

# A Computer-Assisted Method for Estimation of the Partition Coefficient. Monte Carlo Simulations of the Chloroform/Water log *P* for Methylamine, Methanol, and Acetonitrile

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**Abstract:** With use of statistical perturbation theory and Monte Carlo simulation methods, relative chloroform/water partition coefficients for the solutes methylamine, methanol, and acetonitrile were computed. Good agreement was obtained for the experimental and computed relative log *P* values for methanol and methylamine. The log *P* values of acetonitrile relative to the other solutes are overestimated. An analysis of the thermodynamics suggests that entropy plays an important role in the partitioning process. An examination of the solution structure reveals that structure ordering of the solvent chloroform around the solutes via dipole-dipole interactions is rather poor even in the first solvation shells of the polar sites of the solutes. No H...Cl hydrogen bond was found in the solutions of methanol and methylamine.

## Introduction

The partition coefficient for a solute, usually reported or used as its logarithmic transform, is its equilibrium constant for distribution between a nonpolar solvent and water. The parameter is a measure of the relative affinity of the compound for nonpolar phases and has been used in a variety of applications. Reviews of it and its uses have been published.<sup>1,2</sup> In pharmaceutical research, log *P* is an important parameter for use in quantitative structure activity studies.<sup>3,4</sup> In environmental applications, it has been used as an indicator for the bioaccumulation of pollutants<sup>5</sup> and their toxicity to fish.<sup>6</sup> In view of its importance, it is not surprising that significant efforts have been directed toward developing methods to estimate or compute log *P*.<sup>7-9</sup> A widely used program, CLOGP, is available commercially.<sup>10</sup>

With one exception,<sup>9</sup> the methods above are thought to be based on one of two different philosophies. In one case, it is assumed that the solute can be decomposed into substructural fragments to which "hydrophobic" group contribution, or fragment, constants can be assigned. The fragment constants are derived by using multivariable regression methods. These can then be summed to give the log *P* for the solute. In the other case, a regression-based model is derived in which the independent variables are parameters such as charges, volume, dipole moment, etc. These parameters are then computed for a solute, and the log *P* is estimated from the model. While the methods may appear on the surface to be different, they are essentially the same: In the first case, regression determines the value of the fragment constant, and in the latter case, regression determines the coefficient for the variable.

It has recently been shown that Monte Carlo methods coupled with statistical perturbation theory<sup>11</sup> can be a powerful tool for examining solution processes. The basis for simulation of partition coefficients is illustrated in the thermodynamic cycle in Figure 1 for three solutes A, B, and C. The log *P*s for the solutes are related to  $\Delta G_A$ ,  $\Delta G_B$ , and  $\Delta G_C$ . These cannot be directly computed, but their relative values can be obtained indirectly by mutating A to B to C to A in both water and the nonpolar solvent. The results are  $\Delta G_{1(XY)}$  and  $\Delta G_{2(XY)}$  (X, Y = A, B, C) from which relative log *P*s for the solutes can be obtained. The mutation is done by converting the solutes from one to the other in small, well-defined steps. The cycle shown in Figure 1 is closed and internally consistent, providing a check for the computations.

In addition to the relative free energies of solvation of the solutes in water and the nonpolar solvent, simulations provide distribution

Table I. Experimental Chloroform/Water log *P* Data

solute	experimental log <i>P</i>
CH <sub>3</sub> CN	0.43 ± 0.10 <sup>a</sup>
CH <sub>3</sub> NH <sub>2</sub>	-0.90, -1.09, -1.06 <sup>b</sup>
CH <sub>3</sub> OH	-1.26, -1.36 <sup>b</sup>

<sup>a</sup>This work. <sup>b</sup>Reference 10.

functions to characterize the solution structures of the solutes and the solvent-solute and solvent-solvent energy contributions to the solvation enthalpy. These can be informative about processes for which solvent reorganization is important.<sup>12</sup> We are also interested in so-called entropy-controlled processes, e.g., the hydrophobic effect, and the structural factors that contribute or are responsible for them.

Here we report our results of log *P* simulations in which the three solutes methanol, methylamine, and acetonitrile are submitted to the cycle in Figure 1. While this work was in progress, molecular dynamics simulations<sup>13</sup> and Monte Carlo simulations<sup>14</sup> of relative log *P*s were reported for solute pairs.

## Methods and Calculations

The log *P* data for methanol and methylamine were taken from the literature (Table I). The log *P* for acetonitrile was determined in this laboratory by using the shake-flask method.<sup>2</sup> The solvents were mutually saturated prior to the determination. A 5-10- $\mu$ L sample of acetonitrile

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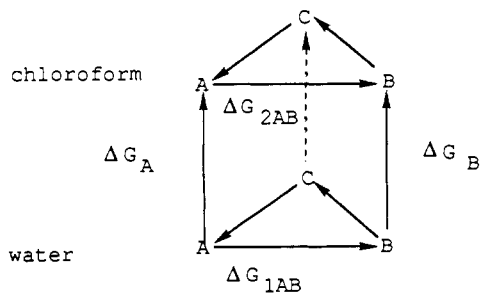


Figure 1. Thermodynamic cycles for transformations A to B to C to A.  $\Delta G_X = -2.303RT \log P_X$  ( $X = A, B$ ).

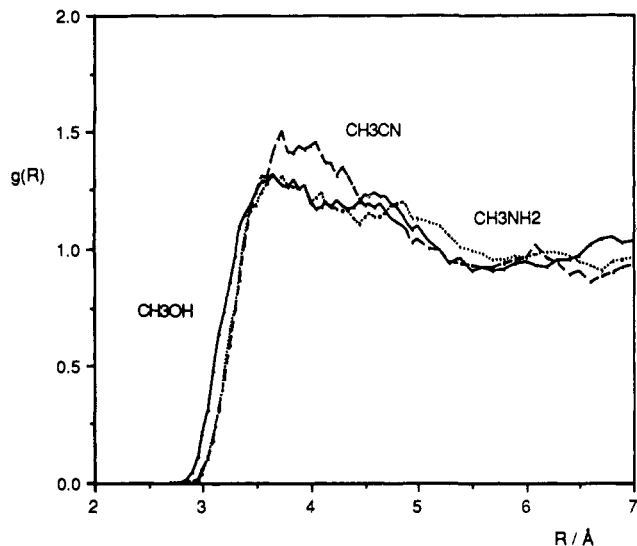


Figure 2. X...Cl ( $X = O, N$ ) radial distribution functions. Solid, dotted, and dashed lines stand for methanol, methylamine, and acetonitrile, respectively.

was introduced into a measured volume of water contained in a 50-mL glass stoppered centrifuge tube and the acetonitrile concentration determined by gas chromatography. A measured volume of chloroform was pipetted into the water-acetonitrile solution, and the system was allowed to equilibrate after shaking. The two-phase system was centrifuged, and the acetonitrile concentration was measured in both phases by using gas chromatography and the log  $P$  calculated. The result is given in Table 1 for 19 such determinations. No concentration dependence was observed.

Monte Carlo simulations of the aqueous systems were carried out via the BOSS 2.0 program and of the chloroform systems via the BOSS 2.8 version,<sup>15</sup> implemented on an IBM 3090 computer in this laboratory. Details of such simulations are published.<sup>16</sup> The NPT ensemble was used with one solute molecule in 264 solvent molecules at 298 K and 1 atm. The 12-6-1 OPLS potential function was used to evaluate intermolecular interactions. Chloroform was selected as the nonpolar partitioning medium because an earlier statistical analysis of log  $P$  data indicates that it is a more suitable solvent.<sup>9</sup> A four-center model for chloroform<sup>14</sup> and the TIP4P model for water<sup>17</sup> were used for the solvents. Previous simulations of methanol,<sup>18</sup> methylamine,<sup>18,19</sup> and acetonitrile<sup>19</sup> gave solute parameters that were used here. Molecular geometries for methanol and acetonitrile were taken from these works. The geometry for methylamine differs from the previous one (case C in ref 19) by changing the C-N-X angle from 125° to 135°, where N-X is the bisector of the H-N-H angle. With use of this value in our preliminary

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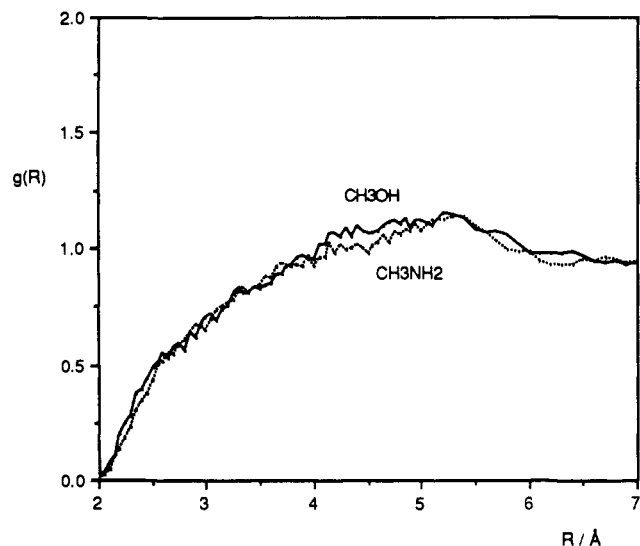


Figure 3. H...Cl radial distribution functions for methanol and methylamine.

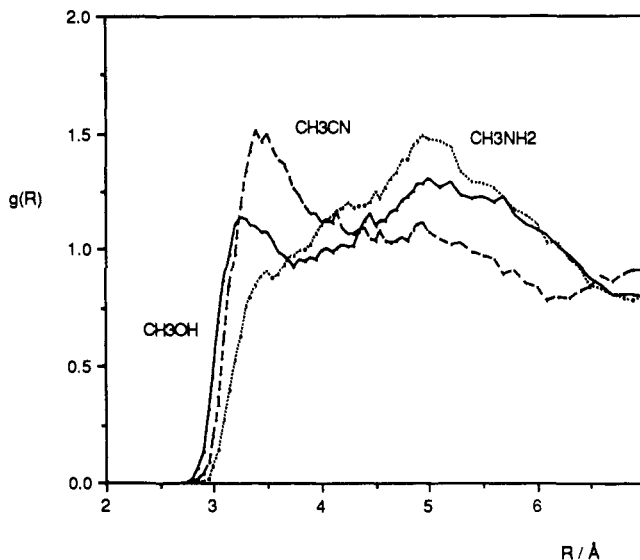


Figure 4. X...CH ( $X = O, N$ ) radial distribution functions. For drawing lines, see Figure 2.

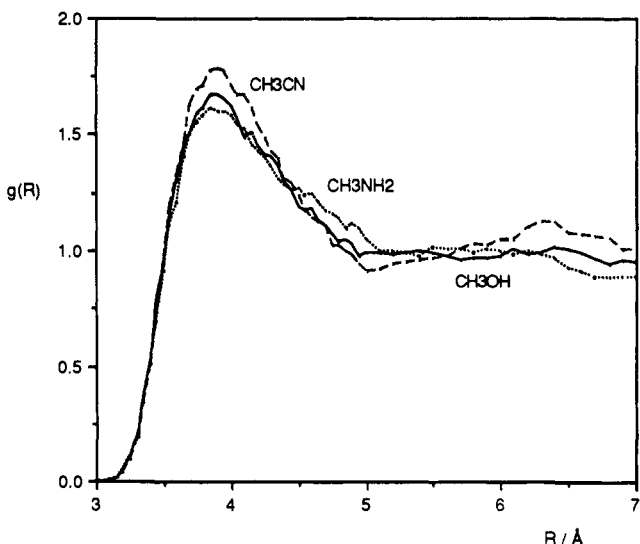
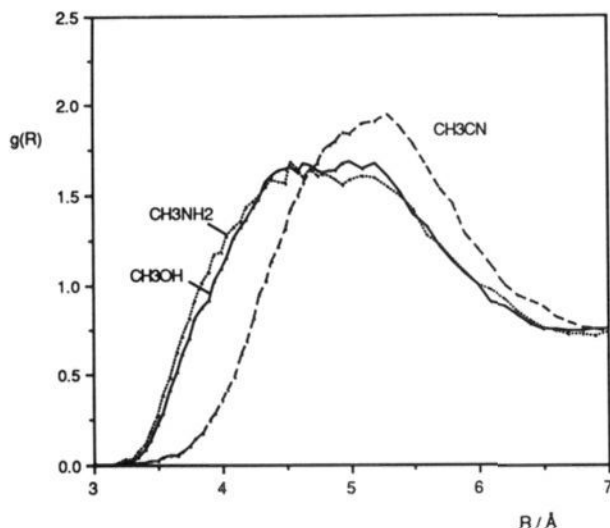
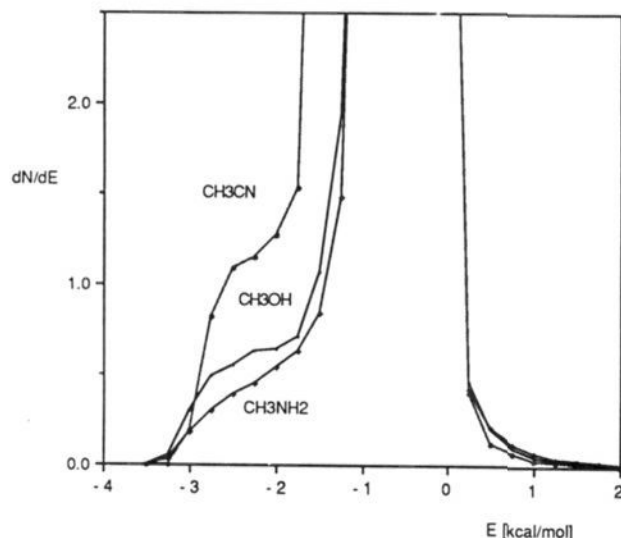


Figure 5.  $\text{CH}_3\cdots\text{Cl}$  ( $X = O, N$ ) radial distribution functions. For drawing lines, see Figure 2.

calculations, a better agreement with the experimental hydration free energy relative to methanol was found.<sup>20</sup> Preferential sampling<sup>21</sup> ac-



**Figure 6.**  $\text{CH}_3\cdots\text{CH}$  ( $X = \text{O}, \text{N}$ ) radial distribution functions. For drawing lines, see Figure 2.



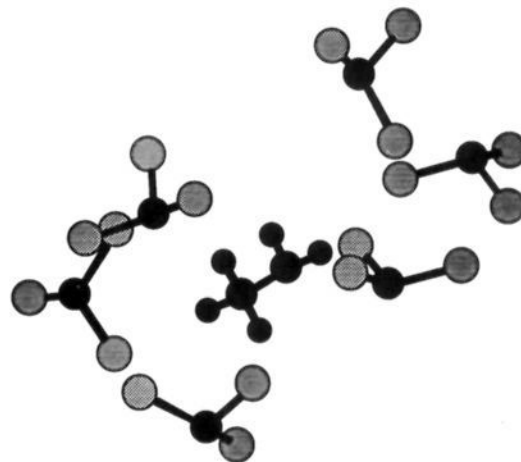
**Figure 7.** Solute-solvent pair interaction energy distribution function.

according to the function  $1/(R^2 + c)$  was used, setting  $c = 250$  for chloroform and  $c = 120$  for water. Cutoff radii for the solute-solvent interactions were taken as 13 and 8.5 Å and for the solvent-solvent interactions were taken as 12 and 8.5 Å for chloroform and water, respectively. Radial distribution and energy pair distribution functions for solutions in chloroform were obtained with equilibration phases of 2000 K configurations followed by averaging phases considering 4000 K configurations. (Figures 2-7). Snapshots to show the closest environments of the methylamine and acetonitrile solutes were taken in the final parts of the averaging process (Figures 8 and 9).

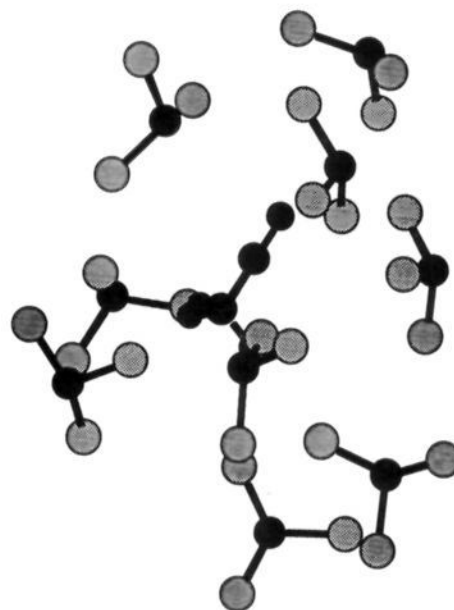
From Figure 1, the relative or  $\Delta \log P$  for solutes A and B is computed from eq 1. Similar equations can be written for the other two combinations of the three solutes. Thus, relative solvation free energies were calculated for all three pairs of solutes.

$$\Delta \log P = (\log P_Y - \log P_X) = [\Delta G_{1(XY)} - \Delta G_{2(XY)}] / 2.3RT \quad (1)$$

The free energy calculations were carried out by using the statistical perturbation theory of Zwanzig.<sup>22</sup> The solutes were gradually transformed into each other by using a linear coupling parameter,  $\lambda$ , for the geometric and potential parameters. Four nonphysical intermediate states were defined in chloroform solution and five states in water. Double-wide sampling<sup>23</sup> allowed the consideration of states differing in



**Figure 8.** Snapshot of the solution structure in nearest environment of the methylamine solute. For clarity, all hydrogen atoms of the solute are indicated. The CH group of the solvent molecules are drawn with a united atom symbol.



**Figure 9.** Snapshot of the solution structure in nearest environment of the acetonitrile solute. For hydrogen atoms, see legend of Figure 8.

**Table II.** Relative Solvation Free Energies and  $\Delta \log P$  Values<sup>a</sup>

A	B	$\Delta G$ (A to B) calcd		$\log P_B - \log P_A$	
		H <sub>2</sub> O	CHCl <sub>3</sub>	calcd	exptl <sup>b</sup>
CH <sub>3</sub> OH	CH <sub>3</sub> NH <sub>2</sub>	0.9 ± 0.2	0.7 ± 0.1	0.2 ± 0.1	0.3
CH <sub>3</sub> OH	CH <sub>3</sub> CN	2.2 ± 0.2	-1.8 ± 0.1	2.9 ± 0.2	1.6
CH <sub>3</sub> NH <sub>2</sub>	CH <sub>3</sub> CN	2.0 ± 0.2	-2.6 ± 0.1	3.4 ± 0.2	1.3

<sup>a</sup> Energy values in kilocalories per mole. <sup>b</sup> For references, see Table I.

$\lambda$  by 0.0625-0.125. Such a choice for  $\Delta\lambda$  gives reasonable results for the systems studied here.<sup>18,19</sup> The relative solvation free energies were obtained by considering 3000 K configurations after equilibration phases with 2000 K configurations for water, and 2500 and 1500 K correspondingly for chloroform. Error bars were obtained by averaging results obtained for separate blocks of 100 K configurations.

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Table III. Relative Energy Data of Solvation<sup>a</sup>

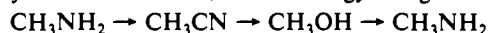
	CH <sub>3</sub> OH to CH <sub>3</sub> NH <sub>2</sub>	CH <sub>3</sub> OH to CH <sub>3</sub> CN	CH <sub>3</sub> NH <sub>2</sub> to CH <sub>3</sub> CN
Water			
$\Delta G$	0.91 (0.16)	2.16 (0.19)	1.99 (0.21)
$\Delta E_{SX}^b$	0.5 (0.5)	2.0 (0.5)	1.5 (0.4)
$\Delta G_{exp}^c$	0.5	1.2	0.7
$\Delta H_{exp}$	0.0, 0.2 <sup>e</sup>	2.5 <sup>f</sup>	2.5, 2.3
$\Delta H_{exp} - \Delta E_{SX}$	-0.5, -0.3	0.5	1.0, 0.8
$T\Delta S^g$	-0.5, -0.3	1.3	1.8, 1.6
Chloroform			
$\Delta G$	0.66 (0.06)	-1.82 (0.10)	-2.61 (0.11)
$\Delta E_{SX}^h$	0.5 (0.2)	-3.4 (0.2)	-3.9 (0.2)
$\Delta H$	2.8 (1.1)	4.5 (1.8)	-1.2 (2.0)
$\Delta H - \Delta E_{SX}$	2.3 (1.1)	7.9 (1.8)	2.7 (2.0)
$T\Delta S$	2.2 (1.1)	6.3 (1.8)	1.4 (2.0)

<sup>a</sup> Energy values in kilocalories per mole. Values in parentheses are the corresponding error bars. <sup>b</sup> References 18 and 19. <sup>c</sup> Reference 20 and references therein. <sup>d</sup> Reference 24. <sup>e</sup> References 24a and 25. <sup>f</sup> References 24a and 26. <sup>g</sup> Calculated as  $\Delta H_{exp} - \Delta G_{exp}$ . <sup>h</sup>  $E_{SX}$  for methanol is -8.0 (0.1) kcal/mol.

## Results and Discussion

**Relative Partition Coefficients.** The simulation results are given in Table II. When the experimental and calculated log *P* differences were compared, the average of the three determinations of methylamine was used and the median for methanol was used. Good agreement with experiment was found for the relative log *P*s for methanol and methylamine. The difference between the present results and those of Jorgensen et al.<sup>14</sup> can be attributed to the different geometry and atomic charges used for the methylamine solute. For the other two solute pairs, over-estimated values were obtained even though these are within the accuracy of the simulation methodology.<sup>14</sup> A major source of variation is attributed to the assumption that the two solvent systems are immiscible, which is not the case experimentally.

This set of solutes was selected and the simulation designed so that the thermodynamic cycle in Figure 1 is closed. This requires that the change of variables of state computed be zero for the cycle. From Table II, the free energy change for the cycle



is  $\Delta G = 2.0 - 2.2 + 0.9 = 0.7$  kcal/mol in water and  $\Delta G = -2.6 + 1.8 + 0.7 = -0.1$  kcal/mol in chloroform. The zero change in a cycle is a theoretical requirement that may not be satisfied in numerical calculations. Attempts to show this for  $\Delta H$  and  $T\Delta S$  for the cycle were not successful as the aqueous phase simulations were done with a version of the program that does not give accurate  $\Delta H$  and  $\Delta S$ . An enhanced version of the software was used for the simulations in chloroform. Though the error bars are too large to study the cycle closure for  $\Delta H$  and  $\Delta S$ , these values are reliable for comparing  $\Delta S$  for the conversions of methanol to methylamine and methanol to acetonitrile. By obtaining experimental data for the transformations in water, the role of  $\Delta S$  in the partitioning process can be assessed.

$\Delta H_{exp} - \Delta E_{SX}$  (Table III) is the difference of the relative experimental solvation enthalpy and the calculated relative solute-solvent interaction energy. It is a good approximation of  $\Delta E_{SS}$ , the relative solvent reorganization energy, if the  $P\Delta V$  term is small, as in the present case. Small  $T\Delta S$  for the methanol to methylamine transformation in water indicates a small reorganization of the solution structure during the process. The  $T\Delta S$  and  $\Delta H_{exp} - \Delta E_{SX}$  terms are larger in magnitude for the other two conversions in aqueous solution. The positive values for  $T\Delta S$  mean less structured solvent. In chloroform solution,  $T\Delta S$  is shown to be significantly larger for the CH<sub>3</sub>OH to CH<sub>3</sub>CN than for the CH<sub>3</sub>OH to CH<sub>3</sub>NH<sub>2</sub> transformations. No such conclusion can be reached when the CH<sub>3</sub>NH<sub>2</sub> to CH<sub>3</sub>CN and the CH<sub>3</sub>OH to CH<sub>3</sub>NH<sub>2</sub> transformations are compared, since  $T\Delta S$  for the former transformation is not reliable.

The transfer of a nonpolar solute, i.e., a hydrocarbon, from water into a nonpolar solvent is thought to be driven by an increase in entropy of the aqueous phase. The increase in entropy is due

Table IV. Relative Energy Data of Solvation in Chloroform<sup>a</sup>

$\lambda_i$	$\lambda_j$	$\Delta G (i \rightarrow j)$	$\Delta H (i \rightarrow j)$	$T\Delta S (i \rightarrow j)$
CH <sub>3</sub> OH to CH <sub>3</sub> NH <sub>2</sub>				
0.000	0.125	0.11 (0.01)	0.34 (0.10)	0.23 (0.10)
0.125	0.250	0.14 (0.01)	0.41 (0.12)	0.27 (0.12)
0.250	0.375	0.21 (0.02)	0.33 (0.17)	0.12 (0.16)
0.375	0.500	0.24 (0.02)	0.12 (0.25)	-0.13 (0.24)
0.500	0.625	0.20 (0.02)	0.56 (0.30)	0.37 (0.30)
0.625	0.750	0.13 (0.03)	0.00 (0.38)	-0.12 (0.38)
0.750	0.875	-0.07 (0.02)	0.72 (0.65)	0.79 (0.65)
0.875	1.000	-0.30 (0.03)	0.35 (0.69)	0.65 (0.68)
$\Delta E_{SX} = 0.5$ (0.2)		$\Delta G = 0.66$ (0.06)	$\Delta H = 2.83$ (1.12)	$T\Delta S = 2.18$ (1.11)
CH <sub>3</sub> OH to CH <sub>3</sub> CN				
0.000	0.125	0.35 (0.04)	0.74 (0.36)	0.39 (0.37)
0.125	0.250	0.11 (0.03)	0.49 (0.37)	0.38 (0.38)
0.250	0.375	-0.20 (0.02)	-0.65 (0.04)	-0.44 (0.35)
0.375	0.500	-0.51 (0.02)	-1.15 (0.34)	-0.64 (0.35)
0.500	0.625	-0.58 (0.02)	-0.31 (0.41)	0.27 (0.42)
0.625	0.750	-0.44 (0.03)	0.11 (0.79)	0.55 (0.79)
0.750	0.875	-0.35 (0.05)	3.86 (1.01)	4.20 (0.99)
0.875	1.000	-0.20 (0.06)	1.41 (0.89)	1.61 (0.87)
$\Delta E_{SX} = -3.4$ (0.2)		$\Delta G = -1.82$ (0.10)	$\Delta H = 4.50$ (1.76)	$T\Delta S = 6.32$ (1.75)
CH <sub>3</sub> NH <sub>2</sub> to CH <sub>3</sub> CN				
0.000	0.125	0.38 (0.05)	3.06 (0.80)	2.68 (0.79)
0.125	0.250	-0.03 (0.04)	1.25 (0.61)	1.28 (0.60)
0.250	0.375	-0.43 (0.03)	-1.19 (0.63)	-0.76 (0.63)
0.375	0.500	-0.68 (0.03)	-2.27 (0.46)	-1.59 (0.45)
0.500	0.625	-0.66 (0.02)	-1.60 (0.31)	-0.93 (0.30)
0.625	0.750	-0.53 (0.03)	-1.23 (0.43)	-0.70 (0.43)
0.750	0.875	-0.36 (0.04)	0.03 (1.08)	0.38 (1.06)
0.875	1.000	-0.30 (0.06)	0.72 (1.02)	1.02 (1.00)
$\Delta E_{SX} = -3.9$ (0.2)		$\Delta G = -2.61$ (0.11)	$\Delta H = -1.23$ (2.03)	$T\Delta S = 1.38$ (2.00)

<sup>a</sup> Energy values in kilocalories per mole. Values in parentheses are the corresponding error bars.

Table V. Relative Free Energy Data of Solvation in Water

$\lambda_i$	$\lambda_j$	CH <sub>3</sub> OH to CH <sub>3</sub> NH <sub>2</sub> $\Delta G (i \rightarrow j)$	CH <sub>3</sub> OH to CH <sub>3</sub> CN $\Delta G (i \rightarrow j)$	CH <sub>3</sub> NH <sub>2</sub> to CH <sub>3</sub> CN $\Delta G (i \rightarrow j)$
0.000	0.0625		1.77 (0.06)	2.33 (0.10)
0.0625	0.125		1.28 (0.05)	1.32 (0.06)
0.000	0.125	0.53 (0.02)		
0.125	0.1875		0.69 (0.04)	0.71 (0.04)
0.1875	0.250		0.43 (0.03)	0.25 (0.04)
0.125	0.250	0.72 (0.02)		
0.250	0.375	1.06 (0.03)	0.45 (0.04)	-0.03 (0.06)
0.375	0.500	1.14 (0.05)	-0.17 (0.04)	-0.70 (0.05)
0.500	0.625	0.82 (0.07)	-0.49 (0.05)	-0.85 (0.05)
0.625	0.750	0.10 (0.08)	-0.55 (0.08)	-0.76 (0.06)
0.750	0.875	-1.11 (0.06)	-0.71 (0.07)	-0.29 (0.07)
0.875	0.9375	-0.93 (0.04)		
0.9375	1.000	-1.42 (0.07)		
0.875	1.000		-0.54 (0.11)	0.01 (0.11)
$\Delta G$		0.91 (0.16)	2.16 (0.19)	1.99 (0.21)

to the distribution of the structured water from the ordered hydration shells into the bulk solvent. Our previous investigations<sup>18,19</sup> showed little differences in the water structure around the methyl groups of methanol, methylamine, and acetonitrile. Also there are small differences in solvating the methyl group with chloroform for the present solutes (see next section). In these solutes, the change is in the polar part, with the nonpolar part of the solute structure constant. Thus, a large difference in the free energy due to a large entropy contribution stemming from the different solvations of the methyl groups is not expected within this series.

With use of the data in Table III, the relative role of  $T\Delta S$  in the overall partitioning process can be assessed. For the conversion of CH<sub>3</sub>OH to CH<sub>3</sub>NH<sub>2</sub>,  $\Delta S_1$ , the entropy of transfer of CH<sub>3</sub>OH from water to chloroform can be compared to  $\Delta S_2$ , the entropy

of transfer of  $\text{CH}_3\text{NH}_2$  from water to chloroform. Thus,  $T\Delta S_1 + 2.2 = T\Delta S_2 - 0.5$ , which leads to  $T\Delta S_1 < T\Delta S_2$ . If  $\Delta S_3$  is the entropy associated with transfer of  $\text{CH}_3\text{CN}$  from water to chloroform, similar reasoning leads to  $T\Delta S_1 \ll T\Delta S_3$  and  $T\Delta S_1 < T\Delta S_2 < T\Delta S_3$ . This is in agreement with the order of experimental and computed  $\log P$ s for the solute set and with the thinking that positive entropy increases are associated with increasing  $\log P$ . We also conclude that the calculated entropy changes are mainly due to the differences in solvation of the polar groups in this solute series.

In all of the above calculations, the united atom model was used for the methyl group. This model has been shown to give acceptable results for aqueous solutions of solutes with limited conformational freedom, as is the case here.<sup>16b,18,23,27</sup> A relative free energy difference of 0.1–0.2 kcal/mol was found in ref 28 by using united or extended methyl group model for describing the gauche–trans equilibria of *n*-butane in water and in the nonpolar solvent carbon tetrachloride. Thus, the united atom assumption is not expected to have a significant influence of the results presented here.

**Solution Structure.** With use of the radial distribution functions for the solutes in chloroform, the number and orientation of solvent molecules around the functional groups in the solutes can be obtained. The energy pair distribution function gives information about the energies of the solute–solvent pairs.

Radial distribution functions (Figures 2–6) indicate basically a similar distribution of the chloroform molecules around the  $\text{CH}_3\text{OH}$ ,  $\text{CH}_3\text{NH}_2$ , and  $\text{CH}_3\text{CN}$  solutes, both at the polar site and in the region of the methyl group.

The X...Cl radial distribution functions (X = O, N, Figure 2) are coincidental for methanol and methylamine. The first peak is at 3.65 Å with  $g(R) = 1.3$ . Then  $g(R)$  approaches the unit value without indicating any further ordered region for the chlorine atoms. A similar conclusion applies to the acetonitrile solute. The peak  $g(R)$  value of 1.5 at  $R = 3.75$  Å suggests a somewhat more stable chlorine structure around the nitrile nitrogen than around the polar groups in the other two solutes. No sign of O–H...Cl or N–H...Cl hydrogen bonds is indicated in Figure 3.

Figure 4 shows the CH (united) group distribution around the polar sites. There are pronounced first peaks for methanol and acetonitrile in the  $R = 3$ –4 Å interval. This definite peak is missing for methylamine. Instead, a very broad band was found with maximum  $g(R)$  values at about 5 Å. These radial distribution functions suggest that in localizing the CH group the charge interaction terms for close atoms do not play a decisive role. Despite that the nitrogen atom in methylamine bears the largest negative charge in the solutes studied here, the positively charged CH group is least localized around the amine nitrogen. Maximum  $g(R)$  values in the  $R = 3.0$ –3.7 Å interval follow the sequence of the dipole moments of the solutes: 3.44, 2.22, and 1.65 D for acetonitrile, methanol, and methylamine, respectively. Thus, the overall charge distribution and remote charge–charge interactions seem to be more important here than in aqueous solution, where the positively charged H atoms of water molecules are bound to the O or N atoms via hydrogen bonds.<sup>18,19</sup>

Figures 5 and 6 show the  $\text{CH}_3$ ...Cl and  $\text{CH}_3$ ...CH radial distribution functions. The Cl distribution about the methyl group is unique for all solutes. There is a peak of  $g(R) = 1.6$ –1.8 at about 4 Å, and the functions reach the  $g(R) = 1$  value around 5 Å. Figures 8 and 9 show that the solvent atoms are oriented in a way in this region that chlorine atoms point toward the methyl group, in accord with their opposite atomic charges. No change in the solvent orientation is expected when the extended instead of united methyl group model is used. The hydrogen atoms of the methyl group have positive charges,<sup>16a,28</sup> allowing the same solvent orientation.

The  $\text{CH}_3$ ...CH radial distribution functions show broad bands in all cases, indicating no preferred position for the CH group of the solvent around the methyl site. This is in contrast to the CH distribution around the polar site for methanol and acetonitrile. Also, in contrast to results shown in Figure 4, the radial distribution functions are very similar here for methanol and methylamine. The maximum of the band for acetonitrile is at a slightly greater distance than those for the other two solutes. The reason is that there is an intermediate C atom in acetonitrile. The  $\text{CH}_3$ ...C radial distribution function (not given in Figure 6) has a plateau of  $g(R) = 1.55$  in the 4.6–4.9-Å interval. Thus, solvent molecules around the methyl group are arranged at a distance further removed from the solute, with a maximal probability at 5.3 Å (Figure 9).

The solute–chloroform interaction energy is –11.4 kcal for acetonitrile, –8.0 kcal/mol for methanol, and –7.5 kcal/mol for methylamine. The solute–solvent pair interaction energy distributions (Figure 7) show a bipolar distribution. The shoulder in the negative interaction energy region is most definite for acetonitrile with largest dipole moment and least pronounced for methylamine with smallest dipole moment. Solvent molecules in a mode repulsive with the solute (interaction energy higher than 0 kcal/mol) are a very small fraction.

Integration of the energy pair distribution functions to the end of the shoulder, –2 kcal for acetonitrile and –1.75 kcal for methanol and methylamine, gives the number of solvent molecules relatively localized around the polar sites. There are 1.1 solvent molecules around the nitrile group and 0.6–0.8 solvent molecules around the  $\text{NH}_2$  and OH groups in methylamine and methanol. The higher value was found for the coordination number of acetonitrile by solvent molecules in the polar region, and is in fair agreement with the conclusions drawn by analyzing the radial distribution functions.

## Conclusions

The relative  $\log P$  values of methanol, methylamine, and acetonitrile in the chloroform/water system were calculated by using the statistical perturbation method and Monte Carlo simulations. The results obtained for methanol and methylamine are in fair agreement with experiment and within the accuracy of the method. The values relative to acetonitrile are overestimated. Entropy changes in the partitioning process, attributed to the difference in the polar groups in this series, follow the order of the  $\log P$  values.

By calculating the free energy change for the closed cycle in Figure 1, it was shown that the method provides consistent results within 0.1 kcal/mol for this variable in chloroform solvent, but this value was 0.7 kcal/mol in aqueous solution.

Solution structures of the three solutes in chloroform show poorly ordered solvent structure around the polar sites of solutes. There is no evidence of hydrogen bond formation of chlorine with methanol and methylamine. The dipole–dipole interaction has an orientational effect on the solvent around acetonitrile and methanol due to their relatively high dipole moments. No ordered chloroform structure was found around the amine group. The methyl regions of the solutes exhibit a rather similar solvent arrangement. The chlorine atoms point toward the methyl groups, with the CH groups located further away by 0.5–1.0 Å and oriented toward the bulk solvent.

The results of this simulation study illustrate that complex processes such as partitioning can be computed with reasonable consistency. The results are also satisfying in that the simulation explicitly includes the solvent–solute interactions. This is not possible with existing methods for computing this parameter.

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Registry No.  $\text{CH}_3\text{NH}_2$ , 74-89-5;  $\text{CH}_3\text{OH}$ , 67-56-1;  $\text{CH}_3\text{CN}$ , 75-05-8; chloroform, 67-66-3; water, 7732-18-5.

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