoretical analysis,^{7,13,14} and with the results of recent neutron scattering studies.³⁵ We will

therefore take the model with a ΔH_U value of 0.3 kJ/mol only and compare it with Muller's original model. Uncertainties associated with the model parameters and with some of the experimental values do not warrant a precise determination of the optimum ΔH_U value. We pick the value of 0.3 simply as a concrete example of small ΔH_U models.

As mentioned before, the parameter values of this model are not too different from those of Muller's original model. Thus, the ΔH_{hs}° , ΔS_{hs}° , and f_{hs} values of this model (Table 5) are essentially the same as those of the original model (Table 2). Essentially the only difference, and a remarkably large difference, is in the ΔS^h values (Tables 2 and 7). Aside from the relatively minor modification of using the previously calculated ΔH_r value for ΔH^h , the main difference between the new model and Muller's original model is the replacement of the assumption $\Delta H_U = \Delta S_U = 0$ with the compensation assumption $\Delta H^h = T\Delta S^h$ at room temperature. The compensation assumption was deliberately adopted here in order to see if such forced assumption will produce an unreasonable set of model parameters. The results presented above show that in fact very small changes in the parameter values are sufficient to produce the compensation. In particular, the values for ΔH_U and ΔS_U that produce the compensation are not far from zero.

The fact that small changes in parameter values will produce such a large change in entropy is initially surprising. For example, in the case of propane, changing ΔH_U from zero to 0.30 kJ/mol and ΔS_U from zero to 3.05 (J/K)/mol (Table 5) resulted in a change in the ΔS^h value from -71.4 (Table 2) to $+22.2$ (J/K)/mol (Table 7) at 25 °C. The reason for such sensitivity is in the fact that the effect of any change in a parameter value is magnified by n^h , the number of hydrogen bonds in the hydration shell, when it applies to the hydration quantities. Thus, in eq 7, the net sum of the terms in the square brackets is small for small values of ΔS_U but can nonetheless give rise to a large value for ΔS^h because of the n^h factor outside the brackets. This is likely to be a general problem with all mixture theory models; many different models can be made to reproduce the observed thermodynamic properties by only a small adjustment of model parameters because of the built-in amplification by the size of the hydration shell. This feature makes it difficult to distinguish the correct from the incorrect models.

In summary, we have shown that Muller's two-state model of bulk and hydrated water can produce compensation with very little modification of the model parameters. In addition, available data on the temperature dependence of the proton NMR chemical shift and of the heat capacity change upon hydration support Muller's model of hydrated water, in which the hydrogen bonds are enthalpically stronger but fewer than in the bulk, rather than the iceberg-like model with stronger and more hydrogen bonds.

JA9538389

(28) Geiger, A.; Rahman, A.; Stillinger, F. H. *J. Chem. Phys.* **1979**, *70*, 263–276.

(29) Rosicky, P. J.; Karplus, M. *J. Am. Chem. Soc.* **1979**, *101*, 1913–1937.

(30) Okazaki, S.; Nakanishi, K.; Touhara, H.; Watanabe, N.; Adachi, Y. *J. Chem. Phys.* **1981**, *74*, 5863.

(31) Mezei, M.; Beveridge, D. L. *J. Chem. Phys.* **1981**, *74*, 622–632.

(32) Rapaport, D. C.; Scheraga, H. A. *J. Phys. Chem.* **1982**, *86*, 873–880.

(33) Jorgensen, W. L.; Gao, J.; Ravimohan, C. *J. Phys. Chem.* **1985**, *89*, 3470–3473.

(34) van Belle, D.; Wodak, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 647–652.

(35) Finney, J. L.; Soper, A. K. *Chem. Soc. Rev.* **1994**, *1*, 1–10.