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Free-energy simulation studies on the hydration of tetramethylurea and tetramethylthiourea

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Abstract

Free-energy simulations are presented calculating the difference between the hydration free energies of tetramethylurea and tetramethylthiourea. The results are combined with estimates of the free energies of evaporation (sublimation) to explain the difference in the solubilities of the two compounds. The free energy simulations used thermodynamic integration and were repeated with two parametrizations and with different polynomial paths.

1. Introduction and background

Aqueous solutions of tetramethylurea (TMU) exhibit a number of anomalous physico-chemical properties [1] and their study by different experimental methods makes possible the investigation of hydrophobic interactions between small solute molecules. Recent small-angle neutron scattering (SANS) studies have shown for example that in the low concentration range water-separated pairs are present in the solution and with increasing concentration contact pair formation becomes more and more important [2–4]. It would be of interest to compare the aqueous solutions of TMU and TMTU (tetramethylthiourea) and to study the effect of oxygen–sulphur substitution on the solute–solute interaction. However, while liquid TMU is miscible with water in all proportions at room temperature the solubility of solid TMTU in water is rather low (about 0.2 mol per liter at 20°C), which makes practically impossible the study of its aqueous solution by SANS. Intuitively this remarkable difference in solubility can be expected to be related to the difference in the strength of hydrogen bonds between water molecules and the carbonyl or thionyl group of TMU or TMTU molecules. Ab initio studies on the interactions of water with TMU and TMTU [5] have shown that although the SCF interaction energy in the neighborhood of carbonyl/thionyl group is smaller in the TMTU–water than in the TMU–water complex the total interaction energies are nearly the same. On the other hand, around the hydrophobic parts of the molecules the total TMTU–H_2O interaction energy is significantly smaller than the corresponding TMU–H_2O interaction energy, which may be one of the factors contributing to the observed solubility difference.

The understanding of the difference in the hydration processes of TMU and TMTU requires, in addition to the energetic considerations discussed above, the inclusion of entropic contributions, therefore we decided to carry out free energy calculations to

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estimate the difference between the hydration free energies of TMU and TMTU using liquid state computer simulations. The calculations also compared various exponent sets used in the polynomial path for thermodynamic integration since that technique was hitherto used only for changes involving full creation or annihilation of atoms.

2. Methods

The liquid state simulations were performed using the force-biased [6] Metropolis Monte Carlo method [7]. The methodology of free energy simulation is a rapidly developing area with several comprehensive reviews [8–10]. The hydration free energy difference was calculated using thermodynamic integration over a path that involved the simultaneous creation and annihilation of TMU and TMTU, respectively, as described by the coupling parameter λ. The attractive features of this technique have been discussed earlier [8,11,12]. This path can be described with the equation

$$E(\lambda) = \sum_{e=12,6,1} (1-\lambda)^{k_e} EI_0(e) + \lambda^{k_e} EI_1(e) \qquad (1)$$

where $EI_0(e)$ and $EI_1(e)$ are the energy terms containing r^{-e} terms in systems 0 and 1, respectively. The path with $k_1 = k_6 = k_{12} = 1$ is a linear path while the path $k_1 = k_6 = k_{12} > 1$ has been referred to as nearly linear. When k_e are different the path is called a polynomial path. Using an exponent larger than 1 is of importance when the path involves the creation of new atom where previously there was none [8]. The advantages of using different exponents for the coupling parameter have been demonstrated in Refs. [10,12].

The hydration free energy difference is then obtained using thermodynamic integration

$$\Delta A = \int_0^1 \sum_{e=12,6,1} k_e\Big[(1-\lambda)^{k_e-1}\langle EI_0(e)\rangle_\lambda + \lambda^{k_e-1}\langle EI_1(e)\rangle_\lambda\Big]\,\mathrm{d}\lambda. \qquad (2)$$

The integration is performed with a Gaussian quadrature.

3. Calculations

The simulations involved 399 water molecules and one solute under periodic boundary conditions in a simulation cell of the shape of rhombic dodecahedron using the canonical (T, V, N) ensemble. The temperature was set to 25°C and the volume was set to maintain the experimental density. Two sets of calculations were performed, one using the OPLS [13] parameter set and TIP4P water model [14] and an other using the AMBER [15] force field with TIP3P [14] water. Partial charges from the standard set were adjusted slightly to maintain neutrality and are listed in Tables 1 and 2 together with the LJ parameters used. Error estimates were obtained by the method of batch means [16,17] and represent two standard deviations (95% confidence interval).

Table 1
TMTU and TMU potential parameters used for the OPLS-TIP4P calculations

Atom name	ϵ (kcal/mol)	σ (Å)	q
C(C=S)	0.105	3.750	0.674
S	0.250	3.550	−0.470
N	0.170	3.250	−0.542
CH_3	0.170	3.800	0.200
C(C=O)	0.105	3.750	0.754
O	0.250	3.550	−0.470
N	0.170	3.250	−0.542
CH_3	0.170	3.800	0.200

Table 2
TMTU and TMU potential parameters used for the AMBER-TIP3P calculations

Atom name	ϵ (kcal/mol)	σ (Å)	q
C(C=S)	0.120	3.296	0.470
S	0.200	3.920	−0.470
N	0.120	3.296	−0.378
$C(CH_3)$	0.060	3.207	0.009
$H(CH_3)$	0.170	2.450	0.038
C(C=O)	0.120	3.296	0.470
O	0.200	2.851	−0.470
N	0.160	3.118	−0.378
$C(CH_3)$	0.060	3.207	0.009
$H(CH_3)$	0.170	2.450	0.038

The free energy difference was calculated with five-point quadratures. Additional calculations with different exponent sets served as further check on the numerical precision of the result. They are also of interest to characterize the shape of the integrand for such systems since previous work using the polynomial path involved the complete creation of atoms while the present system always created new atoms at sites at least partially occupied by the vanishing counterpart.

4. Results and discussion

The difference in the solubilities of TMU and TMTU has two major components: the free energy of separating the molecules of the liquid TMU and solid TMTU (i.e. free energy of evaporation and sublimation, respectively) and the free energy of their hydration. The results of computer simulations will provide an estimate for the second while experimental data were used to estimate the first.

The difference in the free energy change between TMU and TMTU connected with the process of transforming molecules from the condensed phase into the ideal gas phase at 25°C can be estimated by using standard thermodynamic methods (see e.g., Ref. [18]). The initial state is represented by solid TMTU (melting point 76°C) and liquid TMU. The majority of the thermodynamic properties of these compounds required for the calculations are not available in the literature, therefore they were estimated by using different methods [19,20]. Since we are interested in the differences of thermodynamic functions between TMU and TMTU, we can reasonably expect a partial cancellation of the errors due to the procedures employed for the estimation of different thermodynamic parameters. The free energy change was found to be 2.8 kcal/mol higher for the process TMTU (solid, 25°C) ⇒ TMTU(ideal gas, 25°C) than for TMU(liquid, 25°C) ⇒ TMU(ideal gas, 25°C).

The simulated hydration free energies using different potentials and exponent sets are summarized in Table 3. The hydration free energy estimates are consistently below the estimated difference between the free energies of the process connected with the transformation of TMTU (TMU) from the solid (liquid) phase into the gas phase, consistent with the higher solubility of TMU. The results also show that the higher solubility of TMU is due, somewhat counterintuitively, to the higher free energy of sublimation of TMTU, not to its stronger affinity to water.

Table 3
Free energy simulation results

$\{k_{12}, k_6, k_1\}$ [a]	Run length (10^6 steps)	Parameter set	ΔA [b] (kcal/mol)
{1, 1, 1}	5	AMBER	1.5 ± 0.3
{1, 1, 1}	5	OPLS	2.3 ± 0.2
{2, 2, 2}	5	OPLS	2.0 ± 0.2
{3, 3, 3}	5	OPLS	2.5 ± 0.3
{4, 4, 4}	2	OPLS	1.4 ± 0.5
{2, 1, 1}	5	OPLS	2.2 ± 0.4
{3, 2, 2}	2	OPLS	1.5 ± 0.5
{4, 2, 2}	2	OPLS	2.6 ± 1.0
{4, 3, 3}	2	OPLS	1.8 ± 0.7

[a] The λ exponent set, defined in Eq. (2).
[b] Hydration free energy difference between TMU and TMTU.

The comparison of calculations with different λ exponents shows the consistency of the methodology. The calculations with the smallest errors lead to a consensus value of 2.3 kcal/mol for the hydration free energy difference. Significant deviation from this value can be seen when shorter runs are used (with concomitant larger estimated errors). The integrands obtained from the various exponent sets used, shown in Figs. 1 and 2, add additional explanation for the values deviating from the consensus value:

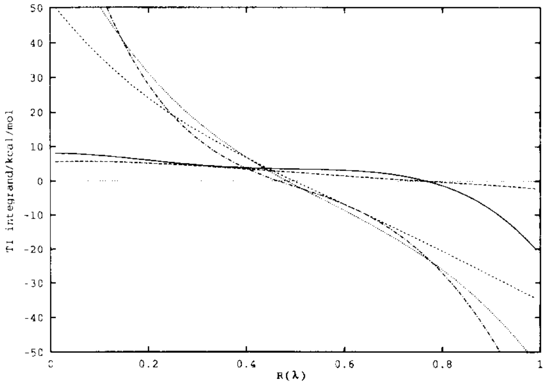

Fig. 1. The integrands of the thermodynamic integration using linear or nearly linear paths. Full line: $k = 1$, AMBER; long dashes: $k = 1$, OPLS; short dashes: $k = 2$, OPLS; dots: $k = 3$, OPLS; dash-dot: $k = 4$, OPLS.

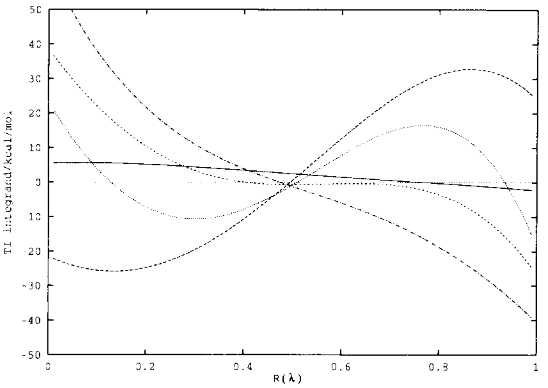

Fig. 2. The integrands of the thermodynamic integration using polynomial paths using the OPLS parametrization. Full line: $k = 1$, OPLS; long dashes: $k_{12} = 2$, $k_1 = k_6 = 1$; short dashes: $k_{12} = 3$, $k_1 = k_6 = 2$; dots: $k_{12} = 4$, $k_1 = k_6 = 2$; dash-dot: $k_{12} = 4$, $k_1 = k_6 = 3$.

They show either much larger variation in the value of the integrand or display extrema. The first case is a source of cancellation errors while the second is a source of quadrature errors. It can thus be concluded that for systems of this type the ‘smoothest’ integrand with the least variation belongs to the {1, 1, 1} exponent set, suggesting that exponents larger than one are only needed when the change involve the creation of entirely new particles or at entirely different places.

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