Chapter 1
Basic Concepts of Allosteric Control

In the late 1950s, a number of workers discovered that in bacteria, metabolic pathways which lead to the synthesis of essential metabolites are subject to feedback (or end-product) inhibition (Novick and Szilard, 1954; Umbarger, 1956; Yates and Pardee, 1956). It was established that, in many metabolic pathways, the terminal metabolite in the pathway functions as a specific inhibitor of the first enzyme in the pathway. Enzymological studies on a number of metabolic pathways revealed that the end-product, which is chemically distinct from the substrates of the initial enzyme in the pathway, inhibits the activity of the enzyme by binding to a site distinct from its active site. Since this feedback inhibitor is not isosteric with the substrate, the term allosteric effector was coined (Monod et al., 1963). It was established that the allosteric effector interacts with a specific allosteric site on the enzyme which is topographically distinct from the active site. The binding of the allosteric effector to the allosteric site brings about the allosteric transition, which consists of a specific conformational change at the active site (and other areas of the protein molecule), thus modulating its activity. It was very quickly realized that allosteric effectors are not necessarily inhibitors. They may also function as activators. In their classical paper Monod et al. (1963) give the example of phosphorylase b activation by 5'-AMP. In the latter case, 5'-AMP functions as a positive effector, switching on the phosphorylase reaction. It was therefore clear that allosteric effectors may be either negative effectors or positive effectors, depending on whether they inhibit or activate the reaction in question.

The essence of allosteric effects involves the interaction between the ligand-binding sites. When the site-site interactions
occur between chemically identical binding sites, one speaks of an interaction between *homologous* sites. When the site-site interactions occur between chemically nonidentical sites, one speaks of an interaction between *heterologous* sites. The binding of oxygen to hemoglobin represents a case of homologous interactions, whereas the inhibition of aspartate transcarbamylase by CTP represents a case of heterologous interactions. Homologous interactions are responsible for the phenomenon of cooperativity. If the binding of a ligand molecule results in a change in the affinity of the remaining sites towards the same ligand, the binding curve obtained is nonhyperbolic, namely the process of ligand binding cannot be described by a Langmuir or a Michaelis type of equation. In the case of hemoglobin, the oxygen-binding curve is sigmoidal, since the binding of oxygen results in an increase of the affinity of the remaining oxygen-binding sites towards oxygen. This progressive increase in affinity is known as *cooperativity* or, more accurately, *positive cooperativity*. As will be shown later, the affinity of ligand-binding sites can in principle decrease as a function of ligand saturation. This situation results in negatively cooperative ligand binding. Today it is well established that many regulatory enzymes also exhibit negative cooperatively in ligand binding. Many of the regulatory enzymes which exhibit cooperatively in ligand binding also possess allosteric sites and, therefore, exhibit interaction between heterologous sites. Monod et al. (1965) already pointed out that many allosteric enzymes such as ATCase (aspartate transcarbamylase) (Gerhart and Pardee, 1963) and threonine deaminase (Changeux, 1961) bind the substrate cooperatively. Furthermore, Monod et al. (1963) noted that treatment of many allosteric enzymes with Hg$^{2+}$ not only desensitizes those enzymes towards their respective allosteric effectors, but also eliminates their substrate cooperative effect. In other words, the desensitized enzyme binds the substrate molecule in a noncooperative (Michaelian) fashion. This observation indicated that cooperative interactions between identical ligand sites (homologous sites) and the interactions between allosteric sites and active sites (heterologous sites) are linked functionally. When the interacting sites are identical, the interactions are termed *homotropic* (example: binding of oxygen to