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NONLINEAR DYNAMICS OF MOLECULAR SYSTEMS AND THE CORRELATIONS OF INTERNAL MOTIONS IN OLIGOPEPTIDES

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The dynamical properties of significantly nonlinear molecular systems with conformational mobility are discussed. The peculiarities of the figurative point movements along the potential energy hypersurfaces with a lot of saddle points are investigated. The methods of dynamical correlation functions of dihedral angles and calculation of free energy maps are developed. These correlation functions and free energy maps can characterize the dynamical properties of the nonlinear systems in detail. The dynamical properties of some oligopeptides are described.

INTRODUCTION

The fundamental physical principles of the dynamical behavior of biomacromolecules have been intensively investigated for more then 20 years.[1] The Mossbauer spectroscopy data and the data on ligand diffusion in proteins were among the starting points of this investigation. These data have been used to prove experimentally the concept of limited diffusion on conformational substates for internal protein dynamics.[2–8] Thermal fluctuations in biopolymers is a natural dynamic background of protein functioning and of relaxation of nonequilibrium states in biomacromolecules.[8]

It can be shown with the help of modern mathematics that the general properties of protein dynamic behaviour are determined by structure

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peculiarities of potential energy level hypersurfaces.[8, 9] Let us consider the main ideas of this approach. A potential energy hypersurface has not only local minima, but also local maxima along the set of degrees of freedom. These maxima have values in a rather narrow (about several kcal/mol) interval of energy. The considered degrees of freedom are connected with rotation around univalent bonds and the formation of hydrogen bonds. The peculiarities of chemical structure result in such conformational energy hypersurface structures, which have a lot of saddle points. Some of the second partial derivatives of potential energy on coordinates have positive and some of have negative values at the saddle points. According to the Morse theory[10] we have the following common structure of a potential energy level hypersurface (Fig. 1).

The molecular system moves along this hypersurface during its thermal motions. There are a lot of attracting regions or locuses in the configuration space of the molecule. They are connected by handles or tubes with fewer dimensions than the loci. It is possible to observe the processes of the such hypersurface formation. In the case of an ideal crystal the potential energy function is a quadratic function of atom displacement. Thus, the potential

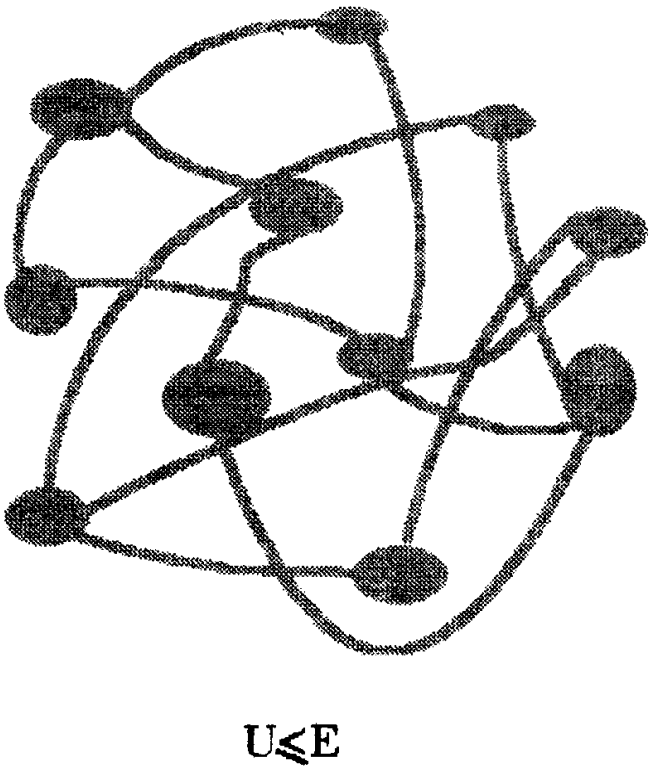

FIGURE 1 The potential energy level hypersurface for conformational labile macromolecular systems (a scheme).

energy level hypersurface is topologically equivalent to a hypersphere (Fig. 2). If there is one defect in a crystal, we have two hyperspheres connected by a handle or a tube (Fig. 3). In a case of protein there are a lot of such saddle points and the structure becomes rather complicated.

Therefore, a very difficult problem appears. The loci (Fig. 1) are connected by a lot of paths that are topologically unequivalent. So, in general there is a

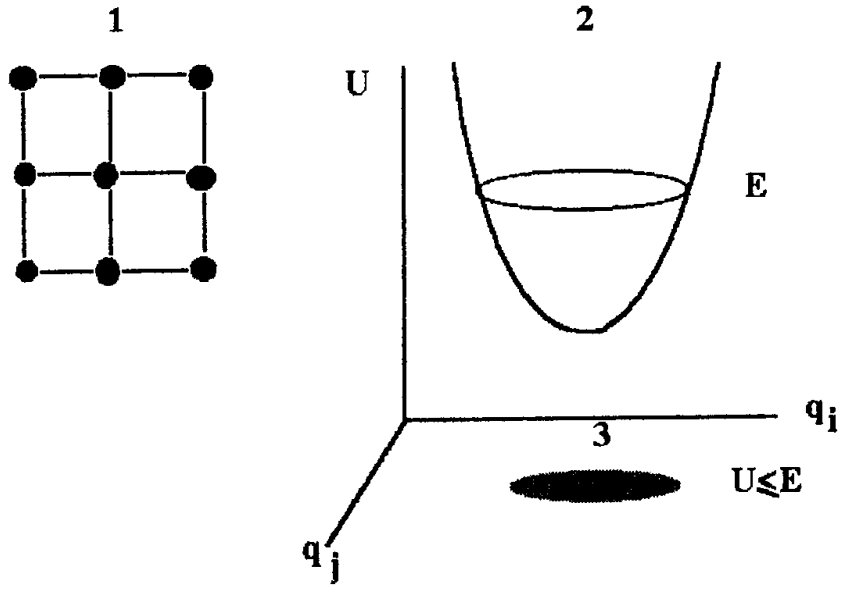

FIGURE 2 The potential energy level hypersurface (3) for the ideal crystal (1). 2 – is the multidimensional paraboloid.

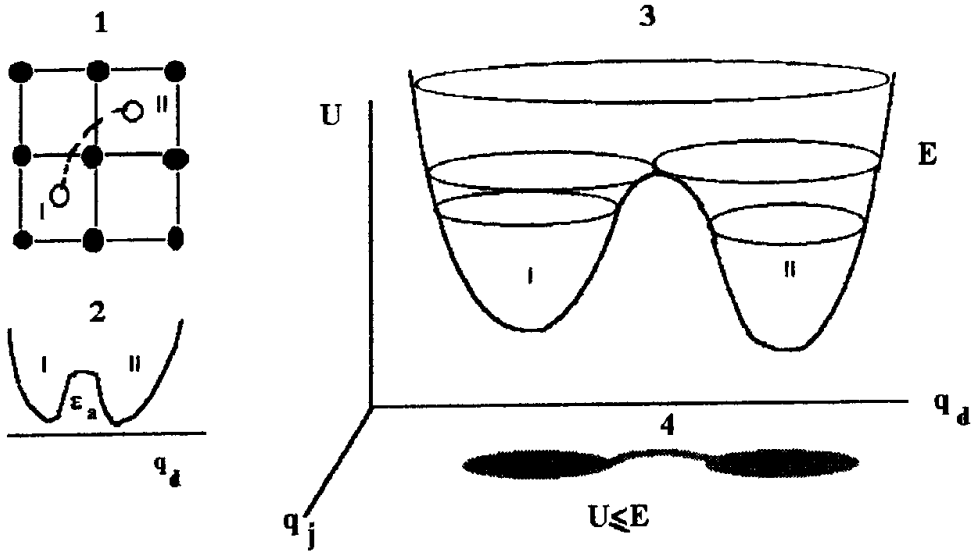

FIGURE 3 The potential energy level hypersurface (4) for the crystal with one defect (1). 2 – is the potential energy profile along defect coordinate. 3 – the potential energy hypersurface.

web of ways of conformational relaxation, but these ways are not equivalent. What are the probabilities of these ways? We don't have any general solution of this problem yet, but we have suggested the approach based on detailed analysis of the dynamical properties. This approach also includes the investigation of corresponding conformational energy level hypersurfaces for protein fragments.[11–13] We consider the series of dipeptides with modified groups on the ends as such fragments (Fig. 4).[14]

The investigation of the configuration space is carried out by the molecular dynamics method. The figurative point scans accessible areas of the configuration space at a given temperature. All atom–atom interactions are included.[1, 15]

The calculation conditions have to be selected so that the molecule trajectories have ergodic properties. Only in this case the trajectory can give us information about probabilities of realization of all accessible states of a molecule. It was established that only long trajectories, about 5000 ps at temperatures above 2000 K have ergodic properties. The results can be transformed to other temperatures by using Boltzmann formula. We use the original method of collisional dynamics.[16] This method considers the molecule in a model solute with low viscosity. The model solute provides an

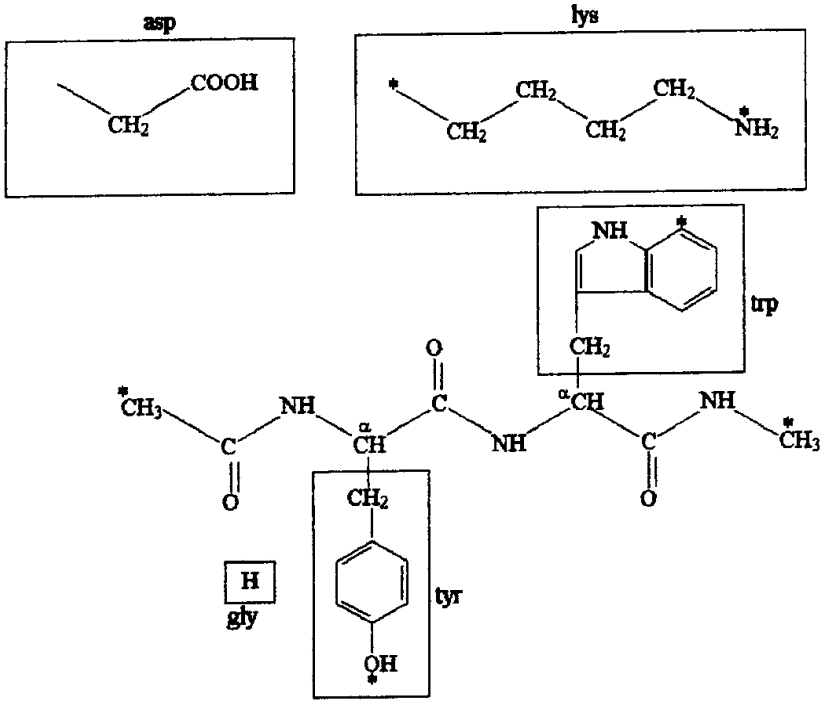

FIGURE 4 The chemical structures of some modified dipeptides. The aminoacid side groups asparagine, lysine, tryptophan, glycine and tyrosine are in boxes. (*) – marks the atoms, the positions of which are discussed in the correlation function analysis.

effective exchange of energy between different intramolecular degrees of freedom.

TWO-DIMENSIONAL DISTRIBUTION FUNCTIONS

Let us see the typical two-dimensional function of probability distribution for the pair of dihedral angles (α_n, α_m) of a dipeptide (Fig. 5). This function was obtained by integration of the multidimensional distribution function

$$P(\alpha_n, \alpha_m) = \int \dots \int P(\alpha_1, \dots \alpha_i, \dots, \alpha_N) \Pi d\alpha_i \quad (i \neq n, m), \tag{1}$$

$P(\alpha_1, \dots \alpha_i, \dots, \alpha_N)$ is the density of probability to find the system in the point of the configuration space (α_i are the series of all independent dynamical variables).

FREE ENERGY MAPS

The peculiarities of the conformational energy level hypersurface structures were investigated by the calculation of the free energy maps. Note that free energy is connected with the probability of the corresponding states realization by the well-known Boltzmann formula. These maps are strongly

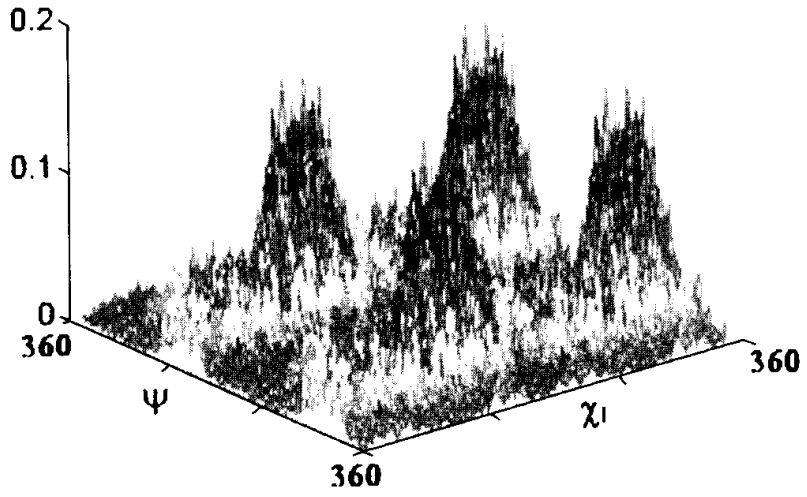

FIGURE 5 The two-dimensional probability function for dihedral angles of tyr–residue in tyr–trp molecule. Angles vary from −360 to 360 degrees in linear scale. (See Color Plate I).

different from, for example, Ramachandran maps or potential energy maps[14] because free energy maps also include the entropic factor. Fortunately, we find only a few typical kinds of free energy level maps for all studied pairs of dihedral angles (about 30 variants of sequences with all twenty aminoacids have been investigated[11-13]). It was obtained that the structures of the corresponding regions on the free energy level maps are directly connected with the dynamical correlation of conformational degrees of freedom.

Let us consider pairs of angles $\varphi_2\,\chi_{21}$ and $\Psi_2\,\chi_{21}$ in the dipeptide gly–asp (Fig. 6). For convenient images, the angle values vary from −360 to 360 degrees. When temperature is ~ 2000 K one can see that on the $\varphi_2\,\chi_{21}$ plane there are four loci. Two of them are connected through a narrow bottleneck (Fig. 7(1)). The free energy level map for the pair $\Psi_2\,\chi_{21}$ looks like a map of a homogeneously rough surface (Fig. 7(2)).

DYNAMIC CORRELATION FUNCTIONS

The dynamic crosscorrelation function for the dihedral angles can be defined as[11-13]

$$F_{\alpha\beta}(\tau) = \left\langle e^{i[\alpha(t)-\alpha(t+\tau)]}\, e^{-i[\beta(t)-\beta(t+\tau)]} \right\rangle - \left\langle e^{i[\alpha(t)-\alpha(t+\tau)]} \right\rangle \left\langle e^{-i[\beta(t)-\beta(t+\tau)]} \right\rangle \tag{2}$$

where α and β are the values of two dihedral angles of a molecule at the moment t or $t + \tau$.

The real parts of these functions for the angle pairs discussed above in the 500 ps time interval are essentially different each from other (Fig. 8). So

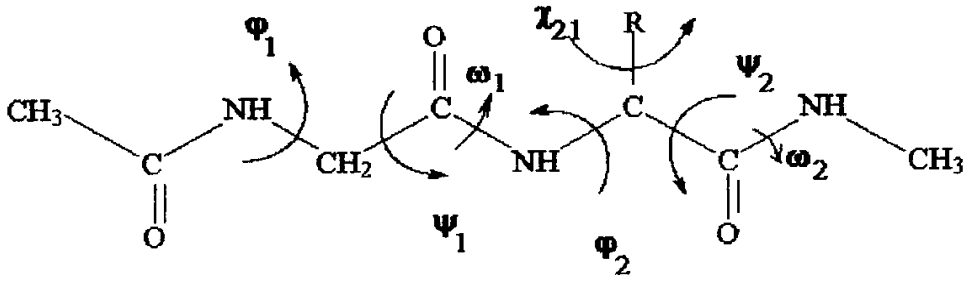

FIGURE 6 Conformational degrees of freedom (dihedral angles) of modified dipeptide gly–asp. R = CH_2 —COOH.

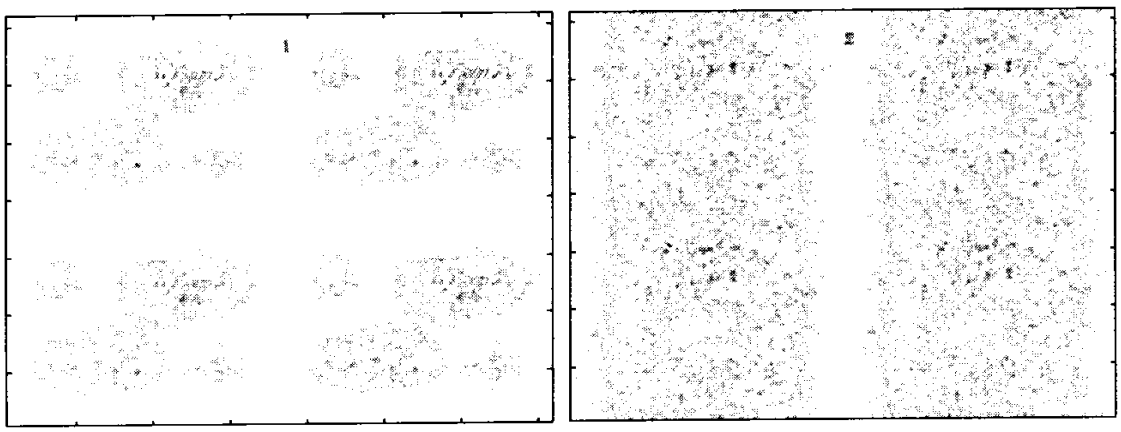

FIGURE 7 Free energy level maps of gly–asp on the $\varphi_2\chi_{21}$ (1) and $\Psi_2\chi_{21}$ (2) planes. Angles vary from −360 to 360 degrees in linear scale (χ_{21} is abscissa).

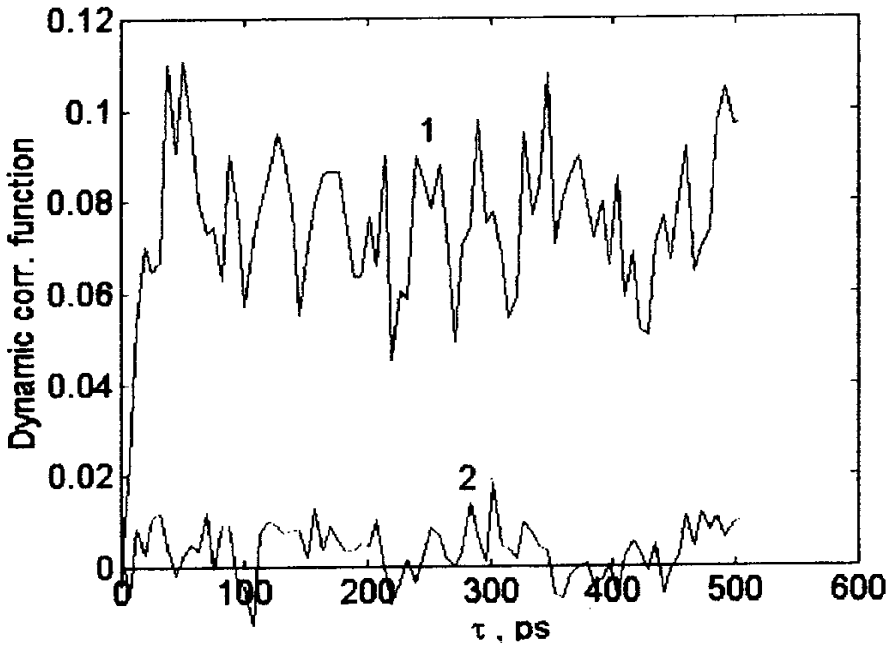

FIGURE 8 The real part of crosscorrelation function (Eq. 2) for $\varphi_2\chi_{21}$ (1) and $\Psi_2\chi_{21}$ (2) dihedral angles.

there is a dynamic correlation for the $\varphi_2\chi_{21}$ degrees of freedom and it is a result of a transition from one locus to the another through the bottleneck (Fig. 7(1)). On the contrary, the second pair of angles $\Psi_2\chi_{21}$ do not correlate one with another during motions. It is a result of the corresponding free energy level map, which looks like the map of a homogeneously rough surface (Fig. 7(2)).

There are several kinds of free energy level maps. There are cases of strongly correlated motions if (1) there is a rather curved valley with great

amplitude of motion, (2) loci are connected with narrow tube, (3) there is a set of ways that look like fingers and connect one locus to another or (4) if there is a long valley going around a locus.

The motions of a pair of degrees of freedom are not correlated if (1) there is no pathway from one locus to another or (2) there is a broad, straightforward and maybe only slightly rough valley.

When oligopeptide molecules are rotated around single bonds the interatomic distances change. The dynamic autocorrelation (if i, j is identical to k, l) and crosscorrelation functions for these parameters are defined as:

$$F_{ijkl}(\tau) = \langle \delta R_{ij}(t+\tau)\delta R_{kl}(t)\rangle \tag{3}$$

where $\delta R_{ij}(t)$ and $\delta R_{kl}(t)$ are the deviations of interatomic distances between i, j and k, l points from their mean values. This autocorrelation function (3) gives the information about the amplitudes and relaxation times of atomic motions and the crosscorrelation functions gives information about collective modes and their correlation times. One can see that the characteristic times of a dipeptide "breathing mode" are about 20 ps and increase up to 100 ps in the case of side groups with large masses (Fig. 9). An interesting effect is demonstrated in Figure 10. The crosscorrelation function

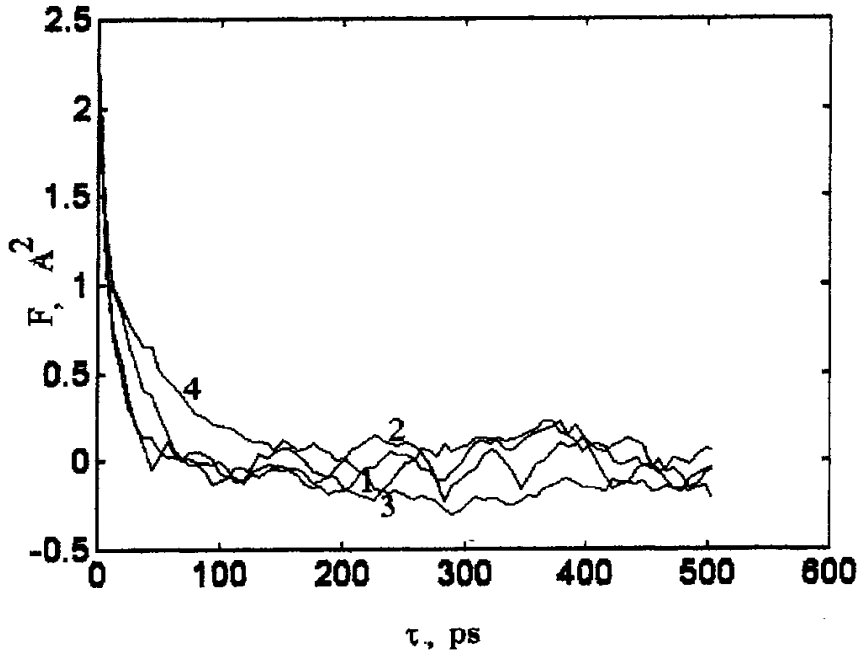

FIGURE 9 The autocorrelation functions (3) for the displacement of interatomic distances from mean value for CH_3 — groups, marked (*) on the ends of molecules (Fig. 4). (1) – asp – asp; (2) – asp – lys; (3) – gly – asp; (4) – tyr – trp.

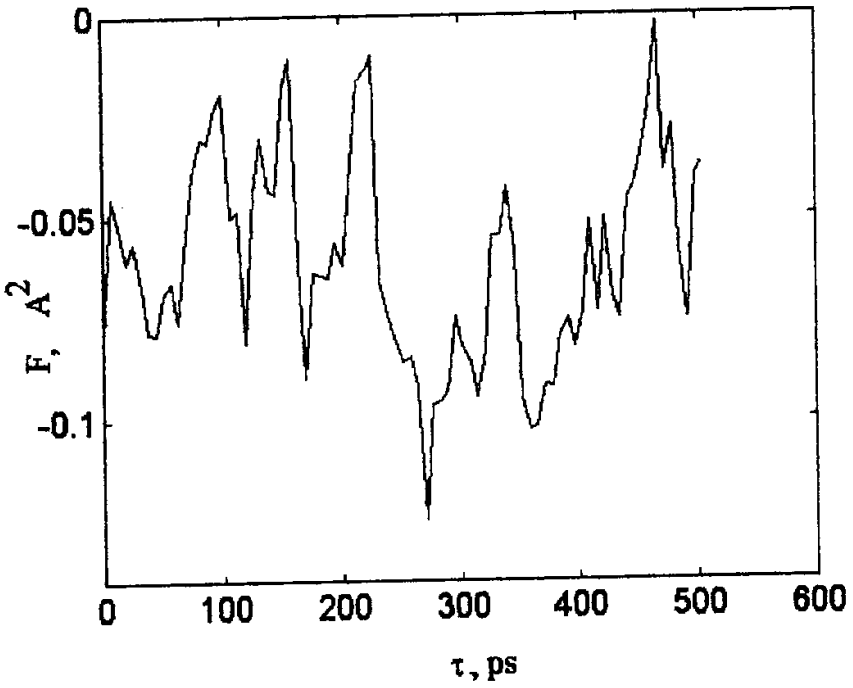

FIGURE 10 The dynamic crosscorrelation function (Eq. 3) for the product of the displacement of interatomic distances from mean values for CH_3— groups on the ends of molecule gly–lys (in the main chain) and for the atoms on the ends of side chain of lys, marked (*) (Fig. 4).

for the deviations of the main and side chain lengths from mean values is negative at all times. Thus the fluctuations of these chain lengths are in correlation and the side group in lys becomes shorter when main chain becomes longer. This effect is a result of van-der-waals interactions between the atoms on the end of side residue and the main chain atoms.

THE DYNAMICAL ISOMORPHISM PHENOMENON

We detected one other interesting phenomenon in the dynamic organization of aminoacid residues and called it dynamical isomorphism phenomenon. It was shown that autocorrelation functions for some aminoacid residues coincide one with another with high precision (Fig. 11). The autocorrelation function is defined as (2) with $\alpha = \beta$. As an example, we can show time dependence of autocorrelation functions for angle φ_1 in asp–asp and angle χ_{11} in tyr–trp (Fig. 11). Such coincidence is not surprising, it is a result of peculiarities of the potential energy level hypersurfaces. These structures look like mosaic structures and these mosaics consist of a few different elements only. Table I illustrates the dynamic isomorphism phenomenon.

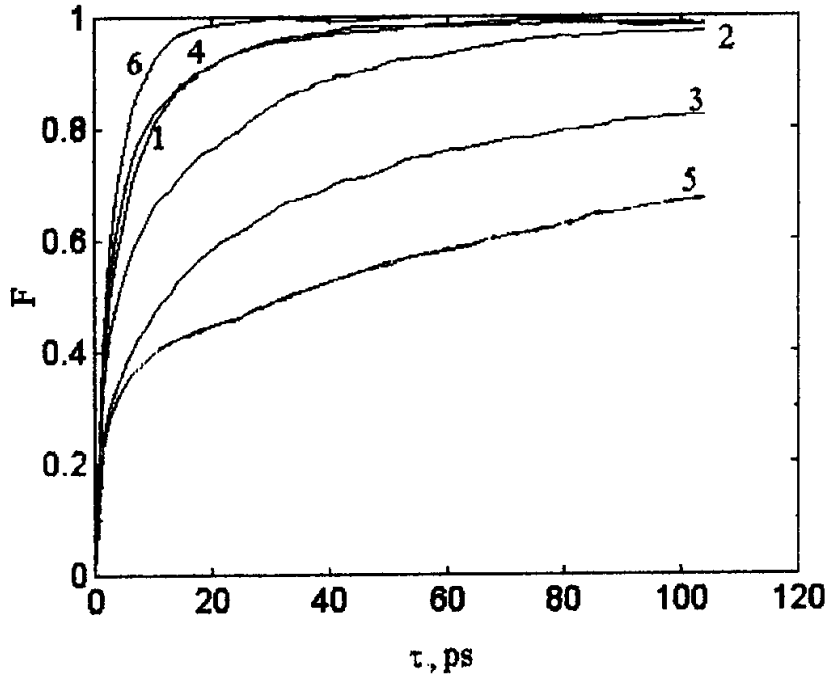

FIGURE 11 The autocorrelation functions (Eq. 2 at $\alpha = \beta$) for dihedral angles in asp–asp φ_1 (1) and in tyr–trp φ_1 (2), Ψ_1 (3), χ_{11} (4), φ_2 (5), Ψ_2 (6).

Identical numbers marks the degrees of freedom that show such phenomenon. The empty boxes correspond to individual properties of the correlation function. It is likely that dynamical isomorphism is a more common characteristic for the aminoacids than structure similarity. We see that, despite differences of chemical structure, there are many degrees of freedom which are very similar each other in biologically important aminoacids.

We investigate this effect by varying of the chemical structure of the natural aminoacids. We demonstrate the effect of tyr modifications (Fig. 12) by another type of autocorrelation function (compare with Eq. 2 at $\alpha = \beta$):

$$F(\tau) = \left\langle e^{i\alpha(t)} e^{-i\alpha(t+\tau)} \right\rangle - \left| \left\langle e^{i\alpha(t)} \right\rangle \right|^2 \tag{4}$$

The autocorrelation functions (2) and (4) result in identical effects for the dynamical isomorphism phenomenon.

It is important that minimal chemical modification of the natural aminoacids leads to strong changes of the dynamical properties and to the breakdown of the dynamical symmetry effects. It can be demonstrated in more details on the free energy maps for these modified molecules (Fig. 13). We select $\varphi_2\chi_{21}$ angles plane. In all native aminoacids strong correlations

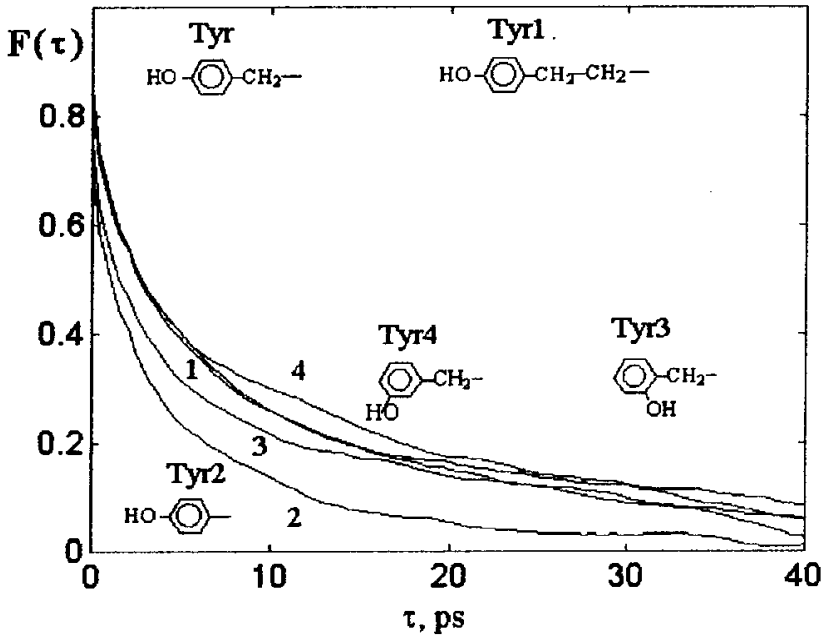

FIGURE 12 The autocorrelation functions (Eq. 4) for dihedral angles φ_1 in the dipeptides (Fig. 6) containing the native and modified tyrosine residues.

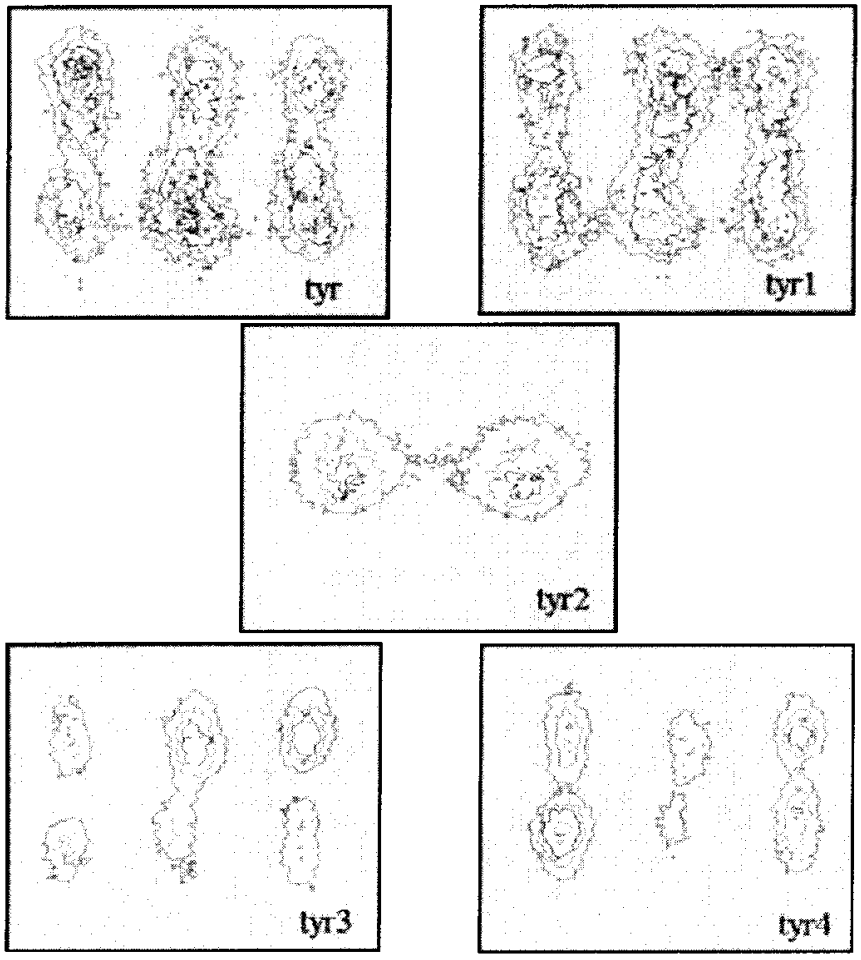

FIGURE 13 Free energy level maps on the $\varphi_2 \chi_{21}$ plane for the dipeptides containing modified tyrosine residues (see also Figs. 6, 12). Angles vary from −90 to 90 degrees in linear scale (φ_2 is abscissa). (See Color Plate II).

for these angles were observed. Under chemical modification conditions only tyr and tyr1 slightly resemble each other. In all other cases there is no dynamical similarity. The most drastic changes occur after CH_2 group elimination from the side residue. When the OH group position in the ring of tyr is changed, serious effects on the maps arise.

We can conclude that biologically important aminoacid residues apparently have some peculiarities. They are determined by the combination of definite chemical structures, mass of groups and force field characteristics.

THE SECONDARY STRUCTURE DYNAMICS AND DESTRUCTION

The dynamics of a modified decaalanine α-helix in vacuum demonstrates some properties of the secondary structure. The simulation shows thermal fluctuations of molecule conformation near helix structure at 300 K and a cooperative drastic conformational transition at a more high temperature (700 K) when the α-helix is destroyed.

Figure 14 shows the possibility for the hydrogen bond to be broken. Thus, there are always some hydrogen bonds that are broken but the helix is stable at 300 K. If temperature increases to 700 K, the bond lengths are increasing

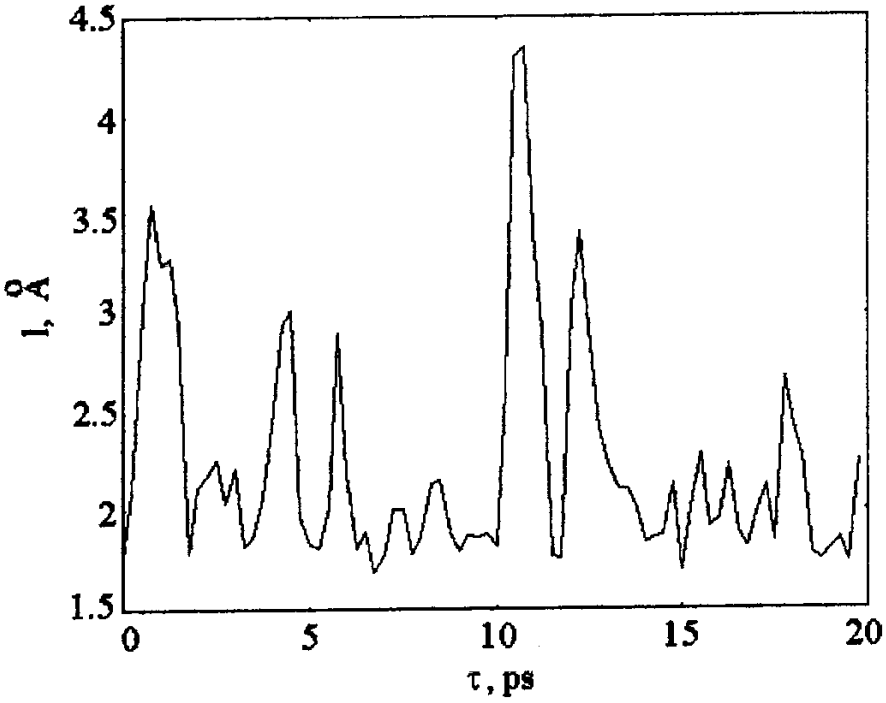

FIGURE 14 The typical time dependence of the hydrogen bond length of simulated decaalanine (between residues 2 and 6) during a 20-ps simulation, averaged over 0.25-ps intervals. The temperature is 300 K.

gradually. The hydrogen bond destruction (melting) occurs as a non-cooperative processes. All hydrogen bonds were destroyed before the time 10 ps (Fig. 15)—the time when the helix shape of this molecule changes irreversibly into the coil.

The time dependences of the dihedral angles of the molecular main chain have one common feature at 700 K (Fig. 16). There is sharp changing at the time about 10 ps. In the other words, the values of the dihedral angles change dramatically at the moment of helix destruction. The motions of the dihedral angles Ψ_i and ϕ_{i+1} are correlated before this changing and, sometimes, after it.

So, there are two stages in the α-helix destruction. In the first stage the hydrogen bonds are broken and it happens gradually and noncooperatively. Then the second stage comes. It is a sharp, cooperative, irreversible transition—the majority of the dihedral angles are changed at the same time. After this α-helix destruction some dihedral angles can return to their old values, but the structure is not a helix any more.

CONCLUSION

The normal modes method of calculation is not applicable for the investigation of the dynamical properties of the molecules with conforma-

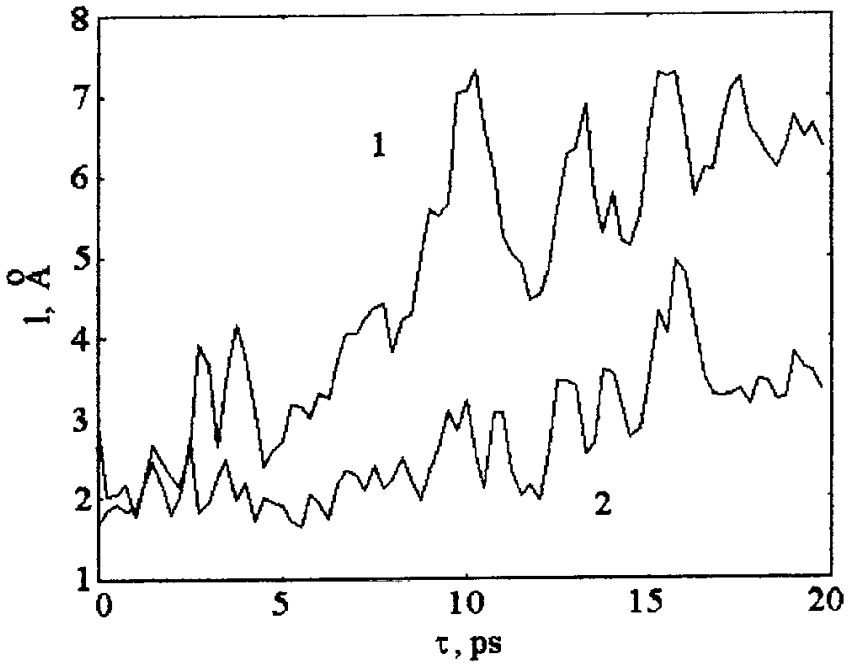

FIGURE 15 The hydrogen bond lengths (between residues 2–6 (1) and 3–7 (2)) as functions of time when temperature is 700 K.

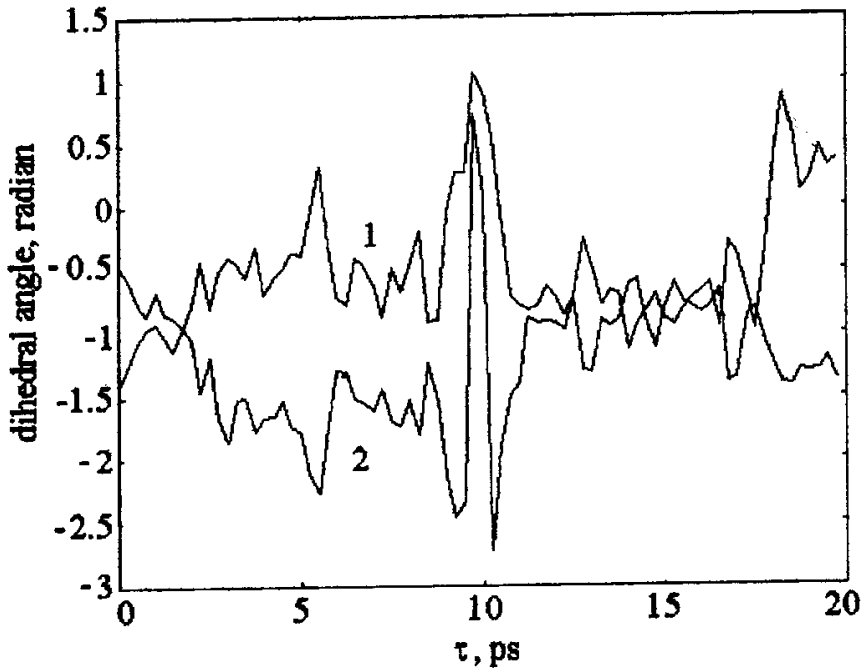

FIGURE 16 The dihedral angles Ψ_5 (1) and ϕ_6 (2) as functions of time at temperature 700 K.

tional mobility. New approaches are developed here; they are based on the analyses of free energy maps and on the investigation of dihedral angle correlation functions. Only a few kinds of free energy maps for all the most important 20 aminoacids were determined. If there are structures such as bottlenecks or curved valleys on this map, then a dynamical correlation between corresponding degrees of freedom takes place. On the other hand, there is no dynamical correlation when the figurative point is moving along a homogeneous rough energy surface or in the one narrow locus only. It is interesting that a strong correlation between displacements of distant atoms can be observed in short peptides.

It is important that the structure of the potential energy hypersurfaces of peptides looks like a mosaic: This mosaic consists of only a few elements. It leads to a dynamical isomorphism phenomenon for peptides. We want to stress that minimal chemical modification of the natural aminoacids leads to strong changes of the dynamical properties and to the breakdown of the dynamical symmetry effects.

The formation and destruction of secondary structures apparently take place as a figurative point moving along some valleys of the potential energy hypersurface. For example, the dynamics of the α-helix destruction has two stages. The first stage is "melting" with the destruction of hydrogen bonds. In this stage a molecule has a helix shape and the process of destruction is

reversible. Then the fast and irreversible stage comes—the "break" of the structure and the formation of new hydrogen bonds.

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