

Picobiology

Picobiology is a field of biology in which we identify the protein(s) that drive physiologically important phenomenon, determine the structure at a resolution of 1 pm and elucidate the reaction catalyzed by the protein(s) with chemistry words. Primary research techniques include protein crystallography and vibrational spectroscopy as well as versatile cellular biology techniques.

All the physiological processes are comprised of chemical reactions catalyzed by enzyme proteins. Therefore, we need to clarify the functional mechanism of proteins in order to understand the life processes. More than several tens thousands of proteins are present in human body and each protein performs a specific function. Therefore, we must first identify the protein performing the function. Any identified protein is a so-called black box and the functional mechanism is not clear even if the function of converting molecule A to molecule B is clarified through biochemical study. Structural analysis is prerequisite to unveil the mechanism of the black box. One of the techniques is protein crystallography by which three dimensional structure is determined at a spatial resolution of 10 pm (0.1 Å).

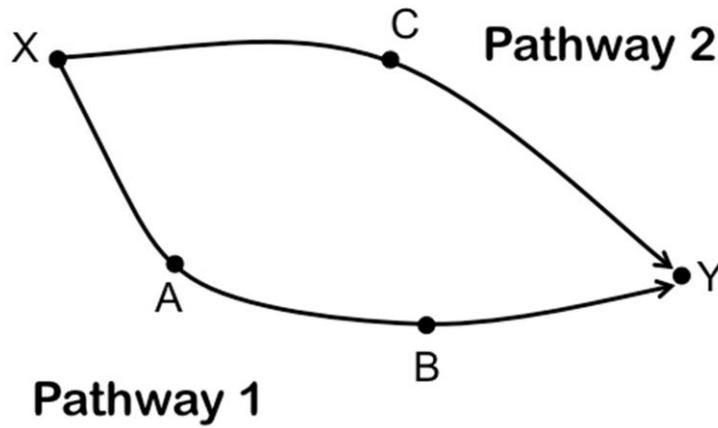
Three-dimensional structure reveals the layouts of functional groups and amino acid residues of proteins. This means that the structural basis for a specific reaction to occur is clarified. However, the resolution of 10 pm is not sufficient to unveil the black box. In order to unveil the black box, vibrational spectroscopic analysis is required as well. It provides us with structure at a resolution of 1 pm (0.01 Å) sufficient to detect the difference of chemical reactivity of functional groups. If a bond length is elongated by only 1 pm from an equilibrium length, the bond becomes less stable. This means that the molecule has a higher energy and therefore a higher reactivity. The relationship between the energy of functional group and its reactivity could be obtained by quantum chemical calculations. Determination of structural information at a 1 pm resolution is crucial to clarify the functional mechanism.

Protein changes its structure during catalysis of chemical reactions. When a protein changes its structure from structure X to structure Y, what kind of pathway does the protein go through? Clarifying the pathway is essential to unveil the black box. Figure 1A depicts two possible pathways of protein structural change during catalysis of a chemical reaction. Protein undergoes structural change either $X \rightarrow A \rightarrow B \rightarrow Y$ (Pathway 1) or $X \rightarrow C \rightarrow Y$ (Pathway 2). In picobiology, stable structures of X and Y are determined by crystallography, and we determine which of the Pathway 1 and Pathway 2 is realized by detecting the short-lived species of A, B and C by vibrational

spectroscopy. For stable structures X and Y, three-dimensional structures are determined by crystallography and at the same time the chemical reactivity of functional groups is determined by vibrational spectroscopy. Based on the results, functional mechanism is clarified. Figure 1B depicts two energy diagrams for pathways 1 and 2, respectively. Structures X and Y are common to two pathways; however, the pathways 1 (left panel) and 2 (right panel) are distinct. Quantum chemical calculations are used to clarify the origin of the energy difference between structures A, B and C, and origin of energy barriers present between these structures. As described above, in Picobiology, we understand the physiological phenomenon by clarifying the chemical reaction steps one by one and by elucidating the chemical reaction based on structures at a resolution of 1 pm.

(Oct. 2014 Version)

(A) Two Pathways from Protein Structure X to Protein Structure Y



(B) Energy Diagram for Pathways 1 and 2

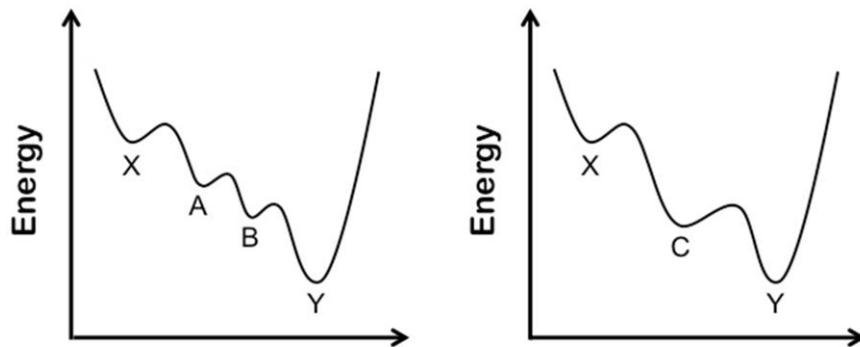


Figure 1. Model Protein Structural Change Pathways (Structure X \rightarrow Y)
(A) Two Pathways from Structure X to Structure Y (B) Energy Diagram for Pathway 1 (Left) and Pathway 2 (right)