I. INTRODUCTION

Ensuring appropriate behavior in molecular simulations has long been a topic of interest, and butane has been an important test molecule as the simplest alkane with a dihedral degree of freedom. In early work on united-atom models, Rebertus, Berne, and Chandler considered solvent effects on butane conformational equilibrium,\(^1\) while Levy, Karplus, and McCammon studied stochastic butane dynamics.\(^2\) Pastor and Karplus later investigated the importance of inertial effects in Langevin dynamics, also using a united atom model of butane.\(^3\) Tobias and Brooks discussed the importance of including hydrogen atoms when considering solvent effects.\(^4\)

One focus of molecular studies has been the dependence of transition rates on the choice of dynamics. In a study of ethylene glycol, which is polar but also possesses a single dihedral angle, Widmalm and Pastor compared rates and other time scales in molecular and Langevin dynamics.\(^5\) Similarly, Loncharich, Brooks, and Pastor explored the effects of the Langevin friction constant on transition rates in the larger “NAMA” molecule with an eye toward speeding up the generation of conformational ensembles in peptides and proteins.\(^6\)

Work in one-dimensional systems, in addition to considering the effects of stochastic dynamics on reaction rates (e.g., Refs. 7–15) has explored transition phenomena on still shorter “microscopic” time scales. Dykman and co-workers have extensively investigated the effects of different noise types and nonequilibrium driving forces on transition events themselves in stochastic settings;\(^16–21\) see also Ref. 22. The present authors previously considered the influence of the local, nonuniform speed along the reaction coordinate on a “dynamic importance sampling” approach to rate computations.\(^23\)

Many “microscopic” questions have remained unanswered regarding molecular transition events. What are their durations, \(t_b\)? (See Figs. 1 and 2.) Is the reaction coordinate traversed at a uniform speed, or is progress more rapid in some regions? Is there sensitivity to the choice of dynamics or potential? The need for detailed answers is more pressing in molecular systems because dynamic importance sampling\(^23–25\) and “transition path sampling” methods\(^26,27\) for computing reaction rates require ensembles of transition event trajectories. A quantitative understanding of transition events could accelerate ensemble generation in these approaches, making larger systems amenable to study. Moreover, because ensembles of transition events are required for rate estimates, the durations set a fundamental minimum on the computer time required to perform such calculations.\(^23\)

In the present study we provide answers to these questions, using a spectrum of simulations. With the CHARMM potential, all-atom butane is studied in explicit water and acetic acid. Low- and high-friction Langevin simulations are also performed with CHARMM, along with a separate high-friction run using the AMBER potential. We compare the butane event-duration distributions and reaction-coordinate speed profiles with those for one-dimensional stochastic systems with white and colored noise.

Two interesting generic features emerge. First, after a simple linear rescaling by the average, the distribution of transition event durations appears to be \textit{universal} across dynamics, solvent, and potential type—regardless of whether butane or a one-dimensional system is considered. The distribution embodies behaviors predicted analytically from a simple one-dimensional model. Second, the reaction-coordinate speed profiles of butane transitions also display a common, accelerating trend, which matches that of colored-noise, one-dimensional simulations.

In the next section, Sec. II, we discuss simulation models and methods. In Sec. III we present an analytic prediction for the distribution of event durations. Section IV contains the simulation results, and we give a summary and some conclusions in Sec. V.
FIG. 2. A schematic view of the butane \((\text{C}_4\text{H}_{10})\) trans and gauche states, showing only the carbon atoms. The dihedral angle, \(\phi\), is defined as that between the planes formed by the first and last three carbon atoms. Note that the two central atoms are also bonded.

**II. SIMULATION MODELS AND SETUP**

Transition behavior was studied in a variety of settings—from all-atom, fully solvated molecular dynamics to one-dimensional Langevin dynamics. In this section we describe the protocols and parameters used.

**A. Fully solvated all-atom models of butane**

To examine solvent effects on barrier crossing behavior, and to ensure a good standard of comparison for stochastic simulations, we performed two all-atom, explicit solvent simulations of butane; see Fig. 2. In one case the solvent was water and in the other it was acetic acid. In both cases the CHARMM program (version C27b2) and parameters (August 1999 release) were used.\(^{28,29}\) The butane molecule was lightly restrained to the center of the simulation cell using a harmonic, molecule-specific, center-of-mass energy term lightly restrained to the center of the simulation cell using a nonharmonic, molecule-specific, center-of-mass energy term loosely restrained to the center of the simulation cell using a CHARMM program (version C27b2) and parameters (August 1999 release) were used.\(^{28,29}\) The butane molecule was lightly restrained to the center of the simulation cell using a harmonic, molecule-specific, center-of-mass energy term (force constant 50.0 kcal/mol Å\(^2\)). The simulations were performed with constant pressure and temperature and a nonbonded-list cutoff of 12 Å. The nonbonded list was generated to 15 Å and the van der Waals force switched to zero between 10 and 12 Å. Electrostatics were shifted to the 12 Å to 15 Å and the van der Waals force switched to zero be-

\[ E_{\text{g}}(x) = E_{\text{g}}(x) + \frac{1}{2}k_x(x - x_0)^2, \]

where \(E_{\text{g}}(x)\) is the potential energy of the gauche state, \(k_x\) is the force constant, and \(x_0\) is the equilibrium position.

**B. All-atom butane in a stochastic “solvent”**

To maintain as much consistency as possible between the explicit- and the implicit-solvent studies, the stochastic simulations used options similar to those for the explicit solvent runs. In particular, the nonbonded energies were cut off at 12 Å, and a center-of-mass restraint was again used on the butane molecule. Temperature was maintained at 300 K. As would be expected, no periodic images were used and there is no pressure control in these stochastic simulations. Dynamics were performed with the leapfrog Langevin dynamics integrator in CHARMM, namely,\(^6\)\(^\text{28,29}\)

\[ \mathbf{x}(t + \Delta t) = \mathbf{x}(t) + \Delta t \mathbf{v}(t + \frac{1}{2}\Delta t), \]

\[ \mathbf{v}(t + \frac{1}{2}\Delta t) = \mathbf{v}(t - \frac{1}{2}\Delta t) + \frac{\mathbf{x}(t) - \mathbf{x}(t - \Delta t)}{\Delta t} + \frac{1}{1 + \frac{1}{2}\gamma\Delta t} \]

\[ + (\Delta t/m) \left[ \mathbf{f}(t) + \mathbf{R}(t) \right], \]

\[ \mathbf{v}(t) = \sqrt{1 + \frac{2}{\gamma\Delta t} \left[ \mathbf{v}(t + \frac{1}{2}\Delta t) + \mathbf{v}(t - \frac{1}{2}\Delta t) \right]/2}, \]

where \(\mathbf{R}\) is a white-noise frictional force, every component of which was chosen from a Gaussian distribution of zero mean and variance \(2m/\gamma k_B T/\Delta t\). We used two values of the friction parameter (\(\gamma = 5, 50\) ps\(^{-1}\)) to implicitly model solvent effects; only the carbon atoms were treated stochastically, while the hydrogen dynamics were governed by the ordinary (\(\gamma = 0\)) leapfrog Verlet algorithm (2.1).

An additional Langevin simulation was performed using the AMBER potential within the Molecular Modeling Tool Kit (MMTK).\(^{31}\) For this “overdamped” (“Brownian”) simulation, dynamics were governed by

\[ \mathbf{x}(t + \Delta t) = \mathbf{x}(t) + (\mathbf{f}(t) + \mathbf{R}(t))/m, \]

\[ \mathbf{v}(t + \frac{1}{2}\Delta t) = \mathbf{v}(t - \frac{1}{2}\Delta t) + \Delta t \mathbf{f}(t)/m, \]

The noise term \(\Delta x_{\mathbf{R}}\) was also chosen to be “white”—in this case, selected independently at every time step from a Gaussian of zero mean and variance,

\[ \sigma^2 = 2 \Delta t k_B T/m \gamma. \]

All atoms were treated stochastically, but we note that overdamped dynamics only make predictions relative to an arbitrary overall time scale\(^3\) embodied here in the convenient choice \(\gamma = 250\).

**C. One-dimensional models**

We also studied the simple bistable potential discussed in Ref. 23 and many other places, namely,

\[ U(x) = E_{\text{g}}[(x/l)^2 - 1]^2, \]

where \(f = -\nabla U\) for potential energy \(U\) and \(m\) is the particle’s mass.

The acetic acid simulations consisted of 253 explicit molecules of acetic acid and box dimensions of roughly 65 Å on a side. This created the appropriate density of solvent for a temperature of 300 K. The water simulations contained 861 TIP3 water molecules and used a box size of roughly 30 Å.
where $E_b$ is the barrier height and $l$ the length scale. This potential is shown in Fig. 3. All one-dimensional simulations used overdamped Langevin dynamics (2.6) with—for simplicity—mass, friction, and the thermal energy scale set to unity: $m = \gamma = k_B T = 1$.

Two types of noise were studied. The first was uncorrelated “white” noise, as discussed above. We also employed exponentially correlated noise simulated via an Ornstein–Uhlenbeck process, in which $\Delta x_R = y$ is considered a position variable executing independent overdamped dynamics (2.6) in a harmonic potential $U(y) = (m \gamma / 2 \tau) y^2$ subject to white noise with fluctuations given by $\sigma_y^2 = (2 \Delta t / \tau)$. This formulation yields the autocorrelation function $\langle y(0) y(t) \rangle = \sigma_y^2 \exp(-t / \tau)$, so that the magnitude of the correlated noise fluctuations is unchanged from the white-noise case. Note, however, that the free energy surface and the transition rates change when the dynamics (2.6) is used with correlated noise because detailed balance is not obeyed.

III. THEORETICAL ANALYSIS OF A SIMPLE MODEL

In this section we discuss an extremely idealized potential characterized by a transition-event-duration distribution with features common among all of the models studied. The reader solely interested in the simulation results could safely pass over this discussion and refer to the asymptotic results quoted later.

The one-dimensional potential is shown in Fig. 4, and the initial state A is defined to be $x < 2$ and state B is $x > 3$. The motivation for studying such an unphysical model is based on the fundamental observation made in the present report (see the next section): because the distribution of durations appears to be universal, it should be derivable from even a trivial model.

The analysis is based on the simulation-step probabilities governing the overdamped dynamics (2.6) with white noise. Explicitly, the potential of Fig. 4 is given by

$$U(x) = \begin{cases} 0 & (x < 2) \\ (E_b/L)(x-2) & (2 < x < 3) \\ E_b & (x > 3). \end{cases}$$

(3.1

For convenience, we introduce the notation $\delta x = f \Delta t / m \gamma = E_b \Delta t / m \gamma L$ for the inclined region $2 < x / L < 3$. As noted after (2.6), fluctuation increments $\Delta x_R$ are chosen from a Gaussian distribution, and the probability density for choosing an increment $\Delta x_j = x_{j+1} - x_j$ in the inclined region is given by

$$T(\Delta x_j) = \frac{1}{\sqrt{2 \pi \sigma}} \exp[-(\Delta x_j - \delta x)^2 / 2 \sigma^2].$$

(3.2

The probability density of a trajectory of $n_b = t_b / \Delta t$ steps, $\xi^{n_b} = (x_0, x_1, \ldots, x_{n_b})$, is simply the product of single-step densities:

$$Q(\xi^{n_b}) = \prod_{j=0}^{n_b-1} T(\Delta x_j).$$

(3.3

Because each of the Gaussian densities $T$ is normalized, so too is the trajectory density; that is,

$$\int d\xi^{n_b} Q(\xi^{n_b}) = 1,$$

(3.4

where $d\xi^{n_b} = \prod_{j=0}^{n_b-1} d\Delta x_j$.

We can now begin to derive an approximate distribution of transition-event durations. The relative probability of a given event duration, $t_b = n_b \Delta t$, is estimated as a product of two factors: (i) the total number of probable $n_b$-step trajectories—whether “crossing” or not—multiplied by (ii) the fraction of $n_b$-step trajectories that cross the barrier (i.e., reach the barrier top at $x > 3$; see Fig. 4). Factor (i) is proportional to $\sigma_b^{n_b}$, because the fluctuation width in (3.2) measures the extent of probable steps; that is, it is extremely unlikely for $\Delta x_j - \delta x$ to greatly exceed $\sigma$. The second factor, the fraction of successful trajectories, may be written formally as

$$f_b = \int d\xi^{n_b} Q(\xi^{n_b}) h_A(x_0) h_B(x_{n_b}).$$

(3.5

where the indicator function $h(x)$ is unity when $x$ is in state Y and zero otherwise. That is, the probability of a transition event occurring in $t_b = t_b / \Delta t$ steps is proportional to $\sigma_b^{n_b} f_b$.

We estimate the fraction of successful trajectories, $f_b$, by considering only those trajectories near to the optimal $n_b$-step crossing trajectory (which differs from the unique, overall-optimal trajectory—for the optimal $n_b$—discussed in Ref. 23). The optimal $n_b$-step trajectory for the constant-force potential of Fig. 4 consists of uniform steps of length $\Delta x_j = L / n_b$, as can be seen by maximizing $Q$ in (3.3) for any pair of steps. We estimate the number of nearby trajectories

FIG. 3. The bistable, one-dimensional potential (2.8) simulated under a variety of conditions discussed in the text. It is shown here for a barrier height of $E_b = 7k_B T$ and length scale $l = 1$.

FIG. 4. A simple one-dimensional potential used to calculate probabilities of event durations, $t_b$. 
as those occurring in a “fluctuation volume” $\sigma^n b$ about the optimal. After substituting $\Delta x_j = L/n_b$ in (3.2) and this result in (3.3), by including the fluctuation volume one finds
\[ f_b \propto c_0^{t_b/\Delta t} \exp \left[ -\frac{m\gamma}{2k_BT} t_b \left( L \frac{E_b}{m\gamma L} \right)^2 \right], \] (3.6)
where $c_0$ is an unknown constant, presumably of order unity.

Finally, the estimate for the probability distribution of event durations is proportional to the product of $\sigma^n b$ and $f_b$, namely,
\[ \rho(t_b) \propto (c_1 \sigma)^{t_b/\Delta t} \exp \left[ -\frac{m\gamma}{2k_BT} t_b \left( L \frac{E_b}{m\gamma L} \right)^2 \right], \] (3.7)
where $c_1$ is again an unknown constant. Using the identity $\sigma^n b = e^{n\log a}$ to incorporate the prefactor into the exponential, we can rewrite this approximation as a two-parameter form for purposes of understanding its behavior,
\[ \rho(t_b) \propto \exp \left[ -t_b \left( \frac{c}{t_b} + d \right)^2 \right]. \] (3.8)

The asymptotic behaviors are of particular interest and are given by
\[ \rho(t_b \to 0) \sim \exp(-c t_b^2), \] (3.9)
\[ \rho(t_b \to \infty) \sim \exp(-d t_b^2). \] (3.10)

It is worth noting that all derivatives of $\rho$ vanish as $t_b \to 0$.

IV. RESULTS

A. Transition-event durations

Here we present results regarding the durations of transition events, $t_b$; see Fig. 1. The universal behavior of the distribution of durations is demonstrated, and limiting behavior is discussed by a comparison to the analysis of the previous section. The average durations are also compared to other time scales that distinguish each system, the correlation time, and inverse reaction rate.

The definition of a transition duration is necessarily somewhat arbitrary. Here we used the time between the last exit from the initial state and the first entrance to the final state; in other words, $t_b$ is the amount of time spent continuously by a trajectory in the transition region. For transitions between the gauche $-$ and trans states in butane, we chose the transition region to be $100<\phi<150$; considering symmetry, the region $210<\phi<260$ was chosen for gauche $+$ and trans. Following convention, the trans state is centered at $\phi = 180$. See Fig. 2.

The principal results for the distributions of event durations are embodied in Fig. 5. The simple linear rescalings, by the system-specific average durations ($\langle t_b \rangle$), cause the data to collapse onto a fairly well-determined universal curve. The empirical fit to the data, detailed below, confirms the asymptotic behaviors predicted analytically in Eqs. (3.9) and (3.10): The gap at small $t_b$ is clearly consistent with $e^{-t_b^2}$ behavior (but not with a more common form like $t_b^q e^{-t_b}$ with exponent $q>0$), and the logarithmic scale of Fig. 5(b) reveals the large $t_b$ behavior to be a simple exponential decay. The collapse of the data indicates that the arbitrary duration definitions do not obscure the fundamental universal behavior.

The empirical fit shown in Fig. 5 depicts the form
\[ \tilde{\rho}(t_b) = \mathcal{N}^{-1} \exp \left[ -t_b \left( \frac{2t_b}{b+b'_f} + \frac{c}{t_b^2} \right) \right], \] (4.1)
where $\mathcal{N}$ is a normalization factor and the three parameters used are $b = 1.5$, $c = 1.4$, $r = 5$. The form was designed, by trial and error, both to display the correct asymptotic behaviors and to capture the inflection point to the right of the peak visible on the logarithmic plot, Fig. 5(b).

B. Time scales

Another question that can be answered based on our data is whether the crossing event durations in a particular system are correlated with other fundamental time scales, like the correlation time and the (inverse) reaction rates. Table I apparently answers this question in the negative. Note that, in the table, the dihedral correlation time is defined by
\[ \tau_{corr} = \langle \phi(0) \phi(0) \rangle^{-1} \int_0^\infty dt \langle \phi(0) \phi(t) \rangle, \] (4.2)

FIG. 5. The collapse of distributions of transition event durations, $t_b$, after simple linear rescaling. Both butane and one-dimensional simulation data are shown, and the probability density function, $p=t\rho$, is plotted for the durations normalized by the average of each dataset. The lower plot shows identical data on a logarithmic scale to emphasize the common behavior in the tails of the distributions. Butane molecular dynamics data reflect water (+ symbols) and acetic acid (×) solvents; butane Langevin dynamics data include low (□) and high-friction (*), as well as high-friction with AMBER (filled boxes). Overdamped, one-dimensional data describe white (○) and colored noise (●). The empirical fit of Eq. (4.1) is shown with a thick, solid line.
TABLE I. A comparison of time scales for butane dynamics with different explicit and implicit solvents. The rates, \( k \), are between the trans (\( t \)) and gauche (\( g \)) states, and the reciprocals define waiting times between transition events. For definitions of the dihedral correlation times \( \tau_{\text{corr}} \) and \( \tau_{\text{decay}} \) see Eq. (4.2) and the subsequent text. The average transition-event duration is denoted by \( \langle t_b \rangle \). All times are in picoseconds.

<table>
<thead>
<tr>
<th>System</th>
<th>( 1/k_{t-g} )</th>
<th>( 1/k_{g-t} )</th>
<th>( \tau_{\text{decay}} )</th>
<th>( \tau_{\text{corr}} )</th>
<th>( \langle t_b \rangle )</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD/acetic acid</td>
<td>55.6</td>
<td>294</td>
<td>0.40</td>
<td>0.136</td>
<td>0.145</td>
</tr>
<tr>
<td>MD/water</td>
<td>35.1</td>
<td>115</td>
<td>0.21</td>
<td>0.049</td>
<td>0.145</td>
</tr>
<tr>
<td>LD/( y = 5 )</td>
<td>38.5</td>
<td>154</td>
<td>0.35</td>
<td>0.023</td>
<td>0.146</td>
</tr>
<tr>
<td>LD/( y = 50 )</td>
<td>32.8</td>
<td>151</td>
<td>0.06</td>
<td>0.08</td>
<td>0.200</td>
</tr>
</tbody>
</table>

where the angular brackets refer here to time averages within the trans state only. Since the dihedral-angle correlation function of the integrand exhibits strong oscillations in molecular dynamics simulations, Table I also includes the decay time of the exponential “envelope,” \( \tau_{\text{decay}} \), resulting from visual fits. The data suggest that the rates are not simply related to correlation times.

C. Reaction-coordinate speed profiles

The reaction-coordinate speed profile\(^{23}\) depicts the local speed of progress along the reaction coordinate, as exemplified in Fig. 6. This subpicosecond behavior (see Table I) is uniquely available from simulations, and critically important for dynamic importance sampling methods for rate calculations: see Ref. 23.

As in the case of the crossing time distributions, the results tell a simple and consistent story. All of the butane simulations show a characteristic “accelerating” speed profile during transitions, as indicated by Fig. 6. While absolute speeds do differ—as is evident from the average crossing times of Table I—the consistent, accelerating profiles from the butane simulations contrast sharply with the white-noise profile of a one-dimensional simulation discussed in detail in Ref. 23 and also shown in Fig. 7.

Because even the Langevin butane simulations—which were performed with white noise—exhibit the accelerating behavior, one can also conclude that molecular fluctuations are inherently colored (i.e., correlated). The reason is straightforward. If one focuses on the dynamics of a particular butane atom, say a methyl carbon, then according to Eq. (2.6) that atom moves based on the force it feels and a white noise increment. The force itself, however, reflects the relatively long-time scale motions executed by the whole molecule. Hence the molecule acts as its own memory, and correlations are not surprising, regardless of the type of noise modeled in \( \Delta x_R \).

V. SUMMARY AND CONCLUSIONS

By comparing butane simulations with explicit and implicit solvents, along with simple white- and colored-noise one-dimensional (1-D) systems, we have found a remarkable degree of commonality in short-time scale kinetic properties. The distributions of transition-event durations \( t_b \) from all systems studied substantially “collapse” onto a single universal function after a simple linear rescaling (Fig. 5), and both the small- and large-\( t_b \) behaviors of the distribution are predicted analytically in Sec. III based on a simple model. Moreover, all the profiles of average local speeds during traversal of the reaction coordinate—the “reaction-coordinate speed profiles”—of the butane systems behave similarly (Fig. 6). These profiles also qualitatively match those from 1-D colored-noise systems, but are clearly distinct from the 1-D white-noise behavior (Fig. 7).

Despite this universal short-time behavior, quantitative estimates for reaction-rate, correlation, and event-duration time scales (Table I) reveal no obvious relationship between...
butane systems with explicit solvents and those with implicit, stochastic “solvent.” This suggests that stochastic simulations, at least at the level considered here, cannot be used for quantitative estimates of time scales in fully solvated computations. While this assessment may be more pessimistic than that of Widmalm and Pastor, it is not surprising that the consideration of an additional time scale, namely $t_b$, makes agreement more difficult. Perhaps more important are two other issues: Do simple stochastic representations become better or worse as larger molecules are considered? What quantity of explicit solvent, say in combination with stochastic boundary conditions, provides a good level of agreement with the array of kinetic quantities in fully solvated systems?

Further theoretical consideration of the connection between simple and molecular systems would also prove valuable. In particular, the study of simple models possessing a one-dimensional reaction coordinate coupled nontrivially to simple orthogonal degrees of freedom (based on, e.g., Refs. 7, 8, 10–12) should permit a better understanding of the effects of noise color on the short-time transition behavior considered here. In a molecular system, as noted in Sec. IV C, the effective noise on any atom must be colored because of the coupling to the nontrivial “bath” of other particles.

Following up on the motivation for the investigation reported here, we believe that an appreciation of the results can inform improved sampling approaches for reaction rate computations within the “transition path sampling” and “dynamic importance sampling” methods. These approaches require ensembles of transition-event trajectories. At a simple level, understanding the transition event duration $t_b$ in molecular systems is critical: as noted in Ref. 23, the duration of molecular crossing events sets, in part, the minimum computation time required to generate a realistic ensemble of transition-event trajectories. Furthermore, given the universal behavior uncovered here, stochastic simulations evidently reproduce key aspects of explicitly solvated transition behavior. Despite the clear importance of solvent effects, this study suggests that trajectories harvested in a computationally inexpensive stochastic context should—at a minimum—provide good starting points for refinement in a solvated context.

ACKNOWLEDGMENTS

A number of people contributed to this project with helpful comments and discussions. The authors would like to thank Mark Dykman, Lucy Forrest, Alan Grossfield, Hirsh Nanda, Richard Pastor, Horia Petrache, and Jonathan Sachs. Bernard Brooks provided a useful clarification regarding the Langevin leapfrog algorithm. Konrad Hinsen graciously provided assistance with the MMTK program. Funding for this work was provided by the National Institutes of Health (NIH) (Grant No. GM54782), the Bard Foundation, and the Department of Physiology. D.M.Z. is the recipient of a National Research Service Award (GM20394) from the NIH.