

Predicting Aqueous Free Energies of Solvation as Functions of Temperature

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This work introduces a model, solvation model 6 with temperature dependence (SM6T), to predict the temperature dependence of aqueous free energies of solvation for compounds containing H, C, and O in the range 273–373 K. In particular, we extend solvation model 6 (SM6), which was previously developed (Kelly, C. P.; Cramer, C. J.; Truhlar, D. G. *J. Chem. Theory Comput.* **2005**, *1*, 1133) for predicting aqueous free energies of solvation at 298 K, to predict the variation of the free energy of solvation relative to 298 K. Also, we describe the database of experimental aqueous free energies of solvation for compounds containing H, C, and O that was used to parametrize and test the new model. SM6T partitions the temperature dependence of the free energy of solvation into two components: the temperature dependence of the bulk electrostatic contribution to the free energy of solvation, which is computed using the generalized Born equation, and the temperature dependence of first-solvation-shell effects which is modeled using a parametrized solvent-exposed surface-area-dependent term. We found that SM6T predicts the temperature dependence of aqueous free energies of solvation with a mean unsigned error of 0.08 kcal/mol over our entire database, whereas using the experimental value at 298 K produces a mean unsigned error of 0.53 kcal/mol.

1. Introduction

Implicit solvation models^{1–4} are widely used to predict a variety of solvent effects including free energies of solvation, solubilities, and vapor pressures. Often, as in industrial, environmental, and pharmacological applications, these quantities are needed over a range of temperatures; however, almost all implicit solvation models have been designed or tested only for predicting these quantities at room temperature. An exception is the work of Elcock and McCammon⁵ who introduced an implicit solvation model for temperature-dependent hydration free energies of amino acids. There remains a need for models designed to treat a broad variety of solutes such as atmospheric pollutants,^{6–8} drug leads,^{6,9} high-energy molecules,¹⁰ and reagents for organic synthesis.¹¹

In the present paper, we present a temperature-dependent extension of our recent implicit solvation model, solvation model 6 (SM6).¹² We refer to this extension as solvation model 6 with temperature dependence (SM6T). SM6T is designed to predict changes in aqueous free energies of solvation as functions of temperature relative to the free energy of solvation at 298 K. In the present study, it was parametrized for compounds composed of H, C, and O in the temperature range 273–373 K (the range over which water is a liquid at 1 atm). SM6T is parametrized on the basis of the solute geometry and the atomic numbers of the atoms in the solute.

The standard-state temperature dependence of the free energy of solvation is given by^{13,14}

$$\Delta G_S^\circ = \Delta H_S^\circ(T) - T\Delta S_S^\circ(T) \quad (1)$$

where T is temperature and ΔH_S° and ΔS_S° are, respectively, the standard-state enthalpy and entropy of solvation. Ignoring the

temperature dependence of ΔH_S° and ΔS_S° yields a linear dependence of ΔG_S° in T ; we call this the van't Hoff model. The temperature dependence of both ΔH_S° and ΔS_S° can be written in terms of the standard-state heat capacity of solvation, $\Delta C_{p,S}^\circ$, which yields¹⁴

$$\Delta G_S^\circ(T) = \Delta G_S^\circ(T_0) - \Delta S_S^\circ(T_0)[T - T_0] + \Delta C_{p,S}^\circ(T)[(T - T_0) - T \ln(T/T_0)] \quad (2)$$

where T_0 is a reference temperature taken throughout as 298 K. Equation 2 with $\Delta C_{p,S}^\circ$ taken as a constant will be the basis of our analysis. Experiment has shown that $\Delta C_{p,S}^\circ$ is not necessarily a constant; for example, Bakk and Høye¹⁵ found that it decreases by 12–35% for methane, ethane, and propane in water when T is increased from 273 to 323 K. One could of course include the temperature dependence of $\Delta C_{p,S}^\circ$ in the model. However, such higher-order effects are probably beyond the resolution of our model. In the method presented here, we go beyond the van't Hoff model by including a nonzero heat capacity, but we do not include the temperature dependence of the heat capacity.

In section 2, we discuss the development of a database of temperature-dependent free energies of solvation in water. Section 3 presents the new model for predicting the temperature dependence of the free energies of solvation. Section 4 summarizes our software plans. The final section discusses the accuracy and applicability of the model.

2. Developing a Database

For a robust parametrization, it was necessary to obtain a database consisting of free energies of solvation as functions of temperature for a variety of compounds. First, we searched the literature for experimental measurements that could be used to obtain free energies of solvation. Next, we analyzed the data and discarded those that failed to meet certain criteria. Finally,

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we recorded the data as free energies of solvation relative to the experimental value at 298 K.

2.A. Compilation of Free Energies of Solvation. We obtained free energies of solvation from a variety of experimental sources including Henry's law constants,^{16–18} saturated vapor pressures^{19–22} of the solute over the pure liquid phase combined with aqueous solubilities,^{23–27} and activity coefficients at infinite dilution^{28–31} for the solutes in water. As with all of our prior models,^{32–34} the free energies of solvation are tabulated for the standard-state choices of 1 M ideal gas and 1 M ideal solution, where the latter behaves as an infinitely dilute solution. As discussed by Ben-Naim,³⁵ such a choice of standard state, involving the same concentration in the two phases, removes the translational entropy of dilution.

To obtain the free energy of solvation, we considered the equilibrium between a solute (A) in the gas phase (g) and in aqueous solution (aq)



In the case of an infinitely dilute solution, the partition coefficient for this process is the Henry's law constant, K_H , which is related to the standard-state free energy of solvation by^{14,36}

$$\Delta G_S^\circ = RT \ln(K_H) \quad (4)$$

where R is the gas constant^{14,37} (1.985 cal K^{−1} mol^{−1}). Henry's law constants are reported in a variety of units, and considerable care must be exercised in converting the experimental data into the appropriate units; Staudinger and Roberts³⁸ provide a useful review on this subject. The Henry's law constant corresponding to our choice of standard states has units of (M of solute in gas phase/M of solute in solution).

Another widely measured quantity is the activity coefficient at infinite dilution. The activity coefficient is the constant of proportionality between the Henry's law constant and the Raoult's law^{14,37} constant and is written as^{28,29,31,36}

$$\gamma_A^\infty = \frac{K_H^X}{P_A^\bullet} \quad (5)$$

where K_H^X is the Henry's law constant in units of mole fractions in the gas and liquid phases and P_A^\bullet is the saturated vapor pressure of solute A over pure liquid solute A. The standard-state free energy of solvation can be calculated from the activity coefficient by

$$\Delta G_S^\circ = RT \ln \left(\frac{\gamma_A^\infty P_A^\bullet}{RT M_w^\bullet} \right) \quad (6)$$

where M_w^\bullet is the molarity of pure water, which serves as the unit conversion between mole fractions and molarity for the solute concentration in dilute aqueous solution. Equation 6 is derived in the appendix, which corrects an error in ref 36.

Alternatively, the solvation process can be considered to occur in two steps. The first is condensing the solute



where l denotes the pure liquid solute. The standard-state free energy associated with moving a solute from a 1 M concentration of solute A in the gas phase to a liquid solute A with ideal behavior in both phases is^{33,34}

$$\Delta G_C^\circ = RT \ln \left(\frac{P_A^\bullet}{RT M_A^1} \right) \quad (8)$$

where M_A^1 is the molarity of the solute in its pure liquid state. The second step of the process is transferring solute A from its pure liquid phase to aqueous solution



The standard-state free energy associated with this step is³⁴

$$\Delta G_T^\circ = -RT \ln \frac{M_A^{\text{aq}}}{M_A^1} \quad (10)$$

where M_A^{aq} is the aqueous molar concentration of solute A in equilibrium with pure liquid; that is, it is the molarity of a saturated solution, which is easily calculated from the solubility. When eqs 8 and 10 are combined, the standard-state free energy of solvation is given by

$$\Delta G_S^\circ = RT \ln \frac{P_A^\bullet}{RT M_A^{\text{aq}}} \quad (11)$$

where eq 11 assumes that the solute is an ideal gas in the vapor phase and that the solution of solute A behaves as though it is very dilute so that a solute molecule only interacts with the solvent.

In practice, several free energies of solvation were computed from eq 11 for highly soluble compounds, for example, benzyl alcohol, which has a solubility of 0.41 mol/L at 293 K.³⁹ Equation 11 is not necessarily appropriate for such compounds; however, we have shown in a previous paper³⁴ that the error introduced by assuming ideal behavior for concentrated solutions is smaller than the inherent error of our solvation models.

A separate issue is that experimental solute vapor pressures and solubilities are rarely available at precisely the same temperature; thus, to calculate free energies of solvation, it was necessary to interpolate experimental vapor pressures to estimate values at the temperatures for which experimental solubilities were available. Fortunately, empirical fits of vapor pressures with accuracies comparable to the experimental errors of solubilities^{39–42} are readily available in the literature.^{43,44}

2.B. Analysis and Removal of Data. Once we obtained an extensive body of experimental free energies of solvation, we proceeded to analyze the data for each compound. We discarded experimental data on the basis of five criteria:

(1) We discarded any source that provided experimental data at only a single temperature for a given compound, except for the case of the free energies of solvation at 298 K obtained from the database used to parametrize SM6.¹² We used this particular criterion because combining such data with data at other temperatures from other sources may lead to spurious temperature dependence. We retained the data from the database used to parametrize the SM6 model because we found these to be reliable values of free energies of solvation at 298 K.

(2) We eliminated all experimental data from sources whose data points systematically deviated by 0.4 kcal/mol or more from values obtained from two or more other sources.

(3) We discarded any compound for which less than four experimental points were available. To estimate the curvature of the temperature dependence of the free energy, at least three data points are necessary. In most cases, the number of data

points is larger, but for a few compounds, such as sparingly soluble alkynes, we did actually use only four data points.

(4) We required that no data point deviate by more than two standard deviations from a fit, as described in section 2.C, to all of the retained experimental data for a given compound. Once a data point was removed, the fit was recalculated using the remaining data. This process was iterated until none of the remaining points deviated by more than two standard deviations from the fit. This criterion was applied to eliminate nonsystematic errors in the experimental data.

(5) In the process of assessing the data, we came to the conclusion that some sources were unreliable either because those sources often disagreed with other workers or because they did not provide complete enough experimental details; data from those sources were not used.

2.C. Evaluation of Experimental Temperature Dependence. With experimental free energies of solvation for a given compound in hand, we calculated the temperature dependence using the following equation

$$\Delta\Delta G_S^\circ = \Delta G_S^\circ(T) - \Delta G_S^\circ(T_0) \quad (12)$$

where ΔG_S° is the experimental free energy of solvation at a given temperature, T . To tabulate $\Delta\Delta G_S^\circ$, one requires a value of $\Delta G_S^\circ(T_0)$ that is consistent with the $\Delta G_S^\circ(T)$ data. In some cases, however, 298 K was not among the available temperatures in the data set produced by the steps in sections 2.A and 2.B. Furthermore, even when available, ΔG_S° at any one temperature such as T_0 is subject to experimental noise. To make the data as consistent as possible, we always obtained $\Delta G_S^\circ(T_0)$ by fitting all of the retained experimental data for a given compound, i , to

$$\Delta G_S^\circ(T; i) = a_i + b_i(T - T_0) + c_i[(T - T_0) - T \ln(T/T_0)] \quad (13)$$

where a_i , b_i , and c_i are fitting parameters. The form of eq 13 is motivated by eq 2, which yields

$$a_i = \Delta G_S^\circ(T_0) \quad (14)$$

During the development of SM6T, we considered using a number of different functions instead of eq 13 including polynomial fits, the van't Hoff model, and a commonly used variant of the thermodynamic equation for the free energy of solvation proposed by Clarke and Glew.⁴⁵ We found that both the equation proposed by Clarke and Glew⁴⁵ and a second-order polynomial produced fits of equal accuracy to eq 13, but as neither was *more* accurate, we retained the form of eq 13.

The overall product of this analysis is a database of evaluated data. A listing of the individual compounds, the number of experimental points used for each compound, the temperature range covered, and the sources for the data used in the database is available in the Supporting Information.

The database is composed of 2364 aqueous free energies of solvation with temperatures ranging from 273 to 373 K for 182 compounds composed of H, C, and O. The database includes a variety of types of compounds including alkanes, alkenes, alkynes, cyclic alkanes, aromatics, alcohols, alkenols, cyclic alcohols, phenols, ethers, cyclic ethers, esters, and carboxylic acids. Table 1 shows that the database has a disproportionately large number of alcohols in comparison to the number of alkynes. Due to the experimental difficulties associated with measuring the equilibria of some of these solutes, particularly branched alkanes and unsaturated alkanes in aqueous solution, we often had to find compounds with combinations of func-

TABLE 1: Number of Free Energies of Solvation in Database

class of compound	no. of points	no. of compounds
unbranched alkanes	123	8
branched alkanes	49	6
cyclic alkanes	96	11
alkenes and alkynes	44	5
aromatics	459	22
alcohols, phenols, and water	702	47
aldehydes	142	13
ketones	236	18
ethers	115	12
esters	332	32
carboxylic acids	58	7
total	2356	181

tionalities that were more soluble. To ensure that the fit does not suffer from this uneven availability of data, the database was divided into 11 classes, based on functional groups, and a weighted error function was used in the parametrization. This will be described further in section 3.C.

3. Model Development

We must first describe certain key aspects of SM6 so that a description of SM6T will be clear. Then, we will introduce the functional form used to predict the temperature dependence of the free energy of solvation. We will also discuss tentative parametrizations of the model. Finally, we will present the final choice of functional form and the parameters used to develop the model.

3.A. SM6. SM6 is the latest in a sequence of closely related solvation models, with the original called SM1^{32,46} and the penultimate called SM5.43R;^{47,48} collectively, the models are referred to as SMx. SM6 is an implicit solvation model^{1,2,49,50} used to calculate the free energy of solvation by approximating the solvent medium as a dielectric continuum, approximating the solute charge density as a collection of atom-centered partial atomic charges and approximating the solute cavity as a set of overlapping atom-centered spheres. In SM6, the free energy of solvation is partitioned into two contributions

$$\Delta G_S^\circ = \Delta G_{\text{ENP}} + G_{\text{CDS}} \quad (15)$$

where ΔG_{ENP} is the contribution due to electrostatic interactions between the solute and the bulk solution and G_{CDS} is a parametrized term designed to account for first-solvation-shell effects and for approximations used in the calculation of ΔG_{ENP} . As discussed elsewhere,^{2,50,51} the decomposition of eq 15 is not well defined. However, a key working principle of the SMx models is that we define ΔG_{ENP} as the Coulombic contribution calculated by bulk electrostatics for a given choice of intrinsic atomic radii called the Coulomb radii, which are assumed to be independent of atomic charge, hybridization state, and solvent. The usefulness of this principle has been validated by the success of the SMx models. To anticipate section 3.B, we note that a key element of SM6T is that these Coulomb radii are independent of temperature.

The bulk electrostatic component of the free energy of solvation is calculated as the sum of two contributions

$$\Delta G_{\text{ENP}} = \Delta E_{\text{EN}} + G_{\text{P}} \quad (16)$$

where ΔE_{EN} is the change in the solute's internal free energy upon insertion into solution from the gas phase and G_{P} is the free energy of polarization. In practice, we usually retain only

the electronic contribution to ΔE_{EN} , assuming that the vibrational–librational–rotational contributions are small enough to be neglected.

The free energy of polarization is the free energy change associated with a bulk electrostatic treatment of the favorable solute–solvent electrostatic interactions that form upon insertion of the solute into the solvent and the accompanying distortion of the solvent molecules and the solvent structure from the pure solvent state. The electrostatic interactions between the partial atomic charges of the solute and the surrounding dielectric medium are calculated using the generalized Born equation^{32,52–54}

$$G_{\text{p}} = -\frac{1}{2} \left(1 - \frac{1}{\epsilon} \right) \sum_{k,k'} q_k q_{k'} \gamma_{kk'} \quad (17)$$

where the right-hand side of the equation is a double sum over all the atoms k and k' in the solute, q_k is the partial atomic charge of atom k computed using charge model 4 (CM4),¹² ϵ is the temperature-dependent dielectric constant of the solvent, and $\gamma_{kk'}$ is the Coulomb integral between atoms k and k' . The Coulomb integral is calculated as⁵⁴

$$\gamma_{kk'} = \frac{1}{\sqrt{R_{kk'}^2 + \alpha_k \alpha_{k'} \exp(r_{kk'}^2/d_{kk}^2) \alpha_k \alpha_{k'}}} \quad (18)$$

where $r_{kk'}$ is the distance between atoms k and k' , $d_{kk'}$ is a parameter,¹² and α_k is an effective Born radius for atom k that depends on the solute geometry and the Coulomb radius of each atom in the solute. The Coulomb radii were determined in a prior paper.¹²

The change in internal energy upon insertion of the solute into liquid solution from the gas phase, ΔE_{EN} , has two contributions: ΔE_{E} which is the energy required to distort the solute electronic structure from its gas-phase optimum and ΔE_{N} which is the equivalent cost associated with distortion of the solute geometry from its gas-phase optimum. The total ΔG_{ENP} is minimized in a self-consistent reaction field (SCRF)^{2,55} calculation. The energy change associated with distortion of the solute geometry, ΔE_{N} , can be calculated by optimizing the solute geometry for the relaxed solute electronic structure. This latter process can be relatively time-consuming, since the solute electronic structure is iteratively computed for each step in the optimization of the solute geometry in solution. One option that has been explored in previous work⁵⁶ is to use the solute gas-phase geometry and to allow only the electronic structure to relax in solution. We have found that this approximation yields reliable results for most cases; in particular, the effect of optimization of the solute structure in solution on the overall free energy of solvation is relatively small for molecules used in our parametrization databases.⁵⁶

As mentioned above, G_{CDS} is an empirically derived term designed to minimize the deviation between experiment and ΔG_{ENP} . It is intended to account for solvation phenomena that are not included in the bulk electrostatic term. It includes the free energy cost associated with forming a solute-shaped cavity in the solvent, changes in solvent structure beyond those included in ΔE_{EN} , nonelectrostatic phenomena such as dispersion and Pauli exchange–repulsion, and any approximations used in the calculation of ΔG_{ENP} . Previous studies^{32,49,57–60} have shown that these phenomena are proportional to the solvent accessible surface area^{61–64} (SASA) of the solute cavity. Note that the atomic radii used to define the SASA for the G_{CDS} term are *not* in general the same as the Coulomb radii. In particular, we use the radii of Bondi⁶⁵ for this purpose.

The G_{CDS} term has the following form

$$G_{\text{CDS}} = \sum_k \sigma_k A_k \quad (19)$$

where the sum is over all atoms k in the solute, A_k is the solvent accessible surface area of atom k , and σ_k is a parametrized functional which is written as

$$\sigma_k = \tilde{\sigma}_{Z_k} + \sum_{m \neq k} \sum_{\tau} \tilde{\sigma}_{Z_k Z_m \tau} F_{Z_k Z_m \tau}(\{r_{km}\}) \quad (20)$$

where the sum is over all the atoms m in the molecule except k , the sum over τ is over one or two types of $F_{Z_k Z_m \tau}$, $\tilde{\sigma}_{Z_k}$ is a coefficient that depends on the atomic number, Z_k , of atom k , $\tilde{\sigma}_{Z_k Z_m \tau}$ is a coefficient that depends on the atomic numbers, Z_k and Z_m , of atoms k and m and the type, τ , of geometric factor $F_{Z_k Z_m \tau}$. The function $F_{Z_k Z_m \tau}$ is designed to account for the dependence of atomic properties on the nature of the functional group in which the atom appears. $F_{Z_k Z_m \tau}$ depends on the set $\{r_{km}\}$ of all of the internuclear distances in the molecule. For compounds containing H, C, and O, SM6 has three σ_Z coefficients, $\tilde{\sigma}_1$, $\tilde{\sigma}_6$, and $\tilde{\sigma}_8$ corresponding respectively to H, C, and O, and six $\tilde{\sigma}_{ZZ\tau}$ coefficients, $\tilde{\sigma}_{161}$, $\tilde{\sigma}_{181}$, $\tilde{\sigma}_{661}$, $\tilde{\sigma}_{662}$, $\tilde{\sigma}_{861}$, and $\tilde{\sigma}_{881}$.

An important point to note is that calculated solute properties depend on the choice of electronic structure theory and basis set. It has been found¹² that the coefficients used to compute G_{CDS} vary somewhat depending on the choice of basis set, but in SM6 and SM6T, we take them to be independent of other aspects of the electronic structure theory chosen (for example, they are independent of which density functional is used).

3.B. SM6T. Using the definition in eq 12 and motivated by eq 15, we partition the temperature dependence of the free energy of solvation as

$$\Delta \Delta G_{\text{S}}^{\circ} = \Delta \Delta G_{\text{ENP}}(T) + \Delta G_{\text{CDS}}(T) \quad (21)$$

where $\Delta \Delta G_{\text{ENP}}$ is the temperature dependence associated with ΔG_{ENP} and ΔG_{CDS} is an empirically derived term designed to account for the temperature dependence of first-solvation-shell phenomena and other approximations associated with use of the generalized Born equation and the way we use it.

The first term on the right-hand side of eq 21 is directly calculated as

$$\Delta \Delta G_{\text{ENP}}(T) = \Delta G_{\text{ENP}}(T) - \Delta G_{\text{ENP}}(T_0) \quad (22)$$

As described in section 3.A, the bulk electrostatic contribution to the free energy of solvation depends on the partial atomic charges of the solute, the Coulomb radii of the solute atoms, the solute geometry, and the dielectric constant of the solvent, all of which might, in principle, depend on temperature. Thus, a strategic decision is required for how to model ΔG_{ENP} .

There has been some discussion^{5,36,66–70} concerning the use of temperature-dependent radii to describe the electrostatics of the solute cavity. An argument⁶⁹ can be made in favor of such an approach based on the observation from statistical mechanical studies that the radial distribution of water around a solute changes as a function of temperature.⁶⁶ There have also been studies^{70,71} that used the isothermal compressibility of the solvent to model the temperature dependence of the solute radii in solution. However, the idea that the radii used to define the solute cavity describe a physical boundary is oversimplified.^{1–3,50} Therefore, on the basis of the principle discussed below eq 15, we treat the Coulomb radii as constant (i.e., independent of T).

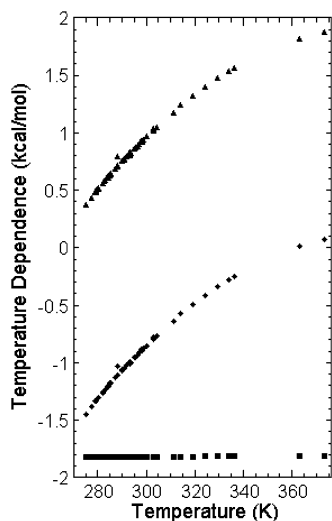


Figure 1. Experimental (◆) free energy of solvation for benzene in water as a function of temperature compared to the corresponding computed values of $\Delta G_{\text{ENP}}(T)$ (■) and $G_{\text{CDS}}(T)$ (▲).

Furthermore, in keeping with the discussion above of ΔE_{N} , we neglect, at least in the parametrization step, the temperature dependence of the geometry of the solute because it is small. (It can be included as desired but will have an effect smaller than the reliability of the aqueous SM6T model.) The temperature dependence of the dielectric constant reflects the ability of the bulk solvent to reorient and polarize in response to the solute charge density. As such, it represents a clear physical phenomenon which can be accurately simulated by incorporating a temperature-dependent dielectric constant into the model. For water, the temperature dependence of the dielectric constant is well approximated by a cubic polynomial.⁷²

The dielectric constant of water changes from 87.90 at 273 K to 55.58 at 373 K; however, G_{P} and consequently ΔG_{ENP} depend on $(1 - (1/\epsilon))$, which changes much less than ϵ . For example, ΔG_{ENP} for ethyl benzene in water changes from -1.68 kcal/mol at 273 K to -1.66 kcal/mol at 373 K, while its experimental free energy of solvation varies by 2.24 kcal/mol (see Figure 1) over this range. The temperature dependence of the bulk electrostatic contribution to the aqueous free energy of solvation remains small even for solutes with larger dipole moments such as furfural (dipole moment of 3.97 D),⁷³ for which the bulk electrostatic contribution to the aqueous free energy of solvation changes from -5.79 at 277 K to -5.74 at 373 K. (The temperature dependence of the electrostatic interaction between the solute and bulk solvent becomes considerably larger for less polar solvents such as octanol. For example, octanol has a dielectric constant that varies from 11.92 to 5.32 over the temperature range 273–373 K,⁷² and the computed value of ΔG_{ENP} for ethyl benzene in octanol varies by 0.19 kcal/mol. Thus, while $\Delta\Delta G$ does not contribute significantly to the temperature dependence of the free energy of solvation in aqueous solutions, it does in nonpolar solvents.)

Throughout the course of this project, the bulk electrostatic contribution to the free energy of solvation, ΔG_{ENP} , both at the reference temperature, T_0 , and at the temperature of interest, T , was computed using SM6 as it is implemented in MN-GSM⁷⁴ (a locally developed code that we cannot distribute due to Gaussian license restrictions), in SMXGAUSS⁷⁵ (a code that is freely available to the general scientific community and that was developed within our group to integrate our solvation models with Gaussian 03⁷⁶), and in HONDOPLUS.⁷⁷

Since the temperature dependence of the bulk electrostatic contribution to the free energy of solvation in water is negligible, the ΔG term incorporates almost all of the temperature dependence of the aqueous free energy of solvation in the SM6T model. This term may be written as

$$\Delta G_{\text{CDS}} = G_{\text{CDS}}(T) - G_{\text{CDS}}(T_0) \quad (23)$$

Comparing eq 23 to eq 2 suggests that we model this as

$$\Delta G_{\text{CDS}} = B(T - T_0) + C[(T - T_0) - T \ln(T/T_0)] \quad (24)$$

where B and C are parameters of the model. As in the SM6 model for G_{CDS} , we model ΔG_{CDS} as being proportional to solvent-exposed surface areas.^{2,32,49–51,78} We applied the same functions and solvent accessible surface areas used in eqs 19 and 20 to calculate B and C

$$B = \sum_k \sigma_k^B A_k \quad (25)$$

$$C = \sum_k \sigma_k^C A_k \quad (26)$$

where σ_k^B and σ_k^C are parametrized as

$$\sigma_k^B = \tilde{\sigma}_{Z_k}^B + \sum_{m \neq k} \sum_{\tau} \tilde{\sigma}_{Z_k Z_m \tau}^B F_{Z_k Z_m \tau}(\{r_{km}\}) \quad (27)$$

$$\sigma_k^C = \tilde{\sigma}_{Z_k}^C + \sum_{m \neq k} \sum_{\tau} \tilde{\sigma}_{Z_k Z_m \tau}^C F_{Z_k Z_m \tau}(\{r_{km}\}) \quad (28)$$

where $\tilde{\sigma}_{Z_k}^B$, $\tilde{\sigma}_{Z_k}^C$, $\tilde{\sigma}_{Z_k Z_m \tau}^B$, and $\tilde{\sigma}_{Z_k Z_m \tau}^C$ are coefficients that depend on the atomic numbers of atoms k and m . Since F_{881} primarily distinguishes peroxides from other oxygen-containing solutes and since the database used here for SM6T has no peroxides, $\tilde{\sigma}_{881}^B$ and $\tilde{\sigma}_{881}^C$ were not used. Thus, there are potentially as many as 16 parameters in SM6T, 8 for B and 8 for C . However, we will reduce the number of independent parameters during the fit, which is discussed in section 3.D.

3.C. Error Function. Several key classes of compounds are under-represented in the database used to develop parameters for the coefficients B and C . The disproportionate number of alcohols versus unsaturated alkanes arose due to the scarcity of experimental solubility data for the latter. To account for this, a weighted error function was used. The error function is defined as

$$D = \sum_{t=1}^{11} \sum_{s_t} \sqrt{\frac{\sum_i^{n_m} (\Delta G_{\text{CDS}}(\text{exptl}; i) - \Delta G_{\text{CDS}}(\text{calcd}; i))^2}{n_m s_t^2 11^2}} \quad (29)$$

where the first sum is over all 11 classes, t , of compounds in the database, the second sum is over all s_t compounds, m , in a given class t , and the third sum is over all n_m experimental data, i , for a given compound, m . $\Delta G_{\text{CDS}}(\text{calcd}; i)$ is calculated using eqs 25–28, and $\Delta G_{\text{CDS}}(\text{exptl}; i)$ is the experimental value obtained by

$$\Delta G_{\text{CDS}}(\text{exptl}) = \Delta\Delta G_{\text{S}}^{\circ}(T) - \Delta\Delta G_{\text{ENP}}(T) \quad (30)$$

where the first term on the right-hand side is obtained from eqs 12 and 13 and the second term is calculated by the generalized Born approximation with temperature-independent radii.

The error function in eq 29 ensures that each class is weighted equally and that each compound within the class is weighted equally with other compounds in the same class; this counteracts the disproportionate number of alcohols and esters in the database. The danger of this approach is that classes with fewer compounds are more subject to the effects of random errors in the experimental measurements for a given compound; this concern has been addressed through the use of strict criteria in selecting experimental data, as described in section 2.B.

The error function, D , was minimized using the generalized reduced gradient code (GRG2) of Lasdon et al.⁷⁹ as implemented in Microsoft Excel. The results produced by this code were compared to those produced by the NAG linear optimizer, and good agreement was found between the two.

3.D. Parametrizations. In this paper, all electronic structure calculations were performed using the 6-31+G(d,p)^{80,81} basis set. Having chosen a basis set, a functional form for the predictive model, and an appropriate error function, we proceeded to determine which parameters, $\bar{\sigma}_{ZZ\tau}^B$ and $\bar{\sigma}_{ZZ\tau}^C$, were necessary to accurately reproduce the experimental temperature dependence of the aqueous free energies of solvation.

As a first step, we considered the case where a unique pair of values for B and C is determined for each individual compound (we refer to this case as “molecular coefficients”) and the case where all of the parameters were set equal to zero (we refer to this case as the “null hypothesis”).

The use of molecular coefficients corresponds to the best case scenario for any model that uses eq 24 to calculate ΔG_{CDS} , and it can also be considered to give a rough estimate of the nonsystematic experimental error in the temperature dependence of the free energies of solvation in our database. Table 2 shows that such nonsystematic errors produce a mean unsigned error of only 0.02 kcal/mol, on average.

The null hypothesis, in contrast, corresponds to assuming that G_{CDS} does not change as a function of temperature. Table 2 shows that this produces a mean unsigned error of 0.53 kcal/mol, which is considerably larger than 0.02 kcal/mol. Clearly then, G_{CDS} does exhibit temperature dependence. Since SM6 can reliably reproduce free energies of solvation to within an average error of ~ 0.5 kcal/mol,¹² a variation of the free energy of solvation by 0.53 kcal/mol is quite significant.

The error in the temperature dependence of free energies of solvation and the error in free energies of solvation, which we estimate⁴⁷ to be around 0.2 kcal/mol, are two distinct properties. The estimated experimental error in the temperature dependence of the free energies of solvation using the molecular coefficients (0.02 kcal/mol) is considerably smaller than the typical estimated error in the experimental determination of absolute free energies of solvation.

Next, we performed a parametrization against the entire database using the full set of 16 coefficients labeled $\bar{\sigma}_1^B$, $\bar{\sigma}_6^B$, $\bar{\sigma}_8^B$, $\bar{\sigma}_{161}^B$, $\bar{\sigma}_{181}^B$, $\bar{\sigma}_{661}^B$, $\bar{\sigma}_{662}^B$, $\bar{\sigma}_{861}^B$, $\bar{\sigma}_1^C$, $\bar{\sigma}_6^C$, $\bar{\sigma}_8^C$, $\bar{\sigma}_{161}^C$, $\bar{\sigma}_{181}^C$, $\bar{\sigma}_{661}^C$, $\bar{\sigma}_{662}^C$, and $\bar{\sigma}_{861}^C$. Analysis of the covariance between the various parameters indicated considerable redundancy in the parameters. The covariance between the parameters in the 16-parameter fit showed that $\bar{\sigma}_H^B$ and $\bar{\sigma}_H^C$ were highly correlated with the remaining parameters and thus could be discarded. This reduces the number of parameters to 14; the resulting fit with 14 parameters is called the “unrestricted” fit, and Table 2 shows that the unrestricted fit produces a mean unsigned error of 0.07 kcal/mol. Table 3 shows the value for each coefficient obtained by parametrizing the unrestricted fit against the entire database. Our next step was to determine how to further reduce the

TABLE 2: Mean Signed Error (MSE), Mean Unsigned Error (MUE), and Root Mean Squared Error (RMSE) for Each Class of Compounds (kcal/mol) for Various Parameterizations of SM6T

	MSE	MUE	RMSE	MSE	MUE	RMSE
	Molecular Coefficients			Null Hypothesis		
unbranched alkanes	0.00	0.05	0.06	−0.39	0.61	0.80
branched alkanes	0.00	0.02	0.02	−0.26	0.62	0.79
cyclic alkanes	0.00	0.01	0.01	−0.04	0.38	0.47
alkenes and alkynes	0.00	0.01	0.01	−0.19	0.28	0.37
aromatics	0.00	0.02	0.03	−0.03	0.31	0.39
alcohols, phenols, and water	0.00	0.03	0.03	−0.58	0.83	1.00
aldehydes	0.00	0.03	0.03	−0.16	0.38	0.46
ketones	0.00	0.03	0.04	−0.36	0.63	0.76
ethers	0.00	0.02	0.03	−0.23	0.58	0.70
esters	0.00	0.02	0.03	−0.39	0.69	0.81
carboxylic acids	0.00	0.02	0.03	−0.22	0.50	0.59
average	0.00	0.02	0.03	−0.26	0.53	0.65
	Unrestricted			van't Hoff		
unbranched alkanes	−0.01	0.07	0.08	0.03	0.10	0.13
branched alkanes	−0.04	0.13	0.15	0.01	0.16	0.21
cyclic alkanes	−0.01	0.03	0.04	0.02	0.06	0.08
alkenes and alkynes	0.03	0.06	0.08	0.01	0.06	0.09
aromatics	0.01	0.06	0.07	0.04	0.07	0.10
alcohols, phenols, and water	0.03	0.09	0.11	0.04	0.11	0.14
aldehydes	−0.01	0.07	0.08	0.00	0.10	0.12
ketones	−0.01	0.06	0.07	0.02	0.09	0.11
ethers	−0.04	0.08	0.09	0.00	0.09	0.11
esters	0.03	0.09	0.11	0.07	0.11	0.15
carboxylic acids	−0.01	0.06	0.08	0.00	0.07	0.09
average	0.00	0.07	0.09	0.02	0.09	0.12
	Final					
unbranched alkanes	−0.01	0.08	0.09			
branched alkanes	−0.04	0.13	0.15			
cyclic alkanes	−0.02	0.04	0.05			
alkenes and alkynes	0.02	0.07	0.09			
aromatics	0.00	0.07	0.09			
alcohols, phenols, and water	0.02	0.10	0.11			
aldehydes	−0.01	0.08	0.09			
ketones	−0.01	0.06	0.07			
ethers	−0.04	0.08	0.10			
esters	0.02	0.08	0.10			
carboxylic acids	−0.01	0.06	0.07			
average	−0.01	0.08	0.09			

TABLE 3: Coefficients Used for Each Parametrization (cal Å^{−2} mol^{−1} K^{−1})

	6	8	161	181	661	662	861
Parameters Used in Calculation of B Coefficient							
unrestricted	38.52	1.96	25.85	73.26	−24.36	−12.51	−8.54
van't Hoff	22.49	17.53	22.34	54.76	−13.07	4.25	−26.23
final SM6T	2.18	2.18	29.47	71.95	2.18	2.18	2.18
Parameters Used in Calculation of C Coefficient							
unrestricted	247.79	−200.07	43.70	294.55	−155.43	−370.03	246.44
final SM6T	−84.45	−84.45	78.59	166.23	78.59	−266.91	166.23

number of parameters without appreciably increasing the error of the model.

For the purpose of testing whether the coefficient C was necessary, we parametrized the model using just the coefficient B . Calculations employing only the coefficient B involved seven parameters, five corresponding to the C, O, H–O, H–C, and O–C bonds and two corresponding to C–C bonds (these parameters are also given in Table 3). Table 2 shows that this “van't Hoff” fit is reasonably accurate, with a mean unsigned error of 0.09 kcal/mol. However, if one inspects the predicted temperature dependence of the aqueous free energies of solva-

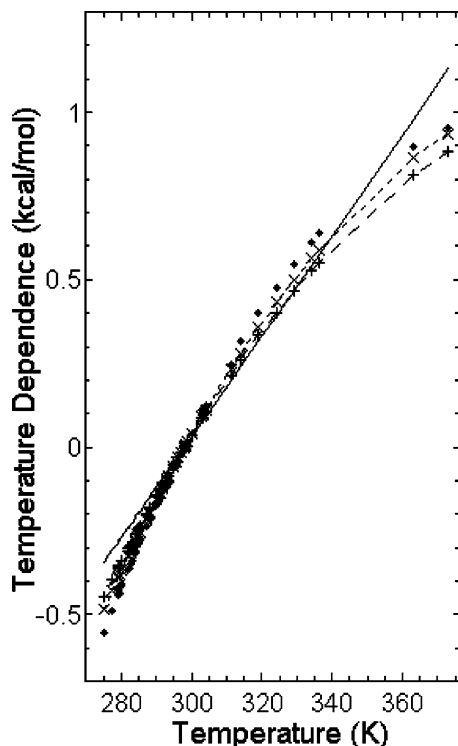


Figure 2. Experimental (◆) value of ΔG_{CDS} for benzene compared to various possible parametrizations of SM6T: unrestricted (- + -); van't Hoff (-); final (- × -)

tion and compares those values to the experimental data for some representative compounds such as benzene (see Figure 2), one immediately sees that the van't Hoff fit fails to capture the obvious curvature in the experimental data.

We also considered combining parameters into a single general parameter. We found after a careful analysis of the covariance matrices, observing the values of the different parameters, and through trial and error that $\bar{\sigma}_6^B$, $\bar{\sigma}_8^B$, $\bar{\sigma}_{661}^B$, $\bar{\sigma}_{662}^B$, and $\bar{\sigma}_{861}^B$ could be set equal to a single "general" parameter, $\bar{\sigma}_{b1}^B$, with relatively little effect on the accuracy or apparent physicality of the model. However, we found that combination of either $\bar{\sigma}_{181}^B$ or $\bar{\sigma}_{161}^B$ with $\bar{\sigma}_{b1}^B$ or removal of either of these coefficients significantly reduced the accuracy of the model. We also observed that $\bar{\sigma}_{b1}^B$ was quite small and that removal of this parameter introduced relatively little additional error into the model.

We also considered combining parameters for the *C* coefficient. The approach which sacrificed the least accuracy involved setting $\bar{\sigma}_6^C$ and $\bar{\sigma}_8^C$ equal to a single parameter, $\bar{\sigma}_{c1}^C$, $\bar{\sigma}_{161}^C$ and $\bar{\sigma}_{661}^C$ equal to a single parameter, $\bar{\sigma}_{c2}^C$, and $\bar{\sigma}_{181}^C$ and $\bar{\sigma}_{861}^C$ equal to a single parameter, $\bar{\sigma}_{c3}^C$ (see "final" parametrization in Table 2). With these restrictions, the mean unsigned error of the model changed by less than 0.02 kcal/mol relative to the unrestricted parametrization.

Our final model uses a total of seven parameters to predict the temperature dependence of the free energy of solvation; three parameters, $\bar{\sigma}_{161}^B$, $\bar{\sigma}_{181}^B$, and $\bar{\sigma}_{b1}^B$, are used to predict the *B* coefficient, and four parameters, $\bar{\sigma}_{662}^C$, $\bar{\sigma}_{c1}^C$, $\bar{\sigma}_{c2}^C$, and $\bar{\sigma}_{c3}^C$, are used to predict the *C* coefficient. This model is the most attractive because it introduces parameters with relatively small values as opposed to those for the unrestricted parametrization (as is shown in Table 3). Parametrizations with smaller values of the parameters are less likely to predict unphysical values when applied to problems outside its applicable range, for example, if the model were to be applied to functional groups

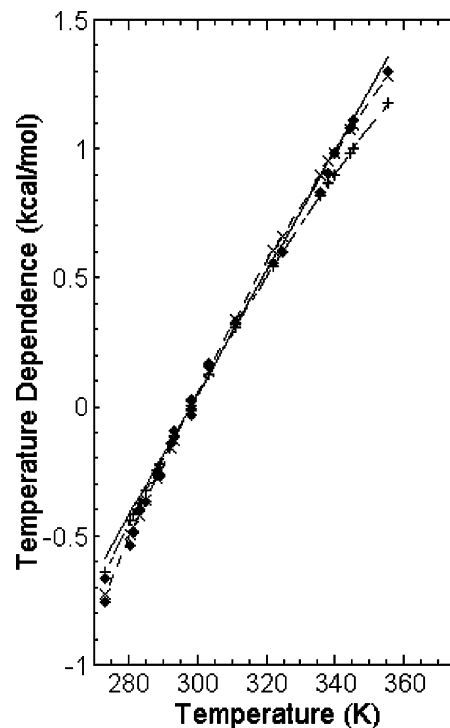


Figure 3. Experimental (◆) value of ΔG_{CDS} for ethoxyethane compared to various possible parametrizations of SM6T: unrestricted (- + -); van't Hoff (-); final (- × -).

that were not included in the data set. The choice of four parameters, $\bar{\sigma}_{662}^C$, $\bar{\sigma}_{c1}^C$, $\bar{\sigma}_{c2}^C$, and $\bar{\sigma}_{c3}^C$, for the prediction of the *C* coefficient is based on the empirical observation that the errors in the model do not change significantly relative to the unrestricted model.

The predictions of the final parametrization do not vary significantly from those of the unrestricted parametrization. Figures 2–4 show each parametrization compared to the experimental temperature dependence of the free energy of solvation for benzene, ethoxyethane, and furfural, and one sees relatively good agreement between the results of the various parametrizations. Even at high temperatures around 373 K, both the final parametrization and the unrestricted parametrization predict very similar values for $\Delta \Delta G_{\text{CDS}}^{\circ}$. The final parametrization reproduces the temperature dependence of the free energy of solvation with more accuracy than the fit using just the *B* coefficient with an equal number of parameters (seven parameters).

The final parametrization uses unique values for the $\bar{\sigma}_{161}^B$ and the $\bar{\sigma}_{181}^B$ parameters. This is physically reasonable because it suggests that the hydrophobic effect, which is proportional to the number of CH groups exposed to the surrounding water, and the formation of hydrogen bonds with OH groups contribute in different ways to the entropy of solvation. The single general parameter, $\bar{\sigma}_{b1}^B$, is retained; while the main contributions to the entropy of solvation in water may arise from the OH and CH groups, this may not necessarily be the case in nonaqueous solvents in which case the general parameter may contribute significantly to the accuracy of SM6T.

3.E. Predicting Thermodynamic Properties. In section 3.D, we showed that a parametrized model based on solvent accessible surface areas can reproduce the temperature dependence of aqueous free energies of solvation quite well. This model predicts two coefficients, *B* and *C*, which for the case of aqueous solutions correspond respectively to the entropy and heat capacity of solvation (compare eq 24 to eq 2). Table 4

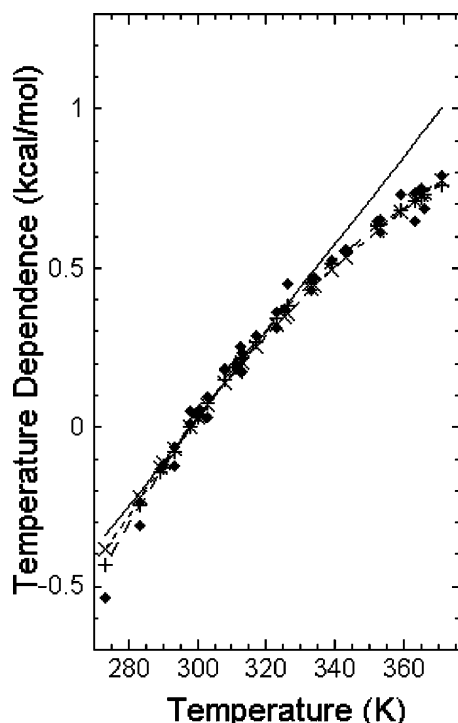


Figure 4. Experimental (◆) value of ΔG_{CDS} for furfural compared to various possible parametrizations of SM6T: unrestricted (— + —); van't Hoff (---); final (— · —).

compares the predicted values of B using the various parametrizations discussed above to experimental^{82–85} and theoretical estimates of the entropy of solvation, such as those based on explicit solvent models by Gallichio et al.,⁸⁶ Cui et al.,^{87,88} Schravendijk et al.,⁸⁹ and Rick.⁹⁰ Table 5 compares the predicted values of C to estimates of the heat capacity of solvation obtained from experimental work^{15,91–101} and from the theoretical work of Graziano.¹⁰² Previous estimates of these thermodynamic properties vary quite considerably between authors. For instance, note the large difference between the values for the entropy of solvation reported by Abraham et al.⁸⁴ and Wilhelm et al.⁸⁵ in Table 4. Furthermore, the values we obtained from a direct fit of the experimental data for each compound in our database (in the column labeled “molecular coefficients” in Tables 4 and 5) can vary quite considerably from other experimental sources. Franks et al.⁹² pointed out that the entropy and heat capacity of solvation are difficult to obtain experimentally and require a considerable number of measurements—they estimated at least 40—over a relatively broad temperature range to accurately obtain such information. In some cases, our final choice of parameters for SM6T produces estimates of the entropy and heat capacity of solvation that agree better with the literature than our molecular coefficients. This may indicate that the final fit is more reliable than fitting each individual molecule because the considerable noise due to the sparsity of data for some compounds is averaged out to some extent when fitting the whole data set.

We emphasized in sections 3.A and 3.B that the partitioning of solvent effects between the two terms of eq 15, ΔG_{ENP} and G_{CDS} , or the two terms of eq 21, $\Delta\Delta G_{\text{ENP}}$ and ΔG_{CDS} , is somewhat arbitrary. We use a fixed cavity size (i.e., our radii are independent of temperature). The extent that the electrostatic terms would change in either of these equations if the temperature dependence of the “true” Coulomb radii were included is, to first order, associated with the region at the solute–solvent boundary, and hence, it is equally well treated by the first-solvation-shell terms. However, changing the Coulomb radii has

the second-order effect that it would also change the calculated partial atomic charges of the solute, which would affect the long-range electrostatic interactions. This effect is not as obviously related to the solvent accessible surface area, but the success of our model argues that either the effect is small or it *can* be modeled well using surface tensions. We have observed this effect numerous times with our prior models.^{12,51,103} That is, the choice of Coulomb radii has little effect on the accuracy of the SMx models for neutral compounds provided that the surface tensions are reoptimized as well, indicating that surface tensions can account for the differences in ΔG_{ENP} due to different Coulomb radii. In our model, since $\Delta\Delta G_{\text{ENP}}$ is small, it was not necessary to partition it into enthalpic and entropic contributions (it is essentially all enthalpic, with negligible entropy and heat capacity). An alternative approach, first implemented by Bonnacorsi et al.,⁷¹ is to compute the change in ΔG_{ENP} due to the temperature dependence of the electrostatic cavity using the coefficient of thermal expansion.^{70,71}

SM6T does not account for the temperature dependence of the heat capacity of solvation, which can be significant.^{15,102} To test the effect of the variation of the heat capacity on the free energy of solvation we compared the free energy of solvation for benzene in water at 373 K computed using a temperature-independent heat capacity obtained from the fit of our experimental data using eq 13 to a temperature-dependent heat capacity predicted using a model reported by Bakk and Høye.¹⁵ We used the same SM6 free energies and SM6T entropies of solvation at 298 K for both types of heat capacities. First, we compared the temperature-independent heat capacity of solvation ($\Delta C_{\text{p,s}}^{\circ} \approx 70.3 \text{ cal mol}^{-1} \text{ K}^{-1}$) to the heat capacity at 298 K obtained from the model of Bakk and Høye¹⁵ ($\Delta C_{\text{p,s}}^{\circ}(298 \text{ K}) \approx 68.8 \text{ cal mol}^{-1} \text{ K}^{-1}$). We found that a difference of $1.5 \text{ cal mol}^{-1} \text{ K}^{-1}$ between the two heat capacities produces a difference of 0.01 kcal/mol in the aqueous free energy of solvation for benzene at 373 K, which is well within the error of SM6T. Then, we compared free energies of solvation computed using the temperature-independent heat capacity and the temperature-dependent heat capacity at 373 K ($\Delta C_{\text{p,s}}^{\circ}(373 \text{ K}) \approx 54.4 \text{ cal mol}^{-1} \text{ K}^{-1}$), and we found a difference of 0.14 kcal/mol between the two calculations. Such an error is comparable to the deviation of SM6T from the experimental temperature dependence of the free energy of solvation of benzene at 373 K, but it is much smaller than the absolute error of SM6. In the interest of minimizing the number of parameters in our model and to avoid including poorly determined small terms, we do not include the temperature dependence of the heat capacity of solvation, but it is evident that the assumption of a temperature-independent heat capacity of solvation does introduce some error.

From the standpoint of our model, which was simultaneously parametrized to predict both linear and logarithmic terms in the temperature dependence of the free energy of solvation, the computation of the entropy and heat capacity of solvation is further complicated because contributions from the linear and logarithmic terms may partially cancel one another to produce reliable and accurate free energies of solvation without necessarily producing a model suitable for predicting the entropy and heat capacity of solvation. In particular, one should note that in Table 3 some of the coefficients for the heat capacity of solvation are negative while experimental heat capacities of solvation are positive. This in itself need not be meaningful because one adds environmentally dependent contributions from all of the atoms in a molecule to obtain the net C coefficient for the molecule. Application of SM6T to the database yields

TABLE 4: Theoretical and Experimental Entropies of Solvation (cal mol⁻¹ K⁻¹) from the Literature Compared to Predictions Based on Various Parametrizations

	SM6T parametrizations				experimental literature	theoretical literature
	molecular coefficients	unrestricted	van't Hoff	final		
methane	-18	-16	-12	-11	-32, ^a -16 ^b	-15, ^c -13 ^d
ethane	-22	-18	-15	-16	-36, ^a -20 ^b	-19, ^c -25 ^d
propane	-24	-22	-18	-21	-39, ^a -23 ^b	-40 ^d
butane	-28	-26	-22	-25	-42 ^a	-26 ^c
hexane	-35	-34	-28	-34	-11 ^e	-32 ^c
cyclohexane	-28	-27	-23	-30	-11 ^e	-30 ^c
benzene	-21	-18	-15	-19	-21 ^f	-19, ^g -15, ^h -8.7 ^h

^a Abraham et al.⁸⁴ ^b Wilhelm et al.⁸⁵ ^c Gallichio et al.⁸⁶ ^d Cui et al.^{87,88} ^e Ben-Naim et al.⁸² ^f Makhatadze and Privalov.⁸³ ^g Schravendijk et al.⁸⁹ ^h Rick.⁹⁰

TABLE 5: Experimental Heat Capacities of Solvation (cal mol⁻¹ K⁻¹) from the Literature Compared to Predictions Based on Various Parameterizations

	SM6T parameterizations			literature
	molecular coefficients	unrestricted	final	
ethane	68	54	34	70, ^a 67, ^b 95, ^c 65 ^d
propane	73	60	47	81, ^a 78, ^b 76 ^d
butane	84	68	59	102, ^a 95 ^b
pentane	70	76	70	108 ^a
hexane	104	84	82	119 ^a
cyclohexane	42	56	79	100 ^e
benzene	70	49	55	69, ^d 67, ^e 72, ^f 84, ^g 70 ^h
methanol	21	30	11	32 ⁱ
ethanol	117	33	30	48 ⁱ
<i>n</i> -propanol	2	40	42	64 ⁱ
butanol	70	48	54	79 ⁱ
2-butanol	92	56	53	83 ⁱ
pentanol	89	52	63	89 ⁱ

^a Olofsson et al.⁹⁶ ^b Dec et al.^{95,97,98} ^c Naghibi et al.^{99,100} ^d Bakk and Hoye.¹⁵ ^e Gill et al.⁹⁴ ^f Arnold et al.¹⁰¹ ^g Franks et al.⁹² ^h Graziano.¹⁰² ⁱ Arnett et al.⁹³

two instances (namely, ethyne and propyne) within the database where the *C* coefficient for a molecule is negative. Also, there are numerous instances within the set where the sum of contributions to the *C* coefficient from all carbon atoms is negative but is counterbalanced by a positive contribution from the H atoms. This reflects the fact that the coefficients used to compute *C* were chosen to best reproduce experimental free energies of solvation with a minimum of parameters and that independent physical meaning cannot be assigned to the value of each coefficient. This is confirmed by a study of the covariance matrices of these parameters, which shows that they are not entirely independent. Noting this, and that we neglected the temperature dependence of the heat capacity of solvation, that we assumed temperature-independent radii, and that an average of only 12 experimental points per compound was used to develop the model, we conclude that, despite the encouraging agreement with data from other groups, the division of the free energy of solvation predicted by SM6T into entropy and heat capacity should be interpreted with caution.

4. Software

New versions of HONDOPLUS,^{77,104} GAMESSPLUS,^{105,106} SMXGAUSS,⁷⁵ NWChem,^{107,108} and Jaguar¹⁰⁹ containing SM6T are planned for the near future.

5. Concluding Remarks

We have developed a model for calculating the temperature dependence of the aqueous free energy of solvation of compounds composed of H, C, and O over the temperature range

273–373 K. This involved creating an extensive database of experimental free energies of solvation, selecting an appropriate functional form for the model, and parametrizing the model against experiment. We found that an accurate model requires a heat-capacity-like term to capture the curvature of the temperature dependence of the free energy of solvation, that a parametrized model based on solvent accessible surface areas produces quite accurate results, and that the temperature dependence of the dielectric constant produces relatively little effect in aqueous solutions, although it is much more significant in organic solutions. The model reduces the mean unsigned error in the temperature dependence of the solvation free energy by a factor of 6.5 relative to the null hypothesis. The next step will be to extend the model to broader classes of compounds and to organic solvents. In future work, it would also be interesting to extend the SM6T model to predict free energies of solvation in near-critical and supercritical water which is the subject of considerable theoretical research.^{110–121}

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Appendix 1. Derivation of eq 6

We start with the standard thermodynamic equation relating the concentration of the solute in the gas phase to the concentration of the solute in solution at equilibrium^{28,29,37}

$$\gamma_a^{g,x} y_a P = \gamma_a^{\infty,x} x_a P_a^* \quad (31)$$

where y_a is the mole fraction of compound *a* in the gas phase, *P* is the total vapor pressure, $\gamma_a^{g,x}$ is the activity coefficient of *a* in the gas phase, x_a is the mole fraction of *a* in solution, P_a^* is the vapor pressure of the pure liquid solute, and $\gamma_a^{\infty,x}$ is the infinite dilution activity coefficient. Assuming that the solute behaves as an ideal gas, eq 31 can be rewritten as

$$\frac{\gamma_a^{\infty,x} P_a^*}{P} = \frac{y_a}{x_a} \quad (32)$$

The free energy of solvation for a standard state of 1 M in the gas phase and 1 M in solution equates to

$$\Delta G_s^0 = RT \ln(K_H) = RT \ln\left(\frac{c_a}{S_a}\right) \quad (33)$$

where K_H is the Henry's law constant, c_a is the molar

concentration of the solute in the gas phase, and S_a is the molar concentration of the solute in solution. Assuming ideality of the solute in the gas phase, we find

$$y_a = c_a \frac{RT}{P} \quad (34)$$

Assuming that the solute is infinitely dilute in the solution yields

$$x_a = \frac{S_a}{M_w} \quad (35)$$

where M_w is the molarity of the solvent, which in this case is water. Combining eqs 34 and 35 with eq 32 and rearranging yields

$$\frac{\gamma_a^{\infty, x} P_a^*}{RT M_w} = \frac{c_a}{S_a} \quad (36)$$

which, when combined with eq 33, results in eq 6.

Supporting Information Available: Tables listing the individual compounds, the number of experimental points used for each compound, and the references for the experimental data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References and Notes

- (1) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027.
- (2) Cramer, C. J.; Truhlar, D. G. In *Solvent Effects and Chemical Reactivity*; Tapia, O., Bertrán, J., Eds.; Kluwer: Boston, MA, 1996; p 1.
- (3) Cramer, C. J.; Truhlar, D. G. *Chem. Rev.* **1999**, *99*, 2161.
- (4) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999.
- (5) Elcock, A. H.; McCammon, J. A. *J. Phys. Chem. B* **1997**, *101*, 9624.
- (6) Grant, D. J. W.; Higuchi, T. *Solubility Behavior of Organic Compounds*; Wiley: New York, 1990.
- (7) Hamad, S.; Lago, S.; Mejias, J. A. *J. Phys. Chem. A* **2002**, *106*, 9104.
- (8) Mirbagheri, S. A. *Int. J. Environ. Sci. Technol.* **2004**, *1*, 141.
- (9) Silverman, R. B. *The Organic Chemistry of Drug Design and Drug Action*; Academic: San Diego, CA, 1992.
- (10) Kelly, C. P.; Cramer, C. J.; Truhlar, D. G. *Theor. Chem. Acc.* **2005**, *113*, 133.
- (11) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997.
- (12) Kelly, C. P.; Cramer, C. J.; Truhlar, D. G. *J. Chem. Theory Comput.* **2005**, *1*, 1133.
- (13) Addison, C. C. *J. Chem. Soc.* **1945**, 1945, 98.
- (14) Klotz, I. M.; Rosenberg, R. M. *Chemical Thermodynamics*, 5th ed.; Wiley: New York, 1994.
- (15) Bakk, A.; Hoye, J. S. *Physica A* **2002**, *303*, 286.
- (16) Sander, R. *Compilation of Henry's Law Constants for Inorganic and Organic Species of Potential Importance in Environmental Chemistry*, 3rd ed.; 1999; (<http://www.mpch-mainz.mpg.de/~sander/res/henry.html>).
- (17) Shiu, W.; Ma, K. *J. Phys. Chem. Ref. Data* **2000**, *29*, 41.
- (18) Dohanyosova, P.; Sarraute, S.; Dohnal, V.; Majer, V.; Gomes, M. C. *Ind. Eng. Chem. Res.* **2004**, *43*, 2805.
- (19) Stephenson, R. M.; Malanowski, S. *Handbook of the Thermodynamics of Organic Compounds*; Elsevier: New York, 1987.
- (20) Yaws, C. L. *Handbook of Vapor Pressures*; Gulf Publishing Company: Houston, TX, 1994; Vols. 1–4.
- (21) Yaws, C. L. *Yaws' Handbook of Thermodynamic and Physical Properties of Chemical Compounds*; Knovel: Norwich, NY, 2003.
- (22) Plyasunov, A. V.; Plyasunova, N. V.; Shock, E. L. *The Database for the Thermodynamic Properties of Neutral Compounds in the State of Aqueous Solution*; Department of Geological Sciences, Arizona State University: Tempe, AZ, 2005 (<http://orchyd.asu.edu/>).
- (23) Yalkowsky, S. H.; He, Y. *Handbook of Aqueous Solubility Data*; CRC Press: New York, 2003.
- (24) Maczynski, A.; Wisniewska-Gocłowska, B.; Góral, M. *J. Phys. Chem. Ref. Data* **2004**, *33*, 549.
- (25) Góral, M.; Maczynski, A.; Wisniewska-Gocłowska, B. *J. Phys. Chem. Ref. Data* **2004**, *33*, 579.
- (26) Góral, M.; Wisniewska-Gocłowska, B.; Maczynski, A. *J. Phys. Chem. Ref. Data* **2004**, *33*, 1159.
- (27) *IUPAC–NIST Solubility Database*; National Institute of Standards and Technology: Boulder, CO, 2005 (<http://srdata.nist.gov/solubility/>).
- (28) Gautreaux, M. F.; Coates, J. *AIChE J.* **1955**, *1*, 496.
- (29) Slocum, E. W.; Dodge, B. F. *AIChE J.* **1964**, *10*, 364.
- (30) Gmehling, J.; Menke, J.; Schiller, M. *Activity Coefficients at Infinite Dilution: C₁₀–C₃₆ with O₂S and H₂O*; Dechema: Frankfurt, Germany, 1994; Vol. 9, Part 4.
- (31) Hovorka, S.; Dohnal, V.; Roux, A. H.; Roux-Desgranges, G. *Fluid Phase Equilib.* **2002**, *201*, 135.
- (32) Cramer, C. J.; Truhlar, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 8305.
- (33) Winget, P.; Hawkins, G. D.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2000**, *104*, 4726.
- (34) Thompson, J. D.; Cramer, C. J.; Truhlar, D. G. *J. Chem. Phys.* **2003**, *119*, 1661.
- (35) Ben-Naim, A. *Solvation Thermodynamics*; Plenum: New York, 1977.
- (36) Cramer, C. J.; Truhlar, D. G. In *Free Energy Calculations in Rational Drug Design*; Reddy, M. R., Erion, M. D., Eds.; Kluwer: New York, 2001; p 63.
- (37) Atkins, P. *Physical Chemistry*, 6th ed.; Freeman: New York, 1998.
- (38) Staudinger, J.; Roberts, P. V. *Chemosphere* **2001**, *44*, 561.
- (39) Stephenson, R.; Stuart, J. *J. Chem. Eng. Data* **1986**, *31*, 56.
- (40) Liabastre, A. A. Ph.D. Thesis, Georgia Institute of Technology, 1974.
- (41) Price, L. C. *Am. Assoc. Pet. Geo. Bull.* **1976**, *60*, 213.
- (42) Stephenson, R.; Stuart, J.; Tabak, M. *J. Chem. Eng. Data* **1984**, *29*, 287.
- (43) Lemmon, E. W.; Goodwin, A. R. H. *J. Phys. Chem. Ref. Data* **2000**, *29*, 1.
- (44) Poling, B. E.; Prausnitz, J. M.; O'Connell, J. P. *The Properties of Gases and Liquids*, 5th ed.; McGraw-Hill: New York, 2001.
- (45) Clarke, E. C. W.; Glew, D. N. *Trans. Faraday Soc.* **1966**, *62*, 539.
- (46) Cramer, C. J.; Truhlar, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 8552.
- (47) Thompson, J. D.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. A* **2004**, *108*, 6532.
- (48) Thompson, J. D.; Cramer, C. J.; Truhlar, D. G. *Theor. Chem. Acc.* **2005**, *113*, 107.
- (49) Cramer, C. J.; Truhlar, D. G. In *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B., Eds.; VHC: New York, 1995; Vol. 6, p 7.
- (50) Cramer, C. J. *Essentials of Computational Chemistry: Theories and Models*, 2nd ed.; Wiley: New York, 2002.
- (51) Hawkins, G.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **1997**, *101*, 7147.
- (52) Daudel, R. *Quantum Theory of Chemical Reactivity*; Reidel: Dordrecht, The Netherlands, 1973.
- (53) Tucker, S. C.; Truhlar, D. G. *Chem. Phys. Lett.* **1989**, *157*, 164.
- (54) Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. J. *Am. Chem. Soc.* **1990**, *112*, 6127.
- (55) Tapia, O. In *Quantum Theory of Chemical Reactions, Vol. 2. Solvent Effect, Reaction Mechanisms, Photochemical Processes*; Daudel, R., Pullman, A., Salem, L., Veillard, A., Eds.; Kluwer: Boston, MA, 1981; Vol. 2, p 25.
- (56) Li, J.; Zhu, T.; Hawkins, G.; Winget, P.; Liotard, D. A.; Cramer, C. J.; Truhlar, D. G. *Theor. Chem. Acc.* **1999**, *103*, 9.
- (57) Giesen, D. J.; Storer, J. W.; Cramer, C. J.; Truhlar, D. G. *J. Am. Chem. Soc.* **1995**, *117*, 1057.
- (58) Makhatazde, G. I.; Privalov, P. L. *Adv. Protein Chem.* **1995**, *47*, 307.
- (59) Lazaridis, T.; Karplus, M. *Proteins* **1999**, *35*, 133.
- (60) Shimizu, S.; Chan, H. S. *J. Chem. Phys.* **2000**, *113*, 4683.
- (61) Lee, B.; Richards, F. M. *J. Mol. Biol.* **1971**, *55*, 379.
- (62) Hermann, R. B. *J. Phys. Chem.* **1972**, *76*, 2754.
- (63) Hermann, R. B. *J. Phys. Chem.* **1975**, *79*, 163.
- (64) Liotard, D. A.; Hawkins, G. D.; Lynch, G. C.; Cramer, C. J.; Truhlar, D. G. *J. Comput. Chem.* **1995**, *16*, 422.
- (65) Bondi, A. J. *J. Phys. Chem.* **1964**, *68*, 441.
- (66) Yu, H.-A.; Roux, B.; Karplus, M. *J. Chem. Phys.* **1990**, *92*, 5020.
- (67) Shock, E. L.; Oelkers, E. H.; Johnson, J. W.; Sverjensky, D. A.; Helgeson, H. C. *J. Chem. Soc., Faraday Trans. 1* **1992**, *88*, 803.
- (68) Rashin, A. A.; Bukatin, M. A. *Biophys. Chem.* **1994**, *51*, 167.
- (69) Kono, H.; Ohtsuki, Y.; Abe, T. *J. Phys. Chem.* **1996**, *100*, 9935.
- (70) Cubero, E.; Orozco, M.; Luque, F. J. *J. Org. Chem.* **1998**, *63*, 2354.
- (71) Bonaccorsi, R.; Palla, P.; Tomasi, J. *J. Am. Chem. Soc.* **1984**, *106*, 1945.
- (72) *CRC Handbook of Chemistry and Physics*; Lide, D. R., Ed.; CRC: Boca Raton, FL, 1995; Vol. 75.
- (73) Abraham, R. J.; Bretschneider, E.; In *Internal Rotation in Molecules*; Orville-Thomas, W. J., Ed.; Wiley: New York, 1974; p 481.
- (74) Kelly, C. P.; Xidos, J. D.; Li, J.; Thompson, J. D.; Hawkins, G. D.; Winget, P. D.; Zhu, T.; Rinaldi, D.; Liotard, D. A.; Cramer, C. J.;

Truhlar, D. G.; Frisch, M. J. *MN-GSM 5.2*; Univeristy of Minnesota: Minneapolis, MN, 2005.

(75) Kelly, C. P.; Thompson, D. J.; Lynch, B. J.; Xidos, J. D.; Li, J.; Hawkins, G. D.; Zhu, T.; Volobuev, Y.; Dupuis, M.; Rinaldi, D.; Liotard, D. A.; Cramer, C. J.; Truhlar, D. G. *SMXGAUSS*, version 2.0.2; University of Minnesota: Minneapolis, MN, 2003.

(76) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nagatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.01; Gaussian: Pittsburgh, PA, 2003.

(77) Kelly, C. P.; Nakamura, H.; Xidos, J. D.; Thompson, D. J.; Li, J.; Hawkins, G. D.; Zhu, T.; Lynch, B. J.; Volobuev, Y.; Rinaldi, D.; Liotard, D. A.; Cramer, C. J.; Truhlar, D. G. *HONDOPLUS*, version 4.7; University of Minnesota: Minneapolis, MN, 2005 (based on HONDO v. 99.6).

(78) Chambers, C. C.; Hawkins, G. D.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem.* **1996**, *100*, 16385.

(79) Lasdon, L. S.; Waren, A. D.; Jain, A.; Ratner, M. *ACM Trans. Math. Software* **1978**, *4*, 34.

(80) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.

(81) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(82) Ben-Naim, A.; Marcus, Y. *J. Chem. Phys.* **1984**, *81*, 2016.

(83) Makhatadze, G. I.; Privalov, P. L. *Biophys. Chem.* **1994**, *50*, 285.

(84) Abraham, M. H.; Matteoli, E. *J. Chem. Soc., Faraday Trans. 1* **1988**, *84*, 1985.

(85) Wilhelm, E.; Battino, R.; Wilcock, R. J. *Chem. Rev.* **1977**, *77*, 219.

(86) Gallicchio, E.; Kubo, M. M.; Levy, R. M. *J. Phys. Chem. B* **2000**, *104*, 6271.

(87) Cui, Q.; Smith, V. H. *J. Chem. Phys.* **2000**, *113*, 10240.

(88) Cui, Q.; Smith, V. H. *J. Chem. Phys.* **2001**, *115*, 2228.

(89) Schravendijk, P.; van der Vegt, N. F. A. *J. Chem. Theory Comput.* **2005**, *1*, 643.

(90) Rick, S. J. *J. Phys. Chem. B* **2003**, *107*, 9853.

(91) Arnold, V. W.; Washburn, E. R. *J. Phys. Chem.* **1958**, *62*, 1088.

(92) Franks, F.; Gent, M.; Johnson, H. H. *J. Chem. Soc.* **1963**, 2716.

(93) Arnett, E. M.; Kover, W. B.; Carter, J. V. *J. Am. Chem. Soc.* **1969**, *91*, 4028.

(94) Gill, S. J.; Nichols, N. F.; Wadso, I. J. *Chem. Thermodyn.* **1976**, *8*, 445.

(95) Dec, S. F.; Gill, S. J. *J. Solution Chem.* **1984**, *13*, 27.

(96) Olofsson, G.; Oshodj, A. A.; Warnstrom, E.; Wadso, I. J. *Chem. Thermodyn.* **1984**, *16*, 1041.

(97) Dec, S. F.; Gill, S. J. *J. Solution Chem.* **1985**, *14*, 417.

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

(99) Naghibi, H.; Dec, S. F.; Gill, S. J. *J. Phys. Chem.* **1986**, *90*, 4261.

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

(101) Arnold, D. S.; Plank, C. A.; Erickson, E. E.; Pike, F. P. *Chem. Eng. Data Ser.* **1958**, *3*, 253.

(102) Graziano, G. *Biophys. Chem.* **2005**, *116*, 137.

(103) Hawkins, G.; Liotard, D. A.; Cramer, C. J.; Truhlar, D. G. *J. Org. Chem.* **1998**, *63*, 4305.

(104) Dupuis, M.; Marquez, A.; Davidson, E. R. *HONDO 99.6*; Quantum Chemistry Program Exchange (QCPE), Indiana University: Bloomington, IN, 1999 (based on HONDO 95.3).

(105) Kelly, C. P.; Pu, J.; Thompson, D. J.; Xidos, J. D.; Li, J.; Zhu, T.; Hawkins, G. D.; Chuang, Y.-Y.; Fast, P. L.; Lynch, B. J.; Liotard, D. A.; Rinaldi, D.; Gao, J.; Cramer, C. J.; Truhlar, D. G. *GAMESSPLUS*, version 4.7; University of Minnesota: Minneapolis, MN, 2005 (based on the General Atomic and Molecular Electronic Structure System (GAMESS)).

(106) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S. J.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347.

(107) Aprà, E.; Windus, T. L.; Straatsma, T. P.; Bylaska, E. J.; de Jong, W.; Hirata, S.; Valiev, M.; Hackler, M.; Pollack, L.; Kowalski, K.; Harrison, R.; Dupuis, M.; Smith, D. M. A.; Nieplocha, J.; V., T.; Krishnan, M.; Auer, A. A.; Brown, E.; Cisneros, G.; Fann, G.; Fruchtl, H.; Garza, J.; Hirao, K.; Kendall, R.; Nichols, J.; Tsemekhman, K.; Wolinski, K.; Anchell, J.; Bernholdt, D.; Borowski, P.; Clark, T.; Clerc, D.; Dachselt, H.; Deegan, M.; Dyall, K.; Elwood, D.; Glendening, E.; Gutowski, M.; Hess, A.; Jaffe, J.; Johnson, B.; Ju, J.; Kobayashi, R.; Kutteh, R.; Lin, Z.; Littlefield, R.; Long, X.; Meng, B.; Nakajima, T.; Niu, S.; Rosing, M.; Sandrone, G.; Stave, M.; Taylor, H.; Thomas, G.; van Lenthe, J.; Wong, A.; Zhang, Z. *NWChem, A Computational Chemistry Package for Parallel Computers*, version 4.7; Pacific Northwest National Laboratory: Richland, WA, 2005.

(108) Kendall, R. A.; Apra, E.; Bernholdt, D. E.; Bylaska, E. J.; Dupuis, M.; Fann, G. I.; Harrison, R. J.; Ju, J.; Nichols, J. A.; Nieplocha, J.; Straatsma, T. P.; Windus, T. L.; Wong, A. T. *Comput. Phys. Commun.* **2000**, *128*, 260.

(109) *Jaguar 6.5*; Schrodinger LLC: Portland, OR, 2005.

(110) Gilson, M.; Sharp, K.; Honig, B. *J. Comput. Chem.* **1988**, *9*, 327.

(111) Tucker, S. C.; Gibbons, E. M. In *Structure and Reactivity in Aqueous Solution*; Cramer, C. J., Truhlar, D. G., Eds.; ACS Symposium Series, Vol. 528; The American Chemical Society: Washington, DC, 1994; p 196.

(112) Bennett, G. E.; Rossky, P. J.; Johnston, K. P. *J. Phys. Chem.* **1995**, *99*, 16136.

(113) Luo, H.; Tucker, S. C. *J. Am. Chem. Soc.* **1995**, *117*, 11359.

(114) Pomelli, C. S.; Tomasi, J. *J. Phys. Chem. A* **1997**, *101*, 3561.

(115) Plyasunov, A. V.; O'Connell, J. P.; Wood, R. H.; Shock, E. L. *Geochim. Cosmochim. Acta* **2000**, *64*, 2779.

(116) Yezdimer, E. M.; Sedlbauer, J.; Wood, R. H. *Chem. Geol.* **2000**, *164*, 259.

(117) Plyasunov, A. V.; O'Connell, J. P.; Wood, R. H.; Shock, E. L. *Fluid Phase Equilib.* **2001**, *183–184*, 133.

(118) Hori, T.; Takahashi, H.; Nitta, T. *J. Comput. Chem.* **2002**, *24*, 209.

(119) Akinfiev, N. N.; Diamond, L. W. *Geochim. Cosmochim. Acta* **2003**, *67*, 613.

(120) Anisimov, M. A.; Sengers, J. V.; Sengers, J. M. H. L. In *Aqueous Systems at Elevated Temperatures and Pressures*; Palmer, D. A., Fernandez-Prini, R., Harvey, A. H., Eds.; Elsevier: London, 2004; p 29.

(121) Majer, V.; Sedlbauer, J.; Wood, R. H. In *Aqueous Systems at Elevated Temperatures and Pressures*; Palmer, D. A., Fernandez-Prini, R., Harvey, A. H., Eds.; Elsevier: London, 2004; p 99.