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Internal Dynamics of Flexible Molecules: Cyclohexane**

Anton Beyer[a] and **Peter Schuster**[b,*]

[a] Permanent address: Institut für Molekulare Pathologie, A-1030 Wien, Austria
[b] Institut für theoretische Chemie, Universität Wien, A-1090 Wien, Austria

Summary. The international motions of a single cyclohexane molecule are studied by molecular dynamics calculations. Classical trajectories are calculated by integrating Newton's equation of motion. The potential functions used are essentially the same as in Allinger's MM2 program which is widely applied for calculations on conformational energies of organic molecules.

Geometries and relative energies are reported for all stable low energy conformers and some transition states of cyclohexane. Vibrational frequencies of classical oscillations of individual bonds – computed for ethane as reference system – are close to the experimental values.

Two trajectories of the molecular dynamics of cyclohexane were simulated. In the first we were able to follow the process of ring inversion: chair → twisted forms → inverted chair. The reaction path is analysed in detail and compared with static approaches. The second trajectory shows the correlated reorientation of the possible twisted forms alone. This process is known as pseudorotation.

Keywords. Cyclohexane; Molecular dynamics; Pseudorotation; Ring inversion.

Interne Dynamik flexibler Moleküle: Cyclohexan

Zusammenfassung. Die inneren Bewegungen des isolierten Cyclohexanmoleküls werden mit Hilfe von molekulardynamischen Rechnungen untersucht. Durch Integration der Newtonschen Bewegungsgleichungen werden klassische Trajektorien erhalten. Die dabei verwendete Potentialfunktion ist im wesentlichen jene des Allinger MM2 Programms, welche vielfach zur Berechung der Konformationsenergien organischer Moleküle verwendet wird.

Die Geometrien und relativen Energien aller stabilen Konformeren und einiger Übergangszustände des Cyclohexanmoleküls werden angegeben. Die berechneten Vibrationsfrequenzen der klassischen Oszillationen einzelner Bindungen – berechnet am Beispiel des Ethanmoleküls als Referenzsystem – stimmen mit den experimentellen Werten gut überein.

Zwei ausgewählte Trajektoren der Molekulardynamik des Cyclohexans wurden näher betrachtet. Die erste beschreibt die Ringinversion: Sesselform → Twist-Bootform → invertierte Sesselform. Der Reaktionsweg wird im Detail analysiert und mit dem statischen Energieprofil verglichen. Die zweite Trajektorie beschreibt die korrelierte Umwandlung der verschiedenen Twist-Bootformen. Dieser Prozeß ist als Pseudorotation bekannt.

Introduction

The study of conformational changes in alicyclic organic molecules has been the subject of numerous theoretical and experimental investigations [1–5]. In contrast

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** Dedicated to Prof. Dr. Karl Schlögl

to these works almost no systematic studies of cyclic organic compounds by molecular dynamics (MD) methods were reported. One reason for this apparent lack of interest in the dynamics of medium size molecules may be seen in the striking success of molecular mechanics computations of equilibrium structures of organic molecules. Several potentials are available, one of the most popular among them is Allinger's MM2 force field [6].

Despite its extensive application to biopolymers and liquids the MD method was rarely used only in studies of small and medium size organic molecules. An investigation of the internal motions in α-*D*-glucose [7] may serve as an example. In this paper we present a study of the internal dynamics of the cyclohexane molecule in isolation. We use the MD method to calculate classical trajectories of all atoms of the cyclohexane molecule. The transition from one chair conformation to the inverted chair form and the pseudorotation of twisted forms are observed and analysed.

Another goal of this work was to test whether or not molecular mechanics potentials can be applied to MD calculations. It is well known that the MM2 potential and other comparable forcefields give excellent results for various minimum energy conformations and molecules in terms of bondlengths, bondangles and dihedral angles [8]. But the same need not be true for arbitrary conformations since the parameters have never been adjusted to an overall fit of the energy surface. We were able to show, however, that the dynamics of cyclohexane on the MM2 potential surface describes the molecular properties fairly well despite the fact that there may be regions of poor fit of the multi-dimensional energy surface.

Method of Computation

The potential and the parameters used are taken from Allinger's MM2 forcefield [6] which reproduces the experimental equilibrium geometry of cyclohexane very well. In order to be able to carry out MD calculations the MM2 potential had to be modified slightly. According to MM2 the contribution of a chemical bond between two bonded atoms i and k to the potential is given by equation (1),

$$V_{ik} = k \cdot (l_{\mathrm{ik}} - l^0_{ik})^2 - k' \cdot (l_{ik} - l^0_{ik})^3 \tag{1}$$

where k and k' are stretching parameters for a given bondtype, l_{ik} is the actual bondlength and l^0_{ik} is the standard bondlength for this bondtype. The cubic term on the right side of equation (1) represents a small correction near the minimum but leeds to an artifical breaking of the bond if l_{ik} is considerably greater than l^0_{ik} and thus the barrier heights turns out to be unphysically low for standard MM2 parameters. The cubic term improves the fit in the close neighbourhood of the global energy minimum but has a disastrous effect at large distances: $\lim_{l_{ik}\to\infty} V_{ik} = -\infty$. To avoid this difficulty we use only the first term of (1) in the bond potential. This is the only modification of the MM2 potential made in the MD calculation presented here. It has very little or practically no influence on the minimum energies and the corresponding geometries of the cyclohexane molecule (cf. Table 1).

The strategy applied in the MD calculations is as follows: we start from a conformation very close to an energy minimum, either local or global. At these geometries the forces at the individual atoms are less than 5–10 kJ/Å. Next we

Table 1. Calculated energies and equilibrium geometries and symmetry constrained geometries of some transition state conformations of cyclohexane. Allinger's MM2 force field was truncated to the harmonic terms (MM2/h). Original MM2 energy values are shown in parantheses. Distances are given in Å, angles in degrees (°) and energies in kJ/mol^{-1}

Atoms*	Conformation and symmetry				
	Chair	Boat	Twist		
	D_{3d}	C_{2v}	D_2	C_s	C_2
1–2	1.535	1.535	1.538	1.530	1.538
2–3	1.535	1.539	1.533	1.530	1.541
3–4	1.535	1.535	1.538	1.533	1.538
4–5	1.535	1.535	1.538	1.540	1.530
5–6	1.535	1.539	1.533	1.540	1.531
6–1	1.535	1.535	1.538	1.533	1.530
1–2–3	110.89	112.77	110.80	107.82	118.51
2–3–4	110.89	112.77	110.80	111.55	118.51
3–4–5	110.89	110.81	112.49	116.70	114.23
4–5–6	110.89	112.77	110.80	119.30	108.79
5–6–1	110.89	112.77	110.80	116.70	108.79
6–1–2	110.89	110.81	112.49	111.55	114.23
1–2–3–4	56.33	0.0	−63.98	64.42	−12.72
2–3–4–5	−56.33	52.51	30.81	−28.61	−8.37
3–4–5–6	56.33	−52.51	30.81	−7.01	49.30
4–5–6–1	−56.33	0.0	−63.98	7.01	−70.78
5–6–1–2	56.33	52.51	30.81	28.61	49.30
6–1–2–3	−56.33	−52.51	30.81	−64.42	−8.37
Energy	27.450	54.568	49.935	71.792	71.596
	(27.419)	(54.526)	(49.887)	(71.753)	(71.555)
ΔE	0.0	27.117	22.485	44.342	44.145
	(0.0)	(27.107)	(22.468)	(44.334)	(44.136)

* Bond length between two neighbouring carbon atoms ($\overline{C_iC_j}$), bond angles between three carbon atoms ($<C_iC_jC_k$) and dihedral angles between four carbonatoms [χ ($C_iC_jC_kC_l$)]

choose randomly oriented initial velocities for all atoms of the molecule, coresponding to a predetermined kinetic temperature. Then Newton's equations of motion (2) are integrated forward in time using a time step of 10–20 femtoseconds.

$$F_k = \left(\frac{\partial V(r_1, r_2, \ldots, r_i, \ldots, r_{3n})}{\partial r_i};\ i = 3k-2, 3k-1, 3k\right)$$
$$= m_k\left(\frac{d^2 r_i}{d t^2};\ i = 3k-2, 3k-1, 3k\right) \tag{2}$$

Herein the Cartesian coordinates of atom k are represented by the vector (r_i; $i = 3k - 2$, $3k - 1$, $3k$). F_k is the force acting on atom k ($k = 1, 2, \ldots, n$) and m_k is its mass. The calculations were performed without any constraints in bondlengths or angles, and in such a way that the concerted motions of all atoms in the molecule can be followed.

In the course of this work we developed a computer program for doing either molecular mechanics or MD calculations on medium size molecules. The highly modular program is able to perform several tasks, the most important are discussed here briefly.

- The first module manipulates molecular structures, choosing thereby between several potential functions and updating the corresponding set of parameters. Currently implemented are MMI, MM2, and a forcefield supplied by Rasmussen [9].
- Several minimization algorithms are available for calculating minimum energy structures: the steepest descent technique, the Newton-Raphson method and the conventional Newton procedure. First and second derivatives are calculated analytically. The formalism applied in our program has been described extensively by Niketic and Rasmussen [10]. In addition we introduced an option of minimizing the energy with several constraints on the molcular geometry. Common constraints are fixed bondlengths, angles and dihedral angles. These constraints are incorporated into the Newton-Raphson minimization algorithm by the method of Lagrange multipliers [11, 12].
- The MD module of the program uses the results of molecular mechanics calculations as input. Newton's equation of motion are integrated by means of a Verlet algorithm [13]. Several simple routines for analysing trajectories are included.

In part our program is based on various other molecular mechanics programs developed by Lifson (QCPE 254), Allinger (QCPE 395), and Rasmussen [9].

Results and Discussion

The discussion of the results obtained by the calculations reported here is split into two parts dealing with the static features of the multi-dimensional energy surface of the cyclohexane molecule and the dynamics simulated on it.

Molecular mechanics calculations on the cyclohexane ring have been carried out by many different groups starting with Hendrickson's pioneering calculations in 1961 [2]. A very compact and uniform treatment of the whole energy surface

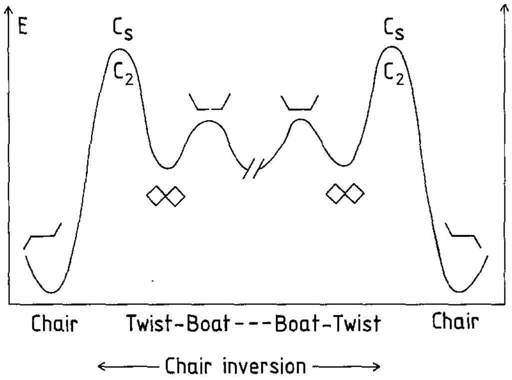

Fig. 1. Schematic cross section of the energy surface of cyclohexane. An energy profile for the interconversion of the two chairforms – called ring inversion – is shown. The height of the barriers separating the two chairforms and the twisted conformations is about 40 kJ/mol

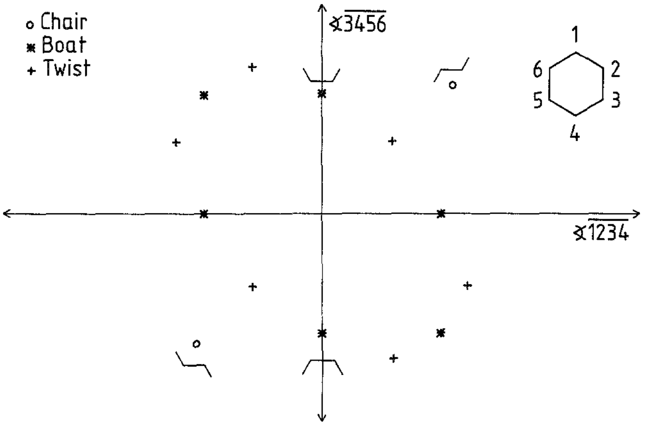

Fig. 2. Schematic sketch of a two dimensional characterization of different conformations of cyclohexane. Two dihedral angles are used as mapping parameters. Two chairforms and several boat and twisted forms are drawn

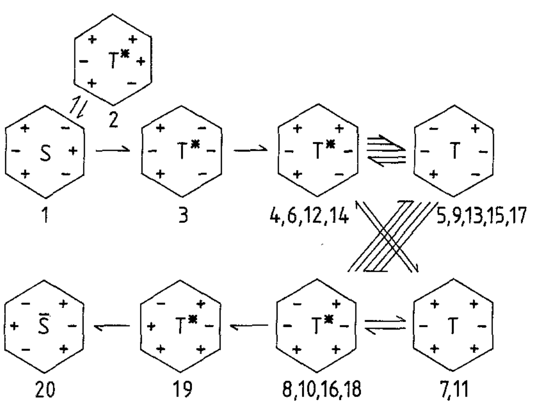

Fig. 3. A sketch of the reaction pathway following one trajectory of cyclohexane inversion. The sequence starts with the conformation denoted by 1 and follows increasing numbers until conformation 20 is reached. The part of the trajectory between conformations 4 and 18 involves only flexible conformations. Each step along the trajectory corresponds to a change of sign of one dihedral angle in the molecule

was given by Picket and Strauss in 1970 [8]. The global minima of the energy surface correspond to the two equivalent chair conformations. Cyclohexane is rather unique among the alicyclic ring compounds since it has a rather rigid minimum energy conformation which is free of geometric strain. Compared to the rigid chair forms twist and boat conformations are more flexible. These conformations are well above the global minimum and hence not easily accessible to experimental investigations. Nevertheless, a vibrational spectrum of the twistboat form of cyclohexane has been reported recently [14].

A schematic two-dimensional cross section of the energy surface which shows the various possible conformations is presented in Fig. 1. The absolut minimum corresponds to the rigid chair form. The various twisted forms are separated by a barrier of about 40 kJ/mol from the chair conformation. The boat conformations

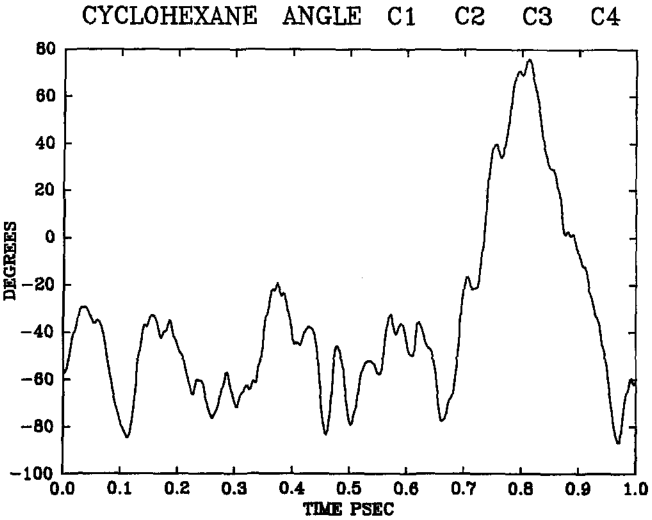

Fig. 4a

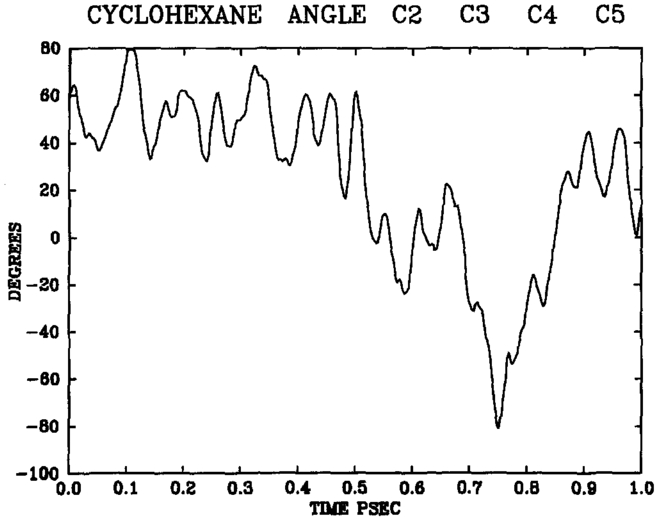

Fig. 4b

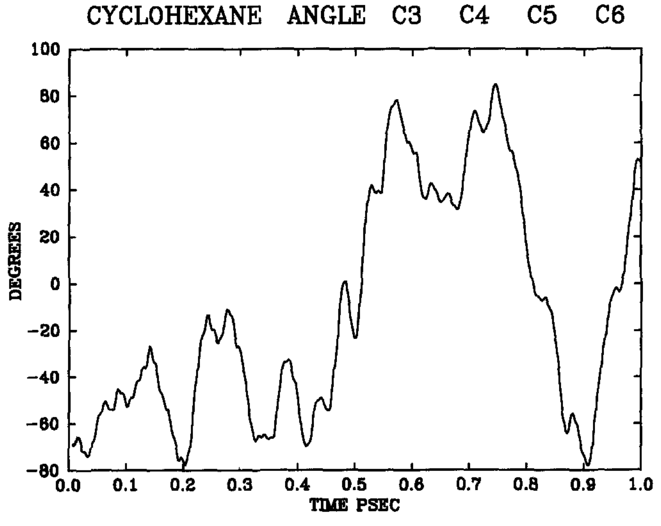

Fig. 4c

Fig. 4. Variation of three consecutive dihedral angles of cyclohecane during the inversion process. The full time range is one picosecond

are only slightly higher in energy than the twisted conformations and hence rapid interconversion between these conformations, commonly called pseudorotation, is possible at room temperature. During the process of chair inversion all equatorial and axial positions are interchanged. Many possible pathways for this process have been proposed [15]. Such pathways are usually constructed by a search scanning the multi-dimensional potential surface and looking for a possible minimum energy path between two conformations. To perform a search is no easy task, however, and various problems are encountered [8]. One goal of this contribution is to complement the static view by looking at the dynamic behavior of the molecule on the energy surface.

For our purpose conformational changes are best described by taking the torsional angles as variables. One possible description of ring geometries is given by the sequence of consecutive dihedral angles. In many cases it is enough to know the sequence of the signs of these angles. Dihedral angles are defined in the conventional way: a positive sign corresponds to clockwise rotation around the middle bond of the four consecutive atoms, the negative sign describes counterclockwise rotation.

Fig. 2 shows a schematic picture of the energy surface with two possible chairforms and several twist and boatforms in between. Two dihedral angles are used as mapping parameters.

Table 1 contains a summary of computed geometries and energies of different conformations and some transition states of cyclohexane. The data demonstrate that energy differences between the original MM2 potential and the modified version which neglects the cubic terms are very small indeed. No energy profile is given because there exist more conformations having essentially the same dihedral angles (1–2–3–4) and (3–4–5–6) which are chosen as variables for appropriate visualization in the diagrams presented here. An appropriate reaction coordinate would necessarily be an involved function of several angles.

In the rigid, minimum energy chair conformation of cyclohexane all torsion angles have the same absolute value of $\varphi \approx 57°$. It is characterized by complete alternation of signs in the torsion angles. During ring inversion all signs of the angles have to be changed. A flexible form is characterized by equal signs in two opposite ring positions (1 and 4, 2 and 5, or 3 and 6, respectively). The well known boatforms and all twisted forms belong to this class of conformations. The interconversion between the six twistboat and six boatforms is usually called pseudorotation. This process has been studied extensively. Since all conformations involved in pseudorotation have approximately the same energy – a fact which is reproduced well by the MM2 potential – rapid interconversion of twistboat conformations is possible at room temperature.

In order to make sure that the computed dynamics reflects the real process we computed the molecular dynamics of the ethane molecule with the MM2 potential. One motion can be easily identified with an – almost sinusoidal – variation of the CC bond length. Its wave number is $930\,\mathrm{cm}^{-1}$ and compares favourably to the experimentally observed value $993\,\mathrm{cm}^{-1}$ which is assigned to the CC bond stretching vibration [15].

One may distinguish between symmetric and asymmetric modes of inversion. In the symmetric mode one symmetry element is retained throughout the inversion process [16]. Fig. 3 shows a reaction path for the inversion as it was obtained in

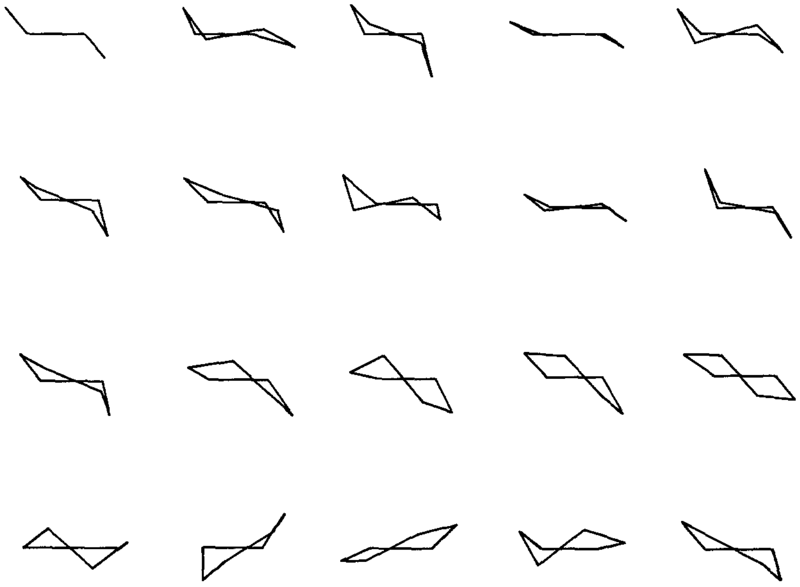

Fig. 5. Time resolved picture of the cyclohexane inversion. The time step between two consecutive frames is 0.05 picoseconds

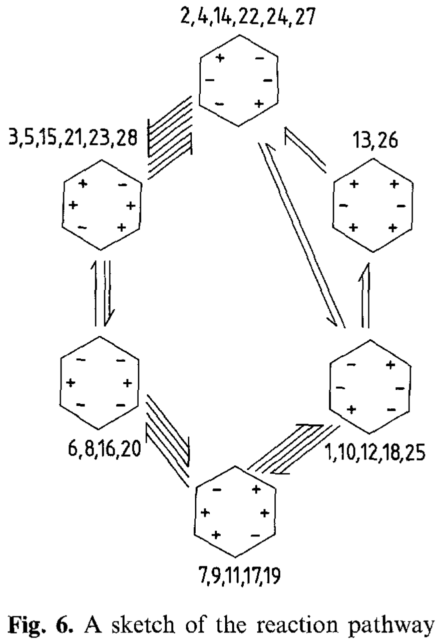

Fig. 6. A sketch of the reaction pathway following one trajectory of cyclohexane pseudorotation. The whole time range covered is 50 picoseconds

one trajectory of our simulations. Every change of one individual sign corresponds to one step in the sketch (individual conformations denoted by 1 to 20). The path obtained from the dynamic simulation corresponds to the asymmetric inversion as described in the literature [16]. The great flexibility of the twisted form is clearly seen in the sequence of pictures (step 4 to 18). The overall process in this region corresponds to pseudorotation. Fig. 4 shows the time-resolved behaviour of three

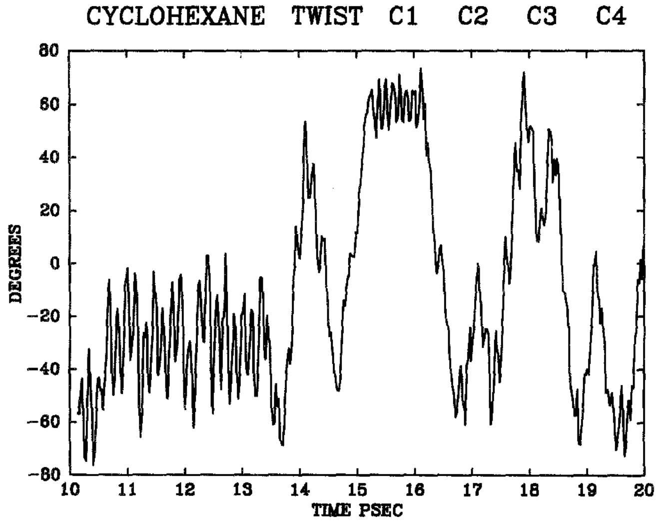

Fig. 7 a

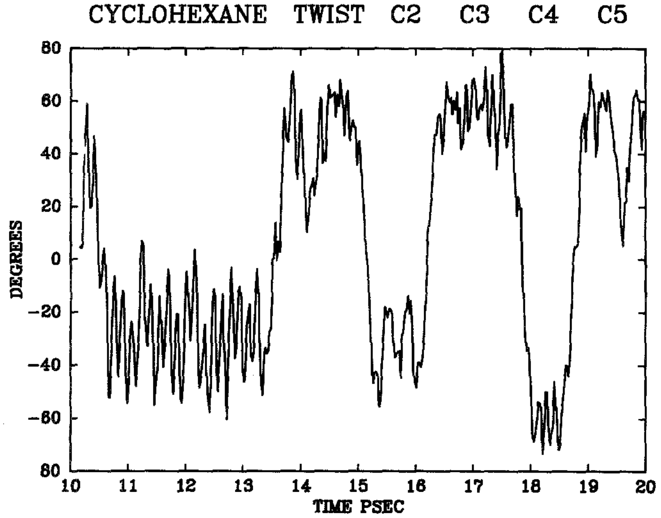

Fig. 7 b

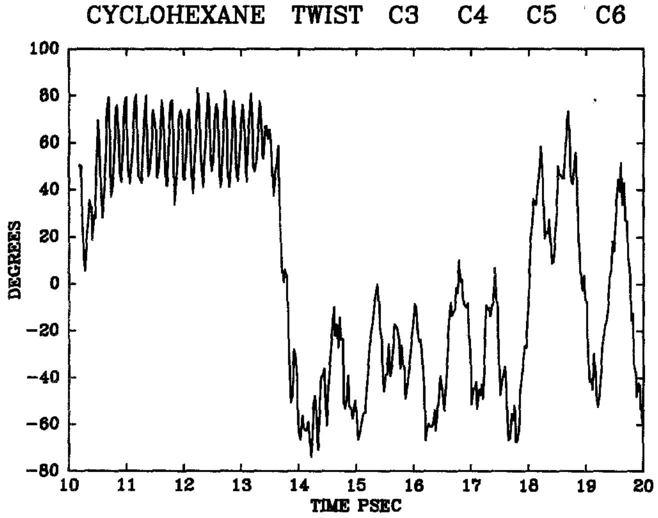

Fig. 7 c

Fig. 7. Variation of three consecutive dihedral angles during pseudorotation. The full time range is 20 picoseconds

consecutive torsion angles. One clearly sees a strong correlation between these angles. The overall time corresponds to one picosecond. A time-resolved picture of the inversion process is shown in Fig. 5. In this simulation we started from a chairform with enough kinetic energy to overcome the high barrier between chair and twist conformations.

The second simulation started from a twisted conformation with low kinetic energy – corresponding to low temperature – in order to keep the molecule inside the potential basin housing the different twisted conformations. The sequence of conformations obtained is comparable to that recorded in the first trajectory. It is shown in Fig. 6. Following the reaction path step by step yields an illustrative documentation of pseudorotation. The time covered by the figure is 50 picoseconds. Fig. 7 shows the variation of three consecutive torsion angles for an overall time of 20 picoseconds.

Concluding Remarks

Using the molecular dynamics (MD) approach we are able to follow the reaction path of an inversion of the chair conformation of cyclohexane. The process can be understood as a sequence of three steps: crossing the barrier separating the chair conformation from the basin of boat and twistboat forms, pseudorotation inside the basin and escape from the basin over the barrier leading to the inverted chair conformation. In a second simulation performed at lower average temperature we recorded a trajectory showing exclusively pseudorotation of the cyclohexane molecule. The results obtained fit nicely to the great amount of data available concerning the flexibility of the cyclohexane molecule.

Our MD calculations demonstrate the applicability of this approach to small and medium size organic molecules for which – in contrast to the great number of investigations on oligopeptides, oligonucleotides and proteins – there is an apparent lack of dynamical studies.

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