# Monte Carlo vs Molecular Dynamics for Conformational Sampling

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A comparison study has been carried out to test the relative efficiency of Metropolis Monte Carlo and molecular dynamics simulations for conformational sampling. The test case that has been examined is liquid hexane. OPLS potential functions have been used with sampling of external motions and internal angle bending and torsions. The BOSS 3.6 and AMBER 4.0 programs were used to perform the internal-coordinate Monte Carlo and Cartesian molecular dynamics simulations, respectively, for samples of 267 molecules in the NPT ensemble at 25 °C and 1 atm with periodic boundary conditions. The initial configurations of the system were equilibrated with the hexane molecules in the all *trans* configuration. The major findings are (1) the Monte Carlo and molecular dynamics results for thermodynamic properties and conformer populations are in accord, (2) the conformer populations reach equilibrium in ca. $10^7$ Monte Carlo configurations or 100 ps of molecular dynamics, and (3) the molecular dynamics calculations require 1.6−3.8 times more computer time to achieve the same level of convergence as the Monte Carlo simulations. The viability of internal-coordinate Monte Carlo methodology contrasts with earlier notions on the inefficiency of Cartesian Monte Carlo methods. Monte Carlo sampling in related contexts such as for side-chain torsional motion in proteins appears promising.

## Introduction

The two most widely used methods for atomic-level modeling of fluids are Monte Carlo statistical mechanics (MC) and molecular dynamics (MD).[1] Both procedures typically have the same system setup including representation of molecules as collections of atom-centered interaction sites, utilization of classical force fields for the potential energy terms, and implementation of periodic boundary conditions. The principal differences are in the modes of sampling the configuration space available to the system. For MC, a new configuration is generated by selecting a random molecule, translating it, rotating it, and performing any internal structural variations. Acceptance of the new configuration is determined by the Metropolis sampling algorithm; application over enough configurations yields properly Boltzmann-weighted averages for structure and thermodynamic properties. For MD, new configurations are generated by application of Newton's equations of motion to all atoms simultaneously over a small time step to determine the new atomic positions and velocities. In both cases, the force field controls the total energy (MC) and forces (MD), which determine the evolution of the systems.

In view of the importance of these methods, there has been surprisingly little comparison of their efficiencies. There is one frequently noted paper by Northrup and McCammon that found MC sampling to yield 10 times less atomic diffusion than MD for a given amount of computer time in simulations of bovine pancreatic trypsin inhibitor (BPTI) in the gas phase.[2] However, Cartesian MC was performed whereby one protein atom was moved at a time to generate a new configuration. This is a highly inefficient procedure that has received no other use for molecular systems to the authors' knowledge. In MC programs like BOSS,[3] molecules are represented in internal coordinates with specification of the connectivity and bond lengths, bond angles, and dihedral angles $(r, \vartheta, \varphi)$ in a "**Z**-matrix", as in most quantum mechanical programs. The internal variables to be sampled during the simulation are also declared in the **Z**-matrix. Then, generation of a new configuration involves translation and rotation of the entire molecule and changes in the variable internal degrees of freedom. The structure of the moved molecule is rebuilt from the modified **Z**-matrix. In this way, correlated motions, particularly internal rotations, are handled efficiently and torsional barriers can be passed over or through.[4a]

It is well recognized that a central problem for molecular simulations is the sampling of conformational degrees of freedom for simple organic molecules to proteins.[4] Such sampling is necessary in flexible molecules to obtain correct distributions of conformers, which, for example, may vary for a molecule in different solvents or bound to a receptor. To test the relative efficiencies of internal-coordinate MC and Cartesian MD methodology for a problem in this area, the present study was carried out for the prototypical case of liquid hexane. This system is attractive for several reasons including its incorporation of typical torsional barrier heights for bioorganic molecules and its symmetry, which provides internal consistency checks on conformer populations. Each monomer has three torsional degrees of freedom along the carbon chain, which is also typical for the side chains of peptide residues in a protein. With the same initial configuration for each molecule in the all *trans* conformation, the convergence of the conformer populations and thermodynamic properties has been monitored with the two methods using standard software. All details including system size, potential functions, and cutoff distances were the same.

## Computational Details

**Fluid Simulations.** The fluid simulations were carried out in the NPT ensemble at 25 °C and 1 atm with 267 hexane molecules in a cubic box ca. 38 Å on a side with periodic boundary conditions. Intermolecular interactions were computed out to a cutoff of 12 Å based on the distance between the $C_3$ atoms; if the $C_3$−$C_3$ distance was within the cutoff, the entire hexane−hexane interaction was included. A united-atom model was used as indicated in Scheme 1 along with the atom numbering and designation of the variable bond angles and dihedral angles. The C−C bond lengths were kept fixed at 1.526 Å by not declaring them as variable in the MC simulations

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**SCHEME 1**
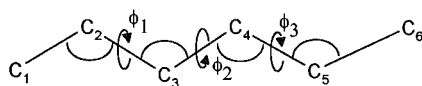


or through the SHAKE algorithm in the MD simulation.[5] The MC calculations were performed with the BOSS program, version 3.6,[3] and the MD was carried out with the minmd module of AMBER 4.0.[6] Both programs are multipurpose modeling programs. Though generally efficient, neither has been optimized for this specific problem. The timings presented here can be used for future comparisons with other programs or as a basis for improvement of algorithms.

The initial configuration was generated using BOSS with its procedure whereby a stored, equilibrated box of liquid argon is expanded to a volume suitable for hexane and the all *trans* hexanes are mapped onto the positions of the 267 argon atoms. This box was then equilibrated with BOSS for $2 \times 10^6$ configurations, which was long enough for the total energy and density to converge. The hexanes were kept all *trans* during this preparation, though the remaining translational, rotational, and angle bending degrees of freedom were sampled. The equilibrated box of all *trans* hexane was then used at the start of all comparison simulations. The decay of the 100% *trans* populations to the equilibrium values is then the critical quantity monitored to assess speed of convergence.

**MC Details.** A decision for the MC simulations is the ranges for the attempted translations, rotations, internal motions, and volume changes. These are normally chosen to yield an overall acceptance rate of about 40% for new configurations.[1] Default values from BOSS were used except for the change in dihedral angles ($\Delta\varphi$). Specifically, for each attempted move, translations of the chosen hexane molecule were performed in all three Cartesian directions within a range of $\pm 0.20$ Å. A rotation of the entire molecule was attempted about $C_3$ by choosing one Cartesian axis at random and rotating about it within a range of $\pm 20°$. The four internal bond angles were changed within a range of $\pm 3.8°$, which is computed by BOSS from the force constant and temperature. Attempted volume changes were performed every 1625 configurations with $\Delta V = \pm 390$ Å$^3$, and the positions of all molecules were scaled accordingly. Three simulations were then run with $\Delta\varphi = \pm 10°$, $\pm 15°$, and $\pm 20°$ and are referred to as MC10, MC15, and MC20. All three dihedral angles in a monomer are varied randomly within these ranges upon an attempted move. The overall acceptance rates for the three simulations were 37%, 31%, and 23%, respectively. It may be noted that in the previous MC study of a series of alkane liquids, $\Delta\varphi = \pm 20°$ was used.[7]

A neighbor list was employed with the MC calculations and updated every ca. 4000 configurations. For the present case, this reduces the computation time by about 20%. In BOSS, a standard cutoff correction is made for Lennard-Jones interactions neglected beyond the cutoff.[1,7] Since this is not done in AMBER, an additional MC run (MC20n) was performed with $\Delta\varphi = \pm 20°$ and with the cutoff correction turned off. The length of each MC simulation was $50 \times 10^6$ configurations. The coordinates were saved every 25 000 configurations for subsequent analysis. The only remaining detail where there is a difference in potential function evaluation between BOSS and AMBER is that BOSS quadratically smoothes the intermolecular interactions to zero over the last 0.5 Å before the cutoff, i.e., between 11.5 and 12.0 Å in the present case, while AMBER performs a sharp spherical truncation at the cutoff. This has little significance, since, as shown below, the differences between the results of the MD and MC20n runs are small.

```
Hexane
  1 C3   71   71   0   0.000000   0    0.000000   0     0.000000
  2 DUM  -1   -1   1   0.500000   0    0.000000   0     0.000000
  3 DUM  -1   -1   2   0.500000   1   90.000000   0     0.000000
  4 C4   71   71   1   1.526000   2  124.000000   3   180.000000
  5 C5   71   71   4   1.526000   1  112.400000   2     0.000000
  6 C6   68   68   5   1.526000   4  112.400000   1   180.000000
  7 C2   71   71   1   1.526000   4  112.400000   5   180.000000
  8 C1   68   68   7   1.526000   1  112.400000   4   180.000000
                        Variable Bonds follow        (I4)
                        Additional Bonds follow      (2I4)
                        Variable Bond Angles follow  (I4)
0005
0006
0007
0008
                        Additional Bond Angles follow (3I4)
                        Variable Dihedrals follow     (3I4,F12.6)
000600650065   20.0
000700650065   20.0
000800650065   20.0
                        Additional Dihedrals follow  (6I4)
                        Domain Definitions follow    (4I4)
                        Final blank line
```

**Figure 1.** **Z**-matrix file for hexane used by the BOSS program.

**BOSS Z-Matrix.** As mentioned above, the internal coordinate MC requires a **Z**-matrix that specifies the atomic connectivity and controls the sampling. The one used here by BOSS for hexane is illustrated in Figure 1. There are entries at the top for the six carbons and two dummy atoms. Each entry gives, in order, the atom number $i$, a label for printing, the OPLS initial atom type, the OPLS final atom type (which may differ from the initial type for free energy perturbations), the atom $j$ connected to $i$, the $i-j$ bond length, the atom $k$ making the $i-j-k$ bond angle, the $i-j-k$ bond angle, the atom $l$ making the $i-j-k-l$ dihderal angle, and the $i-j-k-l$ dihedral angle. Then, the variable bonds, bond angles, and dihedral angles are designated. For hexane, the bond angles used to define atom entries 5–8 and the dihedral angles used to define atoms 6–8 are declared as variable. The dihedral angles are designated as type 65, and the maximum variation is stated as 20.0° for $\Delta\varphi$. The hexane molecules are easily kept all *trans* by setting the dihedral angles for atom entries 6–8 at 180°, as shown, and then by either setting $\Delta\varphi = 0.0°$ or removing the three variable dihedral angle entries. The program looks up the potential function parameters from separate parameter files. Each hexane molecule is built from the **Z**-matrix, and the current values for the variable internal coordinates of each hexane are stored. Upon an attempted move, the variable entries are changed randomly within their designated ranges and the molecule is rebuilt. The atoms are constructed in order, which can affect the sampling efficiency. For a flexible chain like hexane, it is best to build out from the center, as done in Figure 1, rather than proceeding from one end to the other. This causes fewer atoms to be moved on average by the changes in the dihedral angles.

**MD Details.** A leap-frog algorithm is used by the minmd module of AMBER to integrate the equations of motion,[8] and the NPT ensemble is approximated by velocity rescaling and coupling to a constant pressure bath.[9] Use of SHAKE[5] for the bond lengths allowed a time step of 2 fs. It may be noted that not constraining the bond lengths in the MC calculations has negligible effect on the computer time, while it would require a time step of 0.5 ps or less for the MD calculations and 4 or more times the computer time to avoid cummulative integration errors.[10] A nonbonded pair list was used to speed the MD calculations and was updated every 25 time steps. The box of all *trans* hexane was first relaxed with AMBER via 200 steps of steepest descent energy minimization. Initial velocities were assigned from a Maxwell distribution corresponding to a temperature of 200 K. The temperature was then raised to 298 K over 5 ps of NPT MD and maintained at that value for the production run of 500 ps. The energies and coordinates were saved for subsequent analysis every 0.1 ps.

All calculations were executed on the same Silicon Graphics Indigo workstation with a MIPS R4000 processor. FORTRAN/
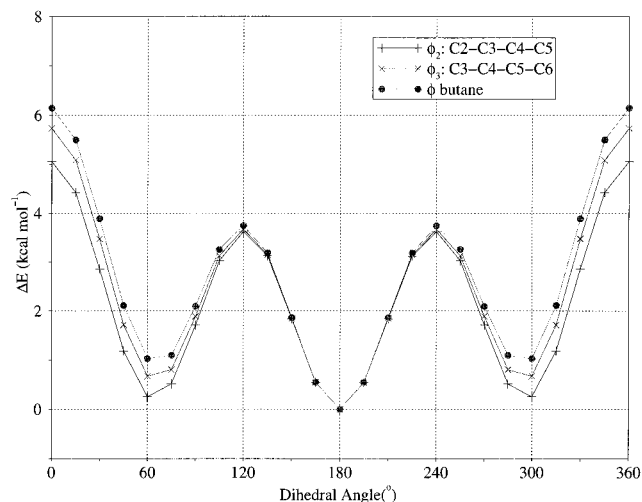
**Figure 2.** Potential energy profiles for variation of $\varphi_2$ and $\varphi_3$ of hexane with the other two $\varphi$'s fixed at 180° and for variation about the central CC bond of butane.

77 compilation was performed with the highest optimization levels for both programs. The calculations required 95.4 s of CPU time for 10.0 ps of MD or for $1.63 \times 10^6$ configurations of MC. In this time, there were 5000 MD time steps or 6105 MC passes, where a pass is an attempted move of each molecule once on average (equals the number of configurations/the number of molecules).

**Potential Functions.** The intermolecular interactions consist of Lennard-Jones 12-6 terms between all atoms with the OPLS united-atom values for $\sigma$ and $\epsilon$. Specifically, $\sigma$ and $\epsilon$ are 3.905 Å and 0.175 kcal/mol for the methyl groups and 3.905 Å and 0.118 kcal/mol for the methylene groups.[7] $\epsilon$ for a $CH_2-CH_3$ interaction was obtained from the geometric mean as 0.1437 kcal/mol, while $\sigma$ for the cross interaction remains at 3.905 Å. The harmonic CCC angle bending parameters have been taken from the AMBER united-atom force field: $k_\vartheta = 63.0$ kcal/mol·rad[2] and $\vartheta_0 = 112.4°$.[12]

The form of the torsional potential is given in eq 1, where the sum is over the three dihedral angles in each hexane molecule.

$$E_{\text{torsion}} = \sum_i \{ V_1(1 + \cos\varphi_i)/2 +$$
$$V_2(1 - \cos 2\varphi_i)/2 + V_3(1 + \cos 3\varphi_i)/2 \} \quad (1)$$

The Fourier coefficients have been chosen to reproduce ab initio 6-31G* results for the conformational energetics of alkanes: $V_1 = -4.040$, $V_2 = 1.226$, and $V_3 = 3.564$ kcal/mol.[13] Intramolecular Lennard-Jones interactions are also included between atoms separated by three or more bonds with the same $\sigma$'s and $\epsilon$'s as above, namely, for hexane the pairs are for carbons 1−4, 1−5, 1−6, 2−5, 2−6, and 3−6. The magnitude of the 1,4-interactions for the 1−4, 2−5, and 3−6 pairs is scaled down by a factor of 2.[12] Resultant energy profiles are shown in Figure 2. The profiles for rotation of $\varphi_2$ and $\varphi_3$ ($=\varphi_1$) in hexane have the remaining two $\varphi$'s fixed at 180° (*trans*). A profile for butane is shown for comparison. The present potential functions have been used with the bond lengths fixed at 1.526 Å and the bond angles optimized at each value of $\varphi$. For hexane, the energy differences between the ttt conformer and the ttg and tgt minima are 0.63 and 0.25 kcal/mol, the *trans* to *gauche* barrier heights are 3.6−3.7 kcal/mol, and the *cis* maxima are 5−6 kcal/mol above the *trans*. These values are in reasonable ranges for alkanes.[7,11,13]
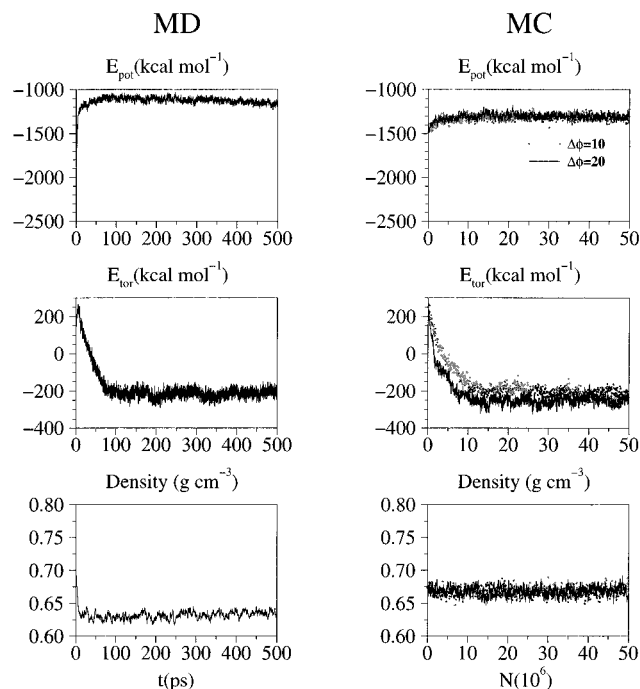


**Figure 3.** Convergence plots from the MD (left) and MC10 and MC20 (right) simulations for the potential energy, torsional energy, and density.

## Results

**Thermodynamic Properties.** The convergence of the total potential energy, the torsional energy, and the density from the MC10, MC20, and MD calculations is illustrated in Figure 3. The instantaneous values are plotted from the saved configurations. The thermodynamic results of all the calculations are summarized in Table 1. They were obtained by averaging over the final 200 ps of the MD simulation and from the final $20 \times 10^6$ configurations for the MC calculations. The reported statistical uncertainties for the averages in Table 1 are $1\sigma$ as obtained from the batch means procedure[1] with batch sizes of $10^6$ configurations for the MC simulations and 10 ps for the MD calculation. The heat of vaporization was computed from the potential energy of the gas obtained from an MC simulation for an isolated molecule minus the potential energy of the liquid plus $RT$.[7] The intermolecular contribution to the heat capacity, $C_p$, the coefficient of thermal expansion, $\alpha$, and the isothermal compressibility, $\kappa$, are computed on-the-fly in BOSS from standard fluctuation formulas[1,7] and are also reported in Table 1 along with the experimental values.[14] The results from the MC15 run will receive little discussion, since they are very similar to those from MC20.

The potential energy and density converge rapidly, since the all *trans* hexane provided a reasonable starting point. The density is 0.035 g cm$^{-3}$ lower from the MD calculation than that from MC10 or MC20. The direction is reasonable with the absence of the cutoff correction in the MD calculation. The computed densities from the MD calculation and the MC20n run differ by only 0.021 g cm$^{-3}$; the remaining discrepancy may be related to the smoothing of the potential at the cutoff with BOSS vs spherical truncation with AMBER and to imperfection in the NPT MD algorithm. All energy terms from the MC20n and MD calculations are in reasonable accord. The OPLS/AMBER potential functions are also providing thermodynamic results and densities close to the experimental values, as expected from earlier work.[7]

The evolution of the torsional energy, which comes solely from eq 1 summed over all 267 molecules, is the more critical issue for assessing the conformational sampling. The Fourier

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**TABLE 1: Summary of Results from Simulations of Liquid Hexane**[a]

| simulation | MC10 | MC15 | MC20 | MC20n | MD | exptl[b] |
|---|---|---|---|---|---|---|
| $\Delta\phi$ | 10 | 15 | 20 | 20 | | |
| cutoff correction | yes | yes | yes | no | no | |
| acceptance % | 36.9 | 31.2 | 22.6 | 23.1 | | |
| $E_t{}^c$ | −1313(1) | −1303(3) | −1307(2) | −1157(3) | −1134(4) | |
| $E_{\text{angle}}$ | 462(2) | 472(3) | 474(1) | 480(2) | 445(2) | |
| $E_{\text{tor}}$ | −211(5) | −244(8) | −247(3) | −256(5) | −214(3) | |
| $\Delta H_{\text{vap}}$ | 7.869(0.004) | 7.831(0.010) | 7.846(0.007) | 7.284(0.010) | 7.198(0.016) | 7.541 |
| $C_p(\text{inter})$ | 14.5(0.8) | 13.0(0.7) | 13.6(0.8) | 12.9(0.8) | | |
| $C_p(\text{l})$ | 46.8(0.8) | 45.3(0.7) | 45.9(0.8) | 45.2(0.8) | | 46.7 |
| $\alpha$ | 124(7) | 119(8) | 133(9) | 123(8) | | 139 |
| $\kappa$ | 152(7) | 142(8) | 147(7) | 172(10) | | 173 |
| density | 0.6692(0.0003) | 0.6680(0.0005) | 0.6690(0.0006) | 0.6549(0.0007) | 0.6338(0.0008) | 0.655 |
| $\phi_1$:g+ | 18.4(0.5) | 13.7(0.3) | 14.9(0.3) | 16.6(0.2) | 16.0(0.3) | |
| $\phi_1$:t | 68.8(0.3) | 70.5(0.6) | 69.1(0.6) | 66.0(0.5) | 71.0(0.5) | |
| $\phi_1$:g$^-$ | 12.8(0.4) | 15.8(0.4) | 16.0(0.4) | 17.4(0.4) | 13.0(0.3) | |
| $\phi_2$:g+ | 23.5(0.4) | 22.4(0.3) | 22.0(0.5) | 20.7(0.6) | 23.4(0.4) | |
| $\phi_2$:t | 60.2(0.4) | 54.3(0.8) | 53.5(0.4) | 55.6(0.7) | 56.2(0.4) | |
| $\phi_2$:g$^-$ | 16.3(0.3) | 23.3(0.7) | 24.5(0.5) | 23.7(0.2) | 20.4(0.4) | |
| $\phi_3$:g+ | 15.5(0.3 | 15.1(0.3) | 14.7(0.3) | 15.3(0.4) | 14.8(0.3) | |
| $\phi_3$:t | 70.9(0.3) | 68.3(0.5) | 69.9(0.5) | 69.2(0.4) | 72.7(0.3) | |
| $\phi_3$:g$^-$ | 15.4(0.2) | 16.6(0.4) | 15.4(0.3) | 15.5(0.3) | 12.5(0.3) | |

[a] Reported averages and standard deviations are calculated over the last 20M for MC or over the last 200 ps for MD. Acceptances and populations are reported in percentages, energies and enthalpies in kcal mol$^{-1}$, heat capacities in cal mol$^{-1}$ K$^{-1}$, $\alpha$ in $10^{-5}$ K$^{-1}$, $\kappa$ in $10^{-6}$ atm$^{-1}$, and densities in g cm$^{-3}$. [b] Experimental data from ref 14. [c] $E_t$ corresponds to total energy for MC and potential energy for MD.

coefficients are such that the torsional energy for $\varphi = 120-240°$ closely follows the total energy profiles in Figure 2, which also include the intramolecular nonbonded and angle bending energies. Then, the Fourier component drops down to about −2 kcal/mol near the *gauche* minima before rising to about −0.5 kcal/mol at the *cis* maximum. This detail is needed to explain the behavior of the torsional energy curves in Figure 3. For the all *trans* hexane starting point, the torsional energy is zero. However, the first data point in the figure for the MD run is after the initial 5 ps warming period and 0.1 ps to the first coordinate output. By that time, the $3 \times 267$ dihedral angles have moved from 180° to yield a total torsional energy near 250 kcal/mol. Similarly, for the MC calculations, the first data point in the figure is for the 25 000th configuration, by which point the torsional energy is also near 250 kcal/mol. The simulations then start populating *gauche* states, which ultimately leads the total torsional energy term to negative values. From Figure 3, it is apparent that it takes at least 100 ps in the MD simulation for the torsional energy to settle into its final range. For the MC simulations, the torsional energy drops faster with the MC20 run than with MC10; it is not surprising that the convergence is more rapid with the larger attempted changes in the dihedral angles. The torsional energy for the MC20 run enters the final range after about $10 \times 10^6$ configurations of sampling.

**Conformer Populations.** The convergence of the *gauche*$^+$ ($\varphi = 0-120°$), *trans* ($\varphi = 120-240°$), and *gauche*$^-$ ($\varphi = 240-360°$) populations is illustrated in Figure 4 for the MC10 and MC20 simulations. The instantaneous values of the populations for each dihedral angle are shown, as obtained from the saved configurations. From the molecular symmetry, the *gauche* populations for each angle should be the same, as well as the *gauche* and *trans* populations for $\varphi_1$ and $\varphi_3$. For the MC20 run, it again takes about $10 \times 10^6$ configurations for the initial *trans* bias to wear off and for the individual populations to start oscillating in the final range. The *trans* bias persists longer with the smaller $\Delta\varphi$ in the MC10 run, particularly for the central dihedral angle, $\varphi_2$. The averages over the final $20 \times 10^6$ configurations are listed in Table 1. The inequivalence in the *gauche*$^+$ and *gauche*$^-$ populations is significantly greater with $\Delta\varphi = \pm 10$, and the *trans* population for $\varphi_2$ is about 5% higher
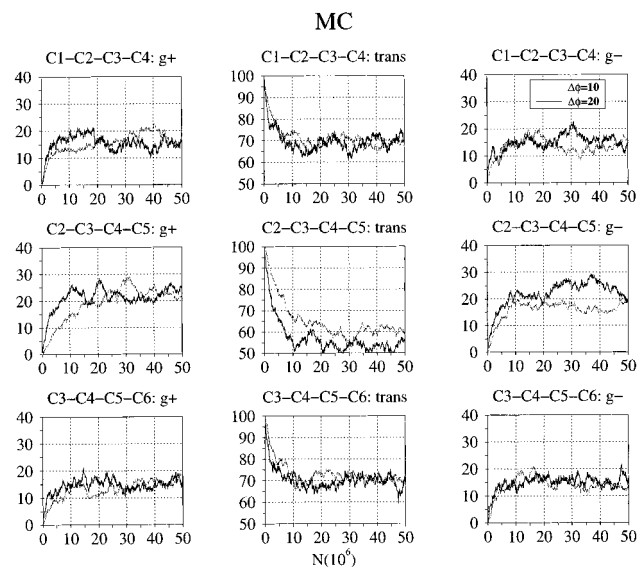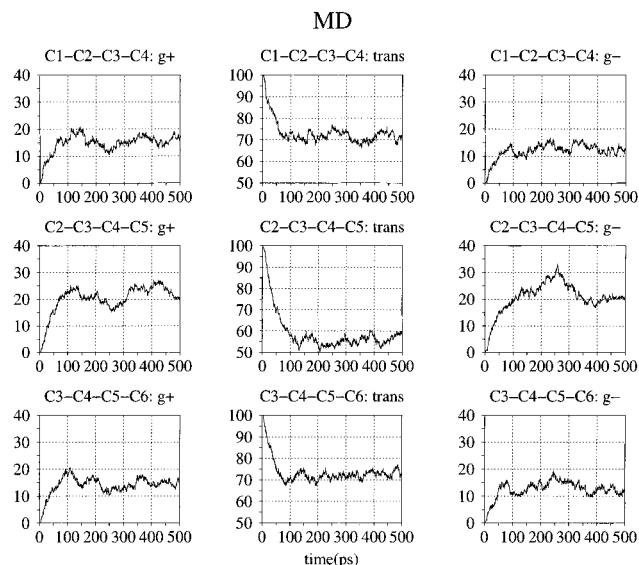
MC



**Figure 4.** Convergence plots for the *trans* and *gauche* populations in percent for each dihedral angle of hexane from the MC10 and MC20 simulations.

than the consensus value from the other simulations. Clearly, choosing $\Delta\varphi = \pm 15$ or $\pm 20$, as in earlier work,[7] is recommended over smaller ranges. The population inequivalences from the other MC simulations of about 2% provide the best estimate of the uncertainties in the final computed populations. The higher *gauche* population for the central dihedral angle, $\varphi_2$, is a real effect that is consistent with the energy for the tgt conformer that is lower than that for ttg, which was mentioned above with Figure 2.

The convergence of the torsional populations from the MD simulation is illustrated in Figure 5. In this case, the initial *trans* bias wears off and the individual populations start oscillating in the final range after 100 ps, which is consistent with the evolution of the torsional energy in Figure 3. The results reinforce the correspondence for convergence of 100 ps of MD with $10 \times 10^6$ configurations of MC. Convergence of the *trans* population for $\varphi_2$ is the slowest in all simulations. The populations from the MD simulation averaged over the final 200 ps are listed in Table 1. The *trans* populations from the

MD



**Figure 5.** Convergence plots for the *trans* and *gauche* populations in percent for each dihedral angle of hexane from the MD simulation.

MD run are all a little higher than from the MC15 and MC20 simulations, which may reflect a lingering bias from the initial configuration. The average asymmetry for the *gauche* populations of 2.8% from the MD calculation is also greater than the 1.4% from the MC15 and MC20 simulations. Thus, it is likely that transitions between conformational states are rarer in 200 ps of MD than $20 \times 10^6$ configurations of MD (the averaging periods for Table 1), though this was not specifically monitored in the present calculations.

Another quantitative measure of the convergence rates can be taken from the progression of the *trans* populations for the three dihedral angles in the early stages of the simulations. Specifically, the periods can be compared for the *trans* populations to decay from 100% to an arbitrary fixed value above the final oscillatory range, e.g., 80%. For the MC10, MC20, and MD calculations the periods are $3.9 \times 10^6$ configurations, $1.7 \times 10^6$ configurations, and 38.8 ps. The correspondence by this measure is less favorable for MD, i.e., 100 ps equates to $4.4 \times 10^6$ configurations of MC with $\Delta\varphi = \pm20°$.

As an additional check, MC with $\Delta\varphi = \pm20°$ and MD calculations were executed in the same manner but with all the hexane molecules initially in the tg$^+$t conformation. The results were basically the same for $\varphi_1$ and $\varphi_3$, i.e., the *trans* populations converge to their final range in about $10 \times 10^6$ configurations of MC or 100 ps of MD. Again, the asymmetry in the four equivalent *gauche* populations is greater with MD varying from 12.8% to 15.7% for averaging over the last 200 ps of the 500 ps run vs 16.0% to 17.3% for the last $20 \times 10^6$ configurations of the MC run of $50 \times 10^6$ configurations. For $\varphi_2$ it takes longer to wear off the initial *gauche*$^+$ bias. About 200 ps of MD or $20 \times 10^6$ configurations of MC are required for the *gauche*$^+$ and *gauche*$^-$ populations of $\varphi_2$ to reach an equivalent point. As usual, the asymmetry is greater with MD and perhaps indicates a memory effect or just a lower transition rate. Over the final 200 ps of averaging the *gauche*$^+$ and *gauche*$^-$ populations for $\varphi_2$ are 26.7% and 19.9% from the MD run, while they are 22.9% and 21.3% from averaging over the last $20 \times 10^6$ configurations of the MC simulation.

## Discussion

First, the overall consistency of the thermodynamic and conformational results for liquid hexane from two different programs, BOSS and AMBER, with very different sampling

algorithms, MC and MD, is reassuring. Such tests for systems other than liquid water have been rare.

In terms of computer time on the SGI R4000 for liquid hexane, two measures can be provided. From the behavior of the torsional energy profiles and conformer populations over the full runs, the roughly $10 \times 10^6$ configurations of MC needed for conformational convergence required 584 s, while the corresponding roughly 100 ps of MD required 954 s or a factor of 1.63 more time. From the periods for the *trans* populations to decay from 100% to 80%, the MC20 calculation required 97 s, while the MD run needed 370 s or a factor of 3.81 more time. There is also a consistent pattern of inequivalence for formally equivalent conformer populations with the MD calculations that is greater than with the MC simulations. The general message for the present system and software is that the Monte Carlo calculations are about $2-3$ times more efficient than molecular dynamics for achieving conformational equilibrium. The correspondence of 10 ps of MD with ca. $0.5 \times 10^6/267 \cong 2000$ MC passes provides a rough rule-of-thumb for comparing the lengths of MC and MD simulations. Similar results are expected for systems with larger numbers of molecules, $N$, because the time required for both MC and MD calculations is proportional to $N^2$.

The present results provide a data point on a prototypical system with torsional barriers of common height using two popular software packages. This study is not intended to be the last word on conformational sampling efficiency, though it does nullify any notion of comparative sampling inefficiency for such problems with sensible MC methods. Other systems could be chosen that could make the comparisons look relatively better or worse for MC or MD. For example, with barriers above 10 kcal/mol, there would be little likelihood of a transition with MD at 25 °C. However, with a large enough $\Delta\varphi$, an MC move could pass through the barrier. A simple example of this would be modeling *cis/trans* isomerization for an amide. Tolerable MC acceptance rates could probably be obtained by alternating between two $\Delta\varphi$ ranges, one normal and one large. On the other hand, advances have been made on more efficient MD procedures such as multiple-time-scale methods.[15] MD would also likely fare relatively better on a longer alkane where the usual internal coordinate MC would suffer from large swings of the tail of the alkane when a central dihedral angle is varied. However, alternative MC sampling algorithms have been devised to enhance transitions for higher alkanes or polymers via crankshaft-like motions.[16] In conjunction with internal coordinate MC for sampling of side-chain motions, such procedures warrant exploration for simulations of proteins as an alternative to MD. Modified MC procedures have also been shown to be highly efficient for conformational sampling of isolated, flexible organic molecules.[17]

Overall, continued effort is needed in optimizing algorithms to enable simulations of larger molecular systems over longer sampling periods. The present results show that MC and MD methods are competitive and should both receive attention. The challenge of simulating slow molecular events is apparent; an MD simulation covering 1 s for liquid hexane would require 300 000 years on an SGI R4000 workstation.

## References and Notes

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