Chapter 2
The Structure of Multisubunit Proteins

I. General Principles

Regulatory enzymes are multisubunit structures. Structural analysis of regulatory enzymes has in every single instance revealed that the subunits interact with each other by way of specific noncovalent bonds. The subunits always form a well-defined geometrical structure, and the architecture obtained determines to a large extent the regulatory properties of the protein. It will therefore be necessary for us to discuss in some detail the principles of design of oligomeric proteins.

The terminology used to describe the structure of multisubunit enzymes is as follows: a protein which is composed of a number of subunits is called an oligomeric protein, or an oligomer. The subunits building the oligomeric structure are referred to as protomers, monomers, or subunits. The subunits (protomers) are bound to each other at specific intersubunit binding domains by noncovalent bonds. A subunit is usually composed of one polypeptide chain, although there are a limited number of cases where each subunit is composed of more than one polypeptide chain. Many regulatory proteins are composed of identical subunits such as glyceraldehyde-3-phosphate dehydrogenase, or from nonidentical subunits as in the cases of hemoglobin, tryptophan synthetase and aspartate transcarbamylase. In hemoglobin the \( \alpha \) and the \( \beta \) subunits have identical functions. In other oligomeric proteins, such as aspartate transcarbamylase and tryptophane synthetase, the two types of subunit are different and also have different functions.

Most oligomeric proteins are composed of a small number of subunits which form closed oligomeric structures that rarely contain more than 12 subunits. In certain cases, such as multienzyme complexes or spherical viruses, the number of protomers is
much larger. In their classical paper Monod et al. (1965) observed that the specificity of subunit-subunit recognition is so great that monomers of an oligomeric protein will associate exclusively with their identical partners even at high dilution and in the presence of other proteins. This principle has been verified by detailed renaturation studies on numerous oligomeric enzymes (Cook and Koshland, 1969). The existence of strong and specific noncovalent inter-subunit interactions which form these geometrically defined aggregates indicates that the subunit interact at specific binding domains. According to Monod et al. (1965), two modes of subunit interactions (Fig. 1) are possible:

![Fig. 1a and b. Modes of subunit association. (a) Isologous association, (b) heterologous association](image)

a) Isologous association: the binding domain is made of two identical binding sets (Fig. 1a), each consisting of an "ab" contact. These binding domains are related to each other by a twofold rotational axis of symmetry.

b) Heterologous association: the binding domain is made of two binding sets (Fig. 1b) which differ from each other: one is a "bc" contact and the other is an "ad" contact. The arrangement of subunits in this case is also known as the head to tail mode of association.

The majority of proteins composed of subunits are either dimers or tetramers. The isologous mode of subunit interactions is the prevalent mode of aggregation in known protein dimers and tetramers. However, some heterologous tetramers such as tryptophanase (Morino and Snell, 1967) and pyruvate carboxylase (Valentine et al., 1966) do seem to have cyclic symmetry ($C_4$). Trimers, pentamers and hexamers, in which the mode of subunit aggregation is heterologous and therefore possess cyclic symmetry, are also known (Klotz et al., 1970).