

DIFFUSIVE DYNAMICS OF ALKANE CHAINS

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I. INTRODUCTION

With the advent of high speed computers that could numerically solve Newton's equations of motion for many particle systems with extreme rapidity, the method of molecular dynamics simulation introduced in 1958 (1), has become an increasingly popular and powerful tool for the study of problems involving the interactions of many particles. Most often applied to the study of equilibrium and dynamic properties of condensed phase systems, the molecular dynamics technique has recently been employed to simulate the motion of a single protein molecule consisting of 458 atoms (2). Even though the speed with which computers can implement integration algorithms is truly amazing (one iteration of a fifth order integration algorithm applied to the 458 atom Pancreatic Trypsin Inhibitor, PTI, requires only 0.25 seconds), it has become evident that the relaxation times of many motions of interest in polymers are too long to make a full molecular dynamics approach feasible. For example, a 100 psec simulation of the small PTI protein required 14 hours of cpu time, yet the relaxation times of sidechain motions are known to range from 100 psec to many nanoseconds or longer; hydrogen exchange rates in proteins vary between microseconds and days; and allosteric transitions probably occur on a millisecond time scale (3). Fortunately, for many applications it is not necessary to consider the motions of all the atoms in the system in detail, rather the coordinates of some of the atoms may be explicitly retained in the Hamiltonian, and the effects of the other atoms incorporated in a statistical manner. Such a subsystem plus heat bath picture of the many particle problem naturally gives rise to a Brownian dynamics approach to the simulation (4-6) for which a phenomenological friction coefficient is used to couple the explicit particles to the heat bath. Brownian dynamics has recently been employed to study the properties of electrolytes in solution (4,5) and to the diffusive motion of polymers in a viscous solvent (6). In this report we examine the diffusive dynamics of relatively short alkane chains in detail, with particular emphasis on the relationship between the explicit form of the molecular potential energy function and the equilibrium and dynamic properties of the hydrocarbon chains. The particular alkanes studied were butane, heptane, and eicosane (4 atoms, 7 atoms, and 20 atoms). We regard this work as a necessary preliminary to the application of similar dynamic simulation methods to systems described by more complex potentials. In sections IIA and IIB the equation of motion used to simulate the diffusive trajectories of the alkane chains is reviewed and the forms employed for the intramolecular potential are described. Section IIC summarizes the parameters used for each of the trajectories. In Section III, the results of the dynamics simulations are presented and the equilibrium and kinetic properties of butane, heptane, and eicosane are discussed.

IIA. Equation of Motion

The problem of describing the motion of a small number of particles which interact both explicitly with each other through the influence of a potential energy function as well as implicitly with a large number of solvent molecules has been approached using a variety of equations of motion that incorporate effects of the solvent on the atoms of interest. The starting point for a general class of equations of motion descriptive of Brownian particles is the assumption that the change in momentum of the Brownian particles is not dependent on the past history of the particles' motion. The time evolution of such a system is described equally well either by solving a boundary value problem corresponding to the time evolution of momenta and displacement distributions that the particles experience (method of Fokker-Planck) or by solving a stochastic (Langevin) differential equation. The Langevin trajectory corresponds to the selection of a single trajectory out of the same distribution of trajectories that is obtained as a solution to the corresponding Fokker-Planck equation. We are interested in describing the diffusive motion of a single hydrocarbon chain in an aqueous solvent. It is characteristic of diffusive systems that the particles' momenta relax to the equilibrium distribution over distances which are small compared to displacements for which the potential energy changes appreciably. In order to discuss the kinetic properties of the alkane simulations it is useful to review the Fokker-Planck description of diffusive motion; the diffusive Langevin equation used to simulate the alkane trajectories is then presented below.

The Fokker-Planck equation in phase space may be derived either from an integral expression for the phase space transition probability as a Markov process (7) or from the Liouville equation (8). The phase space Fokker-Planck equation for a single Brownian particle is:

$$\frac{\partial W}{\partial t} + \vec{v} \cdot \nabla_{\vec{r}} W + \vec{F} \cdot \nabla_{\vec{v}} W = \frac{\beta}{m} \nabla_{\vec{v}} \cdot \left\{ \vec{v} W + \frac{KT}{m} \nabla_{\vec{v}} W \right\} \quad (1)$$

$W(\vec{r}, \vec{v}, t)$ is the phase space probability distribution, \vec{F} the systematic force on the particle is the negative gradient of an explicit potential energy function, and m and β are the mass and friction constant of the Brownian particle. In order to derive a diffusion equation from eq.1 the basic requirements are that the spatial gradient of the potential function and the probability distribution are approximately constant over distances of the order of $[mKT]^{1/2}/\beta$. In this case the complete phase space distribution function is,

for time intervals $t > m/\beta$ approximately separable:

$$W(\vec{r}, \vec{v}, t) \approx \left[\frac{m}{2\pi KT} \right]^{3/2} e^{-\frac{m|\vec{v}|^2}{2KT}} W_1(\vec{r}, t) \quad (2)$$

The configuration space distribution function $W_1(\vec{r}, t)$ satisfies the diffusion (Smoluchowski) equation (7):

$$\frac{\partial W_1}{\partial t} = \frac{1}{\beta} \nabla_{\vec{r}} [-\vec{F} W_1 + KT \nabla_{\vec{r}} W_1] \quad (3)$$

Under steady state conditions the diffusion current is:

$$\vec{j} = \frac{1}{\beta} [-\vec{F} W_1 + KT \nabla_{\vec{r}} W_1] = \text{constant} \quad (4)$$

The momentum Langevin equation for a Brownian particle is (7):

$$m \frac{d\vec{v}}{dt} = -\beta \vec{v} + \vec{F} + \vec{A}(t) \quad (5)$$

Again, m and β are respectively the mass and friction constant of the particle and \vec{F} is the negative gradient of an explicit potential function with respect to the particles' coordinates. $\vec{A}(t)$ a stochastic term, represents a randomly fluctuating force on the particle due to the solvent and is assumed to be gaussianly distributed with first and second moments:

$$\langle \vec{A}(t) \rangle = 0 \quad 6a$$

$$\langle \vec{A}(t) \cdot \vec{A}(t') \rangle = 6\beta kT \delta(t - t') \quad 6b$$

In order to implement a computer algorithm for integrating an equation of motion the time step must be restricted to times small enough such that the gradients of the potential (systematic forces) are approximately constant. With this restriction in mind a first integration of the momentum Langevin equation may be performed:

$$\frac{d\vec{r}}{dt} = \vec{v}_0 \cdot e^{-\left(\frac{\beta}{m}\right)t} + \frac{F(0)}{\beta} (1 - e^{-\left(\frac{\beta}{m}\right)t}) + \frac{e^{-\left(\frac{\beta}{m}\right)t}}{m} \int_0^t e^{\left(\frac{\beta}{m}\right)t'} \vec{A}(t') dt' \quad (7)$$

If the more restrictive requirement discussed above is satisfied, that \vec{F} remain constant over distances $(m kT)^{1/2}/\beta$ and interest is centered on solutions to Eq.7 for times $t \geq m/\beta$ then the diffusive trajectory of the Brownian particle is described by:

$$\frac{d\vec{r}}{dt} = \frac{\vec{F}(0)}{\beta} + \frac{e^{-\left(\frac{\beta}{m}\right)t}}{m} \int_0^t e^{\left(\frac{\beta}{m}\right)t'} \vec{A}(t') dt' \quad (8)$$

The solution to the diffusive Langevin equation (eq.8) is the probability distribution:

$$w(\vec{r}(\Delta t), \vec{F}) = \left[\frac{\beta}{4\pi K T \Delta t} \right]^{3/2} \exp \left[- \frac{|\vec{r}(t + \Delta t) - \vec{r}(t) - \frac{1}{\beta} \vec{F}(t) \Delta t|^2}{4(KT/\beta)\Delta t} \right] \quad (9)$$

The computer algorithm for the diffusive trajectory is then:

$$\vec{r}(t + \Delta t) = \vec{r}(t) + \Delta \vec{r}_{\text{systematic}} + \Delta \vec{r}_{\text{random}} \quad (10a)$$

$$\Delta \vec{r}_{\text{systematic}} = \frac{\vec{F}(t)}{\beta} \Delta t \quad (10b)$$

$\Delta \vec{r}_{\text{random}}$ is chosen from a Gaussian distribution with 0 mean and second moment $6\Delta t$. It should be emphasized again that \vec{F} is required to be approximately constant over Δt for two very different reasons. In the first place it is a necessary condition if the inertial terms in the Fokker-Plack or Langevin equations are to be ignored and less fundamentally it is necessary for numerical accuracy of the integration algorithm. Restricting the time step in the numerical algorithm to $\Delta t \leq \frac{\beta K T}{\bar{F}^2}$ where \bar{F}

is a typical systematic force experienced by the particle may minimize inaccuracy in the numerical integration due to the non constancy of F because the mean square displacement is approximately independent of F in this time regime. We have not however studied this effect in any detail. Eq.10 was used to construct the trajectories of the hydrocarbon chains. A united atom model was used to represent the alkanes so that the skeletal carbon atom coordinates corresponded to point centers of resistance; methyl hydrogens were not explicitly accounted for. The carbon-carbon bond lengths and angles were held constant during the simulation by applying the SHAKE (9) molecular constraint algorithm after each iteration of eq.10. Therefore butane for example, was considered to have 7 degrees of freedom, 6 overall translational and rotational degrees of freedom and 1 intramolecular rotational degree of freedom. One of the primary purposes of the dynamics simulation was to study the effects of an explicit intramolecular potential on the kinetic and equilibrium properties of the alkanes and the different model potentials used are described below.

IIB. Intramolecular Potential Energy Function

In order to implement a stochastic molecular dynamics simulation, a potential surface is required which takes into account the potential energy due to the explicit interaction of particles whose motion is followed as well as effects due to the implicit solvent molecules. The potential due to the direct interaction between extended atom methyl centers was taken to be a sum of terms that account for rotational potential energy about the bonds of the chain and a sum of Lennard-Jones terms representing van der Waals potential energy between methyl centers separated by four or more bonds. The gas phase potential of butane consisted of the rotational term (10):

$$\begin{aligned}
 \text{gas phase} \\
 V(\phi) = 1.99[1.116 + 1.462 \cos \phi - 1.578 \cos^2 \phi - 0.368 \cos^3 \phi \\
 + 3.156 \cos^4 \phi - 3.788 \cos^5 \phi]
 \end{aligned}
 \tag{11}$$

For heptane and eicosane, in addition to rotational terms the Lennard-Jones potential had the form:

$$V(r) = 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right]
 \tag{12}$$

where r is the distance between non-bonded methyl centers, and ϵ and σ are respectively 0.29 kcal/mole and 3.7 Å.

In addition to the stochastic, fluctuating force exerted by the many solvent particles on the solute alkane chain, the solvent may exert a more slowly varying, systematic force on the chain, which depends on the hydrocarbon conformation and possibly on the instantaneous configuration of solvent molecules as well. In Brownian dynamics the solvent molecules are assumed to be distributed over an equilibrium distribution and therefore to account for any systematic force of solvent on polymer, a potential of mean force must be substituted for the gas phase intramolecular potential described above. At CECAM, dynamics of alkane chains in water were studied and an expression for the potential of mean force between apolar solutes dissolved in water is required. Pratt and Chandler (11) have developed a theory which may be used to calculate a solvent modified

intramolecular potential for flexible alkane chains dissolved in water. These authors have established a method for calculating the cavity distribution function $y\{r\}$ for spherical apolar solutes dissolved in water starting from Ornstein-Zernicke type integral equations for the solute-solute and solute-water pair correlation functions. The solvent modified rotational potential for butane dissolved in water is:

$$V(\phi) = V(\phi)_{\text{solvent gas phase}} - K T \ln y\{r\} \quad (13)$$

since $y\{r\}$ is a four point cavity distribution function, approximation method must be used to evaluate it. Pratt and Chandler have shown that for the purposes of calculating $y\{r\}$, butane may be approximated by a pseudo diatomic two cavity model where methyl sites 1 and 2 are replaced by a sphere midway between the 1-2 bond and similarly another sphere is placed midway between the 3-4 bond. The diameters of the two cavities are chosen so as to match the volume of the ethane cavities from which they were formed. The correct diameter for each of the overlapping ethyl cavities at 25°C is 4.5 Å. In this scheme each conformation of butane corresponds to the overlap of 2 ethyl groups where the relation between the dihedral angle ϕ and the center to center distance between the overlapping cavities is easily obtained from the geometry of butane:

$$r = \frac{b_0}{3} [20 + 4 \cos \phi]^{1/2} \quad (14)$$

The coefficients of a polynomial expansion for $\ln y(r)$ for two overlapping cavities of diameter 4.5 Å separated by a distance r are listed in Table II of reference 11. They were used to construct the solvent modified rotational potential for butane; the gas phase and solvent modified potentials are compared in Fig.1. It is clear from the figure that the main difference between the two potentials is a stabilization of the gauche states in the solvent with respect to the gas phase. The differences in energy between the trans and gauche states in the gas and solvent phases are respectively 0.70 kcal/mole and 0.16 kcal/mole. Butane will tend to be more compact in water than the gas phase. Trajectories on the solvent modified potential surface lead to very different equilibrium and kinetic properties of butane as compared with the gas phase potential. The equilibrium and kinetic properties of the solvent and gas phase butane systems are examined in detail in Section III.

In order to simulate the trajectories of heptane and eicosane in water a solvent potential of mean force between non-bonded methyl groups must replace the Lennard-Jones interaction. The potential of mean force is simply related to the pair correlation function (12):

$$\text{solvent} \\ V(r) = -kT \ln g(r) \quad (15)$$

Although g cannot be found exactly for a Lennard-Jones system, an established result from fluid perturbation theory is that g , for a Lennard-Jones system, is approximately equal to g° the pair correlation function for a system of particles interacting through the repulsive portion of the Lennard-Jones potential. Methods have been devised to relate g° to the pair correlation function of a hard sphere system which can be calculated analytically (13). Using these approximations Pratt and Chandler express the potential of mean force between non bonded methyl groups in water as:

$$\text{solvent} \\ V(r) = -kT \ln y(r) + U_o(r) \quad (16)$$

$$U_o(r) = V^{\text{gas}}(r) + \epsilon \quad (\text{for } r \leq 2^{1/6} \sigma) \\ = 0 \quad (\text{for } r > 2^{1/6} \sigma)$$

In Fig.2 the gas phase Lennard-Jones potential between methyl groups is compared with the solvent potential of mean force. The solvent potential is slightly more attractive at the minimum (-0.38 kcal/mole) than the Lennard Jones potential (-0.30 kcal/mole). The minimum in the potential energy occurs at a smaller interparticle separation for the solvent potential (3.9 Å compared with 4.15 Å). At larger separations the attraction is more quickly screened in the solvent than in the gas phase. The construction of $y\{r\}$ is computationally time consuming outside the hard sphere diameter because a Fourier inversion is required at each point. Therefore for the heptane and eicosane trajectories the solvent potential was calculated once by Fourier inversion:

$$y(r) = \frac{\text{hard sphere}}{1 + \frac{1}{2\pi^2 r}} \rho_w \int_0^\infty dk k \sin kr \left\{ \hat{C}_{Aw}^2(k) \times [1 + \rho_w h_{ww}(k)] \right\} \quad (17)$$

ρ_w is the water density, $h_{ww}(k)$ is the structure factor for water and the direct correlation functions $\hat{C}_{Aw}(k)$ are given in Ref. 11, Table I. The final form of the solvent potential of mean force Fig. 2 was then fit to a sum of the first five normalized La Guerre polynomials. This functional form is a good fit to the potential of mean force out to 6 Å and remains slightly more repulsive than the solvent potential at greater interparticle distances. Butane trajectories were generated using both the gas phase and solvent modified rotational potentials. Heptane and eicosane trajectories were constructed using the solvent modified potentials.

IIC. Description of Trajectories Recorded at CECAM

The bond lengths and angles of the alkane chains were respectively 1.523 Å, and 111.3°. A van der Waals radius of 1.85 Å was used for the extended atom methyl groups. Each extended atom group along the chain was considered to be a point center of frictional resistance with a simple Stokes law friction constant.

$$\beta = 6\pi\eta a \quad (18)$$

The viscosity of water, 0.01 poise was chosen for η and a was set equal to the van der Waals radius. Using these parameters $\beta = 3.45 \times 10^{-9}$ g/sec and the monomer momentum relaxation time $t = \frac{m}{\beta}$ is 6.67×10^{-15} sec. The monomer diffusion coefficient estimated from the Stokes Einstein relation is $D = 1.179 \times 10^{-1}$ Å²/psec. An intramolecular rotational diffusion constant about the central bond of butane was estimated from the rms change in dihedral angle during a trajectory performed with the rotational potential turned off. The intramolecular rotational diffusion constant was calculated to be $D = 2.72 \times 10^{-1}$ rad²/psec. Trajectories were constructed with varying time steps between 0.005 psec/step and 0.05 psec/step. Statistics extracted from butane trajectories on average coordinate and force changes per step are shown in Table I. The rms displacement per coordinate contains systematic and random components.

From Table I it can be seen that with the larger stepsize, on the average about 60% of the change in the rotational angle per step may be attributed to the stochastic turn. The fractional change in force (Table I) has contributions from the change in the magnitude of the force along the internal coordinate direction as well as from a change in the direction of the force vector. Most of the time butane is vibrating within $KT/2$ of the rotational potential minima ($|\Delta\phi| \leq 12^\circ$), so that the curvature of the potential in this region gives the dominant contribution to the change in force per step. The slope of the potential surface is more constant further from the potential minimum, changing by 17% between $\phi = 14^\circ$ and $\phi = 34^\circ$, for example.

Part of the motivation for simulating the diffusive dynamics of alkane chains was to prepare for an application of these methods to amino acid sidechain motion in proteins. In an effort to study the effect of increasingly hindered rotational motion about dihedral angles successively closer to a main polypeptide chain, a heptane trajectory was recorded during which three sequential atoms in the chain were kept stationary. There are four dihedral angles in heptane and if three end atoms remain stationary, motion about the dihedral angles becomes increasingly restricted. Motion of four atoms contributes to a change in the dihedral angle at the unrestricted end of the molecule, while the dihedral angle closest to the restricted end of the molecule can only change as a result of the motion of a single atom. The equilibrium and kinetic properties of this hindered rotational model of heptane are compared with the completely flexible heptane trajectory in this report.

Table II contains a summary description of each of the trajectories recorded at CECAM. Ten nanoseconds of the butane trajectory required 15 minutes cpu time on the CIRCE IBM 370/168 computer, while 1.6 nanoseconds of the eicosane trajectory required 40 minutes cpu time.

III. Results and Discussion

In this section the equilibrium and kinetic properties obtained from the butane heptane and eicosane trajectories are reported. Particular emphasis is placed on the butane simulations because it is a relatively straightforward task to calculate the equilibrium distribution of rotational states as well as transition rate constants from the butane rotational potential. These predicted values may then be compared with the results of the diffusive butane trajectories and thus provide important criteria for assessing the accuracy of the diffusive algorithm. In general, inaccuracy in the equation of motion will affect both equilibrium and dynamic properties of the system under study. It should be emphasized that the usual criteria employed to assess the accuracy of a full molecular dynamics trajectory involve the velocity distribution of the system and are not applicable to diffusive dynamics methods. It is therefore important that diffusive dynamics techniques, as they are being developed, be applied to the simplest systems where other means are available for calculating equilibrium and dynamic properties which may then be compared with the simulation.

A. Distribution of Rotational States

The equilibrium distributions of butane rotational states in the gas and solvent phases are given by:

$$S(\phi) = \frac{\text{gas}}{\int_{-\pi}^{\pi} \exp(-V(\phi)/KT) d\phi} \exp(-V(\phi)/KT) \quad 19a$$

$$S(\phi) = \frac{\text{solvent}}{[\int_{-\pi}^{\pi} \exp(-V(\phi)/KT) y(\phi) d\phi]} \exp(-V(\phi)/KT) y(\phi) \quad 19b$$

where y is the cavity distribution function for the two cavity model of butane dissolved in water. The predicted equilibrium fractions of trans and gauche states in the gas phase at 25°C and in water at 25°C and 50°C are listed in Table III. The equilibrium fractions obtained by Boltzmann integrating the potentials (eqs.19) are compared with the value obtained from a simplified three state rotational isomeric model of butane; the two sets of values differ by about 10%. At 25°C in the gas phase, butane is 65% trans and 35% gauche ($K_{EQ} = 0.54$) whereas in water at the same

temperature butane is predicted to be 44% trans and 56% gauche ($K_{EQ} = 1.27$). It is interesting to note that the predicted fractions of trans and gauche states of butane in water are approximately the same at both 25°C and 50°C. The temperature effect on the gas phase distribution, which decreases the fraction of trans states with increasing temperature, is cancelled by the contribution of the solvent, for which the trans conformation becomes relatively more stable as the temperature is increased.

The butane rotational distributions are easily obtained from the dynamics trajectories by dividing the angular space into a large number of rotational states and counting the fraction of the total duration of the trajectory the molecule spends in a particular state. The rotational distributions evaluated from the butane trajectories are shown in Fig.3 and the fractions of trans and gauche states are listed in Table III. It is apparent from Table III, that the fractions of trans states and total gauche states obtained from each trajectory are in good agreement with the predicted equilibrium values. There are however differences between the predicted equilibrium distributions and the distributions extracted from the trajectories. A discrepancy between predicted equilibrium distributions and dynamics results is the fact that for trajectories 2-4 Table III equilibration between gauche + and gauche - states has not been achieved. An analysis of the linear phenomenological rate equations presented in Section B below indicates that close to equilibrium, relaxation of the non-equilibrium distribution between gauche + and - states is only about twice as slow as the relaxation of the distribution between trans and total gauche states. The first concern was to insure that this surprising lack of symmetry in the butane rotational distribution over such a long simulation was not an artifact of the integration algorithm, perhaps related to the method of satisfying constraints. A standard method used to check a full molecular dynamics simulation is to run it backwards in time and check to see if the particles retrace their paths. The Smoluchowski and Langevin equations of motion which determine the diffusive paths are not reversible in time. However, the butane potential is symmetric with respect to the origin ($\phi = 0$) and a diffusive trajectory started at this point should be reversible with respect to a change in the sign of the random displacements; both trajectories will of course correspond to spreading probability distributions. Fig.4 shows the distributions obtained from two such trajectories, each lasting 10 nanoseconds (200,000 steps). The distributions of trans, gauche +, and gauche - states obtained from these are $T = 47\%$, $G+ = 30\%$, $G- = 23\%$ and $T = 47\%$, $G+ = 23\%$, $G- = 30\%$. We therefore conclude that the asymmetry in the rotational distribution over the long simulation is not an artifact of the SHAKE method used to satisfy constraints. The problem of satisfying the ergodic hypothesis which equates a molecular dynamics time average with an equilibrium ensemble average is addressed at the end of this section.

The distributions of heptane rotational states extracted from the heptane diffusive dynamics simulations are listed in Table IV. By symmetry, the rotational distribution of ϕ_1 should equal that of ϕ_4 and similarly the distribution of ϕ_2 should equal ϕ_3 . We might also expect that trans conformations would be relatively less abundant at the ends of the chain because the sequence G+G- is energetically forbidden and gauche states are therefore less restricted at the ends of the heptane chain. As in the case of butane, perfect equilibrium is not achieved in the heptane trajectory. During the last 15 nanoseconds of the heptane trajectory, the distribution of trans states is approximately 50% while each gauche state occurs with a frequency of 25%. Each of the 4 heptane rotational distributions contains a larger percentage of trans states than observed in butane. This is probably due to the inclusion of a van der Waals term in the heptane potential which prevents non-bonded overlaps. The lack of exact symmetry among the distributions along the chain is an indication that equilibrium has not been achieved. The expected increase in the fraction of gauche states at the ends of the molecule is not observed but the effect is probably small enough so that errors in the distribution resulting from too short a trajectory are of the same size as the expected enhancement of gauche states. The distributions of heptane rotational states obtained from the ten nanosecond trajectory for which the first three atoms were held rigid are also reported in Table IV. The rotational distributions are very different from the completely flexible heptane trajectory. Inhibiting the motion of one end of the heptane molecule greatly decreases the rotational transition rates about all four rotational axes, and thus either a much longer dynamics trajectory must be constructed or special techniques used if equilibrium is to be reached for this system. Finally, the distribution of rotational states obtained from the 1.65 nanosecond eicosane trajectory are listed in Table V. The rotational states are distributed with trans and gauche isomers predominating in an alternating sequence down the chain. It is of interest to note that the fraction of trans conformers averaged over all 17 dihedral angles is close to the average number of trans conformers observed in the completely flexible heptane simulation.

When trying to account for any discrepancy between the predicted equilibrium distribution of polymer rotational states and the results of the simulations, the difficult question arises: how long must a molecular dynamics trajectory be run before the ergodic hypothesis is satisfied? This problem has been at least obliquely addressed in the recent literature. Ryckaert and Bellemans have reported a full molecular dynamics simulation of butane in butane (10, 14) over 14 psec at 291 K. The distribution of G+ and G- states averaged over the run is 35% G+ and 11% G-. The authors report that the initial distribution (64 molecules) contained an excess of G+ states which was not corrected during the simulation despite the fact the duration of the simulation is comparable to the predicted relaxation time of the non-equilibrium G+,G- distribution.

These authors also report equilibration between G^+ and G^- states is not achieved during a 19 picosecond simulation of 27 decane molecules at 481°K. Recently, Weber (15) has reported the results of a simulation of liquid butane (100 molecules) at several different temperatures and densities. Unfortunately the distribution between G^+ and G^- states is not reported. Equilibration between trans and total gauche states is reported for 10 psec simulations at 315° and 745°K.

Perhaps more relevant to the interpretation of the "equilibrium" properties of the alkane simulations conducted at CECAM are the recent reports of diffusive Langevin simulations of single polymer chains by Helfand (16) and by Fixman (17). Although neither of these reports deals explicitly with the problem of reaching equilibrium, each author treats the problem implicitly in a different manner. Helfand has studied the dynamics of a single bistable oscillator and chains of such oscillators. Helfand calculates transition rates across a potential consisting of two quadratic wells separated by a quadratic barrier, using a variety of friction constants and barrier heights. Although the equilibrium properties of the Brownian oscillator simulations are not treated explicitly, it is possible to estimate the relative duration of the oscillator simulations. Each of the BBO trajectories was run for 2,000 transitions, where a transition was defined by passage from the bottom of one well to the bottom of the next. Using reported transition rates, the duration of a typical trajectory is about 3×10^6 steps and about 40 steps are required to diffuse from the bottom of one well to the bottom of the next in the absence of the barrier. For comparison with the alkane dynamics time scales it may be noted that using a step size of 0.05 psec, approximately 600 steps are required for butane to diffuse from the gauche+ to the gauche- rotational well in the absence of a barrier and the longest recorded trajectory lasted 8×10^5 steps. It is apparent that on a time scale which is determined by the physical extent of the barrier and the diffusion constant of the system, the number of steps that must be included in the diffusive trajectories of single polymer systems is very large indeed. An analysis of a few butane intra-molecular diffusional trajectories constructed with the potential turned off illuminated a major problem involved in attempting to establish an equilibrium distribution when following the dynamics of a single polymer chain. Fig.5 shows the distributions of three such diffusional trajectories lasting 1,000 steps, 10,000 steps and 100,000 steps (stepsize, 0.05 psec). For these simulations, reflecting barriers were placed at -180° and $+180^\circ$ to prevent the molecule from diffusing from gauche+ to gauche- conformations without passing through trans states. It is apparent that although the diffusional path determined by the Langevin equation (eq.8) represents a "typical" trajectory sampled from the distribution determined by the Smoluchowski equation, the two distributions may for many steps be very different. The solution to the one dimensional diffusion equation with reflecting boundary conditions is of course just a delta function at the initial time which spreads symmetrically about the origin, until a uniform distribution is obtained. From Fig.5 it can be seen that such a spreading distribution is better approximated the longer the single butane trajectory is run.

In an attempt to more efficiently establish equilibrium conditions, Fixman has combined Monte Carlo techniques with diffusive Langevin dynamics of a single polymer chain. The duration of the Fixman trajectories are only slightly longer than the longest relaxation time of interest in his polymer system (17), however many trajectories are run starting from a distribution of initial conditions established by Monte-Carlo methods. For example, when studying the dynamics of a 20 unit chain, Fixman chose 200 different starting conformations and ran each trajectory for about 400 psec (17). Finally it should be pointed out that it is not always necessary to "achieve equilibrium" when studying the dynamics of a particular process using simulation techniques. Rather ingenuity is required in order to combine statistical sampling methods with dynamics techniques so that conformations which are important in determining the rate of a process being studied are correctly accounted for in the simulation.

B. Kinetic Properties of the Alkane Simulations

A correlation function approach (18) has been employed to probe the dynamics of the diffusive alkane trajectories. Again, particular emphasis has been placed on studying the butane dynamics because simple chemical reaction rate theory arguments may be used to predict rate constants for butane isomerization. Most of the kinetic processes discussed in this section involve relatively large reorientations of the alkane chains, and the relaxation times for these motions are very long compared to the monomer momentum relaxation times. We therefore expect a diffusive Langevin description of the motion to be an appropriate representation for the dynamics. The rate of decay of the correlation function $\langle \Delta\phi(t)\Delta\phi(0) \rangle$, where $\Delta\phi(t)$ is the change in the butane dihedral angle from zero at time t , has been evaluated from the butane trajectories. The correlation function decays to zero in less than 1 psec. From estimates of the natural frequency and moment of inertia of trans butane (see below)

the inequality $\left[\frac{\beta_{\text{rot}}}{I} \right]^2 > 4\omega^2$ is satisfied and the local oscillatory motion is predicted to be overdamped. The predicted relaxation time for this mode is $(\frac{\beta_{\text{rot}}}{I})/\omega^2 \approx 0.2$ psec. The remainder of this section is devoted to an examination of the much slower kinetic process involving isomerization along the butane, heptane, and eicosane chains.

The phenomenological rate equations for butane isomerization are:

$$\frac{dN_T}{dt} = -2K_{T \rightarrow G\pm} N_T(t) + K_{G\pm \rightarrow T} (N_{G+}(t) + N_{G-}(t)) \quad 20a$$

$$\frac{dN_{G+}}{dt} = -K_{G\pm \rightarrow T} N_{G+}(t) + K_{T \rightarrow G\pm} N_T(t) \quad 20b$$

$$\frac{dN_{G-}}{dt} = -K_{G\pm \rightarrow T} N_{G-}(t) + K_{T \rightarrow G\pm} N_T(t) \quad 20c$$

Using expressions for the fluctuation in the number of trans molecules at time t from the equilibrium number and for the excess number of gauche+ over gauche- molecules:

$$\delta N_T(t) = N_T(t) - \langle N_T \rangle \quad 21a$$

$$\delta N_{G+}(t) = N_{G+}(t) - \langle N_{G+} \rangle \quad 21b$$

$$\delta N_{G-}(t) = N_{G-}(t) - \langle N_{G-} \rangle \quad 21c$$

$$\delta N_T(t) + \delta N_{G+}(t) + \delta N_{G-}(t) = 0 \quad 21d$$

the rate equations may be solved for the decay of these fluctuations:

$$\delta N_T(t) = e^{-(2K_{T \rightarrow G\pm} + K_{G\pm \rightarrow T})t} \cdot \delta N_T(0) \quad 22a$$

$$\delta N_{G+}(t) - \delta N_{G-}(t) = e^{-K_{G\pm \rightarrow T}t} \left\{ \delta N_{G+}(0) - \delta N_{G-}(0) \right\} \quad 22b$$

The relaxation time for the fluctuation in the number of trans particles is

$$\tau = (2K_{T \rightarrow G\pm} + K_{G\pm \rightarrow T})^{-1} \quad 23$$

The problem now is to extract rate constants from the butane simulations. To determine the rate constant for the decay of $\delta N_T(t)$, the most straight forward approach is to count the total number of transitions out of the trans well and divide by the total duration of the simulation. However, this is a very poor method to use for diffusive trajectories because frequently a molecule will recross the barrier several times before falling into one or another well. The diffusive motion about the transition state leads to an over estimate of the rate constant using this simple counting scheme; furthermore the rate becomes strongly dependent on the time elapsed between conformations included in the sample (see for example heptane isomerization rates determined by this method, Table VIII). We have evaluated butane isomerization rates via associated correlation functions (18) although recently a novel method has appeared which analyzes the problem in terms of first passage time statistics (16). Provided the phenomenological rate equations are approximately valid, the relaxation time can be obtained as an integral of an autocorrelation function:

$$C(t) = \langle \delta N_T(t) \delta N_T(0) \rangle \quad 24$$

$$(2K_{T \rightarrow G\pm} + K_{G\pm \rightarrow T})^{-1} = \int_0^{\infty} \frac{C(t)}{C(0)} dt \quad 25$$

The correlation functions evaluated from the 25°C butane trajectories using both gas phase and solvent modified potentials are shown in Fig.6. The correlation functions are fit well by single exponentials. In order to calculate both $K_{T \rightarrow G\pm}$ and $K_{G\pm \rightarrow T}$ from the trajectories another relation involving the rate constants is required and we have used the detailed balance condition

$$\frac{\langle N_T \rangle}{\langle N_{G+} \rangle + \langle N_{G-} \rangle} = \frac{K_{G\pm \rightarrow T}}{2K_{T \rightarrow G\pm}} \quad 26$$

The butane isomerization rate constants obtained from the trajectories are listed in Table VI. The reciprocals of the rate constants vary between 70 psec and 156 psec. The rates of trans \rightarrow gauche and gauche \rightarrow trans isomerization are both somewhat faster at 50°C than at 25°C using the solvent modified potential despite the fact the equilibrium constant is approximately the same at the two temperatures. The trans \rightarrow gauche isomerization rate is faster in the solvent than in the gas phase and the back reaction rate slower. In order to compare the diffusional dynamics results with reaction rate theory butane isomerization must be idealized as transmission over a barrier of a single particle in a one dimensional potential coupled to a heat bath. Then Kramer's theory (20) may be used to estimate the steady state diffusion flux across the barrier. The reaction rate out of well A across a transition state (TS) barrier is just the diffusion flux at the transition state divided by the number of particles in well A. Assuming the particles are nearly Boltzmann distributed in energy, the diffusion current at the transition state j_{TS} and the number of particles in well A, N_A are:

$$j_{TS} = D \frac{n_{TS}}{L_{TS}} = \frac{KT}{\beta} \frac{n_0 e^{-\Delta E^*/KT}}{\int_{-\infty}^{\infty} dx e^{-m\omega_{TS}^2 x^2/KT}} \quad 27$$

$$N_A = n_0 \int_{-\infty}^{\infty} dx e^{-m\omega_A^2 x^2 / KT} \quad 28$$

n_0 is the concentration of particles at the bottom of well A, n_{TS} is the concentration of particles in the region of the transition state, L_{TS} is the region over which n_{TS} changes appreciably, ΔE^* is the activation energy and ω_T and ω_A are the natural frequencies of motion close to the bottom of the well and at the inverted barrier. In terms of these quantities the Kramers reaction rate is:

$$K^{\text{Kramers}} = \frac{\omega_A \omega_{TS}}{2\pi} \left(\frac{m}{\beta}\right) e^{-\Delta E^* / KT} \quad 29$$

For the butane isomerization problem ω_{trans} and ω_{TS} were evaluated by estimating a rotational force constant and approximate moment of inertia about a rotational axis through the center of mass parallel to the central bond of butane for the trans and transition states. These calculated parameters are listed in Table VII. In the diffusional regime the reaction rate decreases as the inverse first power of the friction coefficient. Eyring, transition state theory (21) may be used to calculate the rate constant in the regime where the friction is small so that the particles stream rather than diffuse over the top of the barrier. In the Eyring theory, the flux across the barrier is just the velocity in the positive direction averaged over an equilibrium distribution of velocities times the density of particles near the top of the well

$$K^{\text{TST}} = \frac{j_{TS}}{N_A} = \frac{KT}{h} \frac{Z^*}{Z} e^{-\Delta E^* / KT} \quad 30$$

where z^* and z are the partition functions of the activated complex and reactant; h is Planck's constant. For the one dimensional quadratic barrier the high and low temperature transition state rate constants are:

$$K_{\text{classical}}^{\text{TST}} = \frac{\omega_A}{2\pi} e^{-\Delta E^*/KT} \quad 31a$$

$$K_{\text{semi-classical}}^{\text{TST}} = \frac{KT}{h} e^{-\Delta E^*/KT} \quad 31b$$

The Kramers estimate of the rate constant is smaller than transition state theory by the factor $\omega_{\text{TS}}/(\beta/m)$. Table VI lists the Eyring and Kramers predicted rate constants for butane isomerization along with the values extracted from the simulations. The rates predicted by the diffusional model are about 5 times smaller than the classical transition state values. The rate constants extracted from the diffusional trajectory are in reasonably good agreement with the Kramer's theory. The rate constants obtained from the small time step trajectory, surprisingly, are exactly equal to the Kramer's theory values, whereas the other rate constants are somewhat smaller than predicted by a simple "diffusion over the barrier" model. The discrepancy (5% - 30% difference between rates calculated from the Kramers theory and rates obtained from the simulation) is not large considering the fact that butane is not a one dimensional system and isomerization involves both rotational and translational motion of the methyl groups. It is interesting to compare the effect of the differences in the shape of the gas phase and solvent modified potentials. Of course the activation energy enters into the rates exponentially and thus dominates any differences between the rates on the gas phase and solvent modified potential surfaces. The activation energy for a trans \rightarrow gauche reaction is 0.15 kcal/mole smaller in water than in the gas phase and thus the rate is expected to be enhanced in water. However, the width of the rotational barrier is larger in the solvent and thus collisions at the top of the barrier are more effective in retarding the rate. This effect enters into the calculation of the pre-exponential factor ($\omega_{\text{TS}}^{\text{gas}}/\omega_{\text{TS}}^{\text{solvent}} = 1.17$) and therefore is not as important

as the differences in the activation energy. Finally with regard to a comparison between rates calculated from the trajectories and rates calculated from reaction rate theory it is important to realize that the equation of motion used to simulate the dynamics is diffusional and it is expected these rates will be much closer to Kramer's theory than Eyring transition state theory regardless of the value used for the monomer friction constant. Recently, the problem of calculating the rate across a barrier has been examined using a kinetic equation approach (22). These authors show the diffusion controlled picture is accurate when

$\left[\frac{\beta}{m\omega_{TS}} \right] > 1.5$. For the present simulations $\left[\frac{\beta}{m\omega_{TS}} \right] \approx 5.6$ and a diffusional model of isomerization is appropriate for this set of parameters

The number of transitions along the heptane chain and the relaxation times obtained by dividing the duration of the simulation by the total number of transitions are shown in Table VIII. When conformations separated by 0.1 psec are included in the sample the average relaxation time is estimated to be about 30 psec whereas when 5.0 psec intervals between conformations are used the relaxation time is closer to 160 psec. Use of a large time mesh to sample the trajectory avoids counting transitions occurring very close together which essentially occur during a "single" transition. Relaxation times obtained using the 5.0 psec mesh are much closer to the rates that would be obtained from a correlation function analysis. There is apparently more mobility about the outer 2 dihedral angles than the central ones. Using the simple counting scheme, the relaxation times for isomerization of ϕ_1 , and ϕ_4 are 130-140 psec whereas for ϕ_2 and ϕ_3 the relaxation times are estimated to be between 170-180 psec. When three atoms of the heptane chain are immobilized, rotational mobility is dramatically reduced. During the 10 nanosecond trajectory for which the first three atoms of the chain remained stationary, there were ten times as many transitions about ϕ_4 as about ϕ_1 (122 transitions about ϕ_4 compared with 11 about ϕ_1). Furthermore, the mobility does not increase proportionally along the chain moving away from the restricted end. Rather ϕ_4 , which is defined by the four atoms that are permitted to move is considerably more mobile than the other three dihedral angles. One measure of rotational mobility is obtained from the correlation function $\langle \cos(\phi(t) - \phi(0)) \rangle$. Plots of this correlation function for each of the dihedral angles of heptane obtained from the 10 nanosecond hindered motion trajectory are shown in Fig.7. The relaxation times obtained from an exponential fit to the correlation function about the most mobile rotational axis ϕ_4 is about 100 psec which is close to the relaxation time obtained for the same dihedral angle when all atoms of the chain are allowed to move. It is hoped that studying hindered rotational models in more detail will be helpful in the interpretation of experiments that probe reorientation about multiple rotational axes, where motion about some of those axes is severely restricted.

The number of transitions about each of the rotational axes of eicosane during the 1.65 nanosecond simulation is listed in Table V. It is interesting to note that the average relaxation time for transitions along the chain is estimated from Table V to be about 150 psec, which is very similar to the rotational relaxation times in heptane. The central dihedral angles do not appear to be less mobile than the dihedral angles closer to the end of the chain. It is clear though from looking at the way the transitions along the eicosane chain are distributed that Monte Carlo and dynamics techniques will have to be combined in order to sample the dynamics of eicosane over an equilibrium distribution of rotational states.

Finally, it should be pointed out that although the diffusive alkane simulation results are internally consistent with respect to the choice of empirical parameters employed for the simulations, no information about the validity of phenomenological subsystem-heat bath coupling parameters can be obtained from an equation of motion derived from an already reduced Hamiltonian. While it is known that Stokes law is useful in the description of a wide range of hydrodynamical problems, the use of a simple Stokes monomer friction coefficient for the simulation of alkane dynamics in water should be considered only as an initial choice of a coupling parameter. A more refined estimate of the friction coefficients for the polymers awaits further work with both Brownian and full molecular dynamics approaches to the problem.

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TABLE I: SAMPLE^a STATISTICS OF BUTANE TRAJECTORIES

TIME STEP:	POTENTIAL ON		POTENTIAL OFF	
	$\Delta t = 0.005$	$\Delta t = 0.05$	$\Delta t = 0.005$	$\Delta t = 0.05$
RMS DISPLACEMENT/COORDINATE ^b	0.028	0.086	0.027	0.084
RMS FORCE/STEP	1.48	1.75	0	0
RMS FRACTIONAL CHANGE IN FORCE/STEP	0.36	1.11	0	0
RMS CHANGE IN ROTATIONAL ANGLE/STEP	3.0	10.6	3.0	9.7

a) Obtained from 5,000 step trajectories for $\Delta t = 0.05$ and 20,000 steps for $\Delta t = 0.005$.

b) Displacements in Å; force in Kcal/(mole-Å); angles in degrees.

TABLE II: TRAJECTORIES RECORDED AT CECAM - SUMMER 1978

ALKANE	POTENTIAL	TEMPERATURE ^a	TIME STEP ^a	COORDINATES SAVED/ DURATION ^b
Butane	Solvent	25	0.005	1 psec/7 nsec
"	"	"	0.05	0.1 psec/1 nsec 1 psec/40 nsec
"	"	50	"	1 psec/20 nsec
"	Gas Phase	25	"	1 psec/20 nsec
Heptane	Solvent	25	0.05	0.1 psec/6 nsec 5.0 psec/15 nsec
"	Solvent 3 Atoms Rigid	"	0.025	0.1 psec/1 nsec 1.0 psec/10 nsec
Eicosane	Solvent	25	0.025	0.5 psec/150 psec 1.0 psec/1.5 nsec

a. Temperature in degrees centigrade; time step in picoseconds.

b. At each step indicated the rotational and non-bonded potential energy were saved as well as Cartesian coordinates and dihedral angles.

TABLE III: DISTRIBUTION OF BUTANE ROTATIONAL STATES

	Gas Phase Potential 25°C			Solvent Potential					
	% Trans	G+	G-	25°C			50°C		
% Trans				G+	G-	% Trans	G+	G-	
Equilibrium Distribution a.)	65	17.5	17.5	44	28	28	43	27.5	27.5
b.)	62	19	19	40	30	30	38	31	31
<u>TRAJECTORY</u>									
1) Step size: 0.005 psec Duration: 7 nsec				45	27	28			
2) Step size: 0.05 psec Duration: 20 nsec	65	21	14						
3) Step size: 0.05 psec Duration: 1 nsec				48	23	29			
10 nsec				41	32	27			
40 nsec				41	36	23			
4) Step size: 0.05 psec Duration: 20 nsec							40	38	22

a. Calculated from full rotational potential using Eq.19.

b. Calculated from 3 state isomeric model.

TABLE IV: DISTRIBUTION OF HEPTANE ROTATIONAL STATES

		<u>% Trans</u>	<u>G+</u>	<u>G-</u>
<u>Solvent Potential - 25°C</u>				
a) First 6 nanoseconds	ϕ_1	55	37	08
	ϕ_2	34	39	27
	ϕ_3	47	32	21
	ϕ_4	36	34	31
b) Additional 15 nanoseconds	ϕ_1	55	22	23
	ϕ_2	48	26	26
	ϕ_3	50	25	25
	ϕ_4	49	25	26
<u>Solvent Potential - 25°C</u>				
3 Atoms Immobile 10 nanoseconds	ϕ_1	97	0.4	2.5
	ϕ_2	34	36	30
	ϕ_3	74	25	1
	ϕ_4	36	35	29

TABLE V: DISTRIBUTION OF EICOSANE ROTATIONAL STATES AND NUMBER OF TRANSITIONS

<u>Eicosane-Solvent Potential^a</u> <u>DIHEDRAL ANGLE</u>	<u>% TRANS</u>	<u>G+</u> <u>G-</u>		<u>NUMBER OF TRANSITIONS</u>		
		<u>TOTAL</u>	<u>G+</u>	<u>G-</u>		
1	78	0	22	18	4	5
2	32	0	68	19	0	10
3	57	0	43	12	0	6
4	38	0	62	15	3	5
5	100	0	0	2	1	0
6	25	21	54	25	6	7
7	97	1	2	9	2	3
8	21	12	67	8	1	3
9	99	0	1	15	1	7
10	25	72	3	10	3	2
11	100	0	0	0	0	0
12	4	0	96	3	0	2
13	100	0	0	2	0	1
14	35	33	32	11	3	3
15	94	6	0	14	6	1
16	9	91	0	11	6	0
17	71	29	0	17	7	2
\bar{x}	56	16	28	11		
σ	36	27	34	7		

a. Temperature 25°C. Timestep, $t=0.025$ psec, and every 1.0 psec saved. Duration, 1.65 nsec. The initial conformation was all trans.

TABLE VI. BUTANE ISOMERIZATION RATE CONSTANTS^a

REACTION RATE THEORY	GAS PHASE POTENTIAL 25°C		SOLVATION POTENTIAL			
	$(2K_{T \rightarrow G \pm})^{-1}$	$K_{G \pm \rightarrow T}^{-1}$	$(2K_{T \rightarrow G \pm})^{-1}$	$K_{G \pm \rightarrow T}^{-1}$	$(2K_{T \rightarrow G \pm})^{-1}$	$K_{G \pm \rightarrow T}^{-1}$
TST (semi-classical)	12	7	9	14	6	9
TST (classical)	22	12	17	22	12	16
Kramers (large friction)	104	56	98	124	58	77
TRAJECTORY	$(K_{T \rightarrow G \pm})^{-1}$					
1) Step size: 0.005 psec Duration: 7 nsec			99	121		
2) Step size: 0.05 psec Duration: 20 nsec	132	71				
3) Step size: 0.05 psec Duration: 40 nsec			108	156		
4) Step size: 0.05 psec Duration: 20 nsec					70	105

a. Reciprocal of the rate constant in picoseconds.

TABLE VII. PHYSICAL PARAMETERS OF TRANS AND TRANSITION STATE BUTANE

	GAS PHASE TRANS		POTENTIAL TRANSITION STATE		SOLVENT TRANS		POTENTIAL (25°C) TRANSITION STATE	
Rotational Force Constant K_{ϕ}	1.628×10^1	6.894			1.500×10^1			5.056
Moment of Inertia I	1.510×10^1	1.232×10^1						
Frequency ω	2.124×10^{13}	1.531×10^{13}			2.039×10^{13}			1.311×10^{13}

Rotational force constant kcal/(mole - rad²), moment of inertia, (grams-Å²)/mole;
frequency radians/sec.

TABLE VIII: HEPTANE KINETICS

TRAJECTORY	NUMBER OF TRANSITIONS				$\frac{\text{psec}^{(a)}}{\text{TRANSITION}}$	τ (b)	
	Angle	Total	G+	G-		(psec)	
1) Heptane; solvent potential 25°C Duration: 1 st 6 nsec i) 0.1 psec between records ii) 5.0 psec between records	i) ϕ_1	208	70	34	29		
	ϕ_2	204	55	47	29		
	ϕ_3	270	74	47	22		
	ϕ_4	199	58	42	30		
	ii) ϕ_1	49	18	7	122		
	ϕ_2	33	10	7	187		
	ϕ_3	38	10	7	157		
	ϕ_4	41	10	11	146		
	2) Heptane; solvent potential 25°C Duration: additional 15 nsec 5.0 psec between records	ϕ_1	117	26	33	128	94
	ϕ_2	86	18	26	174	134	
ϕ_3	83	21	21	181	148		
ϕ_4	100	25	29	142	108		
3) Heptane; solvent potential 25°C; 3 atoms rigid Duration: 10 nsec 1.0 psec between records	ϕ_1	11	3	3	909		
	ϕ_2	33	9	8	303		
	ϕ_3	40	11	10	250		
	ϕ_4	122	31	30	82	101	

a. Duration of trajectory/total number of transitions.

b. Obtained from exponential fit to $\langle \cos(\phi(t) - \phi(o)) \rangle \sim e^{-t/\tau}$.