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Dynamical contribution into enzyme catalytic efficiency

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Abstract

A realistic physical model for the so-called rate-promoting vibration (RPV) at enzyme action is constructed. The origin of the RPV is assumed to be an oscillating electric field produced by long-lived localized vibrational modes in protein dynamics, namely, by the so-called discrete breather (DB) in secondary structure. The strength of interaction of the RPV with the reaction coordinate is evaluated and its effect on the reaction acceleration is assessed within the framework of modern theory for thermally activated escape rate at periodic driving. We reveal the phenomenon of resonant activation in our model elucidating why the frequency of the RPV in the range $100 \div 200\,\mathrm{cm}^{-1}$ was chosen by the evolution of enzymes as an optimal one. The effect of the RPV on the reaction acceleration is shown to vary from moderate one (up to $10^3 \div 10^4$) in the case of three-site DB to enormous (up to $10^6 \div 10^8$) in the case of five-site DB and thus can significantly contribute into enzyme catalytic efficiency. Also the model is shown to be compatible with the known functional dependence of enzymatic reaction rates on solvent viscosity.

Keywords: Enzyme catalysis; Protein dynamics; Discrete breather; Solvent viscosity

1. Introduction

Comprehension that specific protein dynamics contributes somehow into enormous reaction acceleration (up to $10^8 \div 10^{15}$) by enzymes has a long history (see Refs. [1–8] and refs. therein). It is supposed that an enzyme provides more efficient reaction activation compared to corresponding non-enzymatic reaction due to a dynamical mechanism and that the latter is significant enough to be a rival to the effect of lowering of the potential energy barrier (due to transition state stabilization) caused by specific interactions of the substrate molecule in an enzyme active site with catalytically active groups. The latter paradigm going back to Pauling is a cornerstone of traditional chemical enzymology [9] and is developed in a number of vigorously conquering approaches such as transition state stabilization by: (i) electrostatic field of preorganized dipoles in an enzyme active site [10,11], (ii) low-energy barrier hydrogen bonds [12], (iii) entropic, strain and desolvation effects (leading mostly to ground state destabilization) [9], etc. Chemical enzymology is a vast field of activity and it will not be touched upon here. Instead, we deal with physical aspects of enzyme action which are still poorly understood. The reason for that seems to be in the lack of adequate theoretical tools to evaluate the contribution of a dynamical mechanism in the reaction rate and in meager direct experimental evidence for its

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existence. The latter is altered to some extent by recent experiments [13–18]. In these papers the importance of protein dynamics for hydrogen tunneling transfer enzymatic reactions was shown and the notion of the rate-promoting vibration (RPV) was coined [13,15] (some authors call it protein-promoting vibration). To regret hydrogen tunneling transfer is involved only in minor and marginal part of enzymatic reactions and up to now there is no direct experimental evidence for the significance of the RPV in covalent bond cleavage between heavy atoms that is the most typical rate-limiting step at enzyme action. For such enzymes the well-known solvent viscosity effect on the reaction rate (see Refs. [5,19] and refs. therein) still remains the most vivid testimony for manifesting itself of protein dynamics in enzyme catalysis. It is commonly accepted that this phenomenon is mediated by protein dynamics but the detailed mechanism is obscure.

An important question is what kind of motion in proteins is responsible for the dynamical contribution into enzyme catalytic efficiency? Some authors relate protein specific motion producing the RPV with conformational motion of peculiar amino-acid residues which may belong to enzyme active cite or be at a distance from it [17,18]. In our opinion this scenario encounters difficulties at attempts to reconcile it with the experiments [20–23]. The latter unequivocally testify that enzymes retain their catalytic capacity at temperatures below the so-called dynamical ''glass'' transition where conformational motion is considerably suppressed (see, e.g., Refs. [21,24] and refs. therein). Some guess on the origin of the RPV can be obtained by considering its frequency. The authors of [15] conclude that the estimated dominant peaks in the spectral densities of the RPV indicate motions on the $150\,\mathrm{cm}^{-1}$ frequency scale. There are another assessments of this value in the literature: $\leqslant 300\,\mathrm{cm}^{-1}$ [6] and $200\,\mathrm{cm}^{-1}$ [25]. In the latter paper the RPV is attributed to the mode of Amide-VII of a peptide group vibrations. However, this mode requires some torsion of the plane of a peptide group and is very energetically consumptive and unfavorable. In our paper [26], it was shown that there is another possible type of long-lived localized vibrational modes in protein dynamics with required frequency, namely, the so-called discrete breather (DB) in protein secondary structures. The non-linear localized excitations named DBs or else intrinsic localized modes are time periodic spatially localized oscillations with significant amplitudes of several units in a chain of weakly coupled non-linear oscillators while others are at rest or oscillate with negligible amplitudes. They were discovered by Sievers and Takeno [27] and proved by MacKay and Aubry [28] to be structurally stable. By now they are well understood and commonly appreciated as a generic phenomenon in nature (see Ref. [29] and refs. therein). DBs have become a new and very fruitful paradigm in non-linear physics and in particular, much work is being carried out at present to construct models for DBs in biomolecules. The paper [26] is a development along this line. It is shown there that the frequency of a DB in an α-helix can be obtained equal to$115\,\mathrm{cm}^{-1}$ in accordance with the results of the experiments of [30] on far infra-red laser pulse spectroscopy of proteins. The DB is actually an oscillation of the planes of some peptide groups in an α-helix or β-sheet around their equilibrium positions with considerable amplitude (up to $10^{\circ} \div 15^{\circ}$) while neighboring peptide groups oscillate with much less amplitudes and more distant groups oscillate with negligible ones or stay at rest. Thus, the DB is assumed to store and utilize the energy released at substrate binding by an enzyme. It is created by an external cause (binding energy) rather than by equilibrium thermal fluctuations though can be fed by the latter. As a peptide group is known to have a large dipole moment ($\approx 3.6\,\mathrm{D}$) parallel to its plane [31] the participation of the latter in the DB creates an oscillating electric field. Such fields (the so-called electrostatic fluctuations) are for long supposed to be a key factor for enzyme catalysis [4]. The field can interact with the reaction coordinate because during the movement of the system along the latter a separation of charges takes place yielding the dipole moment of the reaction coordinate. Thus, protein dynamics affects the potential surface for the reaction making the latter to be non-stationary. The shape (e.g., the height) of the reaction energy barrier becomes time dependent. As will be discussed below the oscillating electric field in accordance with the general theory of the effect of periodic driving force [32] ""heats up'' the system by changing its effective temperature thus giving rise to lowering of the activation energy of escape which can be much bigger than the real temperature even for comparatively weak fields''.

The aim of the present paper is to construct a realistic physical model for the dynamical mechanism contributing into enzyme action and to evaluate its possible catalytic efficiency. We attain the latter within the framework of the archetypical model for the reaction rate, namely that of the overdamped limit of the Fokker–Planck equation (see Ref. [33] and refs. therein) with non-stationary force field. This equation is a standard tool for studying phenomena with time-dependent potentials mostly within the context of stochastic