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Periodic orbits in biological molecules: Phase space structures and selectivity in alanine dipeptide

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Small and large molecules may localize their energy in specific bonds or generally in vibrational modes for extended periods of time, an effect which may have dramatic consequences in reaction dynamics. Periodic orbits offer the means to identify phase space regions with localized motions. The author demonstrate that techniques to locate periodic orbits developed for small molecules can be applied to large molecules such as alanine dipeptide. The widely used empirical force fields are employed and principal families of periodic orbits associated with local-type motions and emanated from the lowest energy minima and saddle points are investigated. Continuation of these families at high energies unravels the stable and unstable regions of phase space as well as elementary bifurcations such as saddle nodes. © *2007 American Institute of Physics*.
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I. INTRODUCTION

Many body complex systems are studied by two different approaches. Either by using statistical mechanics methods or by the systematic methods of nonlinear mechanics.[1] In the latter case, models of complex dynamical systems are explored by locating hierarchically classical mechanical stationary objects, such as equilibrium points (minima, maxima, and saddles of the potential function), periodic orbits and their bifurcations, tori, reduced dimension tori, as well as stable and unstable manifolds.[2] These multidimensional stationary objects reveal the structure of phase space and they assist us to understand and elucidate nonlinear effects. The progress of nonlinear mechanics in the last decades is immense and the mathematical theories and numerical techniques which have been developed are now powerful tools for the computer exploration of realistic systems.

Molecules are complex many-particle systems and they are usually studied by quantum and (semi)classical mechanical theories. Chemical reactions involve the break and the formation of chemical bonds after the excitation of the molecule at energies above potential barriers. The appearance of nonlinear phenomena, such as resonances and chaos, is inevitable and such phenomena have been observed spectroscopically.[3] Selectivity and specificity are well established concepts in elementary chemical reactions when the role of mode excitation in the reactant molecules and the energy disposal in the products are investigated. Triatomic molecules have been used as prototypes to develop theories as well as to build sophisticated experimental apparatus to study elementary chemical reactions at the molecular level and at the femtosecond time scales.[4] The small number of degrees of freedom in these systems has allowed a detailed analysis of the correspondence between quantum and classical theories.[5]

Studying larger molecules such as biological ones, the application of systematic methods becomes a challenge, since, not only more computer power is needed but also the development of concepts and techniques to extract the physics from the calculations. It is not surprising that up to now statistical mechanics methods have mainly been used, implemented either by averaging over phase space points or transition paths.[6] The latter method is promising for studying rare events in large dynamical systems. On the other hand, the systematic approach to explore polyatomic molecules is usually exhausted by the location of equilibrium points (minima and saddles), to be followed with the calculation of phase space averages.[7]

The hierarchical detailed exploration of the molecular phase space requires first the location of the equilibrium points of the potential function and then the location of periodic orbits (POs), the tori around stable POs, stable and unstable manifolds for the unstable POs, and even transition state objects such as the normally hyperbolic invariant manifolds.[8] Such a program has been implemented up to now to two and three degrees of freedom models for triatomic molecules.[9–11] This work has revealed the importance of periodic orbits in elucidating nonlinear effects in spectroscopy and the good correspondence between classical and quantum mechanics. They have also motivated the development of semiclassical theories.

Efforts to find localized motions in infinite periodic or random anharmonic lattices have led to the concept of discrete breathers.[12,13] The initial observations of localized motions in the work of Sievers and Takeno[14] triggered the discovery of significant mathematical theorems for the existence of periodic orbits in infinite dimensional lattices. However, most of the potential functions employed in the numerical studies were rather simple to describe realistic systems.

In this article, we apply the methods of locating POs that we have developed for small molecules to biological molecules, such as peptides described with empirical potential functions. Using the alanine dipeptide as a prototype system, we show how we can systematically trace regions in phase space where the trajectories stay localized in specific vibrational modes of a minimum or of a transition state. With continuation techniques we obtain families of periodic orbits for an extended energy range and we find elementary bifurcations such as saddle node and Hamiltonian-Hopf type.[15,16] In this way, the road is opened for investigating localization phenomena and selectivity in biological systems.[13,17]

II. COMPUTATIONAL METHODS

To locate periodic orbits in a dynamical system is equivalent of finding the roots of the nonlinear equations which describe the return of the trajectory to its initial point in phase space after the time period T. If $q_1, q_2, \ldots, q_N$ are the generalized coordinates of a dynamical system of N degrees of freedom and $p_1, p_2, \ldots, p_N$ their conjugate momenta, we define the column vector

$$\mathbf{x} = (\mathbf{q}, \mathbf{p})^{+}, \tag{1}$$

where + denotes the transpose matrix. Using $\mathbf{x}$ we can write Hamilton's equations of motion in the form

$$\frac{d\mathbf{x}(t)}{dt} = J\partial H[\mathbf{x}(t)] \quad (0 \leqslant t \leqslant T), \tag{2}$$

where H is the Hamiltonian function, and J is a $2N \times 2N$ dimension matrix which is used to define the symplectic symmetry of a Hamiltonian system

$$J = \begin{pmatrix} 0_N & I_N \\ -I_N & 0_N \end{pmatrix}. \tag{3}$$

0_N and I_N are the zero and unit $N \times N$ matrices, respectively. $J\partial H(\mathbf{x})$ is a vector field, and a matrix M which has the symplectic property satisfies the relation $JMJ^{+}=M$.

If $\mathbf{x}(0)$ denotes the initial conditions of a trajectory at time $t=0$, then this trajectory is periodic if it returns to its initial point in phase space after the time $t=T$

$$B[\mathbf{x}(0);T] = \mathbf{x}(T) - \mathbf{x}(0) = 0. \tag{4}$$

Thus, to find periodic solutions of period T, it is necessary to solve Eq. (2) subject to the two-point boundary conditions, Eq. (4).

The roots of Eq. (4) are usually found by iterative methods, such as Newton-Raphson, which require the examination of the time evolution of neighboring trajectories with respect to a reference one. Taking the difference of two initially neighboring trajectories in time, $\dot{\boldsymbol{\zeta}}(t)=\dot{\mathbf{x}}'(t)-\dot{\mathbf{x}}(t)$ and expanding it as a Taylor series with respect to $\mathbf{x}(t)$, the linear terms result in what is known as *variational equations* (VEs)

$$\dot{\boldsymbol{\zeta}}(t) = J\partial^2 H[\mathbf{x}(t)]\boldsymbol{\zeta}(t) \quad (0 \leqslant t \leqslant T), \tag{5}$$

where the second derivatives of the Hamiltonian with respect to coordinates and momenta of the reference trajectory are needed, and thus, they depend on the curvature of the potential function. The general solution of the linear equation [Eq. (5)] with time dependent coefficients can be expressed as

$$\boldsymbol{\zeta}(t) = Z(t)\boldsymbol{\zeta}(0), \tag{6}$$

where $\boldsymbol{\zeta}(0)$ describes the initial displacement from the reference trajectory $\mathbf{x}$, and Z is the *fundamental matrix*

$$Z(t) = \frac{\partial \mathbf{x}(t)}{\partial \mathbf{x}(0)}. \tag{7}$$

The fundamental matrix is also a solution of the variational equations as can be seen by substituting Eq. (6) into Eq. (5). In other words, Z satisfies the equation

$$\dot{Z}(t) = J\partial^2 H[\mathbf{x}(t)]Z(t). \tag{8}$$

Obviously, at $t=0$, Z is the unit $2N \times 2N$ dimension matrix and it can be integrated in time simultaneously with Hamilton's equations.

Solving the VEs helps us not only to locate POs but also to calculate the Lyapunov exponents which determine the stability of a trajectory. Particularly, for a periodic orbit of period T the fundamental matrix, $M=Z(T)$, is called *monodromy matrix* from the eigenvalues of which we can determine the stability of the trajectories around the periodic orbit. An initial displacement ζ_0 after k periods will become $\zeta(kT)=M^k\zeta_0$. Therefore, the eigenvalues of the monodromy matrix, μ, dictate the stability of the nearby trajectories in the linearized system. Usually, μ is written as

$$\mu = \exp(\lambda T). \tag{9}$$

For conservative Hamiltonian systems the eigenvalues of the monodromy matrix appear as complex conjugate pairs, (μ, μ^*), and one pair is always equal to 1.[18] When all eigenvalues lie on the unit complex circle (λ are pure imaginary numbers) the PO is stable. If one pair of eigenvalues lies on the real axis and out of the unit circle the orbit is singly unstable, if two pairs lie on the real axis the PO is called doubly unstable and so on. For systems with larger than two degrees of freedom it may happen four eigenvalues are out of the unit circle on the complex plane, $(\mu, \mu^*, \mu^{-1}, (\mu^*)^{-1})$. In this case we call the periodic orbit complex unstable.

Once we have located one member of the family of periodic orbits we can use continuation techniques[19] to find trajectories for different periods T. This is done by using T as the control parameter. Usually, for small increments of T linear extrapolation methods are sufficient. By varying T and thus the energy, the eigenvalues of the monodromy matrix move on the unit complex circle, collide, and may come out of the unit circle rendering the PO unstable and vice versa. At every period T for which one pair of eigenvalues becomes equal to 1, a bifurcation takes place and new POs are born.[20,21]

Powerful existence theorems for POs (Refs. 22 and 23) guarantee that the predicted bifurcations in the linearized system will also remain in the nonlinear system. From each minimum of a molecular potential energy surface we expect at least N stable families of periodic orbits, which are called principal or fundamental. They are associated with the N normal modes of the molecule. At a saddle point, the normal modes with pure imaginary eigenvalues (in phase space) give birth to principal families with unstable periodic orbits. The number of unstable directions is equal to the rank of

TABLE I. Energies in kcal/mol, the distance of the two nitrogen atoms in Å, and the harmonic frequencies in cm^{-1} for the 23rd and 24th normal modes of stationary points in the potential energy surface of alanine dipeptide.

	Energy	N–N distance	h.f. 23	h.f. 24
min1	−16.53	3.071	661.87	736.05
min2	−15.59	3.641	668.65	704.07
min3	−14.48	3.108	656.11	735.62
ts1	−15.00	3.566	655.12	700.66
ts2	−8.18	3.211	652.25	695.97
ts3	−7.91	2.900	654.32	713.00

instability of the saddle point. Admittedly, the well developed theory of periodic orbits and their bifurcations has converted the art of solving nonlinear equations [Eq. (4)] to science.

We use multiple shooting techniques and the algorithms and computer codes have been described in previous publications.[24] However, the challenge to extend these methods to many degrees of freedom systems such as alanine dipeptide [2-acetamido-*N*-methylpropanamide, $CH_3CONHCH(CH_3)CONHCH_3$], the molecule that we use in this study, and even larger biomolecules requires the adoption of new practices. We use Cartesian coordinates and empirical force fields to describe the forces among the atoms. We have adopted the molecular mechanics suite of programs, TINKER,[25] to our computer code for locating periodic orbits, POMULT,[26] in order to calculate the potential and its first (in Hamilton's equations) and second (in variational equations) derivatives analytically.

III. RESULTS

Alanine dipeptide has served as a prototype molecule for testing new algorithms in numerous studies in the past.[27–29] We also use this molecule by employing the parameters of CHARMM27 for the force field,[30] Morse functions for the bond stretches,[31] and harmonic potentials for the angles.

A. Equilibrium points

The hierarchical approach for studying the dynamics of this molecule starts with the location of minima and saddle points in the potential energy surface. For a 60 internal degrees of freedom molecule such as alanine dipeptide, the number of stationary points found is large. The lowest three minima are tabulated in Table I together with the saddle points among them. Energies and the distance of the two nitrogen atoms in the molecule are shown in this table as well as the harmonic frequencies of two characteristic vibrational modes to be discussed and studied thoroughly below. Figure 1 depicts the minimum potential energy pathways along a generalized isomerization coordinate. They have been calculated with the method of Czerminski and Elber[27] implemented in TINKER. As we can see in Fig. 1, the two lowest minima are separated by a small barrier of about 0.6 kcal/mol. To open the other reaction channels potential barriers of about 6.5 kcal/mol should be surmounted. In this study we concentrate in the first isomerization pathway and we show that, contrary to our expectation that the small barrier will have negligible influence in the dynamics, domains of phase space where trajectories are trapped for tens of picoseconds even at high excitation energies can be traced from these stationary points. The geometries of the three equilibrium conformations of the dipeptide are shown in Fig. 2.

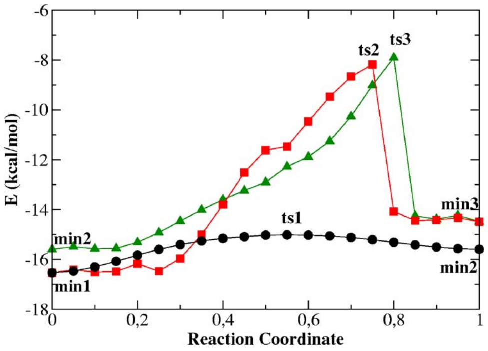

FIG. 1. (Color online) Minimum energy pathways connecting three minima of alanine dipeptide along a generalized reaction coordinate.

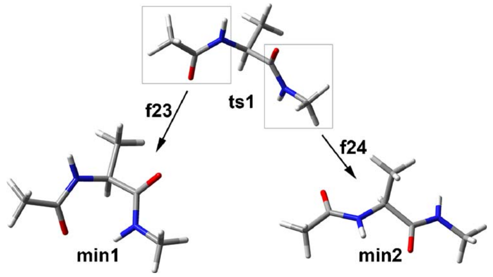

FIG. 2. (Color online) The geometries of the two minima and the transition state for the lowest energy isomerization reaction of alanine dipeptide. The two squares drawn on the transition state enclose the atoms which execute the largest motions in the *f*23 (left) and *f*24 (right) periodic orbits (see text). Quenching the energy from configurations of the *f*23 and *f*24 periodic orbits specifically leads to the minima min1 and min2, respectively. From left to right the tubes correspond to the atoms of the chemical structure $CH_3CONHCH(CH_3)CONHCH_3$.

For the isomerization reaction min 1 ↔ min 2 we find that the distance between the two nitrogen atoms (d_{NN}) is a monotonic function of the reaction coordinate (Fig. 3). In Fig. 4 we plot the minimum energy pathway as a function of d_{NN}. The nitrogen-nitrogen distance varies by 0.57 Å in the two minima and it is used for assigning isomerization events. During this process the peptide folds and unfolds and the time scales of such reactions are important in biology.

B. Periodic orbits

The method that we have proposed to discover domains in phase space with (de)localized trajectories is by locating families of periodic orbits associated with equilibrium points. In this article we investigate in detail the principal families emanating from the minima min1 and min2, and the transition state, ts1. The principal families generated from the minima are initially stable. However, because of the nonlinearity they may turn to unstable at higher energies. The principal families of POs are the natural extensions of the harmonic normal modes, which are valid at energies close to

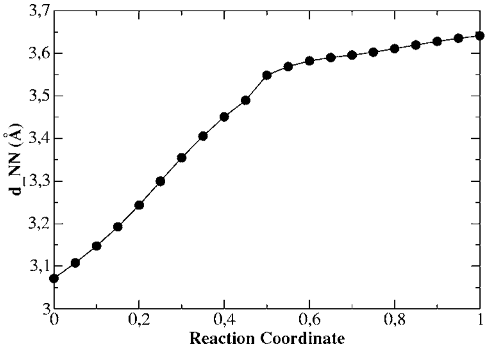

FIG. 3. The variation of the nitrogen-nitrogen distance along the minimum energy isomerization pathway.

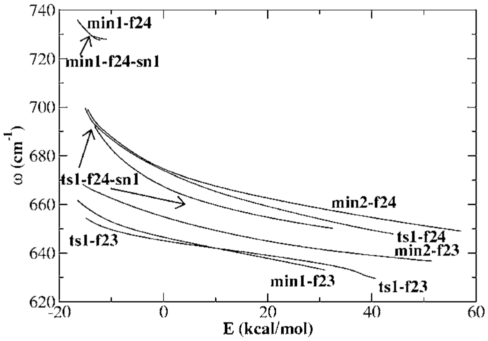

FIG. 5. Continuation/bifurcation diagrams of the principal families of periodic orbits $f23$ and $f24$ originated from the equilibria min1 and min2, and the saddle point, ts1.

the minimum, to high energies where anharmonicity and coupling of the degrees of freedom are unavoidable. Semiclassical quantization of these periodic orbits provides a good approximation to the overtone quantum states of the molecule as previous studies have shown.[3,5,11] The periodic orbits which emerge from the transition state start as unstable with the same rank of instability as the transition state. ts1 has rank-1 instability.

Among the 60 vibrational normal modes, we have chosen to study the 23rd and 24th frequencies of which are also given in Table I. The numbers used to assign the families of periodic orbits are the same as the enumeration of the harmonic normal modes by increasing frequency. Other principal families have been calculated and presented in Ref. 31. The 23rd and 24th normal modes have approximately localized motions that involve the atoms enclosed in the squares of Fig. 2. The NH and CO bonds oscillate in phase executing the largest displacements. Our interest to these particular normal modes came from their specificity. Starting with initial configurations from these oscillations and minimizing the energy we approach a specific minimum, the $f23$ mode leads to min1 and the $f24$ to min2.

In Fig. 5 the continuation/bifurcation (C/B) diagram for the $f23$ and $f24$ families coming out from the three equilibria of the molecule (min1, min2, and ts1) is shown. The anharmonic behavior of the vibrational modes is evident. For the $f24$ families of min1 and the saddle point, ts1, an early saddle-node bifurcation is observed. This means that at a specific energy the continuation line levels off, decreasing its anharmonicity, and a new pair of families of periodic orbits emerge, one of them with stable periodic orbits and the other with unstable ones (we show the stable branch). The mechanism of appearance of such bifurcations has been described before.[15] It is worth noting the higher frequency of the 24th mode of min1 compared to the other two equilibrium points of the potential function. After the appearance of the saddle-node bifurcation (family min $1-f24-\text{sn}1$) it was very difficult to continue this branch at higher energies. We expect a cascade of saddle-node bifurcations as we go up in energy.[3] Plots of some representative periodic orbits are shown in Fig. 6. We project these POs in the plane of nitrogen-nitrogen distance and its relative velocity. The lines in the graph are doubly drawn for the complete periodic orbits.

After locating a periodic orbit we carry out a linear stability analysis to find the eigenfrequencies and the eigenvectors of the monodromy matrix from which we can determine the behavior of the trajectories in the near neighborhood.[15] Those POs which originate from the minima remain stable in most of the degrees of freedom in the examined energy range. However, at the energy of about -15.6 kcal/mol for min1 and -14.1 kcal/mol for min2 we find one quadruplet of eigenvalues which come out of the unit complex circle. We call this kind of instability as complex and we have examined it in the past[32] with respect to the quantum mechanical consequences. The complex instability is associated with what is called Hamiltonian-Hopf bifurcation which leads to the appearance of new POs and tori.[16]

At the saddle point (rank 1) we have always one pair of

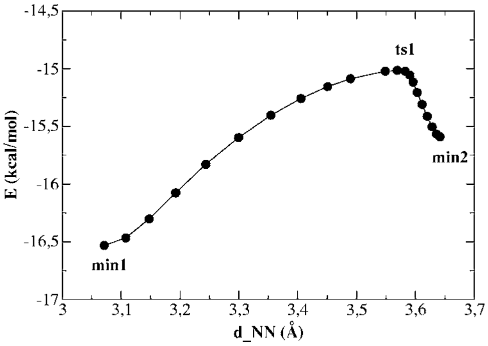

FIG. 4. The minimum energy pathway connecting the two lowest minima of alanine dipeptide as a function of nitrogen-nitrogen distance.

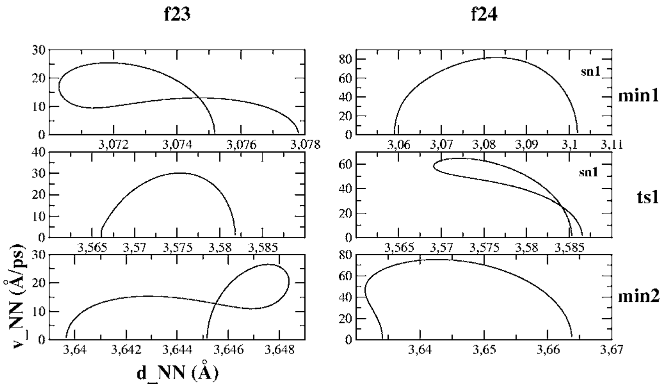

FIG. 6. Plots of representative periodic orbits projected in the plane of nitrogen-nitrogen distance and its relative velocity.

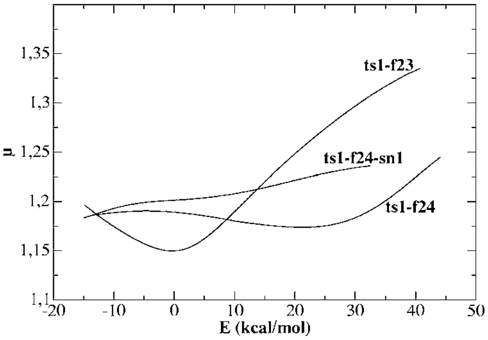

FIG. 7. The instability parameter μ for the periodic orbits at the saddle point.

real eigenvalues, thus the POs born are singly unstable. For the ts1$-f24$ family and at the energy of about -13 kcal/mol we find a saddle-node bifurcation. The new family emerged from the saddle-node bifurcation is also singly unstable and the frequency continuous to decrease as the total energy increases (Fig. 5). The calculated instability parameter is about $\mu=1.2$. From this we can deduce a characteristic time, λ^{-1} [see Eq. (9)], for energy randomization (about 0.3 ps), which determines the time scale for the molecule to develop statistical behavior.[33,34] This time may be interpreted as a lower bound of the lifetime of the molecule at a particular conformation.

In Fig. 7 we depict the instability parameter for the periodic orbits born at the saddle point. We can see that the instability for the ts1$-f23$ family decreases with energy and only for positive energies starts increasing. ts1$-f24$ shows more complex behavior whereas the saddle-node family increases with energy.

C. Localization and selectivity

The location of periodic orbits and their continuation in energy allow one to select trajectories from regions of phase space that are associated with the normal modes of the molecule. This method is free of approximations, such as normal form expansions of the Hamiltonian. Numerically exact periodic orbits are located using the fully coupled anharmonic potential energy surface. At a chosen energy we can sample trajectories from the neighborhood of the periodic orbit to calculate correlation functions or to study isomerization reactions. For example, in Fig. 8 we plot the NN distance as a function of time for 1000 trajectories selected from a Gaussian distribution centered at a PO of the saddle point, ts1 $-f23$, and at energy of -10 kcal/mol. The probability to reach min1 or min2 is about 1/2 with a lifetime distribution in the range of [0.5, 2.5] ps. We propagate the trajectories forward and backwards in time, a technique which speeds up the calculations by carrying the computations parallelly. At times longer than 6 ps the system starts having frequent jumps from one minimum to the other. Contrary to that, trajectories selected from periodic orbits of the same type, $f23$, of the minima min1 and min2 stay localized for 40 ps as can be seen in Fig. 9.

We determine the regular (and localized) or chaotic behavior of the system by calculating autocorrelation functions.

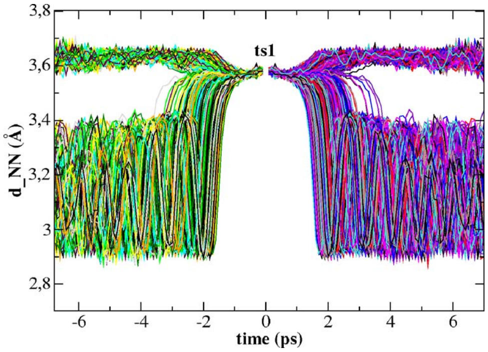

FIG. 8. (Color online) Plots of the NN distance with time obtained from trajectories sampled around a periodic orbit of the $f23$ family of the saddle point at energy of -10 kcal/mol.

By sampling 1000 trajectories from a Gaussian distribution centered on the periodic orbit we calculate the autocorrelation function and from it the power spectra. Examples are shown in Fig. 10. The frequency of the highest peak in the power spectra is that of the periodic orbit whereas the side peaks is the result of the nonlinear coupling among the normal modes. Complexity increases from min2 to the ts1.

Although for a few degrees of freedom systems we can visualize the POs by projections on coordinate planes this is not practical with many degrees of freedom systems. Instead, the motions of the atoms along the periodic orbit are best visualized by using the graphics available for molecular mechanics. We have visually examined the motions of the atoms for all families of POs at several energies. We confirmed that the $f23$ and $f24$ modes are mainly local-type motions involving the atoms enclosed in the squares of Fig. 2, even at high excitation energies. Furthermore, by minimizing the energy starting from phase space points along the periodic orbits, we found that every point in the region of $f23$ leads to min1, whereas by quenching from the region of $f24$ the system converges to min2.

IV. DISCUSSION

Localization in complex systems is currently a subject of intense research.[13,17] For example, energy localization and the theory of breathers have been utilized to argue for the existence of long, nonexponential excited state relaxation in myoglobin.[17] In these studies the authors used simple models

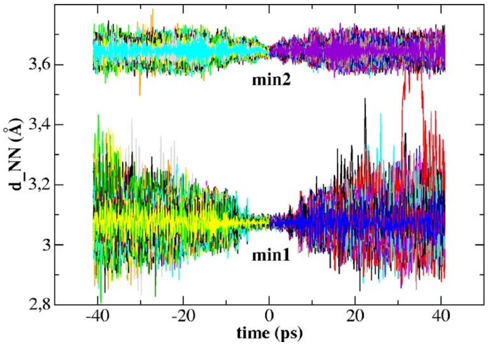

FIG. 9. (Color online) Plots of the NN distance with time obtained from trajectories sampled around a periodic orbit of the $f23$ families of the minima min1 and min2 at energy of -10 kcal/mol.

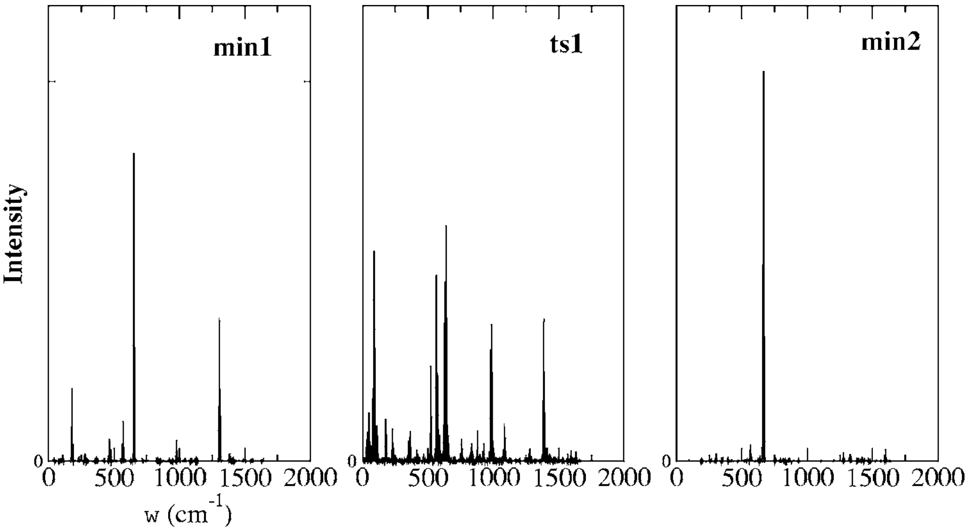

FIG. 10. Spectra obtained by averaging over 1000 trajectories selected from a Gaussian distribution. The centers of the distributions are the periodic orbits of type $f23$ at the energy of -10 kcal/mol.

to argue that localized states may be responsible for the observed long relaxation times. The present study unequivocally demonstrates the existence of stable periodic orbits for substantial energy ranges in alanine dipeptide described with an empirical potential function. Such potentials are widely used in simulations of biomolecules. However, the extention to larger molecules and even the introduction of a solventlike water are necessary to confirm the existence of local-type motions under experimental conditions. The advantage of searching for stationary classical objects such as periodic orbits and their bifurcations is the expected structural stability; in other words small perturbations either in the environment or in the potential function will not introduce major topological changes but only small quantitative differences. Although, one has also to prove that localization remains in quantum calculations, the previous work on small molecules[3] supports our expectations that such phenomena will remain in the quantum world.

We find different time scales in the isomerization process depending on the excitation of specific vibrational modes but from different conformations. In spite of exciting similar modes in the three conformations their dynamics differ substantially. Controlling chemical reactions at such a level is one of the goals of chemical dynamics. However, novel spectroscopic methods have indeed appeared which study small peptides in subpicosecond time scale. In a recent investigation of alanine tripeptide in water by two-dimensional vibrational spectroscopy conformational fluctuations at the time scale of 0.1 ps have been reported.[35]

V. CONCLUSIONS

Families of periodic orbits associated with equilibrium points, the principal ones, of an empirical force field potential function for alanine dipeptide have been calculated with shooting and multiple shooting techniques and propagated in energy by using analytical first and second derivatives. Linear stability analysis of the POs allows one to predict localized trajectories and upper bounds for isomerization rate constants. We have demonstrated that, with the periodic solutions of the classical equations of motion, we can climb up to high energy regions of phase space and select systematically trajectories from specific anharmonic modes, which lead the molecule to specific conformations. The present work has demonstrated that we can systematically explore the dynamics of a small peptide. Currently, we study peptides with ten aminoacids as well as the stability of excited conformations in a solutionlike water. The results will be presented in future publications.

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