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A Study of Enzymes

Volume II Mechanism of Enzyme Action

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Lorsqu'il n'est pas en notre pouvoir de discerner les plus vraies opinions, nous devons suivre les plus probables. (When it is not in our power to determine what is true, we ought to act according to what is most probable.)

René Descartes (1596—1650)

Dedicated to all students of enzymology, both past and present, whose fascination with enzyme mechanisms made this treatise possible.

PREFACE

Although there have been several excellent theses on Enzyme Mechanisms, the time seems unusually ripe for a definitive and selected series of reviews on the subject.

In the past several years, there has been a remarkable resurgence of activity and expansion of knowledge in the area of enzyme mechanisms, both in theory and in data acquisition. Many enzyme proteins, whose primary sequence seemed almost beyond the realm of existing technology have been now had their covalent structures deduced from their complementary DNA's. This then permitted a host of chemical derivatization and modification studies designed to shed light on structure-function relationships. With the recent advent of new techniques, especially in the X-ray deduced macromolecular crystal structures and in the NMR deduced solution structures, and coupled with some specific chemically synthesized and in some cases site-directed mutagenesis experiments (where critical, or noncritical, residues may be substituted in the enzyme molecule, or in peptide fragments of the enzyme molecule), an explosion in enzyme mechanistic studies seems almost imminent.

Structure-function relationships in the future will undoubtedly be assisted by computer modeling, where computer techniques making use of the X-ray crystal and NMR solution structure data, will permit an extension of ideas beyond those of conventional methods.

Together with the application of new or updated spectroscopic approaches, e.g., in nuclear magnetic resonance, in fluorescence, in infra-red Fourier analyses, one will be able to study in greater detail the solution structure of the enzyme-substrate complex(s). A hint of these tremendous advances to be made may be found, e.g., a number of the studies reported here (e.g., on superoxide dismutases, Chapter 21 and on adenylate kinase, Chapter 17).

Molecular dynamics of enzyme proteins are now under vigorous investigation. Interactions of the enzyme molecule with its substrate(s) or modifiers or with specific inhibitors may induce changes in shape and in characteristics. Conformational (or fluctuational) changes on a micro scale lead to ideas concerning the dynamics of such systems (cf. Chapter 1).

Metals in enzyme catalysis have long been the serious study a number of investigators, and ideas concerning complexation in biological systems are only now beginning to be codified (see Chapter 2).

Sound Bioorganic and physical chemical approaches to the study of enzymatic mechanisms are still the preferred method of approach in certain problems of enzyme mechanisms (as illustrated e.g., in Chapters 3 and 4, and in Chapters 19 and 20).

The time is ripe for a detailed review of recent studies on allosteric enzymes (e.g., Chapter 5 on glycogen phosphorylase) and on multienzyme complexes (Chapters 4 and 9).

A remarkable headway has been made in the kinetic studies of certain dehydrogenases, whose X-ray structures are now well known (e.g., dihydrofolate reductase, Chapter 8). Very elegant modification and derivatization experiments, together with the application of a fluorometric approach, is shedding much light on the mechanism of glutamate dehydrogenase (e.g., Chapter 7).

Medical advances are to be anticipated as a result of in vivo and in vitro mechanistic studies (e.g., Chapters 6, 22, 23, and 24).

Since the early days of Michaelis' pioneering experiments, studies of flavo-protein catalysis have been at the forefront of investigations into the mechanisms of redox reaction (Chapters 10, 11, and 12); and ideas concerning semi-quinones and free radicals originated in these studies. Free-radical oxygen (e.g., superoxide anion) has also absorbed the attention of those interested in the dismutation H_2O_2 (e.g., Chapter 21), and the oxygen utilizing reactions, e.g., the monooxygenases and dioxygenases (Chapter 13), will continue to receive the attention they deserve. Now, however, new approaches have permitted deeper insight into the role that the very short-lived intermediates (e.g., with oxygen) play in their mechanisms.

The mechanism of action of the ATP-utilizing enzymes and carriers will continue to occupy much attention especially because of their intrinsic biological importance (Chapters 14, 15, 17, and 18). Their modes of action and those of the phosphotransferases (Chapters 17 and 18) and the nucleotidyl transferases (Chapter 16) are fascinating and absorbing topics for the mechanistic bent of mind.

It, therefore, was the original goal to follow Volume I, which deals with a sound description on enzyme kinetics and ligand binding with Volume II, to deal in detail, with carefully selected topics in enzyme mechanisms, as written by those investigators with a special interest in the particular enzyme mechanism(s) they discuss here.

We hope that we have not been unsuccessful in both of these goals.

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He is a member of the American Society of Biochemistry and Molecular Biology, the American Chemical Society Division of Biochemistry (Chemistry), Sigma Xi, Phi Beta Kappa, American Association for the Advancement of Science, and the New York Academy of Sciences. He has been a member of the Subcommittee on Enzymes, Committee on Biological Chemistry, Division of Chemistry and Chemical Technology, National Academy of Sciences and National Research Council; and also a member of the Physiological Chemistry Study Section, Division of Research Grants, National Institutes of Health, Public Health Service, Department of Health, Education and Welfare. His long list of publications reflect these research interests.

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