

Periodic Orbits in Biological Molecules: Phase Space Structures and Selectivity

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Abstract: 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. We can trace such localization regions in phase space hierarchically by following families of periodic orbits which emanate from minima and transition states of the potential energy surface. Furthermore, we can study the stability of nearby trajectories and we can detect bifurcations which determine new characteristic motions of the molecule as energy or other parameters vary. In this article we demonstrate that our techniques to locate periodic orbits that were developed for small molecules can be extended to biological molecules such as alanine dipeptide.

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1 Introduction

Many body complex systems are studied by two different approaches. Either by using statistical mechanics methods or by the systematic methods of non-linear 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 predict non-linear effects such as resonances and chaos. The progress of non-linear 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, classical and semiclassical mechanical theories. Chemical reactions involve the break and the formation of chemical bonds after the excitation of the molecule above potential barriers. Non-linear phenomena, like resonances, are expected and they have been observed spectroscopically [3]. Selectivity and specificity are well established concepts in elementary chemical reactions when the role of mode

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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].

Moving to more complex systems with many more degrees of freedom such as biological molecules, the application of the 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 large systems is usually exhausted by the location of equilibrium points (minima and saddles), to be followed with the calculation of phase space averages.

The hierarchical detailed exploration of the molecular phase space structure requires 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 normally hyperbolic invariant manifolds [7]. Such a program has been applied up to now to two and three degrees of freedom models for triatomic molecules [8, 9, 10]. This work has revealed the importance of periodic orbits in elucidating non-linear 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 [11, 12]. The initial observations of localized motions in the work of Sievers and Takeno [13] triggered the discovery of significant mathematical theorems. However, most of the potential functions employed in the numerical studies were rather simple to describe realistic systems. In this lecture we show how to extend the methods of locating POs to biological molecules, such as peptides described with the widely used empirical potential functions. It is shown, that we can systematically trace regions in phase space where the trajectories stay localized in specific vibrational modes of a minimum or a transition state. In this way, the road is opened for elucidating localization phenomena and selectivity in biological systems [12, 14].

2 Computational Methods

To locate periodic orbits in a dynamical system is equivalent of finding the roots of the non-linear 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, \dots, q_N are the generalized coordinates of a dynamical system of N degrees of freedom and p_1, p_2, \dots, p_N their conjugate momenta, we define the column vector

$$\vec{x} = (\vec{q}, \vec{p})^+, \quad (1)$$

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

$$\frac{d\vec{x}(t)}{dt} = J\nabla H[\vec{x}(t)] \quad (0 \leq t \leq T), \quad (2)$$

where H is the Hamiltonian function, and J is the matrix

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

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

$$JM J^+ = M. \quad (4)$$

Table 1: 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 three stationary points of the potential energy surface of alanine dipeptide examined in this work.

	Energy	N-N Distance	H.f. 23	H.f. 24
Min1	-16.49	3.068	662.02	738.26
Min2	-15.58	3.640	668.78	704.59
TS	-15.00	3.566	655.12	700.66

If $\vec{x}(0)$ denotes the initial conditions of a trajectory at time $t_1 = 0$, then this trajectory is periodic if it returns to its initial point in phase space after the time $t_2 = T$

$$\vec{x}(T) - \vec{x}(0) = 0. \quad (5)$$

Thus, to find periodic solutions it is necessary to solve Eqs (2) subject to the 2-point boundary conditions, Eqs (5). The roots are found by iterative methods which require the linearization of the equations of motions around properly selected initial conditions. Powerful existence theorems for POs [15, 16] have converted the art of solving non-linear equations to science. We use multiple shooting techniques and the algorithms and computer codes have been described in previous publications [17]. However, the challenge to extend these methods to many degrees of freedom systems such as alanine dipeptide ($\text{H}_3\text{CCONHCH}(\text{CH}_3)\text{CONHCH}_3$) and larger molecules requires the adoption of new practices. We use cartesian coordinate systems and empirical force fields to describe the forces among the atoms. We have adopted the Molecular Mechanics suit of programs, TINKER [18], to our computer code for locating periodic orbits, POMULT [19], in order to calculate the potential and its first and second derivatives analytically. For alanine dipeptide we use the parameters charmm27 adopted in TINKER.

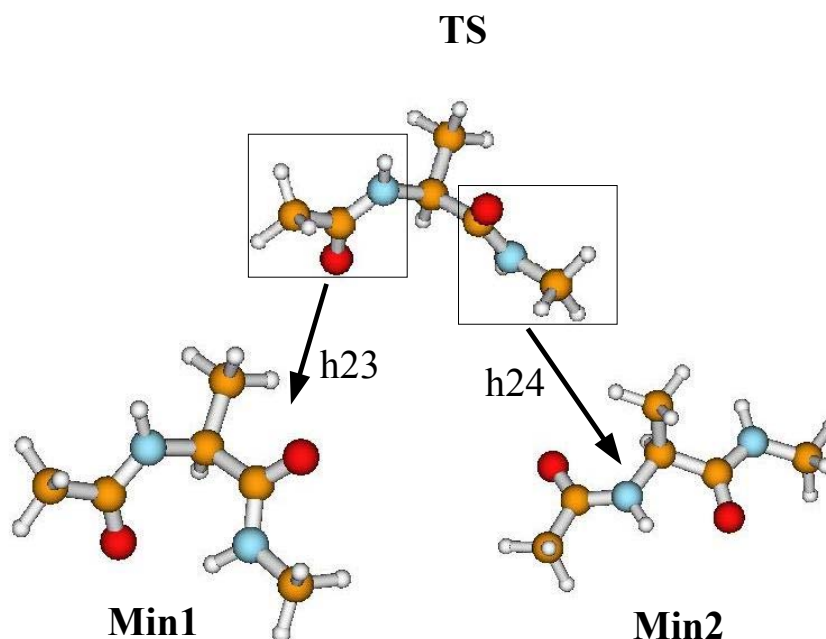
3 Results

In this article we look for periodic orbits emerging from the two lowest minima, that we have found in a search for stationary points, denoted Min1 and Min2, and the saddle point between them representing the transition state (TS) of the isomerization reaction $\text{Min2} \rightarrow \text{Min1}$. In Table I we tabulate the energies of the three equilibrium points, the distance of nitrogen atoms in the two aminoacids and the harmonic frequencies of two characteristic normal modes to be discussed below. We believe that this low barrier conformational change is typical for the class of the molecules we want to examine.

Figure 1 shows the structures of the molecule at the stationary points. Figure 2 depicts the minimum potential energy pathway from Min2 to Min1. It was calculated with the method of Czerminski and Elber [20] implemented in TINKER. On the same figure we show the monotonic increase of the nitrogen-nitrogen distance.

A significant difference of 0.57 Å is found for the nitrogen-nitrogen distance between the two minimum structures. Contrary to that, the harmonic normal mode frequencies show small variations for the three equilibrium points. The 23rd and 24th normal modes shown in Table I, are two out of plane motions that mainly involve those atoms of the dipeptide that are enclosed in the squares of Fig.1. The NH and CO bonds oscillate in phase executing the largest displacements. It

Figure 1: The two minimum conformations and the transition state for the isomerization reaction of alanine dipeptide. The two squares drawn on the transition state enclose the atoms which execute the largest motions in the h23 (left) and h24 (right) periodic orbits (see text). From left to right the balls correspond to the atoms of the chemical structure $\text{H}_3\text{CCONHCH}(\text{CH}_3)\text{CONHCH}_3$.



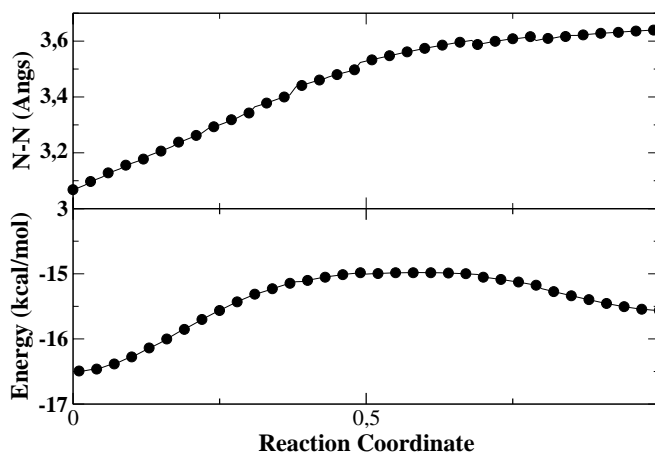
is expected that such motions on the transition state will affect the isomerization of the molecule and this is the reason that we have chosen them in our investigation.

The harmonic normal mode analysis at each equilibrium point helps us to find good initial conditions for the periodic orbits. At least, an equal number of POs to the number of normal modes exists for each equilibrium point according to Weinstein and Moser theorems [15, 16].

In Fig. 3 the continuation diagram of representative periodic orbits for Min2 is shown. Similar plots have been obtained for Min1 and the transition state. The numbers used to assign the families are the enumeration of the normal modes with increasing frequency. We can see that all families show small anharmonicities. After closing the orbit we carry out a linear stability analysis to find the eigenfrequencies and the eigenvectors of the PO from which we can determine its stability. Those POs which originate from the minima remain stable in most of the directions perpendicular to the periodic orbit in the examined energy range, except to the appearance of minor single or complex instabilities. For the transition state we have always one pair of real eigenvalues, thus single instability. The calculated instabilities are small and this justifies the localization of the nearby trajectories as we discuss below. High frequency families not shown in Fig. 3, correspond mainly to stretches with very small anharmonic behavior.

The location of periodic orbits and their continuation in energy allows one to select trajectories from regions of phase space that are associated with the normal modes of the molecule. For example, the behavior of the nearby trajectories to periodic orbits can be followed by calculating

Figure 2: The minimum energy path connecting two minima of alanine dipeptide and the variation of the nitrogen-nitrogen distance along the reaction coordinate.



autocorrelation functions. By sampling a Gaussian distribution of 1000 trajectories centered on the periodic orbit we have produced Fig. 4, which shows the autocorrelation functions and their power spectra for two POs, h23 and h24, emanated from the transition state and at total energies -7.14 kcal/mol and -6.99 kcal/mol, respectively.

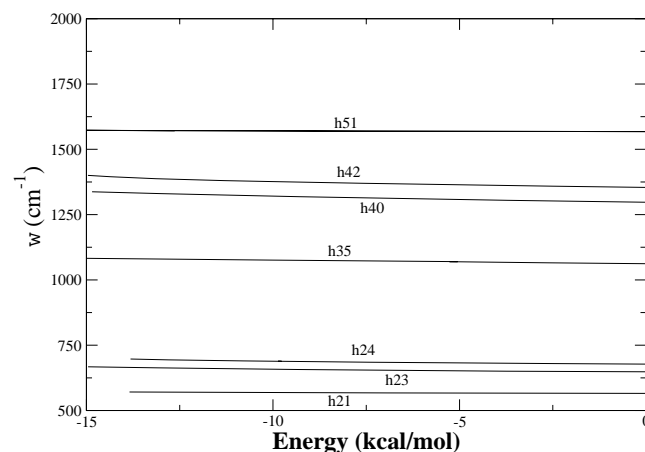
The regularities in the plots reveal the localization and the regularity of the selected trajectories. The frequency of the highest peak in the power spectra is that of the periodic orbit whereas the side peaks is the result of the non-linear coupling among the normal modes.

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 h23 and h24 modes are mainly local type motions involving the atoms enclosed in the squares of Fig. 1 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 h23 leads to Min1, whereas by quenching from the region of h24 we converge to Min2 and in a few times to the saddle point.

4 Conclusions

Families of periodic orbits associated with equilibrium points, the fundamental ones, of an empirical force field potential function of alanine dipeptide have been calculated with continuation techniques and using analytical first and second derivatives. Linear analysis of the POs demonstrate their stability for high excitation energies, and thus the long time localization of the nearby trajectories even for vibrational modes of the transition state. *We have demonstrated that with the periodic solutions of the classical equations of motion we can climb to high energy regions of phase space and select systematically trajectories which can lead the molecule to specific conformations.* Currently, larger peptides are studied to examine the robustness of our methods for locating periodic orbits.

Figure 3: Continuation diagram of the periodic orbits originated from the minimum Min2.



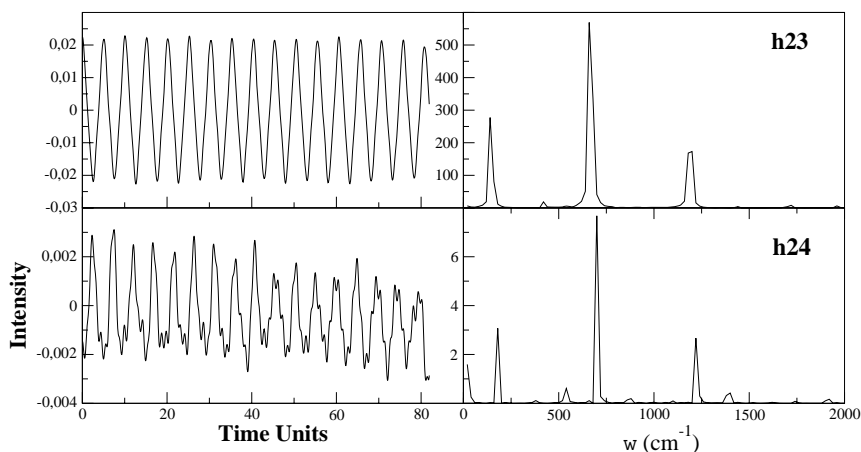
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Figure 4: Correlation functions and spectra averaged over one thousand trajectories selected from a Gaussian distribution. The center of the distributions are the periodic orbits of type h23 and h24 at energies -7.137 kcal/mol and -6.987 kcal/mol, respectively. 1 time unit is equal to 0.01018 ps.



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