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# Enthalpy–entropy compensation in the thermodynamics of hydrophobicity

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**Abstract**

Using Widom's potential distribution theory (J. Chem. Phys. 39 (1963) 2808; J. Phys. Chem. 86 (1982) 869), a general and a special theorems are derived, by means of which one can judge whether a particular sub-process of an overall process will produce compensating changes in enthalpy and entropy. The enthalpy–entropy compensation phenomena that are observed in the transfer process of a hydrophobic molecule from a non-aqueous phase to water are examined in the light of these theorems. It is concluded that most sub-processes involved in the hydrophobic transfer process are compensating except one, that of inserting a cavity corresponding to the solute molecule in the liquid. The reason that this process is non-compensating, and therefore most responsible for the hydrophobicity, is traced to the hard core overlap between solvent and the solute molecules.

*Key words:* Enthalpy; Entropy; Compensation; Hydrophobic; Thermodynamic

## 1. Introduction

Many chemical reactions appear to be accompanied by process(es) that involve large changes in enthalpy and entropy but a relatively small change in the free energy. Many examples of such 'compensation' behavior have been compiled by Leffler and Grunwald [1] and by Lumry and Rajender [2].

In the case of the transfer of a hydrophobic molecule from a non-aqueous phase to water, two different but related compensation behaviors are of interest.

The temperature-dependence of the thermodynamics of this process exhibits a compensating behavior in that the enthalpy and the entropy changes increase rapidly with temperature whereas the free energy change increases relatively more slowly with temperature [3–5]. One result of this behavior is that the hydrophobicity, which is here defined as the free energy change upon this transfer process, is dominated by the entropic effect at low temperatures but by the enthalpic effect at higher temperatures [3]. The enthalpic nature of the hydrophobicity at high temperatures suggests a modification of the traditional view of hydrophobicity as being due to the formation of 'iceberg' or some other low-entropy structures in the vicinity of the added non-polar solute molecule.

The thermodynamics of the process at any one temperature is strongly affected by that of the

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solvent reorganization [5]. However, there are suggestions in the literature [6–9] that solvent reorganization is a compensating process, in which case it becomes irrelevant as far as the free energy change is concerned. If this were the case for all solvent reorganization processes, the true cause of hydrophobicity must be sought elsewhere other than in the solvent reorganization.

In this article, I attempt to clarify this relation between the compensation behavior and the hydrophobicity. It is possible to use Widom's potential distribution theory [10,11] to clearly identify one sub-process that is essential to the hydrophobic transfer process and which is clearly non-compensating. All other sub-processes are likely to be largely compensating and therefore not essential in producing the hydrophobicity.

## 2. Condition for compensation of temperature-dependent change

It is well known [3–5] that the enthalpy and entropy changes upon dissolution of non-polar molecules in water are strongly temperature-dependent whereas the temperature-dependence of the corresponding free energy change is much more mild. This means that the temperature-dependent changes in $\Delta H$ and $T\Delta S$ are large in magnitude but largely compensate one another. An example of this phenomenon is shown in Fig. 1 where the temperature-dependence of the enthalpy, entropy, and the free energy of dissolution of liquid neopentane in water is shown assuming that the heat capacity change, $\Delta C_p^{\bullet}$, is independent of temperature. When $\Delta C_p^{\bullet}$ is independent of temperature, one has

$$\Delta H^{\bullet} = \Delta C_p^{\bullet}(T - T_h), \tag{1}$$

$$T\Delta S^{\bullet} = \Delta C_p^{\bullet} T \ln(T/T_s) \tag{2}$$

$$\approx \Delta C_p^{\bullet}(T - T_s) + (1/2) T_s \Delta C_p^{\bullet} t^2 \tag{3}$$

and

$$\Delta G^{\bullet} = \Delta C_p^{\bullet}[(T - T_h) - T \ln(T/T_s)] \tag{4}$$

$$\approx \Delta C_p^{\bullet}(T_s - T_h) - (1/2) T_s \Delta C_p^{\bullet} t^2, \tag{5}$$

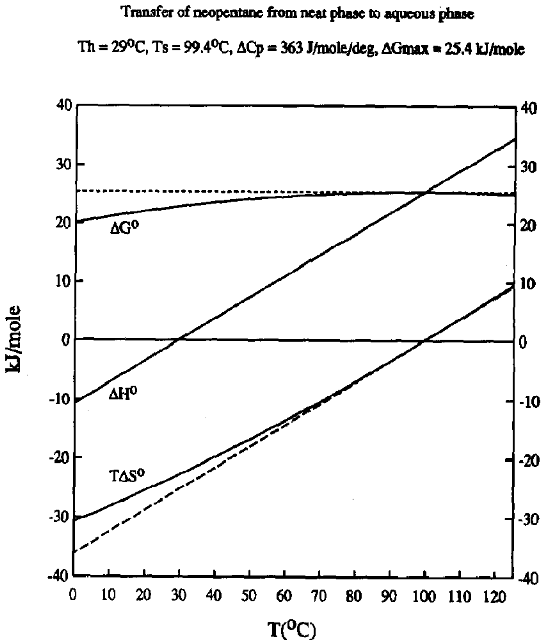

Fig. 1. The temperature-dependence of the changes in the standard free energy, enthalpy, and entropy upon transfer of neopentane from its pure liquid phase to water. The figure was constructed from the room temperature data on $\Delta H^{\bullet}$, $T\Delta S^{\bullet}$, $\Delta G^{\bullet}$, and $\Delta C_p$ given earlier [5] and assuming that the heat capacity change is independent of temperature.

where $T_h$ and $T_s$ are the temperatures at which the enthalpy and entropy changes become zero, which are 29 and 116°C, respectively, for the neopentane transfer process, and $t$ is defined as $(T - T_s)/T_s$. The superscript $^{\bullet}$ in these expressions indicates that the quantities are Ben-Naim's 'local standard' quantities [12], which are the standard quantities used throughout this article. These quantities express changes in the thermodynamic functions for the transfer of the solute molecule from a fixed point in one phase to a fixed position in another. Eqs. (3) and (5) were obtained by expanding $\ln(T/T_s)$ in Taylor series around $t = 0$ and discarding all terms beyond the second power in $t$. The dotted lines in Fig. 1 indicate the temperature-dependence of the entropy and the free energy when the second term in Eqs. (3) and (5) are neglected.

Since $\partial\Delta G^{\bullet}/\partial T = -\Delta S^{\bullet}$, perfect compensation happens at $T_s$ where $\Delta S^{\bullet} = 0$. More generally, the rates of change in enthalpy and entropy upon temperature change are given respectively by

$$\partial \Delta H^{\bullet}/\partial T = \Delta C_p^{\bullet} \tag{6}$$

and

$$\partial (T\Delta S^{\bullet})/\partial T = \Delta C_p^{\bullet} + \Delta S^{\bullet}. \tag{7}$$

Therefore, the temperature-dependence will compensate whenever $\Delta C_p^{\bullet} \gg \Delta S^{\bullet}$. Since $\Delta C_p^{\bullet}$ is large when a hydrophobic molecule is transferred into the aqueous phase, the temperature-dependence will always tend to compensate.

## 3. Implications on the hydrophobic effect

Above result reminds one of the ice–liquid water equilibrium at 0°C. The heat-induced conversion of ice into liquid water at 0°C also involves an (infinitely) large change in the heat capacity and an interconversion of enthalpy and entropy without a change in the free energy. Thus one possible interpretation of the thermodynamic behavior such as that shown in Fig. 1 is the following. At room temperature, insertion of a hydrophobic solute in water is accompanied by a large negative entropy change because of the formation of 'iceberg' [13] or some other low-entropy structure in the hydration shell of water around the solute molecule. At higher temperatures, this negative entropy change is reduced in magnitude as the structure 'melts' with a compensating increase in enthalpy and entropy.

According to this picture, the thermodynamic functions at any one temperature are made of two parts, a non-compensating part, which is nearly independent of temperature, and an additional part which depends strongly on temperature but compensating:

$$\Delta G^{\bullet} = \Delta G^{u} + \Delta G^{c}, \tag{8}$$

$$\Delta H^{\bullet} = \Delta H^{u} + \Delta H^{c}, \tag{9}$$

and

$$\Delta S^{\bullet} = \Delta S^{u} + \Delta S^{c}, \tag{10}$$

with

$$\Delta H^{c} = \Delta C_p^{\bullet}(T - T_c), \tag{11}$$

$$\Delta S^{c} = \Delta C_p^{\bullet} \ln(T/T_c), \tag{12}$$

and

$$\Delta G^{c} = \Delta H^{c} - T\Delta S^{c} \approx 0, \tag{13}$$

where $T_c$ is the temperature where the 'iceberg' has not melted, presumably near or below the room temperature. Since the free energy change comes mainly from the uncompensated part, which in this picture results from the structure formation in the hydration shell, it is this part that ultimately produces the hydrophobicity. The fact that the hydrophobicity becomes almost totally enthalpic at high temperature is dismissed in this picture since it is caused by the superposition of the compensating part [14].

In the last decade or so, a very different view of hydrophobicity has been advanced, by simply changing the temperature $T_c$ to near $T_s$, at which temperature the free energy change is entirely enthalpic. Since the non-compensating part is essentially all enthalpic in this picture, the hydrophobicity is then caused by a rise in enthalpy [4,15–17], presumably due to the breakage of hydrogen bonds. The structure formation at low temperatures, as indicated by the large negative entropy change at these temperatures, is irrelevant to the hydrophobicity in this picture since the structure formation is a compensating process and accompanied by a decrease in enthalpy as well as in entropy.

The debate between these two views is probably serious and not just a matter of semantics. Hydrophobicity, as measured by the free energy change upon transfer of a solute molecule from a non-aqueous solvent to water, is large and changes relatively slowly with temperature. This indicates that there probably is one physical mechanism that produces this large effect at all temperatures. The nature of this mechanism is very different depending on the outcome of this debate. However, it seems that this debate would remain semantic unless one can identify, in a model-free fashion, what processes produce only a compensating change at any one given temperature and what others produce a non-compensating change. This is at least partly possible by means of a theorem that we derive in the following using Widom's potential distribution theory.

## 4. Condition for enthalpy–entropy compensation upon solvent reorganization

We consider the thermodynamics of solvent reorganization upon insertion of a solute molecule at a fixed position in the liquid. A liquid does not have one configuration, but fluctuates among an ensemble of many different configurations. A general way of describing the 'structure' of the solvent is, therefore, by means of the probability density function, $\rho(X)$, defined so that $\rho(X)\,\mathrm{d}X$ gives the probability that the liquid will have a configuration between $X$ and $X+\mathrm{d}X$ at any given time. Here, the variable $X$ refers to the $3mN$ dimensional vector of the $x$, $y$, $z$ coordinates that describe the position of each of the m atoms in each of the $N$ molecules of the liquid solvent. The most general definition of the term 'solvent reorganization' then refers to the change in this probability density function. Thus the enthalpy, entropy, and the free energy changes upon solvent reorganization are *defined* [5] respectively by

$$\Delta H_r = \int H(X)[\rho'(X) - \rho(X)]\,\mathrm{d}X, \tag{14}$$

$$\Delta S_r = -k\int[\rho'(X)\ln\rho'(X) - \rho(X)\ln\rho(X)]\,\mathrm{d}X, \tag{15}$$

and

$$\Delta G_r = \Delta H_r - T\Delta S_r, \tag{16}$$

where the subscript r indicates that these are the solvent reorganization terms, $H(X) = E(X) + pV(X)$ is the enthalpy function for a configuration $X$, and $k$ is the Boltzmann's constant. $\rho(X)$ and $\rho'(X)$ are the probability density functions of the solvent molecules before and after the insertion of the solute molecule, respectively. For the $N$–$p$–$T$ ensemble, these probability densities are given, respectively, by

$$\rho(X) = \frac{\exp[-H(X)/kT]}{\int \exp[-H(X)/kT]\,\mathrm{d}X} \tag{17}$$

and

$$\rho'(X) = \frac{\exp\{-[H(X)+\psi(X)]/kT\}}{\int \exp\{-[H(X)+\psi(X)]/kT\}\,\mathrm{d}X}, \tag{18}$$

where $\psi(X)$ is the interaction energy of the inserted solute molecule with the solvent molecules in configuration $X$.

The total change in the free energy upon insertion of a solute molecule is given by [10,11]

$$\Delta G^{\bullet} = -kT\ln\langle\exp[-\psi(X)/kT]\rangle, \tag{19}$$

where the angled brackets refer to the ensemble average over the pure solvent configurations. The pure solvent ensemble average of any quantity $q$ that is well defined for a solvent configuration $X$ is given by

$$\langle q\rangle = \int q(X)\rho(X)\,\mathrm{d}X. \tag{20}$$

Applying the Gibbs–Helmholtz equation in thermodynamics,

$$\Delta H = -T^2\partial(\Delta G/T)/\partial T, \tag{21}$$

to Eq. (19), and using the definitions (20), (17), (18), and (14), one obtains the total enthalpy change as,

$$\Delta H^{\bullet} = \Delta H_r + \langle\psi\rangle', \tag{22}$$

where the prime on the angled brackets indicates the ensemble average over solvent configurations after the insertion of the solute, i.e., for any quantity $q$ that is well defined for a solvent configuration $X$,

$$\langle q\rangle' = \int q(X)\rho'(X)\,\mathrm{d}X. \tag{23}$$

The total entropy change is obtained either as the temperature derivative of the total free energy change or from the difference between $\Delta H$ and $\Delta G$. Either way, one obtains,

$$T\Delta S^{\bullet} = \Delta H_r - (\Delta G^{\bullet} - \langle\psi\rangle'). \tag{24}$$

In order to focus on the behavior of the solvent, we now assume that the solute molecule is a rigid sphere or that it is rigid and inserted in the liquid in a fixed orientation. In this case, it is clear that all the entropy change that occurs upon this insertion process is due to the rearrangement of the solvent molecules, i.e.

$$\Delta S^{\bullet} = \Delta S_{\mathrm{r}}. \tag{25}$$

Therefore, according to Eq. (24), the enthalpy and the entropy changes due to the solvent reorganization will compensate when and only when $\Delta G^{\bullet} = \langle \psi \rangle'$. This is our general theorem.

One can derive an approximate relation between $\langle \psi \rangle'$ and $\Delta G^{\bullet}$ in the following manner. From (17) and (20), we have

$$\langle \exp(-\psi/kT) \rangle = \frac{\int \exp(-\psi/kT)\,\exp(-H/kT)\,\mathrm{d}X}{\int \exp(-H/kT)\,\mathrm{d}X} = 1 \bigg/ \frac{\int \exp(-H/kT)\,\mathrm{d}X}{\int \exp[-(H+\psi)/kT]\,\mathrm{d}X}. \tag{26}$$

Now, if $\psi(X)$ is not singular, one can write

$$\exp(-H/kT) = \exp(\psi/kT)\,\exp[-(H+\psi)/kT]. \tag{27}$$

Therefore, if $\psi(X)$ is not singular for all configurations of the pure solvent, then (26) can be rewritten as

$$\langle \exp(-\psi/kT) \rangle = 1/\langle \exp(\psi/kT) \rangle'. \tag{28}$$

Note that the average on the left-hand side of this equation is over the ensemble for the pure liquid whereas that on the right-hand side is over the ensemble for the solution after the insertion of the solute. This inverse relation has been derived by others some time ago. (See ref. [11].)

Use of this relation in (19) yields

$$\Delta G^{\bullet} = kT \ln\langle \exp(\psi/kT) \rangle'. \tag{29}$$

Now define $x$ as

$$x = \psi - \langle \psi \rangle' \tag{30}$$

and rewrite (29) as

$$\Delta G^{\bullet} = \langle \psi \rangle' + kT \ln\langle \exp(x/kT) \rangle'. \tag{31}$$

The last term in the above expression is then expanded in Taylor series in $x$. Since $\langle x \rangle' = 0$ from definition (30), the term in the first power of $x$ vanishes and one obtains

$$\Delta G^{\bullet} \approx \langle \psi \rangle' + \langle x^2 \rangle'/2kT \tag{32}$$

if higher order terms are ignored. Thus a necessary, and probably also sufficient, condition for the enthalpy–entropy compensation upon solvent reorganization is that

$$\langle x^2 \rangle'/2kT \ll \langle \psi \rangle'. \tag{33}$$

This is our special theorem that applies when $\psi(X)$ does not become singular for all configuration $X$ of the pure solvent.

## 5. Processes that do and do not compensate

The process of inserting a solute molecule in water can be broken into two steps; creation of the cavity followed by turning on the attractive interaction. The solvent reorganizes in each of these two steps [5]. According to the Monte Carlo calculation by Jorgensen et al. [18], the standard deviation of the fluctuation in the attractive interaction energy between a hydrocarbon and water is only 0.2–0.3 kJ/mol at room temperature. This range corresponds to $\langle x^2 \rangle'/2kT = (8\text{–}18) \times 10^{-3}$ kJ/mol, which is small compared to the average attractive interaction energy of 36.0 kJ/mol between neopentane and water. Thus the solvent reorganization that accompanies the second step of dissolution, that of turning on the attractive interaction on the existing cavity, is likely to be a compensating process.

In contrast, we show below that the solvent reorganization that accompanies the creation of a cavity in water is clearly non-compensating. The interaction energy, $\psi(X)$, for inserting a hard sphere at a fixed position in water is infinite if the position happens to be occupied by a solvent molecule and zero if not. Therefore $\psi(X)$ is singular for many solvent configurations and Eq. (28) becomes invalid. Actually, $\langle \psi \rangle'$ is zero when the solute is a hard sphere and, since $\Delta G^{\bullet}$ is non-zero, cavity creation is never a compensating process. It is important to note that the reason for the non-compensating behavior in this case is not that the fluctuation $\langle x^2 \rangle'$ is large. In fact, when the solute is a cavity, $\langle x^2 \rangle'$ is zero since $\psi$ is identically zero for all solvent configurations of the solution. The reason for the non-compensating behavior is in the fact that $\psi(X)$ becomes infinite for many pure solvent configurations and this is in turn because, in these configurations, the site of the new solute molecule is occupied by a solvent molecule.

## 6. Discussion

Ben-Naim [6,19] and Grunwald [7,20] presented a general dissection scheme for any process in such a manner that one step of the dissection is always an enthalpy–entropy compensated process. When applied to the dissolution process, the dissection scheme is as follows. In the first step, the solute molecule is inserted in water keeping a solvent organization parameter, say $\alpha$, fixed. The process is then completed in the second step by relaxing the solvent so that the parameter $\alpha$ can change to its natural final value for the solution. They show by thermodynamic and statistical mechanical arguments that the second of these two steps is always a compensating process. It should be carefully realized, however, that the solvent reorganizes not only in the second step but generally also in the first step of this dissection scheme. This is because a single parameter, or even a finite set of many parameters, is insufficient to completely specify the organization of the solvent molecules. For instance a solution that contains a solute molecule and therefore cannot have the same probability density function $\rho(X)$ as that of the pure solvent, nonetheless, can be forced to have the same value for the parameter $\alpha$ as that for the pure solvent. Therefore, this dissection scheme does not prove that all solvent reorganizations are compensating. Furthermore, what part of the solvent reorganization will be included in step 2 versus step 1 depends on the choice of the parameter $\alpha$, which is left unspecified or arbitrary by the presenters of this dissection scheme.

Equations that have the same form as Eqs. (22) and (24) have been derived by others using different statistical mechanical routes [6,9]. Noting that the $\Delta H_r$ term appears in both the enthalpy and the entropy expressions, they concluded that the solvent reorganization must be an exactly compensating process. However, if $\Delta H^\bullet$ is written as a sum of two terms, say,

$$\Delta H^\bullet = R + A,$$

then the entropy change can always be written as

$$T\Delta S^\bullet = \Delta H^\bullet - \Delta G^\bullet = R + B,$$

where $B = A - \Delta G^\circ$. Thus the term $R$ appears both in the entropy and the enthalpy expressions regardless of how $R$ is defined and, in particular, even when $R$ is not the entropy change upon solvent reorganization. Therefore mere presence of the $\Delta H_r$ term in the entropy expression is not sufficient; compensation is indicated only if the $\Delta H_r$ term can be independently identified as the entropy change upon solvent reorganization.

I previously [8] derived expressions for the thermodynamic quantities for the solvent reorganization upon insertion of a cavity by considering the solvent reorganization as a process of selecting particular configurations, the solution configurations, from the ensemble of pure solvent configurations. The entropy of the pure solvent system is given by the ensemble average of $k \ln \rho(X)$ over all the pure solvent configurations. The entropy of the solution is given by the sum of two terms; an average of $k \ln \rho(X)$ over the selected solution configurations plus $k \ln z$, where $\zeta$ is the fraction of the selected solution configurations in the ensemble of all pure solvent configurations. It turns out [8] that the first term equals $\Delta H_r/T$ and therefore exactly compensates the enthalpy change. This corresponds to the fact that $\langle x^2 \rangle' = 0$ for the solution configurations with a cavity. The non-compensating part of the entropy change, $k \ln z$, is equal to the total free energy change (with a change of sign and multiplication by $T$) and arises simply from the fact that some pure solvent configurations are excluded from the ensemble for the solution because of the steric overlap between the solvent and the solute molecules.

In summary, we derived a general and a special theorem which can be used to decide whether a process is compensating. While many solvent reorganization processes, and also the temperature variations, yield enthalpy and entropy changes that compensate, one process is clearly not compensating and therefore is the process mainly responsible for the hydrophobicity. This is the solvent reorganization associated with the cavity formation. Moreover, the reason that this process is non-compensating is in the fact that some solvent configurations produce an infinite solute-solvent interaction energy because of the steric overlap between the solute and the solvent molecules. In fact, the non-compensating part is directly related to the number of instances when this overlap happens. Thus the origin of this effect is intrinsically geometrical and entropic; it bears no direct relation to the formation or breakage of hydrogen bonds. This basic feature of the process is, however, masked by the presence of associated compensating processes that alter the enthalpy/entropy mix of the overall dissolution process.

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## Discussion to the paper by B.K. Lee

### *Comments*

*By K. Sharp*

Solvent reorganization upon apolar solute dissolution clearly involves compensating enthalpy/entropy changes, a diagnostic of which is the large heat capacity change. The latter is responsible for the change from entropy domination to enthalpy domination of the hydrophobic effect over the temperature range 25°C to 100°C. B.K. Lee goes further than this and suggests that these solvent reorganization effects (which include the traditional iceberg or low entropy water formation at room temperature) contribute little net free energy contribution to the hydrophobic effect, and that the true cause of hydrophobicity must be due to some other effect which is non-compensating. A 'non-compensating' effect I understand from the discussion preceding Eq. (8), means one that is temperature independent and thus has a small heat capacity change associated with it. I find this somewhat ironic since a large heat capacity increase is more often than not taken as the most reliable signature of, and way to quantitate the hydrophobic effect (e.g., see refs. [1,2]). B.K. Lee's use of Widom potentials provides conditions under which certain solvent enthalpy and entropy changes will compensate (i.e. that $\Delta G_{\text{reorganization}} \approx 0$). However, I still do not see why having $\Delta C_p \gg 0$ requires that the free energy of the process that is giving rise to the heat capacity change, $\Delta G^c$, be zero (i.e. that $\Delta H^c = T\Delta S^c$), which requires one to postulate another process with non-zero free energy but zero heat capacity change. One could equally well assume, with greater parsimony, that there is no $\Delta G^u$, and that $\Delta G^c > 0$: due to entropy at low temperature because water would prefer to be more ordered than lose H-bonds, and due to enthalpy at higher temperature because it is now cheaper to sacrifice a hydrogen bond [3].

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*By Y. Marcus*

At the end of the paper it is stated that "one process is clearly not compensating and therefore is the process mainly responsible for the hydrophobicity. ... (Thus) the origin of this effect is intrinsically geometrical and entropic; it bears no direct relation to the formation or breakage of hydrogen bonds". Why, then, is hydrophobicity limited to water (and solvophobicity to other H-bonded, highly structured solvents)?

*Responses by B.K. Lee to Comments*

*To K. Sharp*

(1) I do indeed think that the large heat capacity change and the large free energy change arise from different physical causes, the former largely from the formation and melting of the "iceberg" or similar low-entropy structures and the latter from the small size of water molecules. This, however, does not diminish the role of $\Delta C_p$ as the signature of the hydrophobic effect, since the small size and the hydrogen bonding property of water go together.

(2) I do believe that the process that produces compensating changes in the enthalpy and entropy is associated with a large change in heat capacity. However, I do not claim that $\Delta G^c$ is zero because the associated $\Delta C_p$ is large. $\Delta G^c$ is zero by definition; this is what I mean by the term "compensation".

(3) $\Delta G^u$ must exist since $\Delta G^c$ is zero by definition and total $\Delta G$ is certainly non-zero. Kim is suggesting that the mechanism that produces $\Delta G^u$ is the formation of more ordered hydrogen bonds at low temperature and hydrogen bond breakage at high temperature. In a sense, he is correct. what I am suggesting are (1) that, in addition to these two mechanisms, the formation of the low entropy structure and the hydrogen bond breakage, there is a third mechanism, that due to size and (2) that the first two mechanisms each have nearly compensating entropy and enthalpy changes whereas the third mechanism has essentially zero enthalpy compenent and therefore non-compensating. Thus we have $\Delta G = \Delta H_{\mathrm{I}} - T\Delta S_{\mathrm{I}} - T\Delta S_{\mathrm{III}}$ at low temperature and $\Delta G = \Delta H_{\mathrm{II}} - T\Delta S_{\mathrm{II}} - T\Delta S_{\mathrm{III}}$ at high temperature, where the subscripts indicate the mechanism, I for the low-entropy structure formation, II for the hydrogen bond breakage, and III for the size mechanism. I am suggesting that $\Delta H_{\mathrm{I}}$ and $T\Delta S_{\mathrm{I}}$ cancel for the low temperature case and $\Delta H_{\mathrm{II}}$ and $T\Delta S_{\mathrm{II}}$ cancel for the high temperature case. However, one could consider that $\Delta H_{\mathrm{I}}$ and $T\Delta S_{\mathrm{III}}$ cancel for the low temperature case and $T\Delta S_{\mathrm{II}}$, which is positive, and $T\Delta S_{\mathrm{III}}$, which is negative, cancel for the high temperature case. One then obtains Kim's picture. What I am trying to point out is that there is a problem with the 'simple' picture, in which the size-dependent mechanism is not considered. This is that each of the mechanisms, I and II, involves changes in both enthalpy and entropy, which nearly compensate each other so that the net free energy remainder is not large enough to account for the hydrophobicity.

*To Y. Marcus*

Enthalpy–entropy non-compensation is clearly a necessary condition for hydrophobicity. But it is not sufficient. In order for a mechanism to produce hydrophobicity, it must produce not only a non-zero free energy change, but also the free energy change produced should be larger in water than in a non-aqueous solvent The solvent reorganization free energy change upon cavity formation does indeed possess this property, but this aspect is not the subject of this paper. The key to understanding this aspect is the realization that hydrogen bonding is not the only property that distinguishes water from common non-aqueous solvents. The other important characteristic of water molecules is their small size. For more details see another paper in this issue, "Role of hydrogen bonds in hydrophobicity: the free energy of cavity formation in water models with and without the hydrogen bonds" by Madan and Lee and references cited therein.