
A Rapidly Convergent Simulation Method: Mixed Monte Carlo/Stochastic Dynamics

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ABSTRACT

Although Monte Carlo and molecular dynamics are the primary methods used for free energy simulations of molecular systems, their application to molecules that have multiple conformations separated by energy barriers of ≥ 3 kcal/mol is problematic because of slow rates of convergence. In this article we introduce a hybrid simulation method termed MC-SD which mixes Monte Carlo (MC) and stochastic dynamics (SD). This new method generates a canonical ensemble via alternating MC and SD steps and combines the local exploration strengths of dynamics with the barrier-crossing ability of large-step Monte Carlo. Using calculations on double-well potentials and long simulations (10^8 steps of MC and 1 μ s of SD) of the simple, conformationally flexible molecule *n*-pentane, we find that MC-SD simulations converge faster than either MC or SD alone and generate ensembles which are equivalent to those created by classical MC or SD. Using pure SD at 300 K, the conformational populations of *n*-pentane are shown to be poorly converged even after a full microsecond of simulation. © 1994 by John Wiley & Sons, Inc.

Introduction

Impressive strides have recently been made in the development of free energy simulation methods; however, such simulations have yet to make a substantial impact as predictive tools for molecular design. The obvious impediments to such applications are the inaccuracies of contemporary molecular mechanics force fields and the

difficulty in obtaining converged, time-invariant results. Although considerable effort has been expended on improving force fields, it seems to us that the second issue, the ensemble sampling problem, is currently the limiting one in using free energy simulations as practical, predictive tools. The unfortunate result of inadequate ensemble sampling is that separate free energy simulations give different results depending on initial conditions or on the length of time the simulation runs. Recent reports¹ suggest that many previously reported simulations (and, by implication, contem-

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porary ones as well) were too short to give free energy results which are converged to sufficient precision (e.g., ± 0.5 kcal/mol) for practical applications.

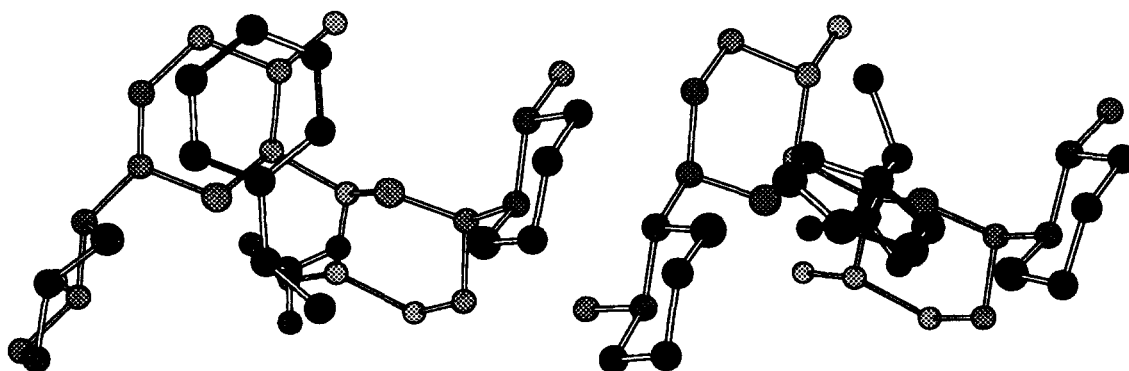
Adequate sampling is particularly difficult to attain when the system studied has multiple conformations separated by large energy barriers. The problem is that stable, converged free energies can be obtained only when all significantly populated conformational isomers are sampled with the correct statistical weights and when the local conformational space of each conformer is adequately sampled as well. Using standard simulation methods, sampling the different conformations of a system becomes highly inefficient when energy barriers separating conformers are large, because barrier crossing then becomes a rare event. In the limit of a very large energy barrier, a classical simulation method would spend all of its time sampling the local space of the starting conformation only. In such a case, simulation results would appear converged but would not represent the ensemble average of the real molecule. Such problems are common with real molecular systems. Even the 3–5 kcal/mol torsional barriers which are characteristic of simple organic molecules can cause serious sampling problems in a simulation and lead to inadequate convergence.²

To illustrate the magnitude of the problem associated with even simple multiple minimum systems, we note the bimolecular complex of a simple, conformationally homogeneous podand host and an α -phenethylammonium ion guest. This system has two low-energy forms (Scheme 1) which are comparable in energy according to molecular mechanics.³ However, neither molecular nor stochastic dynamics at 300 K interconvert these forms during simulations lasting many hundreds of picoseconds (ps). Consequently, standard dy-

namics methodology would appear to require simulation times on the order of nanoseconds (ns) or longer to yield meaningful simulation results with such structures. More flexible or higher barrier systems could be orders of magnitude worse.

Because we wish to use free energy simulation as a tool for designing new molecular receptors which may have multiple binding conformations, we have devised a new simulation method which generates the canonical (Gibbs) ensemble efficiently with simple but conformationally flexible systems. Our method combines the strengths of two common simulation methods: stochastic dynamics (SD),⁴ which searches local space efficiently; and Metropolis Monte Carlo (MC),⁵ which has the capacity to interconvert conformations separated by large energy barriers. Unlike previous approaches which mix MC-like procedures and dynamics,^{4,6} our method puts the two simulation procedures on an equal footing and involves alternating between SD and MC steps during the simulation. The result is a rapidly convergent method which is able to solve the sampling problem with many organic molecules and complexes, including the podand system mentioned earlier.

We have tested the ability of our MC-SD algorithm to generate canonical ensembles with particles in simple double-well potentials and with the molecular system, *n*-pentane. As we will show, the mixing algorithm does not create artifacts, and the final ensemble averages generated by MC, SD, and MC-SD appear indistinguishable. We will also show that dynamics, the most commonly used method for free energy simulations with complex systems, can be extraordinarily inefficient relative to MC and MC-SD at generating converged ensembles even with molecular systems as simple as *n*-pentane.



SCHEME 1.

Method and Tests with a Double-Well Potential

The algorithm we have developed is based on the assumptions that

1. Dynamical methods (e.g., SD) do a good job of sampling phase space to generate a canonical ensemble for systems whose significantly populated states are not separated by large energy barriers.
2. MC methods can sample different conformational states to generate a canonical ensemble even when the barriers between states are large, providing that sufficiently large trial steps are used.
3. A mixing algorithm can be devised which interleaves SD and MC steps in a unified simulation method which samples local and remote regions of phase space efficiently and generates a canonical ensemble.

The objective of the research described in this article is to develop such a mixed MC-SD algorithm which uses MC to drive the system from one conformation to another with the proper statistical weights and uses SD to sample the local space of each conformation. Although alternating between MC and SD steps in a single simulation is simple enough, it was not obvious that a proper ensemble would result from such a procedure. It was also unclear how atomic velocities should be handled after a successful MC step. To evaluate the result of such alternations and of various alternative velocities treatments, we studied double-well potentials of the following form:

$$E = a_0 - a_1 x + a_2 x^2 - a_3 x^3 + a_4 x^4$$

Potential 1: $a_0 = 33.070$, $a_1 = 28.835$, $a_2 = 10.506$,
 $a_3 = 1.568$, $a_4 = 0.082$

Potential 2: $a_0 = 33.339$, $a_1 = 30.082$, $a_2 = 11.382$,
 $a_3 = 1.738$, $a_4 = 0.092$

Potential 3: $a_0 = 33.713$, $a_1 = 31.711$, $a_2 = 12.693$,
 $a_3 = 1.997$, $a_4 = 0.107$

Potential 4: $a_0 = 36.537$, $a_1 = 40.802$, $a_2 = 18.166$,
 $a_3 = 2.975$, $a_4 = 0.160$

The coefficients (a_0 – a_4) were chosen to give two unsymmetrical minima separated by barriers rang-

ing from 1.7 kJ/mol (potential 1) to 12.0 kJ/mol (potential 4) (see Fig. 1). Because the barrier of potential 1 is low, it provides a system whose phase space can be explored efficiently by SD at 300 K. Potential 4, on the other hand, has a relatively large barrier which should be crossed only infrequently by SD at 300 K. Potentials 2 and 3 have barriers of intermediate height (2.9 and 5.2 kJ/mol).

We next wrote a simple simulation program with both SD and MC modes for a one-dimensional oscillator that has potential energy given by the preceding expressions. For our SD algorithm, we used the leap-frog method described by van Gunsteren and Berendsen.⁴ For MC, we took the standard Metropolis algorithm with a Boltzmann probability density function.⁵ First we showed that pure SD and MC simulations gave the same ensemble averages with potential 1, the low-barrier potential which appears efficiently sampled by both SD and MC.

As measures of the properties of the ensemble averages, we took the first two moments of the potential energy distribution (the average and standard deviation) and the particle populations in the two different wells. For our SD simulations, we assigned a mass of 100 amu to the particle and set the simulation parameters as follows: 2 fs timestep, 1.5 ps^{-1} frictional coefficient, 300 K temperature, 1 ns equilibration time, 20 ns total simulation time. Potential energy and particle position in the double-well system were recorded every 50 fs. For our MC simulations, we used a maximum step size of $\pm 6 \text{ \AA}$, a distance large enough to span both energy wells and essentially eliminate the effect of barrier height upon convergence rate. The length of the MC simulations was 2.5×10^7 steps and the

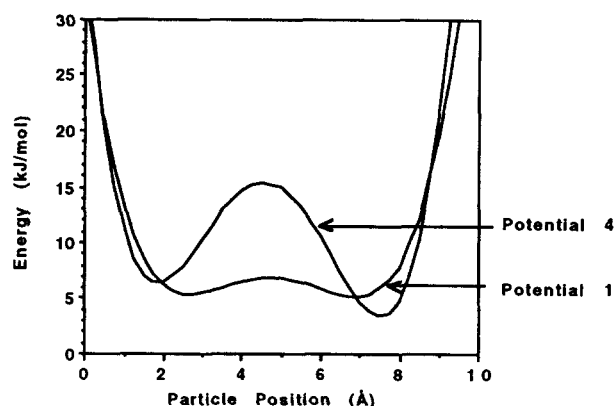


FIGURE 1. Graph of potentials 1 and 4.

temperature was 300 K. Potential energy and particle position were recorded every 20 MC steps.

For our mixed MC-SD simulations, we began with 1 ns of equilibration using pure SD, as described earlier, followed by a 20 ns MC-SD simulation in which every SD timestep was followed by an MC step. We started simply by having the velocities used in the dynamics be unaffected by the MC part of the simulation. Thus, whether an MC step was successful or not, we used the same velocities for the following SD step, and these were given by the standard SD algorithm.⁴ For both MC-SD and pure MC, the acceptance rate for the Monte Carlo steps was found to be ~35%. The results shown in Table I suggest that all three methods give essentially the same ensemble of states in the limit of a long simulation.

In the simulations with potential 1, the lowest barrier potential which is easiest to sample, all three methods give similar results for both potential energy moments and energy well populations. However, as the barrier is increased (potentials 2-4), SD diverges more and more from the MC

results because interconversion between the two wells becomes less and less frequent with SD. Thus the results of our 20 ns SD runs appear converged to three significant figures only in the case of potential 1 having the low 1.7 kJ/mol barrier. With MC, results appear fully converged regardless of the barrier height because the large 6-Å trial step spans the significantly populated region of the entire double-well potential. As Table I shows, the results of our MC-SD runs are essentially the same as those from pure MC regardless of barrier height.

As a second test of our MC-SD algorithm, we computed the free energy difference between a particle in potential 1 and a particle in potential 2 using numerical integration and free energy perturbation with SD and MC-SD. Using standard formulas defining the Helmholtz free energy difference between two states (ΔA) and partition function (Z),⁷

$$\Delta A = A_2 - A_1 = -RT \ln(Z_2/Z_1)$$

where

$$Z_n = \int \exp(-PE_n/RT) dr$$

We used numerical integration of potentials 1 and 2 to establish Z_2 and Z_1 . Our free energy perturbation calculations used the standard expression from Zwanzig⁸:

$$A_2 - A_1 = -RT \ln \langle [\exp(PE_2 - PE_1)/RT] \rangle_1$$

where $\langle \rangle_1$ indicates an ensemble average generated using potential 1. The results using SD and MC-SD to generate the ensembles are given in Table II. In these simulations, we carried out 100 different simulations (blocks) of the time period indicated and used the individual block free energies to compute the standard deviations of ΔA . Central processing unit (CPU) times measured on a Hewlett Packard Model 720 workstation show that MC-SD is approximately 50% slower per timestep than pure SD.

As the data in Table II indicate, both SD and MC-SD converge to similar values for ΔA , and both are very close to the -0.2567 kJ/mol found by direct numerical integration. The rates of convergence are, however, very different, as are the standard deviations of the free energies obtained. The ΔA evaluated using the MC-SD simulation is converged to two significant figures with a simulation using 100 0.10-ps blocks and appears con-

TABLE I.
Ensemble Averages of MC, SD, and MC-SD
Algorithms for a One-Dimensional Oscillator
Using Double-Well Potentials.^a

Simulation method	PE average ^b	PE std. deviation ^c	Well 2 population ^d
Potential 1 (barrier = 1.7 kJ/mol)			
Stochastic dynamics	6.084	1.061	0.5151
Monte Carlo	6.086	1.074	0.5136
MC-SD	6.086	1.070	0.5138
Potential 2 (barrier = 2.9 kJ/mol)			
Stochastic dynamics	6.264	1.251	0.5753
Monte Carlo	6.253	1.243	0.5790
MC-SD	6.252	1.243	0.5795
Potential 3 (barrier = 5.2 kJ/mol)			
Stochastic dynamics	6.589	1.767	0.6676
Monte Carlo	6.545	1.741	0.6743
MC-SD	6.542	1.737	0.6743
Potential 4 (barrier = 12.0 kJ/mol)			
Stochastic dynamics	5.755	2.463	0.6703
Monte Carlo	5.474	2.368	0.7547
MC-SD	5.476	2.367	0.7544

^a The quartic potential functions are described in the text and simulations were carried out at 300 K.

^b Average potential energy (kJ/mol).

^c Potential energy standard deviation (kJ/mol).

^d Proportion of all sampled structures in the low-energy well (right-most in Fig. 1).

TABLE II.
Free Energy Difference (kJ / mol) between Potentials 1 and 2.

Simulation method	ΔA (Std. deviation)	ps / block	CPU time (sec)
SD	-0.2417 (0.421)	0.05	5.2
	-0.2814 (0.377)	0.10	7.0
	-0.2944 (0.295)	0.50	21.2
	-0.2802 (0.232)	1.00	38.9
	-0.2632 (0.090)	10.0	358
	-0.2611 (0.063)	20.0	715
	-0.2564 (0.028)	100.0	3570
MC-SD	-0.2508 (0.094)	0.05	7.4
	-0.2573 (0.068)	0.10	10.5
	-0.2525 (0.031)	0.50	35.6
	-0.2541 (0.022)	1.00	65.0
	-0.2560 (0.007)	10.0	614
	-0.2566 (0.005)	20.0	1220
	-0.2566 (0.003)	50.0	2382

verged to three figures by the time 10.0-ps blocks are used. The analogous simulations using pure SD converge at least two orders of magnitude more slowly, even though the ensemble was generated using the lowest barrier potential function. With the larger barrier potentials, the advantage of MC-SD over SD would be greater.

Thus the ensemble of structures generated by MC, SD, and MC-SD methods appears to be the same with the simple double-well oscillator studied, and the MC and MC-SD methods substantially outperform pure SD in attaining convergence.

Tests with *n*-Pentane

To test our MC-SD algorithm on a more chemically relevant system, we chose *n*-pentane as a simple multiatomic structure having multiple, significantly populated conformations. As with the preceding oscillator tests, our tests involved comparing MC, SD, and MC-SD simulation methods for their ability to generate the same (canonical) ensemble of states. To judge the ensembles generated, we accumulated the first four moments of the potential energy distribution (average, standard deviation, skew, and kurtosis)⁹ and the populations of pentane's nine conformational isomers.

Our pentane simulations were carried out on the united atom (five-particle) representation of *n*-pentane using the AMBER¹⁰ force field. The cal-

culations were performed on Hewlett Packard Model 720 workstations using the MacroModel¹¹ V4.5 distribution of BatchMin, whose performance was verified by comparing MC, SD, and MC-SD oscillator results with the aforementioned special-purpose simulation program. The BatchMin SD used the stochastic leap-frog method.⁴ Our MC employed the standard Metropolis algorithm,⁵ with energy increases greater than 100 kJ/mol always being rejected. The MC-SD simulation algorithm was implemented as described earlier for the one-dimensional oscillator. We have not yet developed a variant of MC-SD which is compatible with SHAKE; hence our simulations were carried out without constraints.¹²

In our first tests with polyatomic systems, we found that the actual temperatures of converged MC-SD simulations were 20–30 K higher than the nominal 300 K temperature used in the MC and SD parts of the algorithm. We also found that the extent of heating varied with the MC acceptance rate. Assuming that this excess kinetic energy might result from numerical inaccuracies in the SD integration algorithm (which anticipates smooth changes in velocities and forces from simulation step to step), we reduced the SD timestep and indeed found a closer agreement between actual and nominal temperatures. With a timestep of 0.15 fs in a nominal 300 K MC-SD simulation, the actual temperature converged to 304 K. To limit the integration errors and still maintain a reasonable dynamics timestep, we implemented and tested a modified MC-SD algorithm which used a 1.5-fs timestep for the SD portion of the algorithm but which reduced the timestep to 0.15 fs for the 20 timesteps following any accepted MC move.

Upon analyzing the effect of random internal coordinate changes on various dynamics integration algorithms,^{4,13} we concluded that the velocity Verlet algorithm¹⁴ would be the most compatible with intervening MC moves because it is a forward-looking algorithm which generates new positions and velocities exclusively from information available at the current timestep:

$$x(t + \Delta t) = x(t) + v(t)\Delta t + f(t)\Delta t^2/(2m)$$

$$v(t + \Delta t) = v(t) + [f(t) + f(t + \Delta t)]\Delta t/(2m)$$

In contrast, the leap-frog, Verlet, and Beeman algorithms utilize information from previous timesteps which is undefined immediately following a successful MC move. Hence we derived a stochastic equivalent of the velocity Verlet algorithm (see Appendix) and implemented it in our MC-SD sim-

ulation code. The results were gratifying. Tests with a simple harmonic oscillator and *n*-pentane (1.0-fs timestep) gave actual simulation temperatures within 0.5 degrees of the nominal simulation temperature (300 K) regardless of the MC acceptance rate. Results of the new SD and MC-SD algorithms with *n*-pentane are detailed in the following paragraphs.

Because *n*-pentane has nine distinct conformations which are separated by energy barriers of 12–25 kJ/mol, we used very long simulations in an attempt to achieve full convergence. In the case of SD and MC-SD, available resources allowed us to use total simulation times of 1 μ s. Both SD and MC-SD simulations used a dynamics timestep of 1.5 fs, a frictional coefficient of 1.5 ps⁻¹, and an equilibration period of 10 ns. In the MC-SD simulations, only torsion angles were varied ($\pm 180^\circ$) by the Monte Carlo part of the algorithm on the assumption that SD would adequately sample local degrees of freedom such as stretching and bending. The simulations themselves were carried out in 10 blocks of 100 ns each. With pure MC, we used a series of simulations totaling 5×10^8 steps with variation of all degrees of freedom. The MC trial moves were limited to $\pm 180^\circ$ for torsion angles, $\pm 3^\circ$ for bond angles, and ± 0.05 Å for bond lengths. These large torsional variations were

found to provide faster convergence than the smaller variations, which are traditionally chosen to give acceptance rates of 30–40%. The use of large torsional variations resulted in acceptance rates of 5.0% for MC and 6.7% for MC-SD. Potential energies and conformational population data were saved every 10 steps with all simulation methods. Conformations of *n*-pentane were characterized by its two torsion angles, in which each angle was designated as anti (*a*, $180^\circ \pm 30^\circ$), *-gauche* (*-g*, $-60^\circ \pm 30^\circ$), or *+gauche* (*+g*, $+60^\circ \pm 30^\circ$).

The energetic results of our three different simulations are summarized in Tables III and IV. These simulations were all carried out at nominal temperatures of 300 K. All three methods ultimately gave potential energy distributions whose moments are essentially identical. One of the most remarkable findings is that simple SD takes an extraordinarily long time to give reasonably converged results, even with such a simple system as *n*-pentane. Thus after a full microsecond of SD, the average potential energy was just barely converged to the nearest 0.1 kJ/mol and the conformational populations were converged to only $\pm 5\%$.

In comparison with the results of pure SD, conformer populations by MC and MC-SD approached convergence much more rapidly. The

TABLE III.
Moments of Energy Distribution in Various *n*-Pentane Simulations.

Simulation method	Simulation length	Average	Potential energy (kJ/mol)		
			Std. dev.	Skew	Kurtosis
MC	1×10^6	12.31	5.67	0.83	1.04
	1×10^7	12.43	5.74	0.84	1.06
	5×10^7	12.44	5.71	0.84	1.08
	1×10^8	12.44	5.72	0.85	1.09
	5×10^8	12.45	5.73	0.85	1.10
SD	15 ns	12.42	5.72	0.86	1.15
	45 ns	12.23	5.74	0.86	1.12
	100 ns	12.30	5.74	0.86	1.13
	300 ns	12.33	5.71	0.85	1.12
	500 ns	12.38	5.73	0.85	1.12
	1000 ns	12.43	5.73	0.85	1.11
MC-SD	1 ns	12.45	5.83	0.89	1.27
	2 ns	12.43	5.78	0.87	1.17
	3 ns	12.45	5.78	0.86	1.13
	4 ns	12.46	5.78	0.87	1.16
	6 ns	12.44	5.77	0.87	1.16
	14 ns	12.45	5.75	0.86	1.13

TABLE IV.
Populations of Conformers in Various *n*-Pentane Simulations.

Simulation method	Simulation length	Conformational population								
		<i>a,a</i>	<i>a,+g</i>	<i>a,-g</i>	<i>+g,a</i>	<i>-g,a</i>	<i>+g,+g</i>	<i>-g,-g</i>	<i>+g,-g</i>	<i>-g,+g</i>
MC	1×10^6	.405	.121	.120	.119	.113	.037	.036	.0032	.0032
	1×10^7	.410	.117	.117	.119	.118	.038	.038	.0031	.0030
	5×10^7	.408	.118	.119	.118	.118	.038	.038	.0031	.0031
	1×10^8	.408	.118	.118	.118	.118	.038	.038	.0031	.0031
	5×10^8	.408	.118	.118	.118	.118	.038	.038	.0031	.0031
SD	15 ns	.402	.132	.133	.072	.142	.028	.048	.0008	.0051
	45 ns	.457	.123	.103	.089	.131	.024	.030	.0018	.0043
	100 ns	.446	.107	.112	.086	.136	.030	.040	.0021	.0030
	300 ns	.429	.110	.102	.123	.128	.036	.031	.0023	.0024
	500 ns	.421	.117	.107	.118	.121	.040	.033	.0026	.0028
	1000 ns	.408	.117	.119	.115	.120	.039	.040	.0030	.0027
MC-SD	0.75 ns	.413	.116	.118	.117	.117	.036	.038	.0026	.0031
	1.5 ns	.414	.115	.116	.118	.117	.037	.038	.0029	.0030
	3.6 ns	.408	.119	.117	.119	.118	.037	.037	.0028	.0028
	6 ns	.408	.118	.118	.119	.118	.038	.038	.0028	.0029
	14 ns	.408	.118	.118	.118	.118	.038	.038	.0029	.0030

MC-SD simulations were particularly well converged, giving stable energy distributions and populations in less than 4 ns. Conformational population convergence can be estimated not only by the stability of the average populations of the various conformers but also by comparison of populations of molecular conformations which are equivalent by symmetry. Thus the populations of *a*, *+g*, *a*, *-g*, *+g,a*, and *-g,a* conformers must all be the same in the limit, as must be the populations of *+g,+g*, *-g,-g* and *+g,-g*, *-g,+g* conformers. As Table IV shows, these equivalent conformer sets are equally populated to only two significant figures by velocity Verlet SD even after a lengthy 1- μ s simulation. Leap-frog SD⁴ gave similar results. MC is significantly better in reaching convergence, but MC-SD is the most rapidly convergent method, giving populations which are stable to almost three significant figures within 5 ns of simulation. Even after a short 1 ns MC-SD simulation, the conformational populations of *n*-pentane were all within 4% of their final values and had fluctuations closely resembling the thousand-fold longer 1- μ s SD populations.

From the final populations found by the three simulations, the corresponding free energy differences between extended (*a,a*) and gauche (*a,g*) *n*-pentane conformations can be calculated to be 3.09 (MC), 3.05–3.15 (SD), and 3.09 (MC-SD) kJ/mol. In comparison, the standard normal mode

analysis with the same force field gives a corresponding free energy difference of 3.14 kJ/mol.

To estimate the rate of convergence of the three methods based on CPU time, we tabulated the standard deviations of populations of the four symmetry-equivalent anti,gauche conformations of *n*-pentane at various CPU times. The results for each method are shown in Figure 2. As indicated earlier, SD converges the slowest and MC-SD converges the fastest. We carried out the MC simulations in two different ways. First we used torsion angle variations that were small enough (maximum step = $\pm 30^\circ$) to give a traditional 30–40% acceptance rate. Those data are shown in Figure 2 as "MC (small step)." The "MC (large step)" entry gives results for the $\pm 180^\circ$ torsional variations (5% acceptance rate) and shows significantly faster convergence.

Conclusion

By mixing classical SD and MC simulation methods, we have developed a new hybrid MC-SD algorithm which samples phase space in the systems we have studied more effectively than does SD or MC alone and generates a canonical ensemble. To validate our new method, we carried out lengthy simulations of *n*-pentane using MC, SD, and MC-SD. Although these methods should all

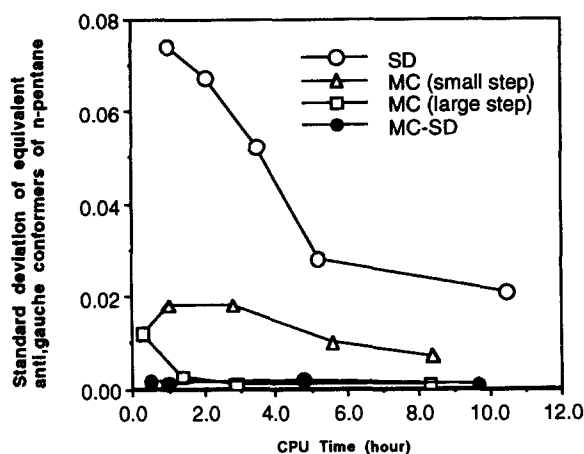


FIGURE 2. Convergence rates of various simulation methods with *n*-pentane.

give the same ensemble in the limit, we were unable to attain sufficient convergence with SD even after a full microsecond of simulation time to allow its detailed comparison with the other methods. We were, however, able to converge the MC and MC-SD simulations. The conformational populations of *n*-pentane found by both methods appeared identical at convergence.

MC-SD gave converged populations at a rate two to three orders of magnitude faster than pure SD in systems having ≥ 3 kcal/mol barriers between significantly populated states. The differences in rates of convergence between MC and MC-SD are smaller, although our MC-SD algorithm appears to converge more rapidly than MC by a factor of ~ 5 in the simple systems studied in this article. We expect the advantage of MC-SD over MC to grow significantly when cyclic systems are studied because of the tightly coupled internal coordinates of rings. For simulations in solution, the MC-SD method is compatible only with continuum treatments of solvent, because explicit solvent molecules limit the ability of the MC part of the algorithm to make large, barrier-crossing movements. When used with a continuum solvation treatment, however, MC-SD can be used to generate high-precision simulation results at a small fraction of the cost of dynamical methods.

We have also applied our MC-SD algorithm to more challenging molecular systems such as the podand ionophore complexes mentioned in the Introduction. With these systems, MC-SD not only gave highly converged free energy simulation results but for the first time provided access to both retrospective and predictive calculations of bind-

ing enantioselectivity which were verified by experiment.¹⁵

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Appendix: Stochastic Velocity Verlet

The stochastic equation of motion with delta function memory is

$$m dv/dt = f[x(t)] + R(t) - m\gamma v \quad (\text{A.1})$$

$$\langle R(t)R(t') \rangle = 2m\gamma kT\delta(t - t') \quad (\text{A.2})$$

where m is the mass, v is the velocity, f is the deterministic force, γ is the friction coefficient, R is the random force, k is Boltzmann's constant, T is the temperature, and the brackets indicate equilibrium ensemble averaging.

Dividing the equation of motion by m , adding γv to both sides, and multiplying by the integrating factor $\exp(\gamma t)$, we obtain

$$d/dt[\exp(\gamma t)v] = \exp(\gamma t)\{f[x(t)] + R(t)\}/m$$

Integrating from t to $t + \Delta t$,

$$\begin{aligned} v(t + \Delta t) &= v(t)\exp(-\gamma\Delta t) \\ &\quad + f(t)[1 - \exp(-\gamma\Delta t)]/(m\gamma) \\ &\quad + \exp(-\gamma t)/m \int_t^{t+\Delta t} dt' R(t')\exp(\gamma t') \end{aligned} \quad (\text{A.3})$$

$$\begin{aligned} x(t + \Delta t) &= x(t) + v(t)[1 - \exp(-\gamma\Delta t)]/\gamma \\ &\quad + f(t)\{\gamma\Delta t - [1 - \exp(-\gamma\Delta t)]\}/(m\gamma^2) \\ &\quad + 1/(m\gamma) \int_t^{t+\Delta t} dt' R(t') \\ &\quad \times \{1 - \exp[-\gamma(t' - t)]\} \end{aligned}$$

Let

$$\begin{aligned} R1(t, t + \Delta t) &= 1/(m\gamma) \int_t^{t+\Delta t} dt' R(t') \\ &\quad \times \{1 - \exp[-\gamma(t' - t)]\} \end{aligned}$$

Integrating the position from t to $t - \Delta t$,

$$\begin{aligned} x(t - \Delta t) &= x(t) + v(t)[1 - \exp(\gamma\Delta t)]/\gamma \\ &\quad + f(t)\{-\gamma\Delta t - [1 - \exp(\gamma\Delta t)]\}/(m\gamma^2) \\ &\quad + R1(t, t - \Delta t) \end{aligned} \quad (\text{A.4})$$

Solving eqs. (A.3) and (A.4) simultaneously to eliminate $v(t)$,

$$\begin{aligned} x(t + \Delta t) &= x(t)[1 + \exp(-\gamma\Delta t)] \\ &\quad - x(t - \Delta t)\exp(-\gamma\Delta t) \\ &\quad + f(t)\Delta t[1 - \exp(-\gamma\Delta t)]/(m\gamma) \\ &\quad + R1(t, t + \Delta t) \\ &\quad + \exp(-\gamma\Delta t)R1(t, t - \Delta t) \end{aligned}$$

Integrating the positions to $x(t + 2\Delta t)$, adding this to $x(t + \Delta t)$, and recalling that velocity in the velocity Verlet MD algorithm is $v(t) = [x(t + \Delta t) - x(t - \Delta t)]/(2\Delta t)$, the velocity integration in the velocity Verlet SD algorithm is

$$\begin{aligned} v(t + \Delta t) &= v(t)\exp(\gamma\Delta t) + [f(t) + f(t + \Delta t)] \\ &\quad \times [1 - \exp(-\gamma\Delta t)]/(2m\gamma) \\ &\quad + [R1(t, t + \Delta t) \\ &\quad + R1(t + \Delta t, t + 2\Delta t)]/(2\Delta t) \\ &\quad + \exp(-\gamma\Delta t)[R1(t, t - \Delta t) \\ &\quad + R1(t + \Delta t, t)]/(2\Delta t) \end{aligned} \quad (\text{A.5})$$

Equation (A.3) is the position integration, and eq. (A.5) is the velocity integration. The integrals of the random variables are solved by assuming that they obey Gaussian distributions with the time correlations given by eq. (A.2).