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MOLECULAR BIOPHYSICS

Molecular Dynamics of Oligopeptides. 3. Free Energy Maps and Dynamic Correlations in Modified Dipeptide Molecules

K. V. Shaitan, M. D. Ermolaeva, and S. S. Saraikin

Biological Faculty, Moscow State University, Moscow, 119899 Russia

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Abstract—A method of free energy maps is proposed for studying the dynamic correlations of fluctuations in molecules with conformational mobility. An agreement was established between the structure of the free energy level map and the type of the corresponding cross-correlation function (in the presence and absence of the correlation of fluctuations in conformational degrees of freedom in modified dipeptides taken as an example).

Key words: modified dipeptides, free energy level maps, amino acid residues, correlations

With this paper we continue a series of works on comparative investigation of the dynamic properties of relatively simple biopolymers aimed at establishing the basic physicochemical patterns and rules, that determine the dynamic behavior of amino acid residues[1–4]. It is important to investigate the inherent dynamic correlation in systems with conformational mobility, not only in order to understand biopolymer properties, but because such a study would be interesting for generalization of the molecular physical notions about the dynamics of a broad class of polymers and organic molecules [5, 6]. It is impossible to use the normal mode approximation in conformationally labile systems, although it has been applied successfully enough to rigid molecule and crystal dynamics [7]. The cause of this is the fundamentally different topological design of the potential energy level hypersurfaces for these systems. For sufficiently large molecules, the general pattern of conformational energy level hypersurfaces is rather complex [8, 9], and it appears expedient to examine the individual elements of this structure on relatively simple examples. Below we discuss the particular arrangement of the free energy level hypersurfaces for a number of peptides and the influence of this structure on their dynamic behavior. We are dealing particularly with the free energy, which includes the entropy contribution of different areas of the phase space of an individual molecule [10] and, therefore, is more closely related to the realization probabilities of different conformational substates and to the dynamics of transitions between these substates.

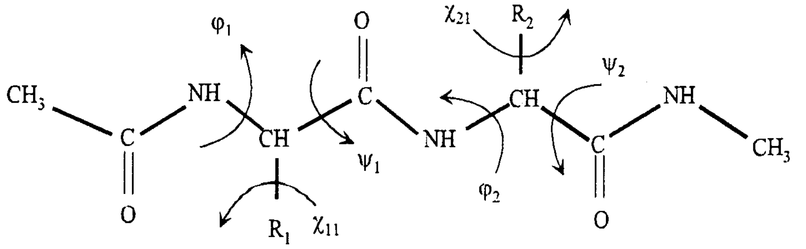

Fig. 1. Structure of molecules of modified dipeptides ($R_1 R_2$) and torsion angle notation.

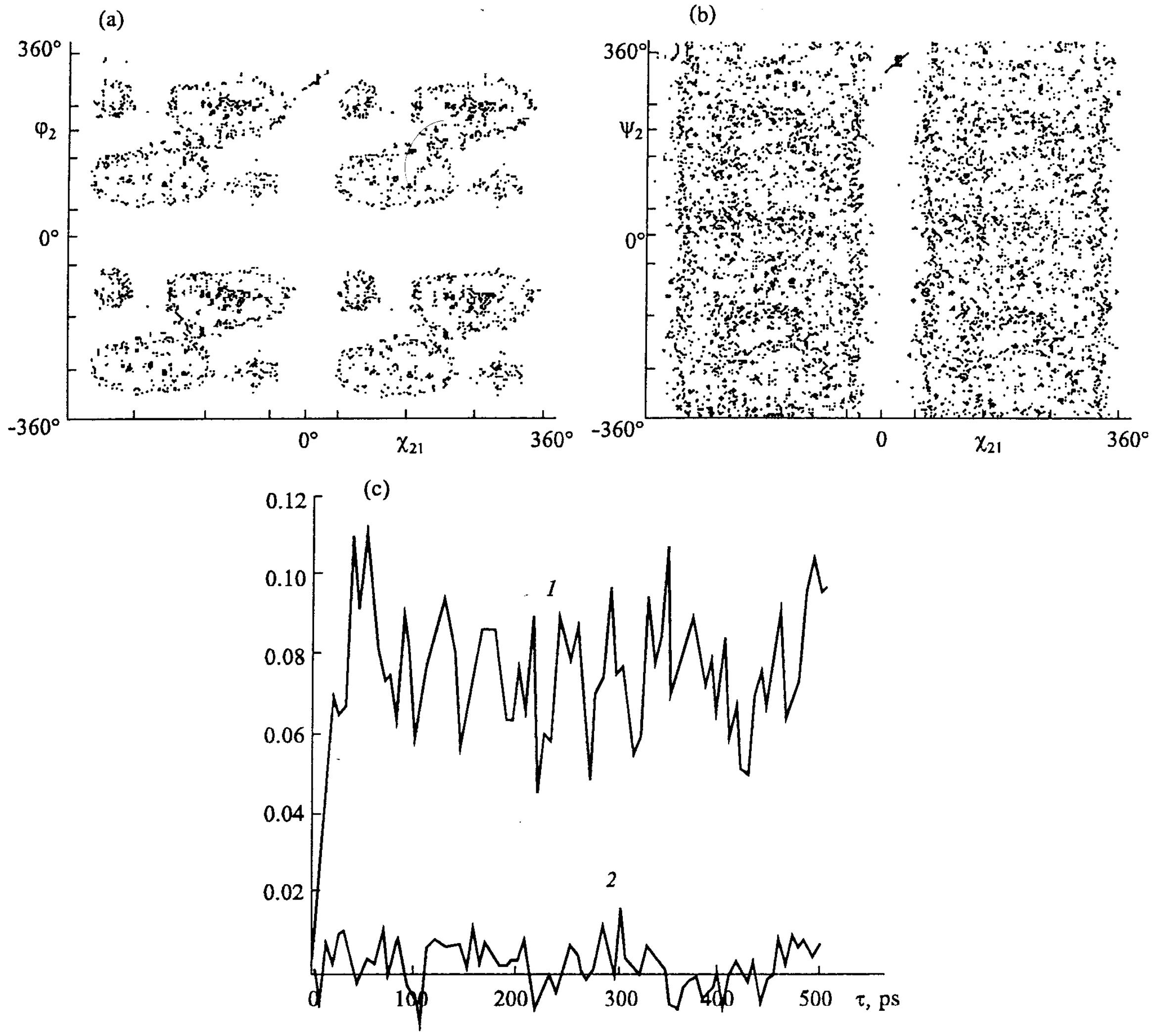

Fig. 2. Free energy level maps for modified dipeptides GLY-ASP on planes: (a) — (φ_2, χ_{21}), (b) — (ψ_2, χ_{21}). Abscissa is χ_{21}. The range of angle variation is from –360 to 360° in linear scale. The transition between lines corresponds to a change of the probability of realization of corresponding conformations by 20%. The white background is pertaius to areas populated with less then 20% probability. Cross-correlation functions F(τ) [2–4] for torsion angles in the dipeptide GLY-ASP (b) are: *1*, φ_2 and χ_{21} (correlation); and *2*, ψ_2 and χ_{21} (no correlation).

The calculation technique and the requirements to trajectories were discussed in detail in a previous paper [1]. We used the collision dynamics method [11]. The effective trajectory length amounted to 5000 ps. Effective temperature was equal to 1000 K. Such values made it possible to scan the allowed area of the configuration space for a sufficient number of times to obtain statistically reliable results. A special investigation showed that the trajectories in question possessed the properties of ergodicity, which in our case meant that the relative probabilities of the figurative point to be found in different areas virtually comply with the canonical distribution [1], and a transfer to lower temperatures would be realized in a standard way [10].

In this work, attention has been focused on a series of modified dipeptides. To reduce the impact of strongly polar terminal groups on the border effect

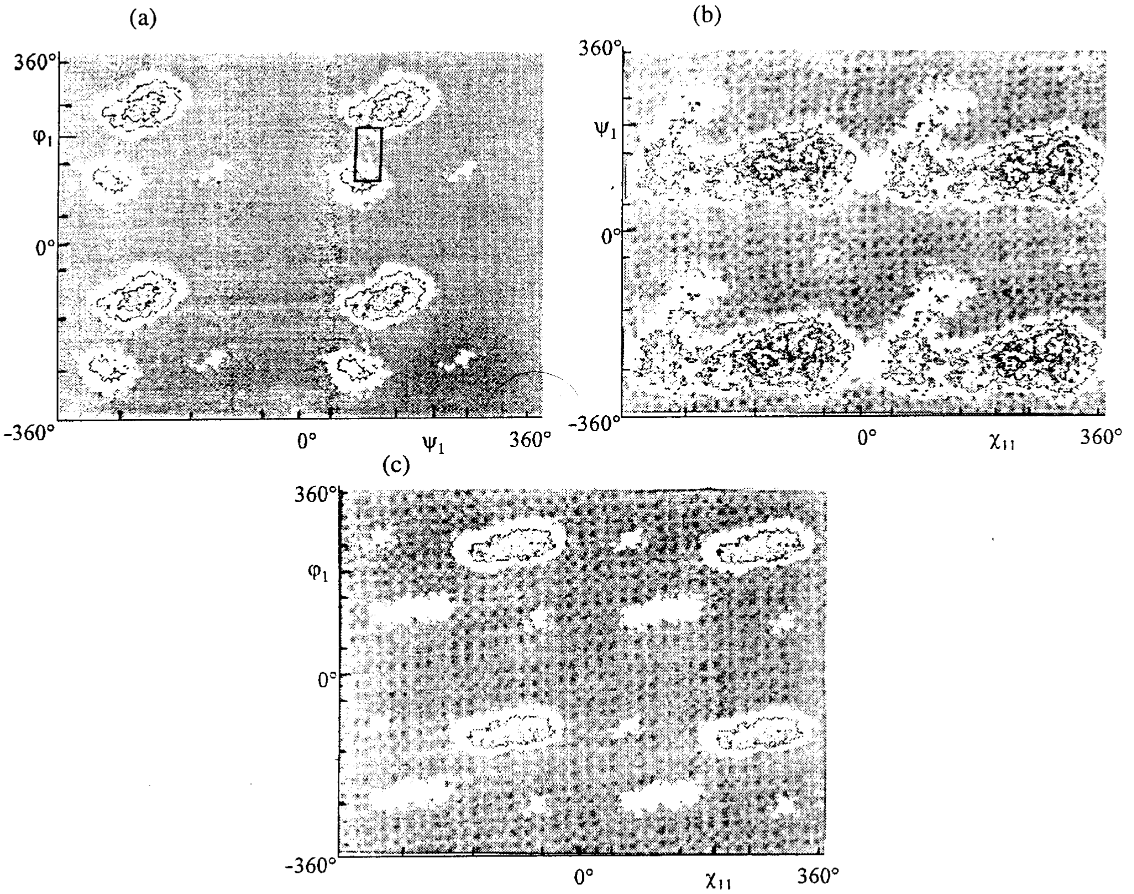

Fig. 3. Free energy level maps for the modified dipeptide TYR-TRP. Range of angle variation is from –360 to 360° in linear scale. The corresponding cross-correlation functions are given in [2] (Fig. 6). The grey background pertaius to the area of the highest energy values. The variable written second is the abscissa axis. (a) Plane (φ_1, ψ_1); the bar means the valley which connects two loci (with pronounced correlation); (b) plane (ψ_1, χ_{11}), a wide curved valley (moderate correlation); (c) plane (φ_1, χ_{11}), the transition between loci requires negotiating a potential barrier; correlation is less pronounced then in the case illustrated in Fig. 2a.

dynamics, the amino end in dipeptides was protected with acetyl, and the carboxy end was protected with N-methylamine, with formation of two additional peptide bonds [1–4]. The results of these changes on the effective atomic charges have beeb determined previously [12]. The general structure of molecules and the notation of torsion angles are shown in Fig.1. In numerical experiments, use was made of the heavy-atom model of a molecule. The potential energy of a molecule $U(r)$ has components responsible for deformations of valence lengths and valence angles, torsion angles, van der Waals and Coulomb nonvalent interactions, as well as hydrogen bonds. The force interaction parameters and the partial charges on polypeptide chain atoms were borrowed from [13], and all pair interactions were taken into account. The dielectric constant of the medium was taken equal to that for vacuum. A procedure of pseudotorsion angle fixation was used in order to block transitions that would have resulted in changes of amino acid residue chirality. Random force pulses, acting on every heavy atom, were used to maintain the preset effective temperature. The average frequency of collisions with each atom was taken to be equal to 100 ps^{-1}, which corresponds to a solvent of relatively low viscosity. Integration of the set of motion equations has been done with a step of 1 fs, while the trajectory was saved into a file after each 0.1 ps.

The trajectories obtained were analyzed by a program package CORREL [1–4]. Two-dimensional $P(\alpha_n, \alpha_m)$ probability distribution functions obtained for the system in different areas of the molecule configuration space. An integral of the form

$$P(\alpha_n, \alpha_m) = \int \ldots \int P(\alpha_1, \ldots \alpha_i, \ldots \alpha_N) \prod d\alpha_i \, (i \neq n, m) \qquad (1)$$

would give a rigorous definition of this value, where α is the set of dynamic variables, and $P(\alpha_1, \ldots \alpha_i, \ldots, \alpha_N)$ is the density of probability of finding the system in the given point of the configuration space. Integral (1) is a partition function of the molecule, with fixed values of the generalized coordinates α_n and α_m. Hence $-k_BT \ln P(\alpha_n, \alpha_m)$, neglecting the additive constant, is equal to the molecule free energy at the corresponding fixed values of the coordinates [10]. According to the conditions under which the trajectory is calculated (constant temperature and pressure, or temperature and volume), the meaning of the free energy changes accordingly. The set of (α_n, α_m) values corresponding to constant $P(\alpha_n, \alpha_m)$, form the free energy level map of the molecule . It should be noted that these maps differ from the conventional Ramachandran maps and the potential energy level maps [14], because they would also include energy and entropy characteristics of the corresponding areas of the configuration space.

Two kinds of system free energy maps for different pairs of conformational degrees of freedom are presented in Fig. 2a,b. Examination of these maps, and also maps in Fig. 3, shows that if dynamic correlations exist (Fig. 2b, curve *1*), there are extended curved valleys or areas, connected with a narrow path (Fig. 2a), on the free energy map. If there is no correlation (Fig. 2, curve *2*), then there are local minima separated by relatively high barriers, as well as extensive and homogeneously rough areas (Fig. 2b). As the correlation time increases, the valley size will also increase, whereas when the correlation time decreases, the valleys decrease in size and are separated by higher barriers. It is necessary to note that the potential energy projections for dynamically isomorphic torsion angle pairs [2–4] have very similar organization.

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