An Analysis of the Thermodynamics of Hydrophobic Solvation
Based on Scaled Particle Theory

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Synopsis

A comprehensive, semi-quantitative model for the thermodynamics of hydrophobic solvation is presented. The model is based on a very simple premise suggested by the scaled particle theory and treats both solute and solvent molecules as hard spheres. A connection between the peculiarly large heat-capacity change for hydrophobic solvation and the large temperature dependence of the thermal expansivity of water is found. Analysis reveals a possible physical origin for the converging behavior of solvation entropies for a series of homologous hydrophobic compounds. The model suggests that the low solubility and the large heat-capacity change of hydrophobic solvation stem from two distinct aspects of water molecules: the static geometry of the molecule and the dynamic hydrogen bonding network, respectively.
Introduction

The scaled particle theory (SPT), a statistical mechanical model for liquids and solutions made of hard spherical molecules, is a powerful conceptual framework and a useful computational tool for molecular solvation.\textsuperscript{1\textendash}4 Even though the SPT was originally developed only for hard spherical molecules,\textsuperscript{5} recent studies have shown that it also provides insight into the solvation of hydrophobic solutes in associative liquid like water. There are several reasons for this wide applicability of SPT:

1) The SPT is not a statistical mechanical theory based on the first principle. Rather, an independently obtained solvent density has to be provided in addition to temperature, pressure, and molecular parameters. This is in contrast to a genuine statistical mechanical theory of liquid, in which density is derived from temperature, pressure, and molecular parameters. Some essential properties of an associative liquid are contained in the density data.\textsuperscript{5,6}

2) Recent studies have shown that the SPT provides accurate numerical calculations for solvation free energy of hydrocarbons in water, but does so with less success for calculating the entropy and enthalpy.\textsuperscript{2,6} This result is consistent with the concept of entropy-enthalpy compensation, which occurs with the solvent reorganization when introducing a solute molecule into a solvent.\textsuperscript{6\textendash}9

3) To apply the SPT to an associative liquid like water, one practical difficulty is how to determine the hard sphere radii for water and the solute molecules.\textsuperscript{2} While these difficulties affect quantitative numerical calculation, it does not alter the qualitative physical insight one obtains from the SPT. In this paper, our primary interest is in the qualitative relationship between different physical quantities, the numerical values are not essential for our analysis.

Based on these arguments, we try to use SPT as a semi-quantitative model for understanding various experimental results which are essential to the solvation of small organic molecules in aqueous solutions. We show that much of the characteristics of hydrophobic solvation can be understood in terms of this over-simplified model. Our approach is very much in the same spirit of the earlier work of Grunwald.\textsuperscript{8} Treating the hydrophobic solutes as inert hard spheres, of course, completely neglects the solute-solvent interaction.\textsuperscript{3,6} This should be kept in mind when applying the result of the present analysis to the solvation of hydrocarbons. On the other hand, the dissolution of inert gases like xenon exhibits all the characteristics of hydrophobic solvation. Hence, neglecting solute-solvent interaction is justified in our present study.

Some Basic Facts
The essential features in the data for dissolution of hydrophobic compounds in aqueous solutions are summarized as follows:

1) Dissolution entropy changes, $\Delta S(T)$’s, associated with transferring a series of hydrophobic solutes from solid $\rightarrow$ water, liquid $\rightarrow$ water, and gas $\rightarrow$ water form three distinct, respective groups. Within each group, $\Delta S(T)$’s for different solute species converge to a common $\Delta S^*$ at a temperature $T^*_s$. While $\Delta S^*$’s are different for the three groups, $T^*_s$’s for all three groups are approximately equal to 110°C. The two groups of data on the transfer from liquid $\rightarrow$ water and gas $\rightarrow$ water are in agreement with the Trouton’s rule.

In order to compare free energies calculated from SPT with experimentally obtained solubility, one has to calculate the solvation free energy from a measurement based on concentration scale in molarity rather than in mole fraction. The numerical difference between the two calculations is $-RT \ln (v_1/v_2)$ where $v_1$ and $v_2$ are the molar volumes of the solvent systems before and after the transfer, respectively. For the gas phase, $v = k_B T/p$ where $p$ is the gas pressure (= 1 atm); for water, $v = 18.08$ cm$^3$/mol. This changing of concentration scale increases the free energy values given by Murphy et al. by about 60 J per degree per mole (e.g., shift the lines in their Figure 1 upward).

2) The heat-capacity changes, $\Delta C_p$’s, for all the dissolution reactions are approximately temperature independent.

3) There also appears to have a convergence temperature for enthalpy changes in dissolution of organic compounds from gas $\rightarrow$ water (see Appendix for more discussion). The temperature is not known, but the corresponding $\Delta H^*$ is about a few KJ/mol.

There have been many different ways of presenting experimental data on the thermodynamics of dissolution. Here we have summarized several key results from the literature which are useful in organizing and relating various data representations. It is important to note that many presentations are in fact concerning same experimental measurements. They are related by the basic thermodynamic formulae, as shown in the following theorems.

**Baldwin’s Theorem**

Based on the observations of Sturtevant and Privalov, R.L. Baldwin gave the following theorem in 1986. For a series of homologous reactions, designated by $i$, with temperature-independent $\Delta C_{pi}$, the following two statements are equivalent:

1) At one temperature $T^\dagger$, there are unique constants $a$ and $b$ such that:

$$\Delta S_i = a + b \Delta C_{pi}$$  \hspace{1cm} (1)

2) there is a unique temperature $T^*_s$ at which $\Delta S(T^*_s)$ is unique. That is, $T^*_s$ and $\Delta S_i(T^*_s)$
are independent of \( i \). Hence:

\[
\Delta S_i(T) = \Delta S(T^*_s) + \Delta C_{p_i} \ln(T/T^*_s)
\]  

(2)

Compare Eq. (1) with (2), we have \( a = \Delta S(T^*_s) \) and \( b = \ln(T^*_s/T^*_s) \). From now on, we will follow Lee\(^{13}\) and refer to the \( \Delta S_i \) versus \( \Delta C_{p_i} \) relation in Eq. (1) as a SMPG plot named after Sturtevant, Murphy, Privalov, and Gill.\(^{10,15}\) Baldwin’s theorem states that a linear SMPG plot is equivalent to having a convergence temperature for \( \Delta S_i \), and the intersection \( a \) in the SMPG plot is the unique \( \Delta S^* \). Conversely, the existence of a convergence temperature indicates a linear SMPG plot at every temperature.

**Lee’s Theorem**

Lee’s theorem\(^{13}\) is an application of the mathematical property of a bilinear function: if a function \( f(x, y) \) is linear as a function of either \( x \) or \( y \), as well as a function of their product, \( xy \), then there exists a \( y^* \) at which \( f(x, y^*) \) is independent of \( x \). To express this by equation:

\[
f(x, y) = a + bx + cy + dxy = d(x + \frac{c}{d})(y + \frac{b}{d}) + \frac{ad - bc}{d}
\]

so when \( y = y^* = -b/d \), \( f(x, y^*) \) is independent of \( x \).

The bilinear function has to be a linear function of either variables when the other one is at a fixed value. To apply this result to the thermodynamics of dissolution, we identify the logarithmic temperature and a certain molecular parameter as the variables \( x \) and \( y \), and the entropy (or enthalpy or Gibbs free energy) of dissolution as the function \( f(x, y) \). Hence, at a given temperature, the entropy is a linear function of the molecular parameter \( X \). Lee proposed the parameter to be a size measure of the solute molecule. In fact, Lee’s proposal of

\[
\Delta S_i(T) = a_s + b_s X_i
\]

(3)

is a structural interpretation of the linear SMPG plot given in (1). The subscript “s” here stands for entropy. (There is a similar relation for enthalpy, with its respective \( a_h \) and \( b_h \).\(^{13}\) ) It is well known that \( \Delta C_p \)’s are proportional to molecular size of a hydrophobic solute. It is also worth noting that a linear relationship due to substituents of a series of functional groups is widely observed in organic reactions.\(^{17}\)

Therefore, the bilinear argument immediately leads to the existence of a convergence temperature from the linear entropy relation in Eq. (3). Combining Lee’s and Baldwin’s theorems, it can be shown that the linear entropy relation is sufficient but not necessary for generating a convergence temperature.

**The BMDW Theorem**
This theorem, which was given by Baldwin and Muller,\textsuperscript{18} and also independently by Doig and Williams,\textsuperscript{19} establishes an intrinsic relationship between the three convergence temperatures for entropy, enthalpy, and Gibbs free energy. Consider a series of homologous reactions designated by $i$ and each has a temperature-independent $\Delta C_p$ of its own. If two out of the three thermodynamics quantities (entropy, enthalpy, and Gibbs free energy) have convergence temperatures, then there is a convergence temperature for the third quantity. If we denote by $T^*_s$, $T^*_h$, and $T^*_g$ these convergence temperatures, we have:

$$T^*_g - T^*_h - T^*_g \ln(T^*_g/T^*_s) = 0$$ \hspace{1cm} (4)

and also a relation for the corresponding thermodynamic quantities:

$$\Delta G(T^*_g) = \Delta H(T^*_h) - T^*_g \Delta S(T^*_s)$$ \hspace{1cm} (5)

This theorem was used by Baldwin and Muller\textsuperscript{18} to explain the intriguing fact of approximately equal convergence temperatures $T^*_s$ and $T^*_h$ for a set of protein folding reactions. It is discovered that this set of proteins have approximately equal melting temperatures, i.e., $T^*_g = 331 \pm 9$ K and $\Delta G(T^*_g) \approx 0$. Using the same theorem, Doig and Williams\textsuperscript{19} have reached a similar conclusion. They pointed out that most proteins of the same set have approximately equal $\Delta G$ per residue at room temperature. These two arguments are consistent with each other if we note that all the proteins in the set have approximately same $\Delta C_p$ per residue.

A Physical Model Based on SPT

The basic results of SPT are summarized here. It is not necessary for the readers to know the technical details of SPT;\textsuperscript{5} rather, our model starts with Eqs. (6) and (7) below. SPT is a rigorous statistical mechanical theory for liquids made of hard spheres. The theory also provides an approximated formula for calculating the free energy of dissolving a hard spherical solute from gas phase into a hard spherical solvent, which is equivalent to introducing a spherical cavity in the hard sphere liquid. The free energy, which is a function of the radius of solute as well as the density and the radius of pure solvent, has three dominant terms. The first term is independent of solute size; it is associated with the reduction of conformational space of the liquid upon introducing a solute molecule of zero physical size into the solvent. With the physical point being present in the middle of the solution, no solvent molecule can occupy the same point in space. Hence such conformations are no longer accessible. This term is a function of the density and the radius of pure solvent only. The second term is proportional to the square of the radius of the solute, i.e., its surface area. And the third term is proportional to the cubic power of the radius, i.e., its volume, and external pressure. It has been repeatedly demonstrated, both theoretically and empirically,
that the volume term is negligible for any molecular size cavity, and the dominant effect is from the surface term which defines a proportional coefficient called surface tension. For hard spherical solvent and solute, SPT gives an expression for the surface tension, and also a minor correction term on the free energy due to different curvature of the solute molecule.

The free energy is given as:\(^5\)

\[
\frac{\Delta G}{k_B T} = -ln(1 - \xi) + \frac{r^2}{a^2} \left[ \frac{3\xi}{1 - \xi} + \frac{9}{2} \left( \frac{\xi}{1 - \xi} \right)^2 \right]
\] (6)

where \(k_B\) is the Boltzmann constant, \(T\) is temperature in Kelvin, \(a\) is the radius of solvent molecule, \(\xi\) is the packing density for pure solvent (the volume fraction occupied by the hard spheres), and \(r\) is the radius of solute molecule.

Our model starts with a very simple premise:

\[
\Delta G(T) = \delta(T, \xi) + \sigma(T, \xi) r^2
\] (7)

where \(\delta\) and \(\sigma\) are solvation energies for a point and surface tension, respectively. Thermodynamics for solvation will depend on the functional form of \(\delta\), \(\sigma\), and implicit temperature dependence of \(\xi\). Eq. (7) offers the possibility for connecting thermodynamics of solvation with the thermal expansion coefficient of pure solvent (see below).

From Eq. (7), it is straightforward to obtain:

\[
\Delta S(T) = -\delta_T - \delta\xi_T - (\sigma_T + \sigma\xi_T)r^2
\] (8)

\[
\Delta H(T) = \delta - T\delta_T - T\delta\xi_T + (\sigma - T\sigma_T - T\sigma\xi_T)r^2
\] (9)

where subscripts “\(T\)” and “\(\xi\)” represent partial derivatives with respect to these variables.

Let’s now estimate the magnitudes of the various terms using values for water\(^3\) (SPT parameters for water at room temperature are \(\xi = 0.363\) and \(a = r_w = 1.38\) Å.) \(\xi_T\) is proportional to the thermal expansion coefficient of the pure solvent: \(\xi_T = -\alpha\xi\), where \(\alpha\) for water is very small. At 1 atm, the values of \(\alpha\) for water range from \(-0.064 \times 10^{-3}\) at 0°C to \(0.7 \times 10^{-3}\) at 100°C, and \(\alpha = 0.257 \times 10^{-3}\) at room temperature (25°C). The thermal expansion coefficients for non-associative liquids are around \(1 \times 10^{-3}\) at 1 atm and between 0°C to 100°C, so these values are not very different from that of water.

Quantitatively, compare Eqs. (6) and (7), we have:

\[
|\delta\xi_T| = \left| \frac{k_B T \alpha\xi}{1 - \xi} \right| \approx k_B \left( \frac{300 \times 0.257 \times 10^{-3} \times 0.363}{1 - 0.363} \right) = 0.04k_B
\]

while

\[
\delta_T = -k_B ln(1 - \xi) = 0.5k_B >> |\delta\xi_T|
\]
where we have used $T = 300K$. Similarly by simple differentiation,

$$\sigma_\xi = k_B T \frac{3(1 + 2 \xi)}{r_w^2 (1 - \xi)^3} = 20k_B T / r_w^2.$$  

Hence $|\sigma_\xi \xi| \approx 0.56k_B / r_w^2$, while $\sigma_T = 3.17k_B / r_w^2 >> |\sigma_\xi \xi|$.

The Heat Capacity $\Delta C_p$

The heat capacity can be obtained from either Eq. (8) or Eq. (9):

$$\Delta C_p = -T(\delta_{TT} + 2 \delta_T \xi_T + \delta_\xi \xi_T + \delta_T \xi_T) - T(\sigma_{TT} + 2 \sigma_T \xi_T + \sigma_\xi \xi_T + \sigma_T \xi_T) r^2 \quad (10)$$

While the values for $\alpha$ are not very different between water and non-associative liquids, there is a dramatic difference between $\alpha$’s dependence on temperature. This difference contributes a large term to the $\Delta C_p$ of solvation in water, in contrast to non-associative solvent. In other words, even though $\alpha$ for water is very small, its temperature dependence is quite large, in contrary to most organic solvents. Hence we will neglect contribution from $\xi_T$ but shall keep the terms with $\xi_{TT}$. Thus we have:

$$\Delta C_p = -T \xi_{TT}(\delta_\xi + \sigma_\xi r^2) \quad (11)$$

where, according to SPT (i.e., Eqs (6) and (7)), both $\delta_\xi$ and $\sigma_\xi$ are explicitly proportional to $T$. Therefore if $\xi_{TT}$ is proportional to $T^{-2}$, then $\Delta C_p$ will be approximately temperature independent.

It is clear from the above argument that, for a non-associative solvent, the solvation of a inert solute should have very small $\Delta C_p$ since non-associative liquid has almost zero $\xi_{TT}$. For water, $\delta_\xi = 1.57k_B T$ and $\sigma_\xi r^2 = 20.0k_B T (r/r_w)^2$. Therefore, Eq. (11) gives a linear relationship between $\Delta C_p$ and molecular surface area $r^2$ with almost zero intersection when $r > r_w$. Note, however, that for hydrocarbon solutes like propane and isobutane, there are significant solute-solvent interactions which contribute to the overall $\Delta C_p$.

Therefore, our present result is only semi-quantitative and has to be augmented with such interactions when applied to real experimental data.

$\Delta S^*$ and $\Delta H^*$

We now return to Eq. (8). According to Lee’s theorem:

$$\Delta S^* = -\delta_T - \delta_\xi \xi_T \quad (12)$$

Note that in order to compare calculation from SPT with experimental measurements, we have to obtain the entropy from experimental measurements according to molarity concentration scale. When this was done, Lee found that the calculation given by SPT compares favorably with experimental results.
Similarly, we have:

\[
\Delta H^* = \delta - T \delta_T - T \delta_\xi \xi_T = -T \delta_\xi \xi_T
\]  

(13)

the second equality is because \( \delta \) is a linear function of \( T \) (see Eqs. (6) and (7)). Numerically, \(-T \delta_\xi \xi_T \) is about 0.034 \( k_B T \), that is, 2.5 kJ/mol. It should be noted that Eq. (13) neglects contribution from solute-solvent interaction. It is known that different hydrocarbons, for example aromatics and aliphatics, have different \( \Delta H^* \). On the other hand, inert gases could be used as a test for the present model.

Thus, according to our analysis, the converging values for entropy and enthalpy are the consequence of point solvation energy. This is an interesting conjecture. A rigorous statistical mechanical treatment of this problem seems possible, but has never been developed. In general, point solvation energy is dependent upon whether it is solid, liquid, or gas, from which the solutes are transferred. A quantitative theory might be able to explain the small differences between the three SMPG plots.\(^{10}\) (Note: after correction according to molarity scale, the intersection, \( \Delta S^* \), for gas \( \rightarrow \) water dissolution is increased by about 60 J per degree per mole, see ref. 10).

\( T_s^* \) and \( T_h^* \)

It is natural to suspect that the unique convergence temperature, \( T_s^* \), for entropy of all three different groups of dissolution transferred from either solid, liquid, or gas, is due to some intrinsic properties of water. \( T_s^* \) is the temperature at which \( \Delta S(T) \) in Eq. (8) equals \( \Delta S^* \) given in Eq. (12). That is:

\[
\sigma_T + \sigma_\xi \xi_T = 0
\]  

(14)

i.e.,

\[
\xi_T(T_s^*) = -\alpha(T_s^*)\xi(T_s^*) = -\sigma_T/\sigma_\xi.
\]

By an approximated calculation, \( \sigma_T/\sigma_\xi = 0.158/T \). Hence:

\[
T_s^*\alpha(T_s^*)\xi(T_s^*) = 0.158.
\]

This is consistent with the laboratory measurements \( T_s^* = 383 \text{ K} \), \( \xi = 0.363 \) and \( \alpha = 1.1 \times 10^{-3} \).

Similarly for \( T_h^* \), from Eqs. (9) and (13) we have:

\[
\sigma - T \sigma_T - T \sigma_\xi \xi_T = 0.
\]  

(15)

According to SPT, the first two terms cancel each other. The third term, as we have indicated, is indeed quite small. Thus unfortunately, Eq. (15) is buried in our various approximations and fails to provide an estimation for \( T_h^* \). A more accurate estimation is required to obtain the convergence temperature for \( \Delta H \).
Discussion

With the physical insight provided by SPT, we now attempt to answer some key questions concerning the thermodynamics of hydrophobic solvation and the hydrophobic effect.

1) What is the Hydrophobic Effect?

Ever since Kauzmann’s seminal paper on hydrophobic effect, people have believed that hydrophobic effect is mostly due to the reorganization of hydrogen bonds among the solvent molecules around the solute, and the contribution of direct interaction between solvent and solute is rather minimal. So what is the relation between the hydrophobic effect and the solvation thermodynamics for hydrophobic solute in water? To address the question, one has to be precise about the meaning of “hydrophobic effect”. There is an experimental (thermodynamic) side and there is a structural (theoretical) side of conventional wisdom on “hydrophobicity”. The experimental side is that non-polar solutes in water have very low solubility and the dissolution has large heat-capacity changes, in contrast to the dissolution in organic solvent. The structural side is that hydrogen bonding arrangement has been altered when a non-polar solute is dissolved in water.

From our analysis, it seems that low solubility and large $\Delta C_p$ in fact stem from two distinct sources. While the large $\Delta C_p$ is associated with rearrangement of water molecules, the low solubility is primarily due to the geometric properties of water molecules. This suggestion is consistent with our understanding of entropy-enthalpy compensation, which says that the ability of rearrangement of solvent should only have minor effect on solubility. The more dynamic aspect of water will be reflected only through quantities like entropy, enthalpy, and heat capacity. The reorganization process within solvent contributes to entropy change through heat capacity $\Delta C_p$, which in turn is related to the peculiar large temperature dependence of $\alpha$, the thermal expansivity, of water. Hence it seems legitimate to identify $\Delta C_p$ with the hydrophobic effect.

However, could one simply identify the $\Delta C_p$ term as hydrophobic free energy? This indeed is the central issue behind the work by Murphy et al. It was, of course, well recognized that the $\Delta C_p$ term is not uniquely determined until an appropriate reference temperature(s) is chosen. Murphy et al. proposed the using of $T_s^*$ and $T_h^*$ as reference temperatures, and thereafter a $\Delta C_p$ term was uniquely defined. However, as we have seen, the existence of convergence temperatures and their values are not the hallmark of the reorganization of associative solvent. We suspect that many other solvation processes might also have such convergent properties. The basis for the existence of convergence temperatures is Eq. (7), and it is clear that this equation is not unique for hydrophobic solvation (more discussion later).

2) What is the Role of Hydrogen Bond?
An inevitable objection to our approach from many readers will be the complete neglect of hydrogen bond which has central importance in Kauzmann’s structural model for hydrophobicity.\textsuperscript{20} We would like to emphasize that we do accept the hydrogen bond in water as the \textbf{structural base} for hydrophobicity, but we want to seek the specific \textbf{thermodynamic aspect} or aspects of the hydrogen-bond structure which are responsible for the thermodynamics of hydrophobic solvation. The large temperature dependence of $\alpha$ no doubt is a manifestation of hydrogen bonding reorganization in water, the ultimate source of hydrophobicity. However, other aspects of the water molecules might also be relevant or even crucial; for example, the tetrahedral chemistry of hydrogen bonding,\textsuperscript{20} or more generally the non-isotropic pair-wise interaction between two water molecules,\textsuperscript{23} and the high ratio between physical volume and thermodynamic volume of water.\textsuperscript{3} In our model, SPT indeed uses all these properties of water, though not explicitly. The fact is that water molecule in the SPT model has large thermodynamic volume, i.e., low packing density, but at the same time a small radius leads to high solvation number around a cavity.\textsuperscript{3} This indicates that the solvent molecule is not isotropic, and there are preferences for these molecules to surround a cavity, which is exactly the Kauzmann’s argument! A crude analogy will be a wedge-shaped molecule, and that is quite consistent with water molecules.

3) \textit{What is the basis of convergence temperature?} As pointed out by Lee,\textsuperscript{13} the presence of convergence temperature is due to some kind of linear free energy dependence on molecular substituents, i.e., Eq. (7).

4) \textit{What determine the magnitudes of $\Delta S^*$ and $\Delta H^*$?} They are determined primarily by the thermodynamics of solvation of zero size point solutes.

5) \textit{Why is there a large $\Delta C_p$?} The $\Delta C_p$ of hydrophobic solvation stems from the peculiar large temperature dependence of thermal expansion coefficient, $\partial \alpha / \partial T$.

6) \textit{How to Obtain Molecular Interaction Energy From the Thermodynamic Data?}

This is an age-old question. Twenty-five years ago, T.H. Benzinger proposed a new definition for enthalpy of chemical reaction.\textsuperscript{24} His argument was that for a chemical reaction with non-zero $\Delta C_p$, there would be no unique heat of formation for the reaction. Since the true heat of formation is mechanical (athermal), Benzinger suggested to use $\Delta H(0)$ at zero Kelvin as the “true” heat of formation, and argued that the remains of free energy should be lumped into one term:

$$\Delta W(T) = \Delta H(0) - \Delta G(T).$$

When taking into account the fact $\Delta S(0) = 0$, he obtained:

$$\Delta W(T) = \int_0^T \Delta C_p(X) \left( \frac{T}{X} - 1 \right) dX$$

10
In some sense, what Benzinger did was similar to what Murphy et al. did. They were both trying to divide the total free energy into a part with direct (mechanical) interaction and the rest part with surrounding effect due to thermodynamics. They both realized that $\Delta C_p$ term was related to the latter since it characterizes the fluctuation in enthalpy due to thermal agitation. The crucial question is of course whether it is possible to find an appropriate reference temperature(s) based on purely thermodynamic analysis without any molecular model. Chan and Dill recently have extensively discussed this issue, and they concluded that without a molecular model, purely thermodynamic analysis would not provide much meaningful result.\textsuperscript{12}

7. The Validity of Using SPT to Model Hydrophobic Solvation.

Let’s now reiterate the rationales for using SPT to model solvation in associative solvents. In SPT, the reorganization of solvent is considered implicitly through experimental data on $\xi$ as function of temperature. This approach is consistent with the assertion that the ultimate reason for reorganization in a solvent is its temperature dependence as a pure liquid.\textsuperscript{7} The presence of hydrogen bonds between solvent molecules is manifested in the experimental data on water density and its temperature dependence. SPT, of course, completely neglects the soft interaction between solute and solvent.

Our second defense is based on a recent analysis of how thermodynamic systems respond to small perturbations.\textsuperscript{7} It has been shown that if we classify thermodynamic quantities by the orders of derivative of free energy, there is a relationship between thermodynamic of perturbation and the thermodynamics of unperturbed system. Since one can treat solvation as a perturbation, one only needs the thermodynamics of one order higher for pure solvent in order to calculate the thermodynamics of solvation. For example, $\alpha_T$ of solvent gives $\Delta C_p$ of solvation. All the structural changes in hydrogen bonding will be captured in these thermodynamic quantity of pure water, and our analysis made use of them.

Finally, we would like to emphasize that we are not attempting to use SPT to model the properties of water; rather, we are merely using SPT to relate the thermodynamics of dissolution of an inert solute in water to that of pure water. In the past, many models for water which are based on multi-state of water conformation have been successful in providing calculations for thermal expansion coefficient, $\alpha$, but have failed to deal with its temperature dependence.\textsuperscript{25} This situation is completely in accord with our analysis.

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hydrogen exchange, DNA flexibility, and hydrophobic effect have been guiding lights for my research.

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Appendix: A possible $\Delta H^*$ in gas to water dissolution?

Let's proceed with the dissolution of a gas into water \((g \rightarrow w)\) by first liquefying the gas \((g \rightarrow l)\) and then transferring the liquid into water \((l \rightarrow w)\):

\[
\Delta H_{g\rightarrow w} = \Delta H_{g\rightarrow l} + \Delta H_{l\rightarrow w}.
\]

There seems to be a convergence temperature for dissolution enthalpy change from liquid \(\rightarrow\) water at about 20°C, and corresponding $\Delta H^*$ is about few KJ/mol. According to Trouton’s rule, we can write

\[
\Delta H_{g\rightarrow l} = -88T_b \text{ J/mol}
\]

It is well known that the boiling temperature $T_b$ is scaled with molecular size, hence $\Delta H_{g\rightarrow w}$ and $\Delta H_{l\rightarrow g}$ should have similar converging $\Delta H^*$ but at different temperatures. Mathematically, if we have:

\[
\Delta H_{l\rightarrow w} = \Delta H^* + b_1(T)r^2
\]

where $b_1 = 0$ when $T = 20^\circ C$, and

\[
\Delta H_{g\rightarrow l} = b_2(T)r^2
\]

then:

\[
\Delta H_{g\rightarrow w} = \Delta H^* + [b_1(T) + b_2(T)]r^2
\]

the convergence temperature is the value of $T$ at which $b_1 + b_2 = 0$. 