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CHAPTER 4
Principles of Enzyme Catalysis
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4.3. The Relaxation Concept of Enzyme Catalysis

The theories on the conformational changes of the enzyme molecule in the course of a catalyzed reaction and the crucial role of these changes for enzyme functioning were put forward many years ago. The history of this problem has been considered in brief in the preceding section of this chapter.

The first approach toward the relaxation concept of enzyme catalysis was probably formulated in 1970 in the pioneering work by Sidorenko and **Descherevsky**. According to [**18**], after the completion of the enzymatic cycle and the liberation of a product, the free enzyme molecule remains in a conformationally non-equilibrium state. The relaxation time of this state may be comparable with the time interval between two consecutive catalytic acts related to a single enzyme molecule. In this case, catalytic activity of an enzyme will depend on the time moment of a substrate attachment to the enzyme molecule after product dissociation in the preceding cycle of enzyme turnover. Two mathematical models have been analyzed. According to the first, "discrete" model, an enzyme can exist only in two states: the "excited" state (after disintegration of the Michaelis complex) and the relaxed state (after the relaxation of the "energized" state). In the second, "continuous" model, the "excited" enzyme molecule relaxes to equilibrium through a continuous set of intermediate states. Analysis shows that both models lead to the kinetic behavior declining from the required by the Michaelis-Menten.

The main feature of the Sidorenko-**Descherevsky** approach was the statement that conformational relaxation of the functioning enzyme molecule can acquire an important role in enzyme activity. Meanwhile, the mechanism of the chemical transformation of the substrate was considered as the conventional one. The conformational changes in the course of enzyme relaxation influence the activity of an enzyme, but do not take an immediate part in performing the elementary chemical act.

The first notion on the deviation of elementary catalytic acts of enzyme reaction, from that prescribed by classical thermodynamic and kinetic approaches, was, probably, formulated in 1971 [19]. It had been shown that the application of basic postulates of activated state theory to the majority of enzyme processes can lead to physically meaningless values of the activation parameters (energy and entropy of activation). It was emphasized that enzyme functioning is more similar to the work of a mechanical construction than to the catalytic homogeneous

chemical reaction. The self consistent phenomenological relaxation theory of enzyme catalysis was proposed in 1972 [20, 21].

What is the principal idea of the relaxation concept? This is not simply a question of the conformational relaxation of the substrate-enzyme complex associated with changing the enzyme catalytic activity. The substrate binding to an enzyme active center initiates the conformational relaxation acting as the driving force that pushes the chemical system (substrate molecule attached to the catalytic center) along the reaction coordinate.

Speaking, for certainty, of the "substrate binding" as the factor triggering the conformational transition of a system to the new state of equilibrium, we have to remember other factors. As noted in Section 4.1, any local chemical change in the protein molecule (the substrate or inhibitor binding to the active center, redox change of a group in the prosthetic group, ionization of acid or base group, etc.) can lead to the appearance of a conformationally non-equilibrium state. The fast vibrational relaxation ($\tau \sim 10\text{-}12$ s) of the active center and its nearest surroundings takes place immediately after the local disturbance, while the structure of the whole protein globule still remains practically the same. However, the structure of the unchanged globule becomes the non-equilibrium one. The new kinetically available equilibrium state for the whole system (the enzyme-substrate complex) will correspond to the conformationally changed structure of the protein globule with the product bound to an enzyme active center. The relaxation concept of enzyme catalysis assumes that the transformation of a substrate molecule into the product is realized in the course of the enzyme-substrate complex conformational relaxation to the state of equilibrium. As has been stressed above, this transition can proceed extremely slowly compared with the time scale of vibrational relaxation.