PREFACE

It is 14 years since I wrote the second edition of *Enzyme Structure and Mechanism,* at a time when we were just entering the age of protein engineering. Since then, the spectacular advances in determining biological structure, manipulating genes, engineering proteins, sequencing whole genomes, and computing have made each successive year more exciting than the last. We are now entering a new age of protein design, a time when the fields of protein folding and enzymology converge. Inspired by these developments, I have expanded *Enzyme Structure and Mechanism* into a more general book about mechanism in protein science that shows the unity of concepts in folding and catalysis.

So much is now known about enzyme mechanisms that the latest compendium on just the chemical aspects takes up four volumes of more than 1500 pages. In the past year alone, more than 20,000 scientific papers on enzymes and more than 2000 on protein folding and design were published. This book is intended to be a guide to the study of structure, activity, and mechanism, and so to provide a path through the vast subject of protein science. I believe that the understanding of mechanism is based on knowing the structures and properties of the reagents and the kinetics and thermodynamics of their reactions, as well as how the kinetics and other properties change when the structures of the reagents are modified and the reaction conditions are altered. Accordingly, the key to understanding proteins and their action is understanding basic chemistry, kinetics, thermodynamics, and structure, and how they are related. I concentrate on the fundamental principles, illustrated by representative examples in depth, rather than providing a comprehensive survey. The emphasis is on simple, direct observation and simple, direct measurements. The method of this book is to discuss basic principles, with an emphasis on the fundamental physical and chemical processes behind them to develop an intuitive feel for the handling of formulas, kinetics, and elementary thermodynamics.

Structure and Mechanism in Protein Science has evolved naturally from *Enzyme Structure and Mechanism,* because the same strategies apply to studying mechanism in both catalysis and folding. The advent of protein engineering allows the structure of proteins to be modified in a manner similar to small molecules so that structure–activity relationships may be studied. There are four new chapters, all based on the impact of protein engineering on protein folding and catalysis. One chapter illustrates the uses of protein engineering in enzymology, with two examples: the tyrosyl-tRNA synthetase as a model case for studying and exemplifying the principles of catalysis; and subtilisin for protein redesign. There are three chapters on protein folding, dealing with protein stability, the kinetics of folding, and the pathways or "energy landscape" of folding. Several chapters—Chapters 1 (The Three-Dimensional Structure of Pro-

teins), 6 (Practical Methods for Kinetics and Equilibria), 10 (Conformational Change, Allosteric Regulation, Motors, and Work), 11 (Forces Between Molecules), 14 (Recombinant DNA Technology), and 16 (Case Studies of Enzyme Structure and Mechanism)—have been extensively rewritten. Other chapters have had varying degrees of updating and pruning, but those on classical enzymology have largely been left alone. I have tried to maintain a balance between historical development and current knowledge.

The ribbon diagrams were drawn with the program MolScript, which Per Kraulis has so generously distributed to the scientific community.

Much of this book was written while I was a Scholar-in Residence at the Fogarty International Center for Advanced Study in the Health Sciences, National Institutes of Health, Bethesda, Maryland, USA. I am indebted to several colleagues for their useful comments, especially those of Attila Szabo on Chapters 17, 18, and 19. I thank in particular Sophie Jackson for her critical reading of the entire manuscript and for her help with the proofs.

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