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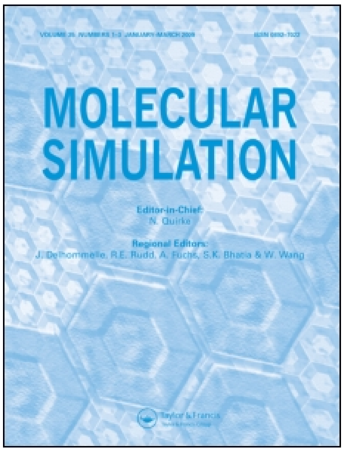

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CONVERGENCE OF THE CHEMICAL POTENTIAL IN AQUEOUS SIMULATIONS

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The chemical potential of a sphere in water is calculated using a molecular dynamics simulation. The convergence of a continuous sampling method is examined. Free energy calculations for forming a cavity or methane site in water with a thermodynamic integration are found to be strongly dependent on total simulation time length out to hundreds of picoseconds. The implications of insufficient sampling are given and related to relaxation time scales in the solvent about the solute in an Eisenberg-Kauzmann like analysis. Implications for more complex liquids are discussed.

KEY WORDS: Chemical potential, free energy

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Chemical potentials in solution are the basis of solubilities and are determined by the liquid state structure around the species of interest. A number of different theoretical methods for evaluating the free energy per particle or the chemical potential of solutes in liquids are in common use [1, 2]. One method based on integrating an exact differential of the state function along an arbitrary convenient path connecting the initial and final states, the thermodynamic integration, and other formal equivalents have been used on a wide variety of systems including a number of complex systems of biochemical interests [1–5]. We show how the convergence of this method using a continuous simulation path, sometimes called the slow-growth method, depends on the configurational sampling and therefore, the relaxation events in the solvent.

Thermodynamic integration [2] was employed to calculate the Gibbs free energy corresponding to enlarging the cavity from one of a thermal diameter of 1 Å to one of 3.6 Å. The thermal diameter is defined as the size of the particle where the potential is equal to kT. In the Gibbs ensemble the free energy change, ΔG, associated with changing an ideal atomic solute into one with solvent-solute potential $U(r) = A/r^{12}$ is given by integrating the ensemble averaged derivative of the potential with respect to a coordinate, λ, that connects the initial state, i, with the final state, f.

$$\Delta G = \int_0^1 \left\langle \frac{\partial U(\lambda)}{\partial \lambda} \right\rangle_\lambda d\lambda \tag{1}$$

The derivative in equation (1) for our choice of potential is given by

$$\frac{\partial U(\lambda)}{\partial \lambda} = \frac{\partial}{\partial \lambda}\left(\frac{\lambda A_f + (1 - \lambda)A_i}{r^{12}}\right) = \frac{A_f - A_i}{r^{12}}. \tag{2}$$

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Here, $A_f = RT(3.6\,\text{Å})^{12}$ and $A_i = RT(1\,\text{Å})^{12}$. RT is the gas constant times absolute temperature. Substituting equation (2) into equation (1), replacing the integral with a sum and substituting an ensemble average by a single step average over a small change in λ, the free energy difference is calculated as

$$\Delta G = \sum_{j=1}^{N} \left(\frac{A_f - A_i}{r^{12}} \right)_j \Delta\lambda_j \tag{3}$$

Where N is the number of molecular dynamics steps and $\Delta\lambda_j$ is the change in path coordinate λ at step j.

All molecular dynamics simulations described in this note were performed in an $18.6 \times 18.6 \times 18.6\,\text{Å}^3$ box with periodic boundary conditions containing 216 molecules of SPC water [6] and 1 solute. The SHAKE algorithm [7] was employed to maintain the solvent bond lengths at their equilibrium values. The temperature and pressure were maintained at 298 K and 1 atm, respectively, through a weak coupling to an isothermal and isobaric reservoir with couplings as given in reference [8]. All interactions were calculated up to a separation of 9 Å and the pair lists were updated at each step. The time step for integration of the equations of motion was 1 femtosecond. The only interaction between the solute and the solvent was in the form of a twelfth power repulsive term. The 1 Å particle should have nearly zero free energy change for solvation in water by scaled particle estimates and, starting at that finite size, avoids known singularities in the integrand [10]. In order to facilitate evaluation of the integral in terms of a solute cavity thermal radius, λ was made a function of time such that $\lambda(t)$ went from 0 to 1 as the simulation time went from 0 to t_{tot} where t_{tot} is the total time for the thermodynamic integration. We chose our scaling function based on the analytic results for $\lambda \rightarrow 0$. For a power law potential of order m this results in a scaling of time with λ^{m+2}. Thus, for an r^{-12} potential we used, $\lambda = (t/t_{\text{tot}})^{10}$. Here, t is the simulation time. This results in a path for λ vs. time which deviates from linearity and significantly improves the use of sampling time available since, even though the singularity in the integrand [10] is formally avoided, the effects of the pole remain and this curve more nearly correctly weights the important region of the integration [9]. While this form is an asymptotic result for the small λ limit comparisons with linear and smaller power ramps (not shown) indicates that not only is this more efficient in the critical small λ region where the integrand is largest but it is quite adequate as λ approaches unity.

From Figure 1, we find that the calculated free energy for forming a cavity in water via thermodynamic integration is dependent on total simulation time length out to a few hundred picoseconds. For an independent estimate, from scaled particle theory [10], we expect a cavity of 3.6 Å diameter to have a Gibbs free energy of solvation of 33–35 kJ/mol. The simulation of intermediate length, 30 to 80 ps, seem to yield a false convergence near the SPT estimate. Clearly, the sign of the change and order of magnitude for this example converge fast. However, it is only at considerably longer times that the calculated free energy seems to asymptotically approach a highly converged value, e.g., to within a couple of kJ/mol. While this is a typical amount of time used in other non-Boltzmann sampling techniques associated with free energies [10], this is a longer time scale than most calculations of the type presented here have employed [2, 11]. We analyze the appearance of the false minimum in convergence of the ensemble averages in Eisenberg and Kauzmann like terms [12]. They found it convenient to separate the time scales into the instantaneous structure (I), the vibrationally averaged structure (V) and the diffusive structure (D). The I-structure

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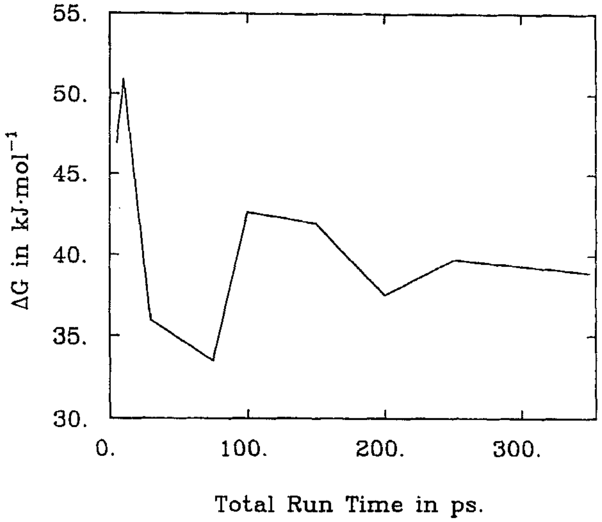

Figure 1 The change in the resultant calculated chemical potential of a sphere in water as a function of total simulation sampling time, t_{tot}. The results are from nine simulations, from 5 ps to 350 ps, starting from the same initial condition.

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may be thought of in terms of the individual "snapshots" found along a discrete integration of a simulated trajectory, while the *V*-structure is an average over the librations as well [13]. The *D*-structure has been left for all the undifferentiated long time averages including reorientations, translational diffusion and the true equilibrium average.

The results in Figure 1 suggest the existence of a time scale longer than that for the *V*-structure (which is a few tenths of a picosecond) [13] which may not be the long-time *D*-structure. This may be an important relaxation process, limiting sampling in a continuous thermodynamic integration. A preliminary analysis shows a poorly defined frequency in the position and rotational autocorrelation spectrum of these simulations between 60–80 ps. Periods of this length have been seen in other long time (hundreds of ps) aqueous simulations [9, 15], the possibility of contamination due to the recurrence time dependent on the box size and the speed of sound makes an unequivocal physical interpretation of such events difficult. It is not possible to say how other windowing thermodynamic methods will converge from this study [1, 2].

Preliminary analysis of our trajectories reveals that there are certain collective events, involving the rearrangement of a number of molecules around the solute which happen for cavity growths longer than 75–80 ps. It appears to be important for the cavity growth problem to be able to average over these slow collective "rotations" to ensure proper sampling as when a number of simulations in windows are strung together producing a rather long effective sampling time [10]. More complicated rigid solutes could be thought to further impede sampling due to such solvent events. In a recent study of this method for a strong field case, i.e., an ionic solute in water, the pattern of convergence was very similar up to about 80 ps [14]. Whether the solute-induced solvent structure in those strong field systems would lead to a similar phenomenon as that explored here is unclear, but such systems are typically dominated by Born terms and would not be expected to show as great a percentage of change as this case. Considering this problem of convergence in more complicated fluids such as polymers or biopolymers [3–5] will require an understanding of the timescales associated with the persistent structures in those liquid systems.

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