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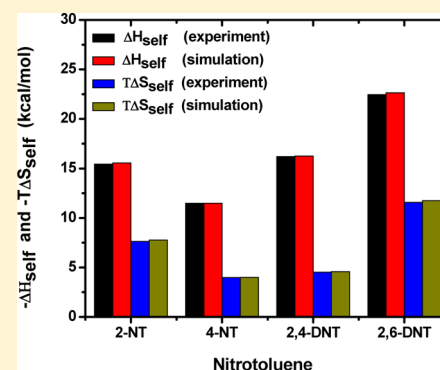
# Temperature-Dependent Physicochemical Properties and Solvation Thermodynamics of Nitrotoluenes from Solvation Free Energies

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**S** Supporting Information

**ABSTRACT:** Expanded ensemble molecular dynamics simulations are used to calculate the free energies of hydration and self-solvation of low polarity nitrotoluenes over the temperature range of 273 K to 330 K. From this information the liquid, subcooled, and solid-phase vapor pressures, solubilities, Henry's law constants, hydration and self-solvation entropies, enthalpies, isobaric heat capacities, and enthalpies of vaporization or sublimation are then computed. The values obtained are compared to the limited experimental data available. At a reference temperature of 300 K, the hydration enthalpies are found to be larger in magnitude than hydration entropies for the nitrotoluenes, and vary with the number of nitro groups, while the hydration entropies are almost unchanged as functions of either the number of nitro groups or the solvent accessible surface area. Consequently the variation in the hydration free energies among the nitrotoluenes is due to the variation in their hydration enthalpies. In contrast, both enthalpies and entropies change with the number of nitro groups in self-solvation, and both contribute to the variation of the self-solvation free energy. Also, the isobaric hydration heat capacities are found to change only slightly with temperature.



## I. INTRODUCTION

The temperature dependence of physicochemical properties is important in environmental modeling, drug discovery, and industrial applications.<sup>1–3</sup> Koga<sup>4</sup> recently compared and contrasted the behavior of water and simple liquids on the basis of their temperature-dependent solvation free energies and related thermodynamic quantities. Here we consider the nitrotoluenes (NTs), low polarity organic pollutants that are difficult to eliminate from the contaminated sites because of their low aqueous solubilities,<sup>5</sup> so that they remain in the soil, sediment, and clay. The highly exothermic, indeed explosive, nature of the nitrotoluenes makes experimental measurements of their temperature-dependent properties difficult.

An understanding of the different contributions to the thermophysical properties of these compounds can be obtained using molecular simulation. The thermodynamic decomposition of the hydration (solvation in water) free energies into enthalpic and entropic contributions using simulation has been limited to apolar compounds.<sup>6–10</sup> Levy and Gallicchio<sup>11</sup> presented an extensive review of the different approaches for the determination of the enthalpy and entropy of solvation and discussed the rationale of doing so. A large body of work can be found on the temperature dependence of the solvation free energies of nonpolar solutes in water, and the enthalpic or entropic dominance in different temperature ranges (see the review by Dill<sup>6</sup> and the references therein); however studies of solutes with polar functional groups are rare.

While an understanding of the thermodynamic properties leading to the low aqueous solubility and volatility of the nitrotoluenes is important, the separate contributions of the

solvation free energy, enthalpy, and entropy have not been studied systematically. The isobaric heat capacity of pure liquids as a function of temperature is important in some applications, for example, in energy balances, in phase and reaction equilibria,<sup>12</sup> and for theory.<sup>13</sup> However, measured heat capacities for the compounds of interest here are limited and several empirical predictive methods<sup>14,15</sup> have been proposed. The prediction of the solvation heat capacity using molecular simulation is quite sensitive to the polarity of the solvent and solute.<sup>16</sup> Ben-Amotz and Widom<sup>16</sup> have identified the factors affecting the self-solvation and hydration heat capacities using interrelationships among the derivatives of the thermodynamic variables, and have provided a way of experimentally verifying the components of the solvation heat capacity.

Here we present a study of the temperature dependence of solvation free energies, solvation thermodynamics, and the physicochemical properties of the nitrotoluenes. We determine the relations among the solvation free energies, the solvation thermodynamics, and the number of nitro groups, and also compute physicochemical properties from the solvation free energies. Specifically, hydration and self-solvation free energies are computed for a range of temperatures using expanded ensemble molecular dynamics simulations. The entropy, enthalpy, isobaric heat capacity of hydration, vapor pressure, aqueous solubility, and the Henry's law constants as functions

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of temperature are then calculated from these temperature-dependent solvation free energies.

## II. METHODOLOGY

**Models.** We have used the TraPPE<sup>17–20</sup> force field parameters with CHELPG<sup>21</sup> charges for the calculations of the nitrotoluenes (NTs) as it has been found previously that this combination reproduces the experimental hydration free energies reasonably well.<sup>22</sup> Also, the transferability of the TraPPE model is advantageous for the study of temperature-dependent properties within a class of compounds. The CHELPG charges were calculated at the B3LYP/6-311G-(d,p)<sup>23–26</sup> level using the gas-phase optimized geometry at the B3LYP/6-31G(d) level; all the quantum mechanics calculations were done using Gaussian 09.<sup>27</sup> The NTs chosen for study are 2-nitrotoluene (2-NT), 4-nitrotoluene (4-NT), 2,4-dinitrotoluene (2,4-DNT), 2,6-dinitrotoluene (2,6-DNT), and 2,4,6-trinitrotoluene (2,4,6-TNT). The TIP3P<sup>28</sup> forcefield was used for water.

**Simulation Conditions.** All simulations were carried out in the NPT ensemble using the expanded ensemble (EE) molecular dynamics algorithm<sup>29,30</sup> in the MDynaMix Package, version 5.2.4.<sup>30</sup> The solvation free energies in water (hydration) and the self-solvation free energies were computed at four temperatures in the range of 273 K to 330 K at a pressure 1 atm. Temperatures and pressures were controlled using the Nose–Hoover thermostat and barostat, respectively. Only 2-NT is liquid over the temperature range. Among the other NTs only 4-NT is liquid at temperature 330 K. Consequently, we can only compute self-solvation free energies from measured vapor pressures for 2-NT (for the entire temperature range) and 4-NT (at 330 K). For all other compounds, we can only predict subcooled self-solvation free energies. For comparison, our 4-NT results at 330 K have been singled out to demonstrate the predictability of the method.

For compounds that are solids in the temperature range studied, the subcooled self-solvation free energies were computed following the protocol described elsewhere.<sup>31</sup> In all cases the solvation free energies were calculated by inserting a single NT solute molecule into the solvent consisting of 500 water molecules (for hydration calculations) and 250 molecules of its pure or subcooled liquid (for self-solvation calculations).

The number of expanded ensemble (EE) subensembles  $M$  used in the simulations was 20 for hydration calculations and 30 to 40 for the self-solvation calculations. Values of the insertion parameter ( $\lambda_m$ ) were evenly spaced using  $\lambda_m = (M - m)/(M - 1)$ , where  $m$  is the index of the current subensemble. The partial atomic charges were scaled as the square of the  $\lambda_m$  and the Lennard-Jones well-depth parameters were scaled with the fourth power of  $\lambda_m$ ; the rationale for choosing this power law scaling scheme is described elsewhere.<sup>32</sup> Compatibility of this scaling method with the so-called “soft-core” potential<sup>33–38</sup> has been verified by implementing the soft-core potential in the framework of the EE algorithm and found to reproduce results within the standard deviations of each (see Supporting Information of ref 32). Also, the applicability of the power law scaling scheme used here has been verified previously by comparing the results with other methods (e.g., thermodynamic integration and Bennett acceptance ratio methods) that use the soft-core potential scheme.<sup>39–41</sup> The balancing factors were determined and optimized in an automated way using the Wang–Landau (WL) algorithm.<sup>42</sup> At first, 10 ns of each EE simulation was used to optimize the balancing factors and then

an additional 10 ns run was used to collect the solvation free energies and the statistical errors. The convergence of the EE method was examined using two checks. First, we made sure that adequate sampling was done in the two extreme subensembles (the first and the last) during a WL iteration by observing the number of visits to those subensembles. Second, the probability distribution over the subensembles and the forward and reverse acceptance ratios were examined for their equal orders of magnitude.

**Solvation Free Energies and Physicochemical Properties.** All solvation free energies and corresponding thermodynamic quantities reported here are at the commonly used “1 M fixed concentration standard-state”<sup>43</sup> of Ben-Naim.<sup>44</sup> Here the calculated Gibbs free energy changes are for transferring a solute molecule from a pure ideal gas at a concentration of 1 mol/L into an aqueous phase at a solute concentration of 1 mol/L (for the hydration free energy) or into its pure liquid or subcooled<sup>45</sup> liquid phase at a concentration of 1 mol/L (for the self-solvation free energy). Then the solvation entropy, enthalpy, and heat capacity are calculated from the temperature derivatives of the “1 M fixed concentration standard-state” solvation free energies.<sup>44</sup>

The temperature-dependent vapor pressure  $P^X(T)$ , with  $X$  being a subcooled (subco) or liquid (liq) phase, were calculated from the temperature-dependent self-solvation free energy using

$$P^X(T) = P^T M_X \exp\left(\frac{\Delta G_{\text{self}}^X(T)}{RT}\right) \quad (1)$$

where  $P^T$  is the ideal gas pressure in atm at the temperature  $T$  in K and a density of 1 mol/L, and  $M_X$  is the molarity of the solute in its pure liquid or subcooled liquid state. For the NTs that are solid at a temperature of interest, the solid-phase vapor pressures,  $P^{\text{sol}}(T)$ , as a function of temperature were calculated from the subcooled liquid vapor pressures,  $P^{\text{subco}}(T)$ , using the thermodynamic corrections reported elsewhere.<sup>31</sup>

The liquid and subcooled aqueous solubilities,  $C_w^X(T)$ , were then estimated from the hydration and self-solvation free energies of the solutes using

$$C_w^X(T) = M_{\text{aq}}^X(T) = M_X \exp\left[\frac{\Delta G_{\text{self}}^X(T) - \Delta G_{\text{hyd}}^X(T)}{RT}\right] \quad (2)$$

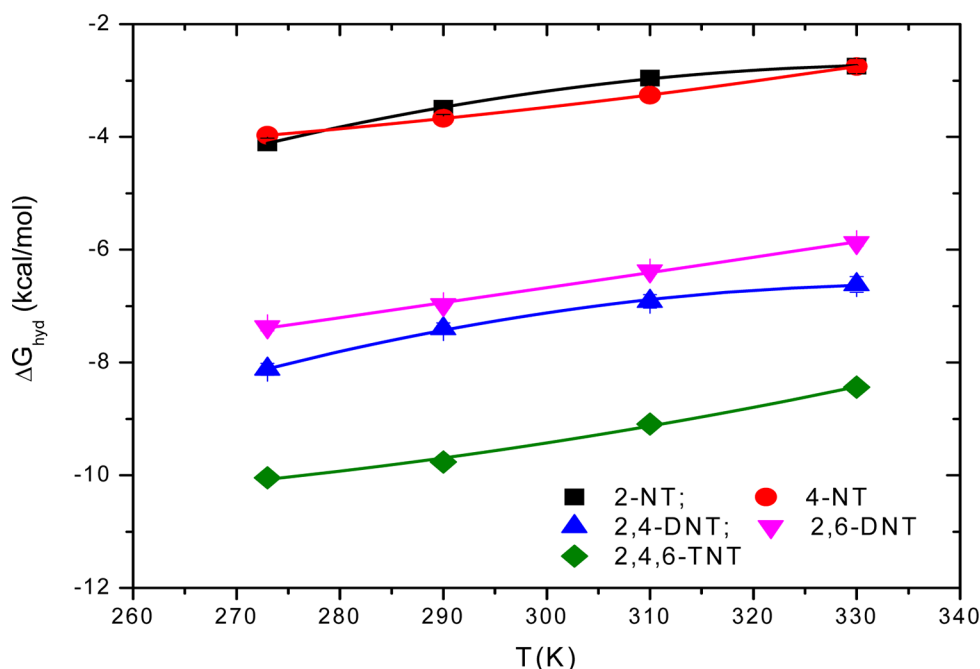
where  $M_{\text{aq}}^X$  is the aqueous solute solubility in molarity units. When the solute is a solid at the temperature of interest its aqueous solubility,  $C_w^X(T)$ , was calculated from the solid-phase corrected vapor pressure and the hydration free energy as in our previous work.<sup>31</sup> The Henry’s law constants (HLCs),  $K_{\text{hyd}}^X(T)$ , were calculated from the ratio of solute vapor pressure to its solubility

$$K_{\text{hyd}}^X(T) = \frac{P_{\text{vap}}^X(T)}{C_w^X(T)} \quad (3)$$

**Analyses of the Solvation Thermodynamics.** The computation of the solvation entropy, enthalpy, and heat capacity from temperature-dependent solvation free energies is common in literature;<sup>6,11,44</sup> however, there exists several numerical approaches, and most were used only for the temperature-dependent hydration (solvation in water) free energies,<sup>16,46–49</sup> not self-solvation free energies. Other

Table 1. Experimental (expt) and Simulated (sim) Hydration Free Energies of the Nitrotoluenes as a Function of Temperature

compound	$\Delta G_{\text{hyd}}/(\text{kcal/mol})$							
	273 K		290 K		310 K		330 K	
	expt	sim	expt	sim	expt	sim	expt	sim
2-NT	-4.43	-4.11 $\pm$ 0.08	-4.00	-3.50 $\pm$ 0.10	-3.49	-2.96 $\pm$ 0.09	-2.99	-2.75 $\pm$ 0.13
4-NT	-4.77	-3.97 $\pm$ 0.09	-4.25	-3.67 $\pm$ 0.11	-3.67	-3.26 $\pm$ 0.09	-3.12	-2.75 $\pm$ 0.11
2,4-DNT	-7.29	-8.12 $\pm$ 0.11	-6.74	-7.40 $\pm$ 0.10	-6.16	-6.92 $\pm$ 0.12	-5.64	-6.62 $\pm$ 0.14
2,6-DNT	-6.84	-7.37 $\pm$ 0.08	-6.30	-6.98 $\pm$ 0.06	-5.73	-6.37 $\pm$ 0.06	-5.19	-5.87 $\pm$ 0.06
2,4,6-TNT	-9.00	-10.04 $\pm$ 0.10	-8.54	-9.77 $\pm$ 0.09	-8.01	-9.09 $\pm$ 0.07	-7.55	-8.44 $\pm$ 0.06



**Figure 1.** Calculated hydration free energies of the nitrotoluenes as a function of temperature. The lines are second order polynomial fits of the temperature-dependent hydration free energies.

thermodynamic state functions can be obtained as temperature derivatives<sup>44,47</sup> of  $\Delta G_{\text{hyd}}(T)$  and  $\Delta G_{\text{self}}(T)$ . The entropic ( $\Delta S_Y$ ) ( $Y = \text{hyd}, \text{self}$ ), enthalpic ( $\Delta H_Y$ ), and isobaric heat capacity ( $\Delta C_{p,Y}$ ) contributions to the solvation free energies  $\Delta G_Y(T)$  at any temperature are obtained from the first and second temperature derivatives of the solvation free energy as follows:

$$\Delta S_Y(T) = -\left(\frac{\partial \Delta G_Y}{\partial T}\right)_{P,N} \quad (4)$$

$$\Delta H_Y(T) = -T^2 \left[ \frac{\partial(\Delta G_Y/T)}{\partial T} \right]_{P,N} \quad (5)$$

$$\Delta C_{p,Y}(T) = -T \left[ \frac{\partial^2 \Delta G_Y}{\partial T^2} \right]_{P,N} \quad (6)$$

Several methods have been used to estimate these derivatives; including nonlinear regression, polynomial fits of the temperature-dependent solvation free energies, and finite difference methods directly using data derived from experiment or simulation. Each of these numerical approaches has limitations and advantages (see the review of Levy and Gallicchio<sup>11</sup>); outlines of the methods are discussed in the Supporting Information. All of these methods lead to essentially similar

results here for  $\Delta H_Y$  and  $T\Delta S_Y$  calculated from the solvation free energies.

**Compilation of Experimental Data.** Data on the temperature-dependent physicochemical properties of the nitrotoluenes are scarce in the literature. Only vapor pressure and aqueous solubility data as functions of temperature are available, and then only for some of the nitrotoluenes. Since the measurements were made by different researchers, they are often not at the same temperature or in our temperature range. Calculating the hydration free energy at a given temperature from the experimental data requires the measured vapor pressure (for  $\Delta G_{\text{self}}$ ) and aqueous solubility (for  $\Delta G_{\text{self}} - \Delta G_{\text{hyd}}$ ) at that temperature. Vapor pressures were calculated either from the temperature-dependent equations (often of the Clausius–Clapeyron type) provided in the original literature, or by fitting to the reported data.<sup>50–55</sup> These equations are valid only in the experimental temperature range, which was not always from 273 K to 330 K as considered here, so that when used to calculate the vapor pressure in this temperature range in some cases either the low-temperature or high-temperature vapor pressures are extrapolations. Table S-1 of the Supporting Information gives the equations and parameters collected from the original literature with the temperature range of their validity. A similar approach has also been used for compiling the experimental solubility data.<sup>56–60</sup>

**Table 2.** Experimental (expt) and Simulated (sim) Self-Solvation Free Energies of the Nitrotoluenes as a Function of Temperature

compound	$\Delta G_{\text{self}}/(\text{kcal/mol})$							
	273 K		290 K		310 K		330 K	
	expt	sim	expt	sim	expt	sim	expt	sim
2-NT	−8.70	−8.79 ± 0.26	−8.38	−8.18 ± 0.19	−8.02	−7.52 ± 0.17	−7.66	−7.50 ± 0.24
4-NT <sup>a</sup>		−7.88 ± 0.07		−7.69 ± 0.08		−7.33 ± 0.07	−7.87 <sup>b</sup>	−7.16 ± 0.08
2,4-DNT		−13.75 ± 0.46		−12.28 ± 0.31		−12.32 ± 0.27		−11.53 ± 0.26
2,6-DNT		−12.38 ± 0.42		−11.49 ± 0.26		−10.51 ± 0.21		−10.41 ± 0.14

<sup>a</sup>Melting temperature, 324.60 K. <sup>b</sup>Liquid at 330 K.

The values of the temperature-dependent self-solvation free energies from experiment for liquid 2-NT were calculated using the measured vapor pressures as a function of temperature. Experimental vapor pressures of the subcooled liquids were not found for the NTs that are solids over the temperature range. However, 4-NT is a liquid at the highest temperature considered here, 330 K, and its self-solvation free energy was calculated directly from its measured liquid vapor pressure.

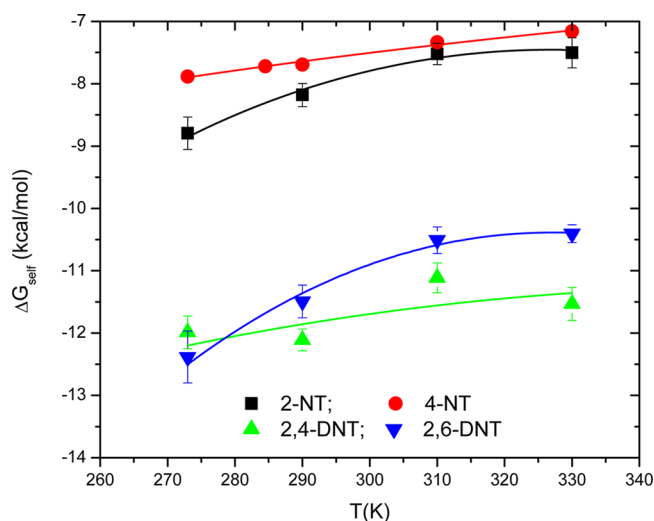
Since experimental data for hydration and self-solvation enthalpies, entropies, and isobaric heat capacities of the NTs are not available in the literature, for comparison these were estimated from the solvation free energies derived from experimental data using the methods discussed in the next section.

### III. RESULTS

**A. Temperature Dependence of the Solvation Free Energies.** Table 1 gives the hydration free energies  $\Delta G_{\text{hyd}}$  obtained directly from simulation and derived from experiment at each of the temperatures (also plotted in Figure 1). The hydration free energies of the NTs studied are all negative, and their absolute magnitude decreases with increasing temperature. For most of the NTs here the TraPPE/CHELPG model reproduces the temperature-dependent measured hydration free energies, when available with an average unsigned error (AUE) of only about 0.5 kcal/mol, except for 4-NT for which the AUE is larger but still below 1 kcal/mol. This level of accuracy is reasonable considering the uncertainties in the measured vapor pressure and solubility data over the temperature range from which the hydration free energies were derived and the force fields and partial charges used.

Table 2 gives the self-solvation free energies ( $\Delta G_{\text{self}}$ ) at each of the temperatures, which are also shown in Figure 2. The  $\Delta G_{\text{self}}$  values are all negative and decrease in magnitude with increasing temperature. The temperature-dependent self-solvation free energies of 2-NT computed here as a function of temperature are compared with the available self-solvation free energies derived from the measured vapor pressures. Except for the 310 K results, the  $\Delta G_{\text{self}}$  values derived from the experimental data are within the standard deviations of the simulation results. However, even at 310 K the difference is only 0.5 kcal/mol. Also, a comparison between the simulation result of  $-7.16 \pm 0.08$  and the measured datum of  $-7.87$ , both in kcal/mol, of 4-NT at 330 K (liquid) shows only a 0.71 kcal/mol difference.

Table 3 summarizes the average unsigned errors between the simulation results and those derived from experiment for the hydration and self-solvation free energies (and also the vapor pressure and the solubility to be considered later) for the nitrotoluenes studied. Figure 3 shows the hydration free

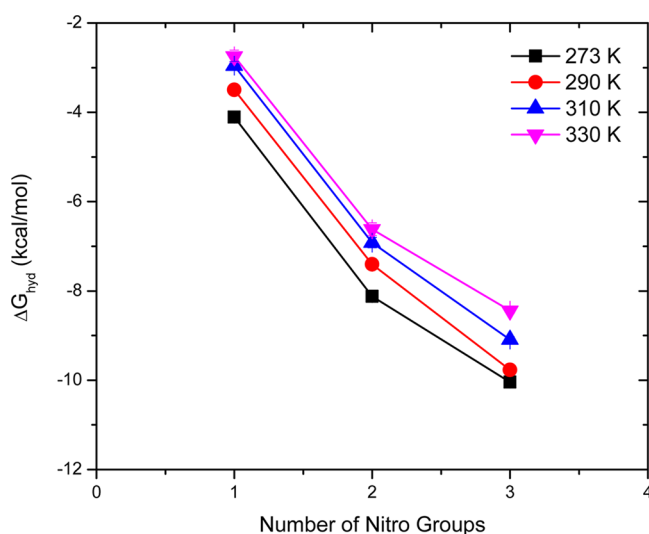
**Figure 2.** Self-solvation free energies of the nitrotoluenes as a function of temperature. The lines are second order polynomial fits of the temperature-dependent self-solvation free energies.**Table 3.** Average Unsigned Error (AUE) of the Results from Simulations over the Temperature Range ( $T = 273 \text{ K}$  to  $330 \text{ K}$ )

physicochemical property	2-NT	4-NT	2,4-DNT	2,6-DNT
$\Delta G_{\text{hyd}}/(\text{kcal/mol})$	0.40	0.54	0.81	0.63
$\Delta G_{\text{self}}/(\text{kcal/mol})$	0.24			
$\log_{10} P/(P \text{ in Pa})$	0.28	0.77	0.41	0.56
$\log_{10} C_w/(C_w \text{ in mol/L})$	0.32	0.86	0.26	0.93

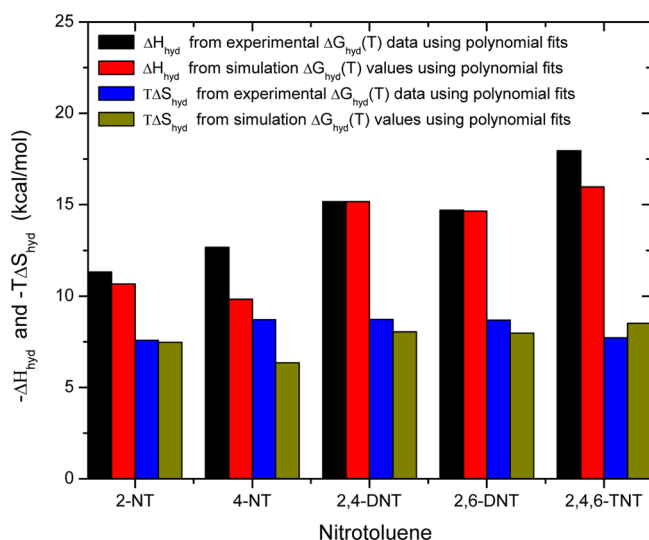
energies of the NTs as a function of the number of nitro groups at different temperatures in the range of 273 K to 330 K. The hydration free energies become more negative with an increasing number of nitro groups, and also with decreasing temperature. For a fixed number of nitro groups, the hydration free energies depend on the intramolecular spatial distribution of the nitro groups. Also the magnitudes of the self-solvation free energies increase with decreasing temperature and the number of nitro groups.

**B. Solvation Thermodynamics.** (i). *Solvation Thermodynamics at 300 K.* Figure 4 (also Table 4) gives the hydration enthalpies and entropies, respectively, at a temperature 300 K calculated from the hydration free energies derived from experiment and from simulation using the polynomial fits (eqs 10 to 13 of the Supporting Information). Also, Tables S-3 and S-4 of the Supporting Information summarize the isobaric solvation heat capacities of the NTs at 300 K. The values of the solvation thermodynamic properties obtained as derivatives of the hydration free energies are very sensitive to the shape of the





**Figure 3.** Hydration free energies as a function of the number of nitro groups in the NTs at different temperatures.



**Figure 4.** Hydration enthalpies and entropies of the NTs at a reference temperature of 300 K.

**Table 4.** Experimental (expt) and Simulated (sim) Hydration Enthalpy ( $\Delta H_{\text{hyd}}$ ) and Entropy ( $T\Delta S_{\text{hyd}}$ ) at  $T = 300$  K Based on a Polynomial Fit

compound	$\Delta H_{\text{hyd}}/(\text{kcal/mol})$		$T\Delta S_{\text{hyd}}/(\text{kcal/mol})$	
	expt	sim	expt	sim
2-NT	-11.33	-10.74	-7.58	-7.55
4-NT	-12.67	-9.80	-8.72	-6.32
2,4-DNT	-15.19	-15.25	-8.75	-8.12
2,6-DNT	-14.72	-14.64	-8.71	-7.97
2,4,6-TNT	-15.99	-17.91	-7.72	-8.46

$\Delta G_{\text{hyd}}(T)$  vs  $T$  curves, especially the isobaric solvation heat capacity, which is the second derivative of the free energy and is numerically small in value. Since 4-NT is a liquid at 330 K (above its melting point), its subcooled thermodynamic properties were computed from the polynomial fits of subcooled self-solvation free energies over the temperature range of only 273 to 310 K.

The predicted  $\Delta H_{\text{self}}$  and  $T\Delta S_{\text{self}}$  values for 2-NT were validated by comparison with the values obtained from the available measured data (Table 5 and Table S-4 of the

**Table 5.** Experimental (expt) and Simulated (sim) Self-Solvation Enthalpy ( $\Delta H_{\text{self}}$ ) and Entropy ( $T\Delta S_{\text{self}}$ ) at  $T = 300$  K Based on a Polynomial Fit

compound	$\Delta H_{\text{self}}/(\text{kcal/mol})$		$T\Delta S_{\text{self}}/(\text{kcal/mol})$	
	expt	sim	expt	sim
2-NT	-13.67	-15.55	-5.48	-7.76
4-NT		-11.49		-3.99
2,4-DNT		-16.25		-4.57
2,6-DNT		-22.65		-11.75

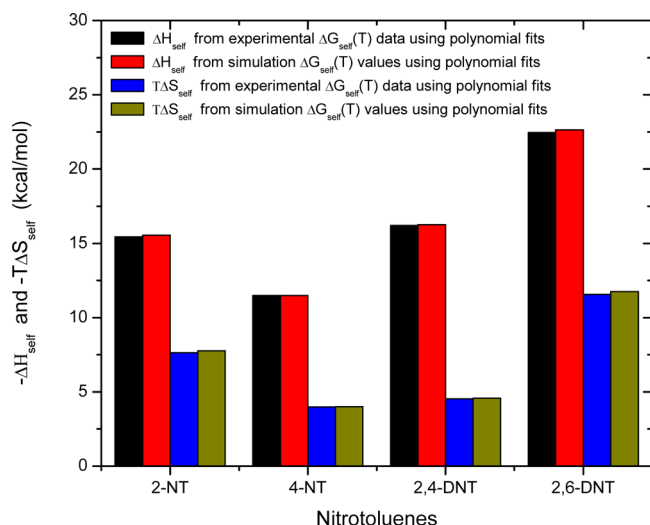
Supporting Information for details). Table 3 summarizes the average unsigned errors (AUE) of the self-solvation free energies compared to those derived from the measured vapor pressures.

Comparison of the values of  $\Delta H_{\text{hyd}}$  and  $T\Delta S_{\text{hyd}}$  obtained from simulation with those derived from experimental data suggests that both are of comparable accuracy. Our predictions for both  $\Delta H_{\text{hyd}}$  and  $T\Delta S_{\text{hyd}}$  from simulation are within  $\pm 1$  kcal/mol of the values derived from the experimental data. The differences between the measured and predicted values can be attributed to several factors. Among these are the uncertainties in both the measured and computed hydration free energies, the temperature grid used in estimating the derivatives, and most importantly the water and solute force fields and the partial atomic charges used.

The predicted isobaric solvation heat capacity is different among the different fitting and numerical methods mentioned earlier, and this is detailed in Section I of the Supporting Information. Although the three methods of predicting the solvation thermodynamics give  $T\Delta S_{\text{hyd}}$  and  $\Delta H_{\text{hyd}}$  values in reasonable agreement with one another, the predictions of  $\Delta C_{p,\text{hyd}}$  are different in magnitude and in some cases also in sign. However, all of the latter are very small in value (ranging from  $-0.15$  to  $+0.25$  kcal/(mol·K)), and all the methods indicate an increase in the magnitude of  $\Delta C_{p,\text{hyd}}$  with the number of nitro groups. The estimated  $\Delta C_{p,\text{hyd}}$  values from the finite difference method are larger in magnitude and more negative than from the other methods, so these are not used here for comparison and interpretation.

Figure 5 (data given in Table S-4 of the Supporting Information) presents the self-solvation enthalpies ( $\Delta H_{\text{self}}$ ) and entropies ( $T\Delta S_{\text{self}}$ ) at the reference temperature of 300 K calculated from the simulation results using the polynomial-fit method. Since 2-NT is liquid over the whole temperature range, the thermodynamic properties are for the liquid. For the other NTs, which are solids over the temperature range, the thermodynamic properties calculated are those of the subcooled liquid.

A comparison of the hydration thermodynamic properties obtained from simulation and derived from experimental data, presented in Table 4, shows that the TraPPE/CHELPG 2-NT model can reproduce the pure liquid-phase thermodynamic properties to within approximately 2 kcal/mol for both  $\Delta H_{\text{self}}$  and  $T\Delta S_{\text{self}}$ . The thermodynamic properties of the subcooled liquids reported here for the solid NTs at the reference temperature of 300 K cannot be compared with measured data as none are available in the literature. Unlike hydration thermodynamics, in which the hydration entropy is approx-



**Figure 5.** Self-solvation enthalpies and entropies of the NTs at a reference temperature of 300 K.

imately constant, there is a larger variation in self-solvation. However, in both hydration and self-solvation, the enthalpy change is larger in magnitude than the product of the temperature and the entropy change.

(ii). *Effect of the Number of Functional Groups on Solvation Thermodynamics.* As seen in the results (Table 4 and Figure 4), hydration entropies vary little with an increase in the number of nitro groups. Also, the changes in the solvation entropies due to the spatial location of the nitro groups are small, though not negligible. For example, there is an approximately 1 kcal/mol difference in the  $T\Delta S_{\text{hyd}}$  values between 2-NT and 4-NT, which suggests that the steric interaction between the methyl and nitro groups makes some contribution to the hydration thermodynamics.

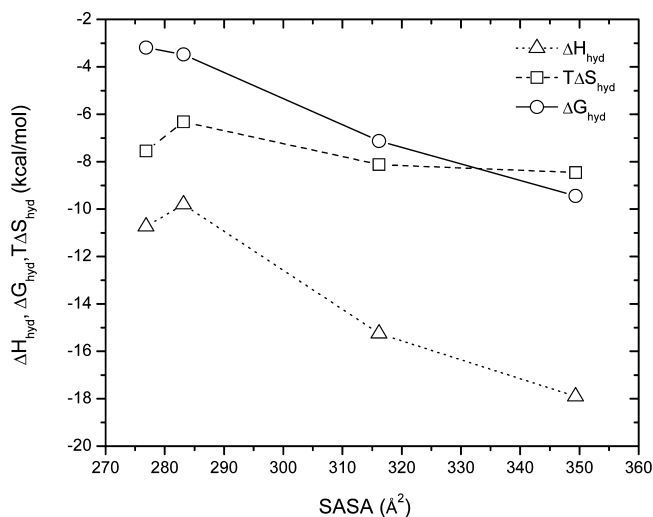
In contrast,  $\Delta H_{\text{hyd}}$  increases significantly in magnitude (though negative in sign) with an increasing number of nitro groups as shown in Figure 4. Consequently, the variation in the hydration free energies among the NTs is largely determined by the variation in their hydration enthalpies. Also,  $\Delta H_{\text{hyd}}$  values of the different NTs vary with the spatial position of the nitro groups relative to the methyl group and to one another, which suggests that the effects of functional groups on the hydration enthalpy are nonadditive, at least for the NTs studied here.

Both  $\Delta H_{\text{self}}$  and  $T\Delta S_{\text{self}}$  in Figure 5 (these are subcooled values for the solid NTs) are negative, and their magnitudes increase with an increasing number of nitro groups. Also, the spatial distributions of the nitro groups relative to one another and to the methyl group have significant effects on both  $\Delta H_{\text{self}}^{\text{subco}}$  and  $T\Delta S_{\text{self}}^{\text{subco}}$ . As in hydration, the self-solvation enthalpic and entropic contributions are nonadditive.

The values of  $\Delta C_{p,\text{hyd}}$  and  $\Delta C_{p,\text{self}}$  increase with the number of nitro groups (see Tables S-3 and S-4 of the Supporting Information). Also, the spatial distributions of the nitro groups relative to the methyl group and to one another have a significant effect on the isobaric hydration and self-solvation heat capacities.

(iii). *Solvation Thermodynamics and Solvent Accessible Surface Area.* The solvent-accessible surface area (SASA) is an important quantity in predicting partition coefficients<sup>61</sup> using structure–activity relationships (QSAR), in determining conformational equilibrium,<sup>62</sup> and in many implicit solvation models.<sup>63</sup> Therefore, it is of interest to examine the

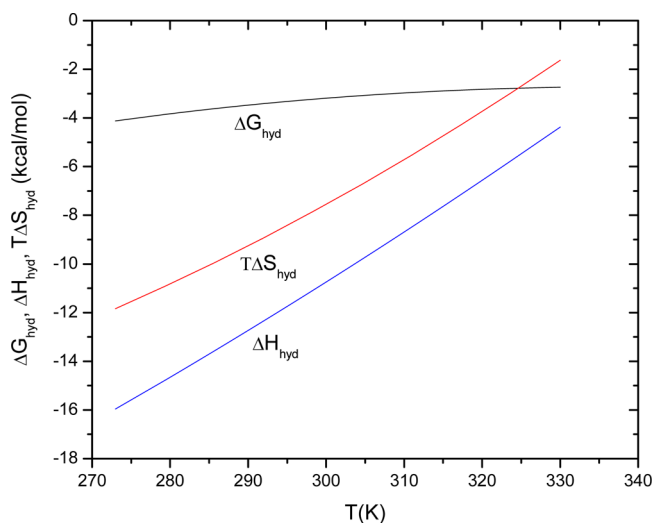
relationships between SASA with the hydration free energies ( $\Delta G_{\text{hyd}}$ ), the enthalpies ( $\Delta H_{\text{hyd}}$ ), and the product of temperature and hydration entropies ( $T\Delta S_{\text{hyd}}$ ). Figure 6 shows  $\Delta G_{\text{hyd}}$



**Figure 6.** Hydration free energies, enthalpies, and entropies of the NTs as a function of the solvent accessible surface area, SASA.

$\Delta H_{\text{hyd}}$  and  $T\Delta S_{\text{hyd}}$  for the NTs at 300 K as a function of the solvent accessible surface areas (the SASA was calculated using the Gerstein calc-surface program<sup>64</sup>). For the NTs considered here, at 300 K, the entropic contributions are almost independent of the SASA. However, the addition of a nitro group significantly increases the magnitude of the enthalpic contribution so that this term largely results in the variation of the free energy change on solvation with changes in SASA. The spatial distribution of the nitro groups changes both the SASAs and the magnitude of enthalpic contribution.

(iv). *Temperature-Dependent Solvation Thermodynamics.* Figures 7 to 11 show the temperature dependence of the enthalpic and entropic contributions to the hydration free energies obtained from the temperature derivative of the second order polynomial fits (eqs 10 to 13 of the Supporting Information) of the hydration free energies. A qualitative



**Figure 7.**  $\Delta G_{\text{hyd}}$ ,  $T\Delta S_{\text{hyd}}$  and  $\Delta H_{\text{hyd}}$  of 2-NT as functions of temperature.

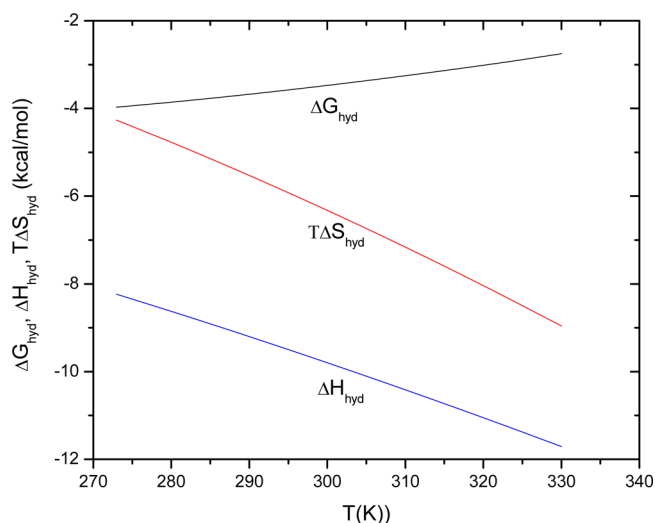


Figure 8.  $\Delta G_{\text{hyd}}$ ,  $T\Delta S_{\text{hyd}}$ , and  $\Delta H_{\text{hyd}}$  of 4-NT as functions of temperature.

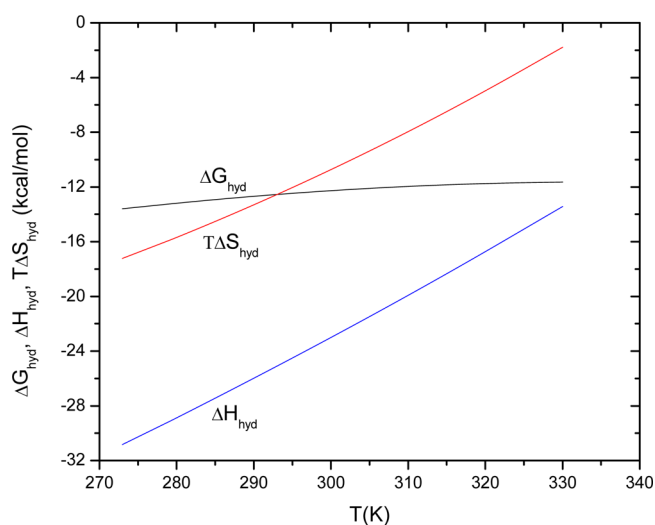


Figure 9.  $\Delta G_{\text{hyd}}$ ,  $T\Delta S_{\text{hyd}}$ , and  $\Delta H_{\text{hyd}}$  of 2,4-DNT as functions of temperature.

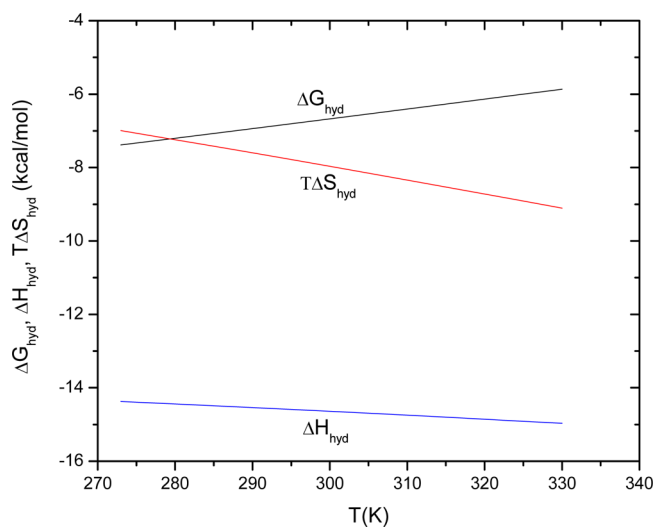


Figure 10.  $\Delta G_{\text{hyd}}$ ,  $T\Delta S_{\text{hyd}}$ , and  $\Delta H_{\text{hyd}}$  of 2,6-DNT as functions of temperature.

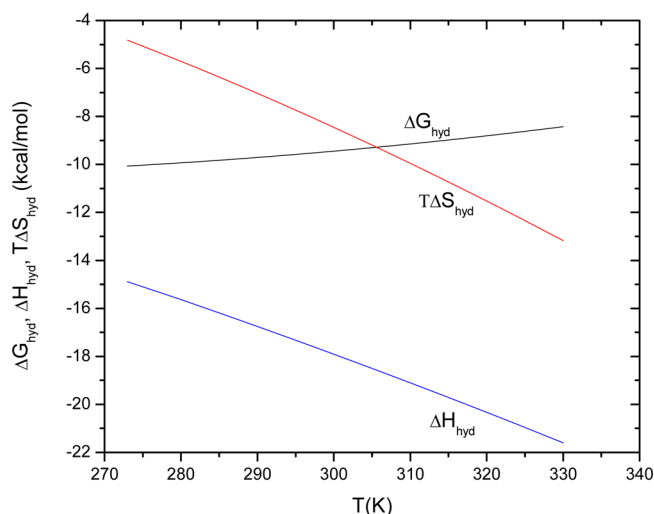


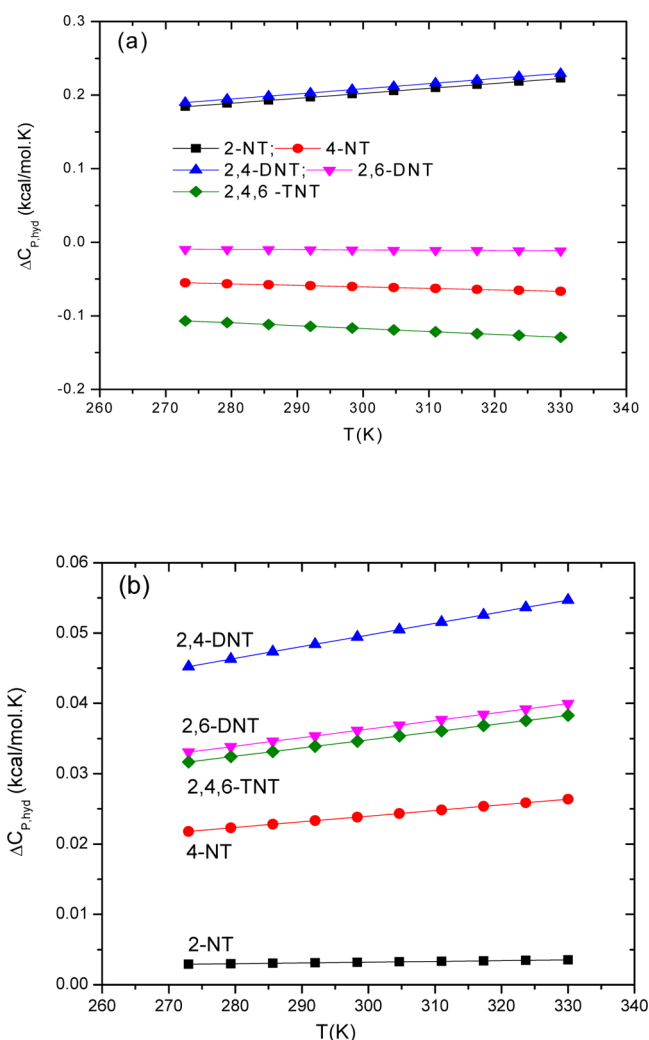
Figure 11.  $\Delta G_{\text{hyd}}$ ,  $T\Delta S_{\text{hyd}}$ , and  $\Delta H_{\text{hyd}}$  of 2,4,6-TNT as functions of temperature.

understanding of the effects on the entropic and enthalpic solvation components result from an examination of the temperature derivatives. Systematic errors as a result of the polynomial fit in the computation of solvation enthalpies and entropies should not have a significant effect in the comparisons since temperature derivatives of both the experimental data and the simulation results were obtained using the same second order polynomial fit method. For the NTs studied here, the hydration enthalpies dominate over the hydration entropies. At low temperatures the difference between these two contributions is slightly larger than at high temperatures as a result of the increasing of the entropic contribution. Variations of  $\Delta H_{\text{hyd}}$  and  $T\Delta S_{\text{hyd}}$  both from experimental data and simulations (Figures S-9 and S-10 of the Supporting Information), do not show any regular trend as functions of temperature.

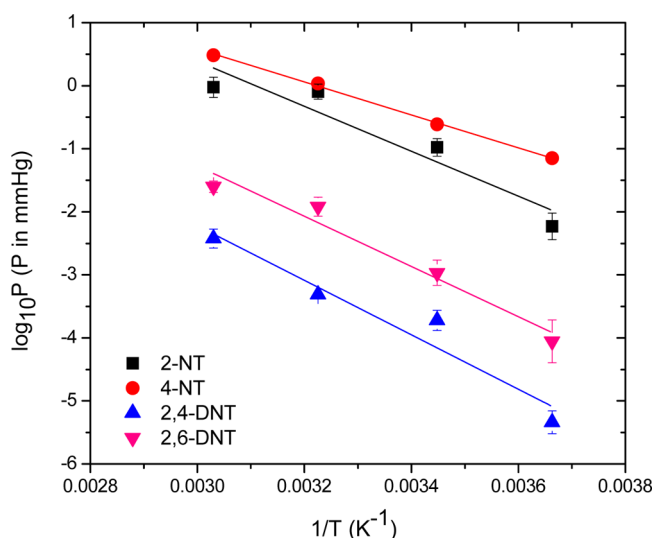
Figure 12a shows the temperature dependence of  $\Delta C_{p,\text{hyd}}$  which is quite small. Although the signs and magnitudes of the isobaric hydration heat capacities are different among the different NTs, a simple linear form,  $\Delta C_{p,\text{hyd}} = \Delta C_{p,\text{hyd}}^0 + \alpha T$ , fits the results quite well. The spatial distribution of the nitro groups relative to the methyl group has an effect on the hydration heat capacities (compare results for 2-NT and 4-NT, and also 2,4-DNT and 2,6-DNT). We also estimated  $\Delta C_{p,\text{hyd}}$  as a function of temperature using a second-order polynomial fit of the hydration free energies derived from experiment (Figure 12b). Comparison of these (Figure 12b) and the simulation results (Figure 12a) shows a similar linear dependence of  $\Delta C_{p,\text{hyd}}$  on temperature; however, the magnitudes and signs are different among the NTs. These differences are the result of the slight curvatures (Figure 1) of the hydration free energies with temperature, and the heat capacities are obtained from the second-order temperature derivative of  $\Delta G_{\text{hyd}}$ .

**C. Temperature Dependence of the Physicochemical Properties.** Figures 13 and 14 show the vapor pressures and Henry's law constants (HLCs), respectively, as functions of temperature computed using the hydration and self-solvation free energies obtained from simulation. (The values of these properties are also given in Tables S-5 to S-9 of the Supporting Information.) The figures show the variation in the solvation properties with increasing number of nitro groups. Table 3 summarizes the average unsigned errors (AUE) compared to

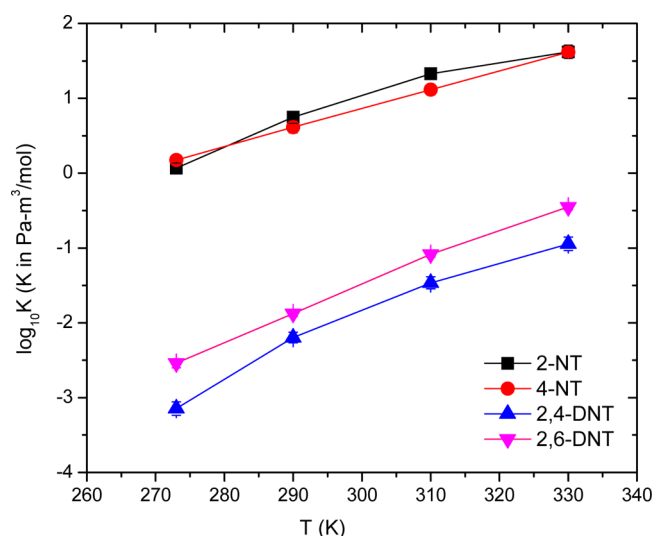




**Figure 12.** Isobaric hydration heat capacity of the NTs as a function of temperature obtained from (a) simulation and (b) derived experimental hydration free energies using polynomial fits.



**Figure 13.** Vapor pressures of the NTs as functions of temperature obtained from simulation. Lines are the fits of the form  $\log_{10}P$  (mm Hg) =  $A - B/T$ , where  $A$  and  $B$  are fitting parameters.



**Figure 14.** Henry's law constants of the NTs as functions of temperature obtained from simulation.

the measured vapor pressures and solubilities over the temperature range studied here.

For 2-NT (liquid over the temperature range), using the TraPPE/CHELPG model leads to vapor pressures with an AUE of only 0.28 log unit (pressure in Pa) compared to experimental data. Also, the vapor pressure of 4-NT at its liquid temperature (330 K) deviates only 0.47 log unit from the measured value. There are no measured subcooled vapor pressure data to compare with for the other NTs. Considering the uncertainties involved in the extrapolated experimental vapor pressures and the limitations of all force field-based simulations (solute and solvent models and charges), this level of accuracy is considered to be quite satisfactory. Except for the vapor pressure of 4-NT, all other models are generally capable of reproducing the experimental data with an AUE of less than 0.5 log units.

The enthalpies of vaporization/sublimation of the NTs calculated from the measured vapor pressures are given in Table 6. The predicted enthalpies of sublimation are generally a

**Table 6.**  $A$  and  $B$  Parameters (Valid for the Temperature Range 273 K to 330 K) in the  $\log_{10}P$  ( $P$  in mm Hg) =  $A - B/T$  (K) Fits of Vapor Pressures Calculated from Simulation Results. Enthalpy of Vaporization for 2-NT and Enthalpy of Sublimation for the Remainder of the Compounds

compound	$A$	$B$	$\Delta H_{\text{vap}}$ or $\Delta H_{\text{sub}}$	
			kcal/mol	
			sim	expt
2-NT	11.08	3564.55	$16.31 \pm 3.80$	
4-NT	8.43	2616.36	$11.97 \pm 0.36$	
2,4-DNT	10.73	4318.66	$19.76 \pm 3.60$	22.52 to 23.34 <sup>54,55,69</sup>
2,6-DNT	10.68	3983.96	$18.23 \pm 2.50$	23.52, 23.81 <sup>54,55</sup>

few kcal/mol lower than the measured values. The temperature-dependent solubilities (for the liquid, solid, and subcooled phases) and the Henry's law constants (Table 7 and Figure 14) calculated from simulation also show reasonable agreement with the experimental data considering the uncertainties involved in both the measurements and the calculations.

Table 7. Henry's Law Constants  $K$  of the Nitrotoluenes as a Function of Temperature

compound	$\log_{10}K$ ( $K$ in Pa-m <sup>3</sup> /mol)			
	273 K	290 K	310 K	330 K
2-NT	0.07 ± 0.07	0.75 ± 0.08	1.33 ± 0.06	1.62 ± 0.09
4-NT	0.18 ± 0.07	0.62 ± 0.08	1.11 ± 0.07	1.62 ± 0.07
2,4-DNT	−3.15 ± 0.09	−2.20 ± 0.07	−1.47 ± 0.08	−0.94 ± 0.09
2,6-DNT	−2.54 ± 0.06	−1.88 ± 0.04	−1.08 ± 0.04	−0.45 ± 0.04

#### IV. DISCUSSION

Recently, Bhatnagar et al.<sup>65</sup> developed a variant of the TraPPE-UA<sup>17–20</sup> force field for an extended set of 12 nitro compounds and also computed solvation free energies in water and 1-octanol, Henry's law constants, and 1-octanol/water partition coefficients at room temperature. Although, we did not report room temperature results here, it is interesting to compare our data with that of Bhatnagar et al. Previously, we had computed a wide range of physicochemical properties at room temperature,<sup>22,31</sup> including the ones computed by Bhatnagar et al.,<sup>65</sup> using the same FF parameters and partial atomic charges used here. Since the prediction of physicochemical properties are based on the solvation free energies in water and in 1-octanol, a comparison of solvation free energies computed by Bhatnagar et al. with our results, and with the recommended experimental data are presented in the Supporting Information (Table S-10) for the interested reader. Note that the parameters and the partial atomic charges of the new TraPPE-UA version developed by Bhatnagar et al. are different from the original ones used here as follows. First, the values of the parameters developed/used by Bhatnagar et al. to introduce flexibility are different from the original TraPPE-UA<sup>17–20</sup> parameters used here. The implications of the Lennard-Jones parameters and flexibility on the computation of solvation free energies can be found elsewhere.<sup>22,40,66,67</sup> Second, we computed CHELPG charges at the B3LYP/6-311G (d,p) level using the gas-phase optimized geometry at the B3LYP/6-31G(d) level.<sup>22,31</sup> However, Bhatnagar et al.<sup>65</sup> computed the CHELPG charges of single nitro compounds employing HF/6-31+G(d,p) and then used an "empirical optimization" (a scaling factor of 0.9) scheme for di- and tri-nitro compounds. The implications of different theory/basis set combinations in the computation of partial atomic charges and solvation free energies can be found elsewhere.<sup>22,33,40</sup> Also, the effects of using scaled partial atomic charges are discussed elsewhere.<sup>68</sup>

Equation 2 shows that the hydration free energy is not the only determinant of solubility; solubility results from the difference between the self-solvation and hydration free energies. So estimating the solubility of a compound looking only at its hydration free energy can be misleading. The nitrotoluenes with their low solubilities are examples of compounds for which the aqueous solubility increases with increasing positive hydration free energies as a result of the compensating effect of the self-solvation free energies. Generally one would assume that increasing hydration free energy would result in lower aqueous solubility.

At all temperatures  $\Delta H_{\text{hyd}}$  is the largest contribution to the hydration free energy, though with increasing temperature the magnitude of the difference between the enthalpic and entropic contributions decreases. For self-solvation, the magnitudes of both  $T\Delta S_{\text{self}}$  and  $\Delta H_{\text{self}}$  increase with an increasing number of nitro groups, that is, they become more negative. On the basis of the self-solvation free energy, separating a multifunctional

toluene from its own pure liquid/subcooled phase is more difficult than for a NT with a single nitro group, and this results in the vapor pressure decreasing with an increase in the number of nitro groups.

#### V. CONCLUSIONS

For the nitrotoluenes it has been demonstrated that using the TraPPE/CHELPG models with the TIP3P water model can reproduce the temperature-dependent solvation free energies (hydration and self-solvation), physicochemical properties (vapor pressure, solubility, and Henry's law constant), and solvation thermodynamic properties (solvation enthalpy, entropy, and isobaric heat capacity) with reasonable accuracy for those compounds for which experimental data are available. This study demonstrates the value of molecular simulation methods for the prediction of physicochemical properties and solvation thermodynamics provided that an appropriate force field/charge model is known in advance. Also, the use of the TraPPE/CHELPG and TIP3P models for the prediction of a range of physicochemical properties, over the temperature range of 273 to 330 K, has been verified for the compounds studied here.

An important feature of the hydration thermodynamics of the NTs is that the largest contribution is from the hydration enthalpy. This observation for low polarity NTs is in contradiction with the solvation thermodynamic behavior of apolar compounds for which entropic contributions are dominant. The hydration enthalpies of the NTs have been found here to change significantly with an increasing number of nitro groups, whereas the solvation entropies remain almost unchanged. This suggests that the intramolecular spatial distribution of the functional groups and their relative positions does not strongly affect the solvation entropies. Thus, the variation in the hydration free energies with the number of nitro groups is the result of variations in the hydration enthalpies.

The self-solvation free energy is also dominated by the enthalpic contribution, though in this case the entropic contributions also show significant variations with number of nitro groups. Consequently, the variation in the self-solvation free energy with the number of nitro groups is a result of both enthalpic and entropic contributions.

Another observation from the calculated temperature-dependent thermodynamic properties is that the isobaric hydration heat capacities are almost unchanged over the temperature range studied here. This verifies the commonly used approximation of constant isobaric hydration heat capacities in obtaining thermodynamic functions from the temperature-dependent solvation free energies.

The use of simulation to obtain enthalpies of vaporization/sublimation (estimated from the temperature-dependent vapor pressures computed directly from simulation) may be useful as an alternative to experimental measurement, especially, for

hazardous compounds such as the nitrotoluenes considered here.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

Figures S-1 to S-4: fitting of experimental data for vapor pressures and solubilities of NTs. Figures S-5 to S-8: self-solvation free energies, entropies, and enthalpies of NTs as a function of temperature. Figures S-9 and S-10: hydration enthalpies and entropies of NTs as a function of temperature. Figures S-11 to S-15: atomic configurations of NTs referenced in Table S-15. Tables S-1 and S-2: compilation experimental vapor pressure and solubility data of NTs as a function of temperature. Tables S-3 and S-4: hydration and self-solvation entropy and enthalpy for NTs. Tables S-5 to S-9: subcooled vapor pressures, vapor pressures, aqueous subcooled solubilities, aqueous solubility, and Henry's law constants of the NTs as a function of temperature. Table S-10: comparison of simulation results between two variants of TraPPE-UA force field. Tables S-11 to S-15: TraPPE-UA force field parameters used here. Equations 1 to 13: equations used in the calculation of solvation thermodynamic properties. Equations 14 to 18: potential functions of the TraPPE force field. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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