

# Simulation of Conformational Dynamics with the MM3 Force Field: The Pseudorotation of Cyclopentane

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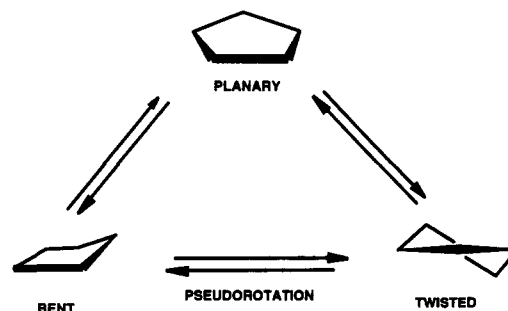
Received October 7, 1992

**Abstract:** A conformational molecular dynamics simulation of cyclopentane has been carried out for 100 ps at room temperature. The conformational interconversion through the pseudorotational pathway was found to be the only conformational motion observable during the simulation. The energetics of the pseudorotational motions match well with the previous predictions of energy minimization studies. Through the energy component analysis, the origin of the lack of a barrier to the pseudorotational pathway was clearly identified. On the kinetic aspect of the pseudorotational motion, an average time cycle of 0.2 ps for pseudorotation was calculated. This time cycle has been estimated on this order of magnitude experimentally. Our study offers a concrete example of the capability within, and accuracy achieved by, the conformational dynamics simulation of organic molecules during the MM3 force field.

## I. Introduction

The conformational dynamics of cyclopentane has received considerable attention ever since Kilpatrick, Pitzer, and Spitzer proposed the concept of pseudorotation from a thermodynamic analysis of the cyclopentane system.<sup>1</sup> Over the last 40 years, a large body of experimental data from infrared and Raman spectroscopy, and from X-ray crystallography, has proved the existence of pseudorotation, and provided valuable information about the energetics and kinetics of cyclopentane dynamics.<sup>1-8</sup> A number of computational formulas were proposed to describe the pseudorotation.<sup>1,7,10</sup> Both *ab initio* and force field methods have been applied to study the energetics of cyclopentane.<sup>9-16</sup> As a result of these investigations, it was found that the interconversions between the bent and twisted conformations of cyclopentane are through the pseudorotational pathway (Figure 1). There are no significant barriers along this pathway.<sup>4</sup> The pseudorotation of cyclopentane takes place on the picosecond or subpicosecond time scale.<sup>2,4,5</sup>

The pseudorotational motion in cyclopentane conformational dynamics arises from the coherent movement of the atoms imposed



**Figure 1.** The two possible pathways for the interconversion between the bent and twisted conformations of cyclopentane. The interconversion through the pseudorotation pathway involves a concerted movement of all the ring atoms and is virtually barrierless. An alternative pathway for the interconversion involves a planar ring conformation as an intermediate. The barrier on this pathway was determined to be around 5 kcal/mol.

by the five-membered ring constraints. Because the five-membered ring would be highly strained if it were held in a planar conformation, the stable conformations are puckered. Two parameters, the puckering phase angle  $P$  and the puckering amplitude  $q$ , have been used to describe the deviation of cyclopentane from planarity.<sup>7</sup> The puckering phase angle  $P$  indicates which part of the ring is farthest from planarity. The puckering amplitude  $q$  was defined as the maximum distance of a ring atom from the plane of the ring, and was used to measure the magnitude of the deviation from planarity. The conformational energy of cyclopentane depends strongly upon the puckering amplitude but is relatively independent of the puckering phase angle.<sup>9</sup> In the five-membered-ring pseudorotational motion, the puckering amplitude  $q$  is kept at a constant nonzero value while the puckering phase angle  $P$  changes significantly, indicating that the deviation from planarity is passed around the ring. When the puckering amplitude was kept at a constant value, the conformational energetics were found to be constant, and, therefore, a barrierless pathway is available for the interconversion of the bent and twisted conformations.

The conformational dynamics of cyclopentane presents an interesting challenge to molecular dynamics simulations. It demands accuracy in both the force field and dynamic integration scheme. Even though the pseudorotational pathway is virtually barrierless, the endocyclic torsion angles change over the range of  $-50$  to  $50^\circ$  within a pseudorotation cycle.<sup>29</sup> This requires the

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 (1) Kilpatrick, J. E.; Pitzer, K. S.; Spitzer, R. *J. Am. Chem. Soc.* **1947**, *69*, 2483-2488.  
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 (10) Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354-1358.  
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force field to be able to accurately represent the whole potential surface of this system, especially the smooth barrierless valley along the pseudorotational pathway rather than only the local area around a minimum, as is the case for most local energy minimization studies. Additionally, the pseudorotational is an extremely fast motion with a rate estimated to be in the range between subpicoseconds and picoseconds. The dynamics integration scheme employed is required to be accurate enough so that the kinetic parameters produced are comparable to those observed experimentally. Most of the reported theoretical investigations on cyclopentane used either energy minimization or torsion driver techniques. These investigations were quite successful in characterizing the pseudorotational pathway and conformational energetics. However, the techniques used in those studies were not capable of carrying out a direct and rigorous simulation of the conformational dynamic process itself.<sup>18</sup> Thus, some fundamental questions of conformational dynamics, such as the pseudorotational velocity or time scale, were not previously answered.

We report in this publication a direct conformational dynamics simulation of cyclopentane using the MM3 force field. Our objectives in this study were 2-fold. First, the cyclopentane system is used to evaluate the usefulness and accuracy of molecular dynamics using the MM3 force field, in terms of conformational dynamics simulations of organic molecules. In a similar fashion, cyclopentane was used to evaluate a molecular mechanics calculation using the MM2 force field.<sup>11</sup> We will try to evaluate the dynamics simulations against the following criteria. First, we seek to find if the pseudorotational motion is produced as the natural result of the dynamics without any special treatment. We then seek to see how well the kinetic parameters of the pseudorotation, such as the pseudorotational velocity, calculated from this simulation compare with the experimental data. Our second objective is that, if the properties of the system calculated from simulation compare well with the experimental observables, we will seek the insight and details at the molecular level of this conformational motion by analyzing the dynamic trajectories. Through the energy component analysis, we seek to show the origins of the lack of barriers on a pseudorotational pathway for conformational interconversions. The dependence of the torsion, valence angle, and even the bond length on the pseudorotational motion will be examined. This information is useful for validating the predictions of the dynamic behavior of this system previously based solely on the energetic calculations. Furthermore, this simulation will provide insight into the conformational motion of this system in details that could not be obtained experimentally.

This study is part of our effort to rigorously evaluate the validity of molecular dynamics simulations with the MM3 force field. Recent progress provided us the necessary components for a rigorous study of this subject. The latest MM3 force field achieved a satisfactory level of accuracy in calculating vibrational frequencies that are directly relevant to the internal dynamics of molecular systems.<sup>19</sup> A molecular dynamics integration procedure was recently implemented with the MM3 force field.<sup>20</sup> On the experimental front, the recent publications by the Laane and MacPhail groups<sup>2-4</sup> on the vibrational spectroscopic studies of the conformational dynamics of cyclopentane provide relevant

dynamics information for us to make a direct comparison with the simulated results.

## II. Method

**A. Dynamics Simulation.** A direct simulation of the conformational dynamics of cyclopentane was carried out, using the leap-frog algorithm of Verlet as implemented in the MM3-MD computer program.<sup>20</sup> The initial geometry of cyclopentane was generated and optimized with MM3. The initial velocities were assigned according to a Maxwell distribution at the simulation temperature of 298 K. The temperature was kept constant around 298 K by coupling to an external thermal bath.<sup>21</sup> The time step for the dynamics integration was chosen to be 0.2 fs except for the cases where the coupling between the stretching motion of the carbon-hydrogen bond and the pseudorotational motion was examined. In that case, an extremely small time step of 0.02 fs was employed. This small time step would give 100 steps of integration for a cycle of C-H stretch.<sup>22</sup> There were no constraints applied to any internal coordinates, since the extremely small time step used allowed the full relaxation of the simulated system. The center of mass motion was removed every 100 steps of integration. The instantaneous, average, and fluctuation of energy, temperature, and geometry were calculated from the history file of the simulation. The frequency of sampling was every 0.2 fs for the motions related to the C-H stretching, and every 10 fs for other motions. Ten runs of lengths ranging from 10 to 100 ps each were carried out. A total of 50 000 conformations were collected for the statistical analysis. All of the simulations were performed on the SGI 4D series of computers using the UNIX version of the MM3-MD program.

**B. Data Analysis.** The simulation generated a large amount of data on the kinetics, energetics, and molecular geometries. We will describe here the methods we used for processing these data for the purpose of presenting the results in the most clear and understandable fashion.

**Calculation of the Pseudorotational Coordinates.** The major conformational motion of cyclopentane is pseudorotation. This motion has been described conventionally by two pseudorotation coordinates: the pseudorotation phase angle  $P$  for describing how the deviation from planarity passes around the ring, and the ring puckering amplitude  $q$  for describing the maximum deviation from planarity.<sup>7</sup> We did not use this special coordinate system for the dynamics simulation. Instead, the Cartesian coordinate system was used for defining geometry and integrating dynamics trajectories. This choice of coordinate system allowed us to simulate the conformational dynamics of cyclopentane using MM3-MD directly without any special tailoring for the cyclopentane system. However, for the purpose of analysis and display of the dynamics simulation results, it is better to use the pseudorotational coordinates ( $P$ ,  $q$ ), since this coordinate system gives a much more intuitive and pictorial description of the dynamic process. The connections between these two coordinate systems are the endocyclic torsion angles of the cyclopentane system. The pseudorotation phase angle  $P$  may be calculated from the five endocyclic torsion angles using the formulation of Altona and coworkers.<sup>7a</sup>

$$\tan P = \frac{(\theta_2 + \theta_4) - (\theta_1 + \theta_3)}{2\theta_5(\sin 36^\circ + \sin 72^\circ)} \quad (1)$$

where  $P$  is the phase angle for pseudorotation and  $\theta_i$  is the endocyclic torsion angle in degrees. The puckering amplitude  $q$  (in angstroms) is calculated from the maximum deviation of the endocyclic torsion,<sup>7b</sup>

$$q = \theta_m / 102.5 \quad (2)$$

where  $q$  is the ring puckering amplitude, and  $\theta_m$  is the maximum deviation of endocyclic torsion from  $0^\circ$ . We could calculate  $\theta_m$  as follows:

$$\theta_m = \frac{2}{5} \sqrt{(\sum \theta_j \cos \alpha_j)^2 + (\sum \theta_j \sin \alpha_j)^2} \quad (3)$$

where  $\alpha = 4\pi/5$  and the sum is taken from  $j = 0$  to  $j = 4$ .

**Calculation of the Pseudorotational Velocity.** The major objective of our simulation was to obtain kinetic information from the dynamics trajectories. The most important piece of kinetic information is the pseudorotational velocity. We calculated the root-mean-square average pseudorotational velocity as follows:

(21) Berendsen, H. J. C.; Postma, J. P. M.; van Gunsteren, A.; DiNola, A.; Haak, J. R. *J. Chem. Phys.* **1984**, *81*, 3684.

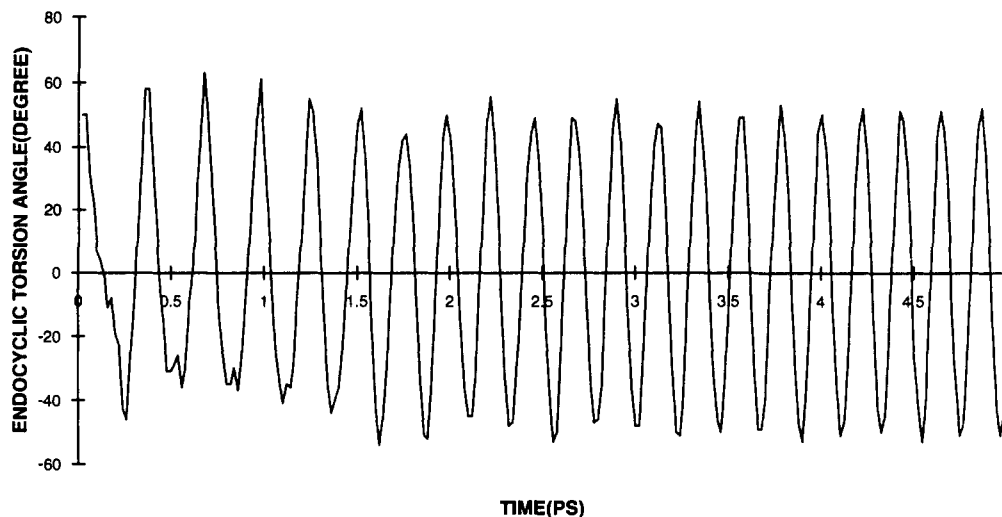
(22) The C-H stretching mode at  $3000 \text{ cm}^{-1}$  corresponds to a time scale of 2 fs per cycle.

(17) Harvey, S.; Prabhakaran, M. *J. Am. Chem. Soc.* **1986**, *108*, 6128-6136.

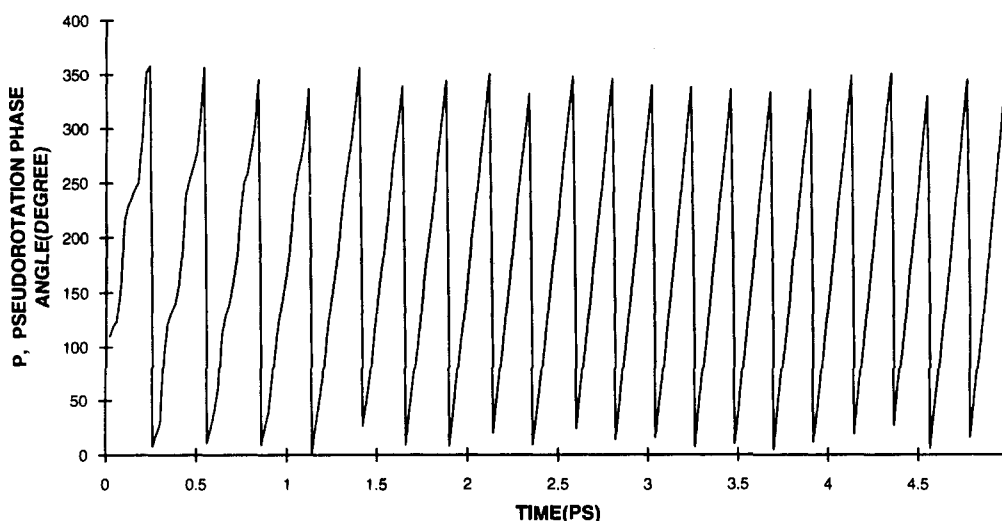
(18) There is no report on a direct simulation of the conformational dynamics of the cyclopentane system to the best of our knowledge. Harvey and Prabhakaran had reported a simulation of the pseudorotation of sugar ring system in DNA.<sup>17</sup> However, the pseudorotation in that system is a much slower motion, estimated to be on the nanosecond time scale. This is about three orders of magnitude slower than the cyclopentane system. MacPhail and Variaye used the molecular dynamics technique in the simulation of Raman spectrum of cyclopentane.<sup>2</sup> However, neither the objective of their study nor the information presented in their publication duplicates the results of our study.

(19) Lii, J. H.; Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8566.

(20) MM3-MD User Manual, Chemistry Department, University of Georgia.



**Figure 2.** The time course of a particular endocyclic torsion angle of cyclopentane over the first 5 ps of simulation. The significant changes in this torsion angle indicate that the conformational interconversion is taking place.



**Figure 3.** The time course of the pseudorotational phase angle  $P$ . During one cycle of pseudorotation, the value of  $P$  will go through 0 to  $360^\circ$ .<sup>30</sup> The periodic change in  $P$  clearly indicates the occurrence of pseudorotation.

$$V_{\text{rms}} = \sqrt{\sum_i (\frac{dP}{dt})_i^2 / N} \quad (4)$$

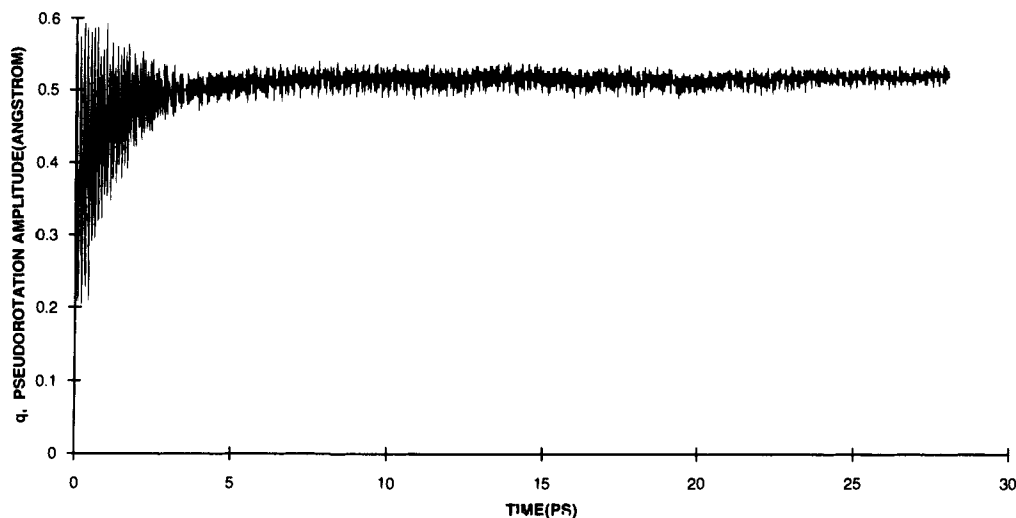
where  $V_{\text{rms}}$  is the root-mean-square average of the pseudorotational velocity,  $dP$  is the change of the pseudorotational phase angle within the increment of time  $dt$ , and  $N$  is the number of time increments.

### III. Results and Discussions

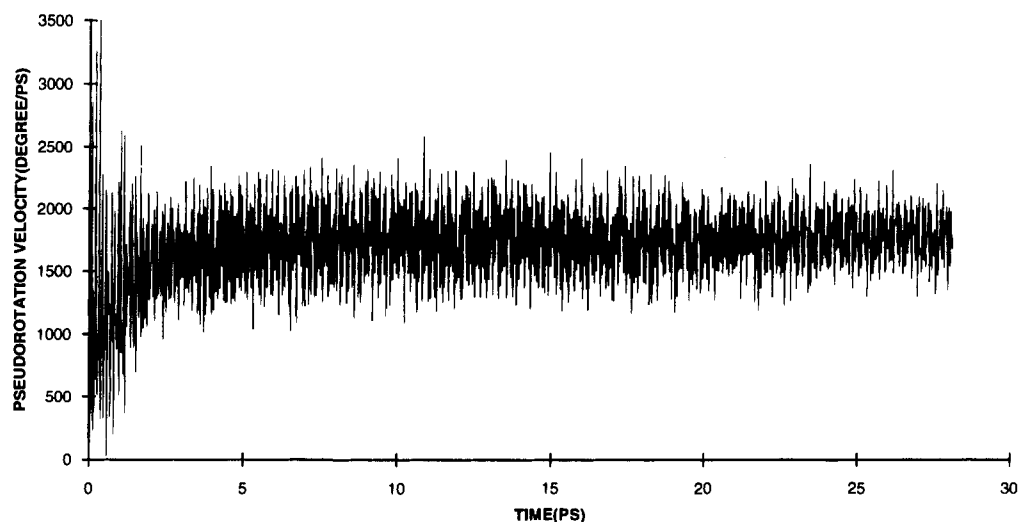
We will first demonstrate the validity of the dynamics simulation by showing that the pseudorotational motion was produced directly by the dynamics integration, and that this motion dominated the conformational dynamics of the cyclopentane system. Second, we will give an assessment of the accuracy of the dynamics simulation by comparing the calculated kinetic parameter of the pseudorotational motion with the one determined from the Raman spectroscopic study. We will then present a detailed analysis of the energetic and structural data generated by the dynamics simulation.

**A. Conformational Interconversion through the Pseudorotational Pathway.** The conformational dynamics of a molecular system consists of two major components, the local thermofluctuation around individual major conformational states and the interconversions between major conformational states. For cyclopentane, the major conformational states are the bent and twisted conformations. The interconversion between these conformations can take place either along the pseudorotational pathway or by passing over a more or less planar conformation

as a transition state (Figure 1). On the basis of numerous calculations and experimental observations, it was concluded that the dominant conformational motion in cyclopentane is pseudorotational, since the barrier to interconversion through the planar state has been determined to be about 5.5 kcal/mol, while that of the pseudorotation pathway is almost zero.<sup>4</sup> The dynamics simulation clearly supports this conclusion. In our dynamics simulation of 100 ps, we observed hundreds of cycles of pseudorotation, while the conformational interconversion through a planar conformation was not observed. It can be seen in Figure 2 that smooth interconversions between the bent and twisted conformations take place as the endocyclic angle changed with time.<sup>23</sup> The endocyclic torsion angle underwent 20 cycles of periodic changes in the first 5 ps.<sup>29</sup> The pseudorotational motion started almost immediately at the beginning of the molecular dynamics simulation with a velocity 2.5 cycles/ps. After about 5 ps of equilibrium, the speed of pseudorotation accelerated to 5 cycles/ps, and it continued for the rest of the 100-ps simulation. The conventional formalism for describing pseudorotation can also be used. We calculated the pseudorotational phase angle  $P$  and ring puckering amplitude  $q$  from the endocyclic angles as described in the Methods section. The time courses of  $P$  and  $q$  are shown in Figures 3 and 4, respectively. The continued change of  $P$  from 0 to  $360^\circ$  indicates that the maximum deviation from the ring plane is passed around the ring, while a constant value of  $q$  indicates that the pseudorotational pathway was closely



**Figure 4.** The time course of the puckering amplitude. The ideal puckering amplitude for the pseudorotation of cyclopentane system is about 0.48 Å. This value is reached and maintained after 5-ps equilibration. The nearly constant value after the initial 5 ps indicates that the pseudorotation pathways are closely followed.



**Figure 5.** The time course of the instantaneous pseudorotational velocity  $V$ . The value of  $V$  starts at around 200 deg/ps. During the first 3 ps, the value of  $V$  continues to increase even though large fluctuations are observed. It reached the value of 1700 deg/ps and stabilized around this value after 5 ps.

followed by the simulated molecular system. The puckering amplitude  $q$  was determined to be about 0.48 Å from Raman spectroscopic studies.<sup>4</sup> The average  $q$  calculated from the simulated molecular dynamics trajectory is about  $0.5 \pm 0.03$  Å. It has been clearly demonstrated (Figures 2–4) that the cyclopentane pseudorotational motion was reasonably well reproduced.

**B. Kinetics.** One of the most important kinetic properties of a pseudorotational process is the velocity with which the

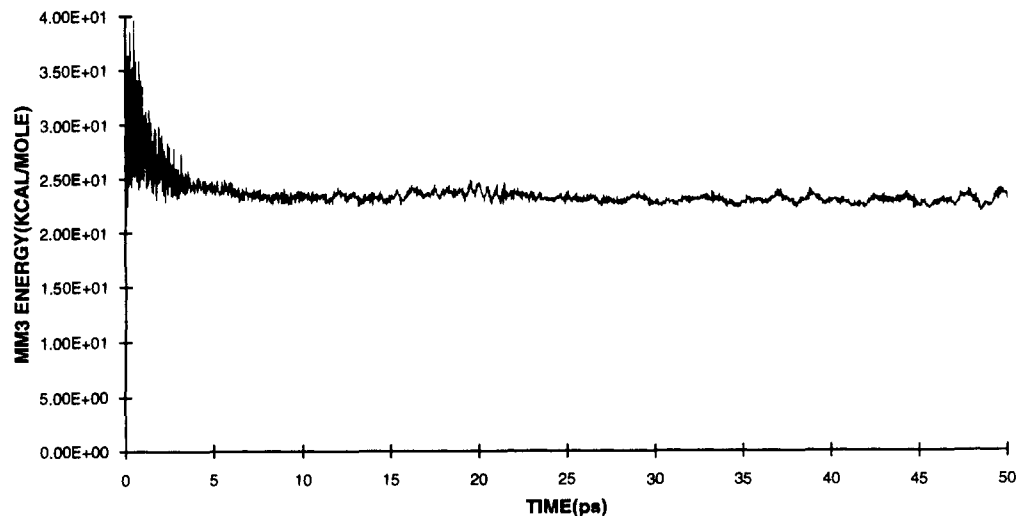
(23) A zero value of this torsion angle indicates a perfect bent conformation ( $C_2$ ), while a perfect twisted conformation ( $C_2'$ ) is reached when the value of this torsion is at  $-45$  or  $+45^\circ$ . The starting conformation was a twisted conformation. It went through a cycle of pseudorotation within the first 0.4 ps. Within this cycle, these torsion angles go through the 0 value twice and reach the  $-45$  once and  $+45$  once. This indicates four interconversions between bent and twisted conformations. Because the symmetric nature of the cyclopentane ring, all of the five endocyclic torsion angles went through similar changes. Thus, a total of 20 interconversions take place within one cycle of pseudorotation.

(24) The general energy functions of MM3 include more terms, such as  $E_{\text{dipole}}$  for the dipole–dipole interaction. For cyclopentane, the energies for all these additional terms are always zero according to the MM3-91 parameter set. Thus, these additional terms do not change the total MM3 energy of the cyclopentane system.

(25) In the two most recent publications on the calculation of the cyclopentane system, the MM2 force field was employed to characterize the energetics of the pseudorotation pathway. The calculation by Rosa, Cooper, and Laane<sup>11</sup> concluded that there is no barrier for pseudorotation within the limit of accuracy of the MM2 force field. The barrierless pathway for the conformational conversion of cyclopentane on the MM2 potential surface was further illustrated by Jaime using the torsion driver technique.<sup>11</sup>

pseudorotation take place. This can be expressed as the change in pseudorotational phase angle over time. The time course of the instantaneous pseudorotational velocity is plotted in Figure 5. The average pseudorotational velocity over the first 0.05 ps is  $340 \pm 230$  deg/ps. It increases quite rapidly to reach a value of  $1300 \pm 750$  deg/ps in the first 2 ps. As the simulation continues, the forces imposed on the atoms by the MM3 force field overcome the initial randomly assigned velocities, and the movements among the atoms become more coherent. The pseudorotational velocity increased to, and then stabilized at  $1650 \pm 330$  deg/ps. A total of 20 simulations starting with different initial structures have been carried out for 10 ps to explore the kinetic aspects of these dynamic pseudorotational processes. Although the initial pseudorotational velocity has a dependency on the initial structures and atomic velocities, all of the simulations converged to the same pseudorotational velocity ( $1700 \pm 300$  deg/ps) after a few picoseconds. This converged value represents the intrinsic pseudorotational velocity of a cyclopentane molecule in the MM3 force field at a constant temperature of 298 K.

A direct experimental determination of the cyclopentane pseudorotational velocity has not been reported. The experimental observable of pseudorotation which can be related to the kinetics of cyclopentane pseudorotation, is the reduced mass obtained from the Raman spectrum.<sup>4</sup> The pseudorotational velocity was estimated from this reduced mass. Strauss and co-workers<sup>5</sup>



**Figure 6.** The time course of the instantaneous potential energy. After the initial equilibration of 5 ps,  $E_{\text{pot}}$  stabilized around 25 kcal/mol. It remained at this value through out the entire course of simulation.

estimated a value of 400 deg/ps for the root-mean-square angular velocity of cyclopentane pseudorotation at 300 K. This estimation is based on an assumption that there is no significant energy barrier to pseudorotation. Thus, the pseudorotational velocity is determined by the kinetic energy as

$$\frac{1}{2}m_r\nu^2 = \frac{1}{2}kT \quad (5)$$

where  $m_r$  is the reduced mass for the pseudorotational mode of cyclopentane, and  $\nu$  is the root-mean-square angular velocity for pseudorotation.

In order to assess the accuracy of our dynamics simulations, we calculated  $\nu$  from the MM3-MD dynamics trajectory of cyclopentane to make a direct comparison with the data estimated experimentally. The average values of  $\nu$  were calculated to be 400 deg/ps over the first 0.05 ps and  $1700 \pm 300$  deg/ps over the entire course of our dynamics simulations. It is important to know if any part of our simulation is comparable to the experimental conditions under which the reduced mass of cyclopentane pseudorotation was determined.<sup>13</sup> The beginning part of our simulations corresponds to a short period of time following a random collision. During this period, the velocity of each atom has a high degree of randomness. The intrinsically favored motion, pseudorotation, does not have its optimal speed because of the counter forces from these random movements. After this period, the forces imposed on each atom by the MM3 force field overcome the randomness and force the atoms to move coherently. The pseudorotation is simultaneously accelerated to its intrinsic velocity. Since the time between molecular collisions in the gas phase of Raman experiments was estimated to be 200 ps,<sup>26</sup> it is reasonable that the average  $\nu$  over the entire 100-ps simulations should be chosen to compare with the experimentally estimated  $\nu$ , even though the value of  $\nu$  calculated from the initial phase of the simulations agrees better with the experimentally estimated value. Therefore, the kinetic parameter  $\nu$  calculated from our simulations is about four times larger than that estimated from experimentally determined reduced mass. We view this as a satisfactory agreement between the simulation and experiment, given the fact that both the simulation and the experimental estimation have limitations in terms of accuracy. It is difficult to put an error bar on the experimental estimation at this time. The reduced mass for cyclopentane pseudorotational motion was determined quite accurately<sup>4</sup> with an error of about 5%. However, the estimation of the pseudorotational velocity from the reduced mass involved making an assumption that no significant barrier exists along the pseudorotation pathway. There is no experimental evidence against this assumption. However, the possibility of existence of a small barrier could not be ruled out.<sup>4</sup>

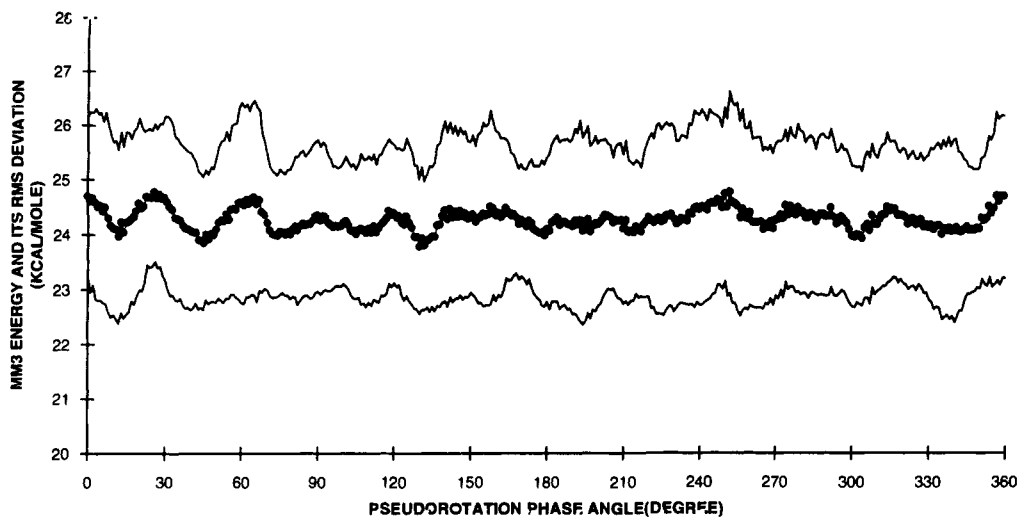
(26) MacPhail, R. A. Private communication.

**C. Energetics.** There are two issues that we would like to address in the energetic analysis of the simulated cyclopentane pseudorotation. The first is the conformational strain energy dependency on the pseudorotational phase angle. We examined the dependence of potential energies on pseudorotations by plotting the simulation time course of the potential energies. As can be seen in Figure 6, there is no barrier climbing observed during 50-ps simulations. One could argue that the large thermofluctuation of energies at room temperature can keep small barriers from being observed. To deal with the random thermofluctuation, we calculated the average potential energy and rms deviations of the energies, as a function of pseudorotation phase angles from the ensemble of conformations generated by the dynamics simulations<sup>27</sup> (Figure 7). The energy remained constant around 25 kcal/mol with a rms deviation of 2 kcal/mol. There are several regions in which the average potential energy and fluctuation have small peaks. The small deviations of the average energy from the base line in Figure 7 in these regions do not lead to any obvious pattern of dependency on the phase angle. Thus, we conclude that no significant barrier has been observed to pseudorotation in the dynamics simulations.

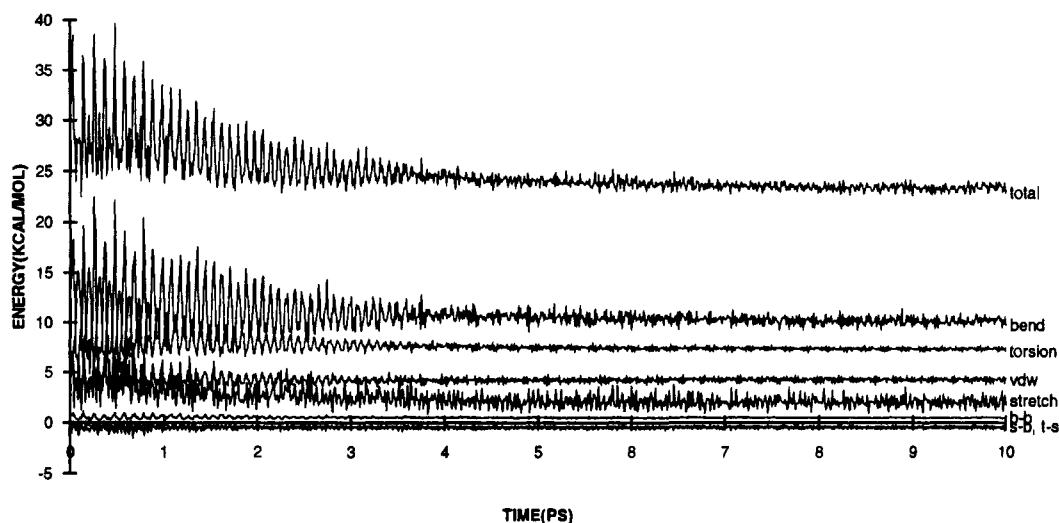
The existing experimental data on this subject also lead to a general conclusion that the potential energy of the system is virtually independent of pseudorotational phase angle, and that the barrier for pseudorotation is extremely low or nonexistent.<sup>1-8</sup> The most recent data on this issue came from a Raman spectroscopic study of cyclopentane.<sup>4</sup> Bauman and Laane concluded that there is no evidence for the existence of any barrier, except that barriers smaller than  $25 \text{ cm}^{-1}$  around the pseudorotation phase angles of 90 and 270° could not be ruled out. The theoretical calculations on the energetics of cyclopentane are generally in agreement with the experimental observations.<sup>25</sup> The energetic analysis based on our dynamics simulations provides further support for the general conclusion that the potential energy is independent of the pseudorotational phase angle, and the pseudorotation pathway is virtually barrierless.

The second issue on the energetic analysis of cyclopentane we want to address is the origin of the lack of barriers on its pseudorotation pathway. It is intriguing to see why the potential

(27) The dynamic simulation shows quite significant thermofluctuations at room temperature. To produce a representative picture of the pseudorotational motion, we took the average over several hundreds of cycles of pseudorotation. For the examination of the dependence of the potential energy on the pseudorotational phase angle, we calculated the potential energy and the pseudorotational phase angle for each of the conformations we sampled during the entire molecular dynamics simulation (amounted to 50 000). Then, for a given pseudorotational phase angle, the values of potential energy of all the conformations with this particular pseudorotational phase angle are averaged. The plot of this average potential energy over the pseudorotational phase angle represents the averaged behavior of the molecule over the several hundreds cycles of pseudorotation.



**Figure 7.** The average potential energy ( $E_{\text{pot}}$ ) is plotted against the pseudorotational phase angle  $P$ . The value of  $E_{\text{pot}}$  is the average<sup>31</sup> of the potential energies of all the conformations whose endocyclic torsion angles give rise to the corresponding  $P$ . The curve with solid circle marker is the  $E_{\text{pot}}$  curve. The curve about it is the average upper bound of the thermofluctuation in  $E_{\text{pot}}$  calculated as  $E_{\text{pot}} + \text{rms deviation}$ . Similarly, the curve below the  $E_{\text{pot}}$  curve is the lower bound.



**Figure 8.** The time course of the instantaneous potential energy and its components.  $E_{\text{total}}$  is the total potential energy. The other seven curves correspond to the seven components of total potential energy as show in eq 6. Note that the curves for stretch–bend energy and torsion–stretch energy overlap each other.

energy of cyclopentane remained constant while its ring geometry underwent significant changes from the twisted to bent conformation during the pseudorotation. The origin of this type of energy profile could be identified through energy component analysis. We decomposed the MM3 energies of cyclopentane into two levels of components.<sup>20</sup> At the first level, the total potential energy could be decomposed into terms of different types of intramolecular interaction energies as shown in the equation<sup>24</sup>

$$E_{\text{total}} = E_{\text{stretch}} + E_{\text{bend}} + E_{\text{torsion}} + E_{\text{vdw}} + E_{\text{stretch-bend}} + E_{\text{bend-bend}} + E_{\text{tor-stretch}} \quad (6)$$

The time courses of each of these components are plotted in Figure 8. It is apparent that the constant value of the total strain energy is not a result of compensations among these energy components, but rather each of these components itself maintains a constant value during the pseudorotation. If we focus on the torsion energy, it remains at a constant value throughout the course of pseudorotation. However, we know that the torsion angles change from  $45^\circ$ , passing  $0^\circ$ , to  $-45^\circ$ . There is a substantial barrier associated with the change of each torsion angle.<sup>20</sup> For the torsion energy to remain constant, the energy terms associated with each torsion angle must compensate each other almost exactly. A further decomposition of the strain energy was carried out such

that each term in eq 6 is decomposed to its components. For instance, the decomposition of the torsion energy term is given in:

$$E_{\text{torsion}} = E(\omega_1) + E(\omega_2) + \dots + E(\omega_j) + \dots + E(\omega_n) \quad (7)$$

where  $\omega_j$  is the  $j$ th torsion and  $n$  is the number of torsion angles in the molecule. The torsion energies of each of the five endocyclic torsions and summation of these five terms against the pseudorotational phase angle are plotted in Figure 9. The energy of each torsion angle changes significantly from a value of 0.0 to 0.6 kcal/mol, while the summation of these five energy terms remained at a constant value of 1.8 kcal/mol. The changes in the energies of the different torsion angles compensate each other. The compensation results in a constant value for the total torsion energy. The same behavior is observed for the energy terms associated with endocyclic valence angle bending and endocyclic bond stretching. It is the compensation among the energy terms at this lower level that makes the pseudorotational pathway free of barriers.

#### D. Cooperative Movement along the Pseudorotational Pathway.

The energy component analysis presented in the previous section clearly indicated that the cooperative movements among the internal coordinates are crucial for a pseudorotation pathway to be barrierless. In this section, we will take the advantage of a

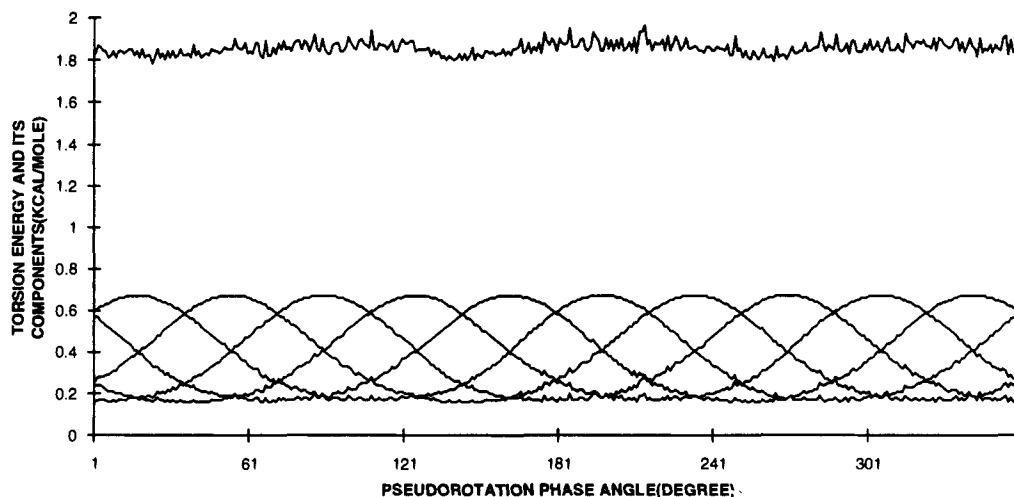


Figure 9. The compensation among the components of the torsional energy. Each data point is the average<sup>31</sup> over all the conformations that give rise to the corresponding  $P$ .

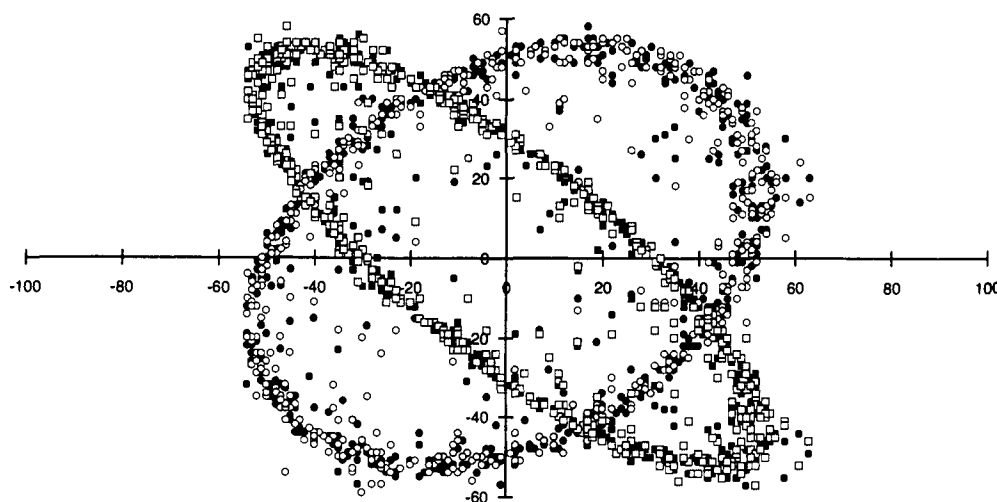


Figure 10. The coupling among the five endocyclic torsion angles. The values of four endocyclic torsion angles are plotted against the fifth one. The solid circle is for torsion 1, open circle for torsion 4, solid square for torsion 2, and open square for torsion 3. The conformations are sampled from the first 10 ps of simulation.

large amount of structural data generated from the dynamics trajectory to directly examine the cooperative intramolecular movement itself. The dependencies of the torsion, valence angle, and bond length on the pseudorotational phase angle will be examined.

It has been suggested that a conformational change in the cyclopentane ring would involve concerted changes of the five endocyclic torsion angles, since these angles are tightly coupled due to constraint posed by the ring structure. In Figure 10, we plotted four endocyclic torsion angles against the fifth endocyclic torsion angle calculated from the conformations sampled from the dynamics trajectories. The conformations used in Figure 10 are selected from the first 10-ps dynamics trajectory. The two ellipses represent a tight coupling among the endocyclic torsion angles, while the off-ellipse data points indicate a deviation from the pseudorotation. Most of the off-ellipse data points correspond to the first 5 ps of dynamics when a large thermofluctuation is observed as a result of the initially assigned velocities. As the simulation went on, the initial random velocities were overcome by the influence of the MM3 force field. The cyclopentane system then undergoes a smooth pseudorotation without much deviation, and more data points fall on the two ellipses. These plots clearly demonstrated that these five endocyclic torsion angles move quite cooperatively along the pseudorotation pathway.

The interdependence of the valence angles of cyclopentane on the pseudorotation is less obvious than that of the endocyclic torsion angles. Because of the ring restriction, the pseudorotation

of cyclopentane changes the ring geometry significantly and should inevitably have an effect on the valence angles. On the other hand, the valence angle bending motions are of higher frequencies than the pseudorotational motion. The time course of the values of the endocyclic valence angles did not give a clear picture of the puckering dependence, owing to the large thermofluctuation of the valence angle. However, the scatter plot of the valence angle over puckering phase angle based on a large number of conformations clearly showed a pattern of periodic dependence on the pseudorotational phase angle  $P$  (Figure 11). This type of periodic dependence of the endocyclic valence angle upon pseudorotation was previously observed in an energy minimization study<sup>28</sup> and in a dynamics simulation of the ribose ring in DNA.<sup>17</sup>

The dependence of the C-H bond stretching motions on pseudorotation is of significant practical interest. The C-H bond lengths of cyclopentane assume slightly different values when in axial and equatorial positions. The C-H bond is longer when it is at an axial position due to the steric repulsion of the 1,3 axial hydrogen atoms. The C-H stretching frequencies in deuterated cyclopentane (cyclopentane- $d_5$ ) show an extremely precise correlation with C-H bond length.<sup>2</sup> Since the pseudorotational

(28) Olson, W. K. *J. Am. Chem. Soc.* **1982**, *104*, 278-286.

(29) This endocyclic torsion angle underwent about 20 cycles of periodic changes in the first 5 ps. Each cycle corresponds to a complete cycle of pseudorotation. Because of the symmetry of cyclopentane, there are actually 20 interconversions between various bent and twisted conformations within each cycle of pseudorotation. Therefore, a total of 400 interconversions between bent or twisted conformations take place in the first 5 ps.

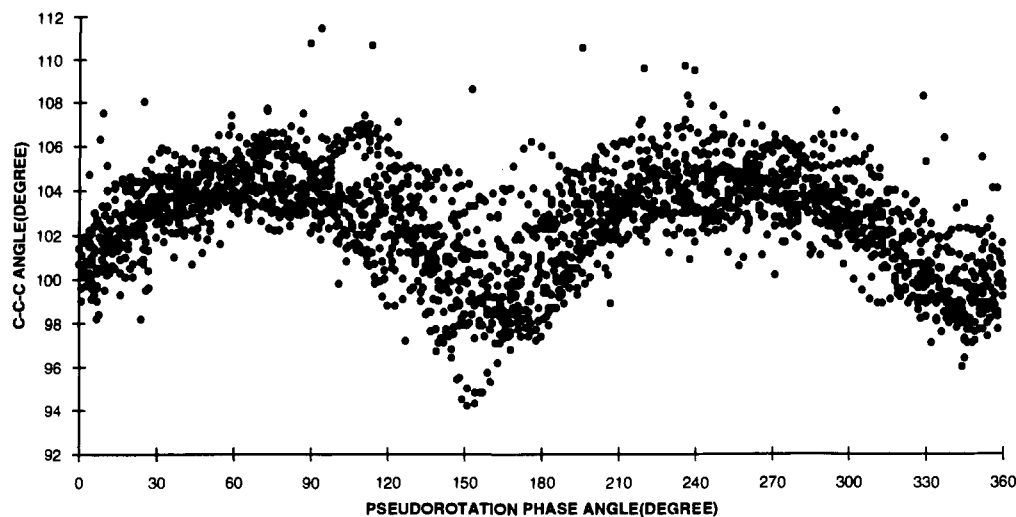


Figure 11. The periodic dependence of the endocyclic C-C-C valence angle on the pseudorotation phase angle  $P$ .

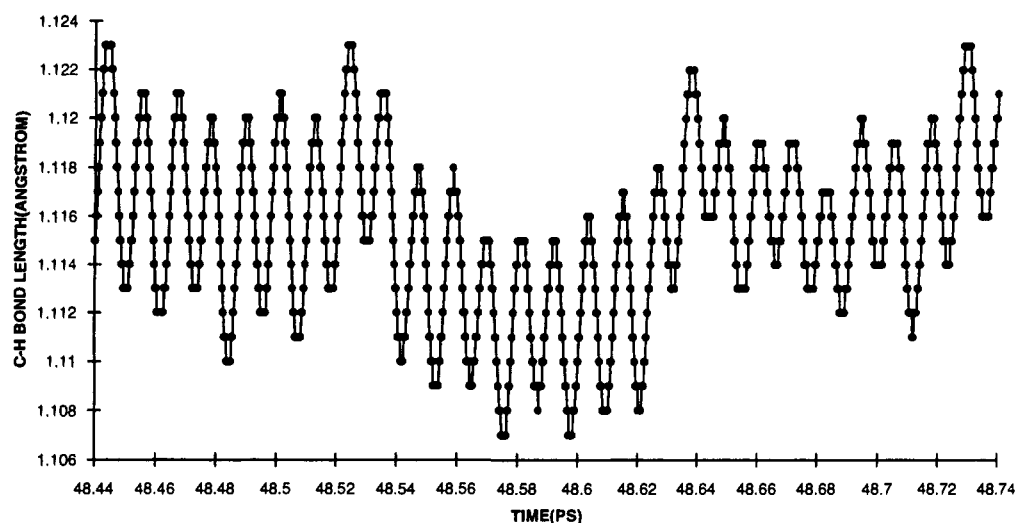


Figure 12. The time course of the C-H bond length over a time period during which an extremely smooth pseudorotation was maintained. It corresponds to 1.5 cycles of pseudorotation.

motion should cause the C-H bond in cyclopentane to rapidly change character from axial to equatorial, the C-H bond stretching band in the Raman spectrum has played a major role in probing the pseudorotation of the cyclopentane system.<sup>2-4</sup>

The coupling between the C-H stretching and pseudorotation presents itself as an interesting test case for molecular dynamics with the MM3 force field. The C-H stretching is extremely fast and is a local movement in terms of the changing molecular geometry, while the pseudorotation as a global movement involves significant conformational changes. The dynamics simulation has to sample not only the local movements with a high resolution, but also the global movements quite well. We used an extremely small time step of 0.02 fs for integrating the bond stretching motion, and the length of the simulation covers several hundreds of pseudorotation cycles. Figure 12 shows the time courses of the C-H bond length. During a cycle of pseudorotation, the hydrogen atoms spend half of the cycle around an axial position and the

other half around an equatorial position. The time cycle of the pseudorotation is around 0.2 ps. Thus the hydrogen atom should be at an equatorial position for 0.1 ps, then being converted to an axial position for 0.1 ps, and so on. As a consequence, the equilibrium length for a C-H bond should show a change every 0.1 ps. This type of periodic dependence of the equilibrium length of a C-H bond upon pseudorotation is clearly reflected in Figure 12. It could be observed during the time period when the pseudorotation is very smooth and thermofluctuation is small. However, a general pattern of the periodic dependence of the C-H bond length on the pseudorotation could also be observed in Figure 13. In this plot, the length of the C-H bond is calculated by averaging over all the conformations that have a specific  $P$  value. Thus, the experimentally observed coupling between the C-H bond stretching motion and pseudorotation is reproduced quite directly by this dynamics simulation.

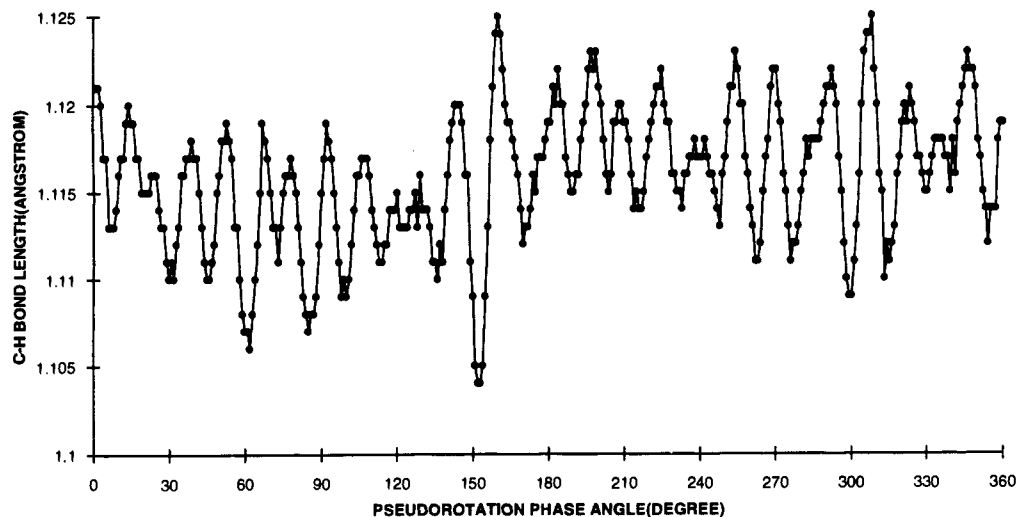
#### IV. Conclusions

The conformational dynamics of cyclopentane has been directly simulated using the conventional molecular dynamics method and the MM3 force field. The unique conformational motion, pseudorotation of cyclopentane, has been reproduced by this simulation. The simulated conformational changes followed closely the pseudorotational pathway. The five endocyclic torsion angles are tightly coupled with each other and move cooperatively throughout the dynamics simulation. It was found that the valence angle bending and C-H bond stretching are also coupled with the

(30) The relationship between the pseudorotational phase angle  $P$  calculated according to eq 1 and the pseudorotational motion is best depicted in Figure 3 of ref 7a. An interconversion between bent and twisted conformations takes place for every 18° change in  $P$ . The starting conformation of cyclopentane will be converted to its mirror image conformation when  $P$  changes from 0 to 180°, and the ring comes back to its initial conformation when  $P$  changes from 0 to 360°.

(31) The pseudorotational phase angle  $P$  of each conformation sampled from the dynamics trajectory was calculated from the five endocyclic torsional angles of this conformation according to eq 1. We separated the conformations into 360 groups according to the value of the pseudorotational phase angle of each conformation. For each group, we then calculated the average and rms deviation of potential energies of this group of conformations.





**Figure 13.** The coupling between C-H bond stretching and pseudorotation. Twenty thousand conformations sampled from the dynamics simulation were used to calculate the average C-H bond length for each value of  $P$ .

pseudorotational motion. The average time scale for the pseudorotational cycle was found to be about 0.2 ps. This time scale was previously estimated to be on the order of picosecond or subpicosecond, based on experimental data from vibrational spectroscopic studies of cyclopentane. The observed dependence of the valence angle bending and C-H bond stretching upon the pseudorotation in this simulation are also in good agreement with the Raman data. The energy component analysis based on the dynamic trajectories provided a straightforward answer to the interesting question of the origins of the lack of barriers on the pseudorotation pathway. The encouraging results from this straightforward simulation demonstrated the usefulness of MM3 force field molecular dynamics simulations for conformational dynamics studies of organic compounds. We have carried out

similar molecular dynamics simulations on various molecular systems in which the time scale of conformational changes range from a few picoseconds to the order of nanoseconds as part of our efforts to expand applications of the MM3 force field into molecular dynamics. We will report these simulations shortly.

**Acknowledgment.** We are grateful to Drs. J. Stevenson, J. Laane, and R. A. MacPhail for valuable discussions on Raman experiments of the cyclopentane. We would like to thank Dr. Wangkan Lin for his contribution in the development of MM3-MD program and Dr. W. W. Ogilvie for his advice on improving the manuscript. We express our gratitude to BioMega and Syntex for supporting this research project.