Hermann Dugas

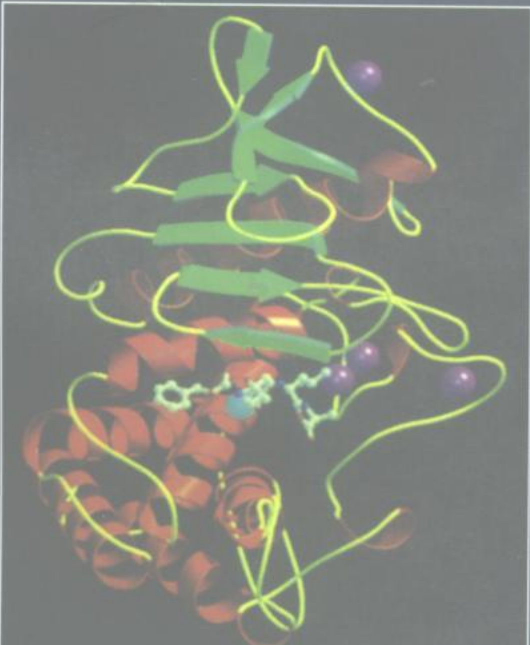
Bioorganic Chemistry

A Chemical Approach to Enzyme Action

Third Edition

生物有机化学

第3版



Springer-Verlag

世界图书出版公司

Hermann Dugas

Bioorganic Chemistry

A Chemical Approach to Enzyme Action

Third Edition

With 112 Figures, 6 in Full Color

Springer-Verlag
世界图书出版公司
北京·广州·上海·西安

Hermann Dugas
Département de Chimie
Université de Montréal
Montréal, Québec
Canada H3C 3J7

Series Editor:
Charles R. Cantor
Boston University
Center for Advanced Biotechnology
Boston, MA 02215, USA

Cover illustrations: Foreground: The figures shows thermolysin with an inhibitor that is believed to be an analog of the transition state (in white) bound to the near active-site cleft. The inhibitor is the tripeptide Cbz-*Phe*^{P}-Leu-Ala. The active site zinc is shown in blue and the four calcium ions are in mauve. β-sheet regions are in green, helices are orange, and irregular regions of the enzyme are shown in yellow. Section 7.3.1 of the book can be consulted for more detail. (Courtesy of Dr. Ingrid Vetter and Prof. Brian Matthews, University of Oregon). **Background:** X-ray structure of the extended thermolysin active-site cleft. Reproduced with permission from *Biochemistry* **26**, 8542–8353 (1987).

Library of Congress Cataloging in Publication Data
Dugas, Hermann.
Bioorganic chemistry : a chemical approach to enzyme action / Hermann Dugas. — 3rd ed.
p. cm. — (Springer advanced texts in chemistry)
Includes bibliographical references and index.
ISBN 0-387-94494-X (alk. paper)
1. Enzymes. 2. Bioorganic chemistry. I. Title. II. Series.
QP601.D78 1996
574.19'25—dc20 95-8361

Printed on acid-free paper.

Acquiring editor: Robert C. Garber
Production coordinated by Chernow Editorial Services, Inc., and managed by Terry Kornak; manufacturing supervised by Jeffrey Taub.
Typeset by Best-set Typesetter Ltd., Hong Kong.

This reprint has been authorized by Springer-Verlag(Berlin/Heidelberg/New York) for sale in the People's Republic of China only and not for export therefrom.
Reprinted in China by Beijing World Publishing Corporation. 1998

ISBN 0-387-94494-X Springer-Verlag New York Berlin Heidelberg

Springer Advanced Texts in Chemistry

Springer
New York
Berlin
Heidelberg
Barcelona
Budapest
Hong Kong
London
Milan
Paris
Santa Clara
Singapore
Tokyo

Springer Advanced Texts in Chemistry

Series Editor: Charles R. Cantor

Principles of Protein Structure
G.E. Schulz and R.H. Schirmer

Bioorganic Chemistry: A Chemical Approach to Enzyme Action (Third Edition)
H. Dugas

Protein Purification: Principles and Practice (Third Edition)
R.K. Scopes

Principles of Nucleic Acid Structure
W. Saenger

Basic Principles and Techniques of Molecular Quantum Mechanics
R.E. Christofferson

Energy Transduction in Biological Membranes: A Textbook of Bioenergetics
W.A. Cramer and D.B. Knaff

Principles of Protein X-ray Crystallography
J. Drenth

Biomembranes: Molecular Structure and Function
R.G. Gennis

This book is dedicated to
all those professors, teachers, students, and friends
who have realized and appreciated
the pleasure of transmitting human knowledge.
What else could be more noble?

Series Preface

New textbooks at all levels of chemistry appear with great regularity. Some fields such as basic biochemistry, organic reaction mechanisms, and chemical thermodynamics are well represented by many excellent texts, and new or revised editions are published sufficiently often to keep up with progress in research. However, some areas of chemistry, especially many of those taught at the graduate level, suffer from a real lack of up-to-date textbooks. The most serious needs occur in fields that are rapidly changing. Textbooks in these subjects usually have to be written by scientists actually involved in the research that is advancing the field. It is not often easy to persuade such individuals to set time aside to help spread the knowledge they have accumulated. Our goal, in this series, is to pinpoint areas of chemistry where recent progress has outpaced what is covered in any available textbooks, and then seek out and persuade experts in these fields to produce relatively concise but instructive introductions to their fields. These should serve the needs of one semester or one quarter graduate courses in chemistry and biochemistry. In some cases the availability of texts in active research areas should help stimulate the creation of new courses.

Charles R. Cantor

Preface to the Third Edition

It was over 100 years ago that Emil Fischer postulated his ingenious "lock-and-key" principle, which was subsequently applied to the development of a modern theory of enzyme catalysis. Later, the molecular recognition concept was used as the basis for the elaboration of the different fields of bioorganic chemistry. I am tempted to say that if Emil Fischer had lived in our time, he would undoubtedly be a leader in what is now called supramolecular chemistry, an important discipline of bioorganic chemistry. As we know, enzymes, by their complexity, set chemists a high standard for developing synthetic catalysts to imitate nature's highly selective enzymatic reactions. With the end of the twentieth century and the approach of a new millennium, bioorganic chemistry and enzyme mimetics are becoming more and more fashionable disciplines, particularly with the recent development and application of novel "molecular devices" that are expanding the frontiers of molecular science. With this point of view in mind, the third edition of the book was undertaken.

The publication of this third edition also coincides with the 75th anniversary of the Department of Chemistry of the Université de Montréal and my 25 years of teaching in this department.

To keep the book to a reasonable size, some sections from the second edition have been removed. Indeed, each chapter has been updated with new biomimetic examples, references, and/or review articles. At the same time, this exercise provided an opportunity to correct various graphic and typographic errors present in the previous edition. However, the major change in the third edition is a new chapter on molecular devices, in which the protocols of self-organization and self-assembly at the supramolecular level are exploited. Topologically complex molecules have until recently been regarded as mere academic curiosities, but their potential as components of molecular-scale devices is now being realized. Expressions such as *molecular meccano* and *molecular tectonics* or even *molecular cybernetics* are now used on a daily basis by a growing number of bioorganic chemists, and it is in these new domains, with an obvious analogy to molecular construction kits, that the fastest progress in bioorganic chemistry is taking place.

The reference section is composed of a list, although not exhaustive, of no less than one hundred review articles on bioorganic chemistry that appeared in the last 15 years. This impressive number is a strong barometer of the vivacity and growing popularity of the field.

Again, as in the previous editions, the emphasis is more on the concepts of bioorganic chemistry than on the details of synthetic and mechanistic difficulties of preparing the molecules within each individual project or field of application.

One of the goals of bioorganic chemistry is to mimic and understand via models the living processes in nature. This book is a tribute to this goal. However, the biomimetic approach is not limited to natural processes. Many biomodels go beyond the natural pathways and allow us to learn more about chemistry and nature, and often open new avenues in science. In this book I hope that I have succeeded, in a modest way, in transmitting this taste for knowledge.

Montréal, Canada Hermann Dugas
January 1995

Preface to the Second Edition

The design and synthesis of molecules to mimic biological events can no longer be considered a new field. This is particularly true since the last decade where we have witnessed a real explosion of new biomodels of enzymatic transformations. The growing importance of bioorganic chemistry is easily measured by the impressive number of review articles (over seventy) written on various bioorganic subjects. The list is given in the reference section, at the end of the book.

Indeed, increasing numbers of chemists and biochemists are studying simple synthetic molecules as models of enzymes. The aim is to fashion molecules that will catalyze useful reactions without the need of the bulky polypeptide backbone of proteins. The major concept behind this approach is *molecular recognition*. The importance of this discipline was recognized worldwide when the 1987 Nobel Prize in chemistry was awarded to D.J. Cram, J.M. Lehn, and C.J. Pedersen, three pioneers and leaders in this field.

In this second edition, Chapters 2 and 3 have been completely restructured to emphasize new developments in amino acid and nucleotide chemistry in the past ten years. Therefore, the aspect of chemical and biological synthesis of proteins and polynucleotides has been replaced by new subjects such as developments in asymmetric synthesis of amino acids, chemical mutations and protein engineering, and other exciting new fields such as antibodies as enzyme and RNA as catalyst and a section on DNA intercalating molecules. Among other modifications, a general presentation of the biomimetic approach to model design has been added in the first chapter, and molecular recognition in Chapter 2 focuses on structure-activity relationship in neuropeptides and drug design. In my experience, this section was particularly appreciated by students. It became also important in this new edition to develop a section on transition state analogs.

Chapters 4 to 7 retain the same basic structure but each section has been updated with new and enlightening examples. All those examples stress the talent of those chemists for imaginative chemical architecture in bioorganic models of biological processes. Chapter 4 has been expanded to include a section on enzyme analogs using polymers, another section on the use of enzymes in organic synthesis, and one on the design of molecular clefts. A new section in Chapter 6 covers recent advances in photosynthetic models.

An honest and judicious selection of pedagogically relevant and appealing biomimetic models among the astonishing number of exciting new synthetic receptors that have emerged in the last decade was not in any way an easy task. Consequently, choices had to be made and not all aspects of bioreceptors could be adequately covered. Detailed synthetic and mechanistic implications related to other applications can be found by looking up the appropriate references where particularly useful aspects can be prepared and developed further. This way, this edition could be kept to a reasonable size.

I tried to incorporate the most recent and key observations, but I also deliberately decided to put the emphasis more on the beauty of the molecular architectures than on their detailed descriptive synthetic difficulties. As such, I believe that there is little need to go into too much elaborated and sophisticated development of mechanistic considerations. Although the course is addressed to the final undergraduate and/or first-year graduate level, the presentation should remain simple and concise, yet lively. This is why more general background materials have been added in the first two chapters. This should create a better link with the rest of the material in the book.

I am once more indebted to my very devoted secretary, Miss C. Potvin, for her cheerful and persistent competence throughout the preparation of the second edition.

Montréal, Canada Hermann Dugas
February 1988

Preface to the First Edition

Bioorganic chemistry is the application of the principles and the tools of organic chemistry to the understanding of biological processes. The remarkable expansion of this new discipline in organic chemistry during the last ten years has created a new challenge for the teacher, particularly with respect to undergraduate courses. Indeed, the introduction of many new and valuable bioorganic chemical principles is not a simple task. This book will expound the fundamental principles for the construction of bioorganic molecular models of biochemical processes using the tools of organic and physical chemistry.

This textbook is meant to serve as a *teaching* book. It is not the authors' intention to cover all aspects of bioorganic chemistry. Rather, a blend of general and selected topics are presented to stress important aspects underlying the concepts of organic molecular model building. Most of the presentation is accessible to advanced undergraduate students without the need to go back to an elementary textbook of biochemistry; of course, a working knowledge of organic chemistry is mandatory. Consequently, this textbook is addressed first to final-year undergraduate students in chemistry, biochemistry, biology, and pharmacology. In addition, the text has much to offer in modern material that graduate students are expected to, but seldom actually, know.

Often the material presented in elementary biochemistry courses is overwhelming and seen by many students as mainly a matter of memorization. We hope to overcome this situation. Therefore, the chemical organic presentation throughout the book should help to stimulate students to make the "quantum jump" necessary to go from a level of pure memorization of biochemical transformations to a level of adequate comprehension of biochemical principles based on a firm chemical understanding of bioorganic concepts. For this, most chapters start by asking some of the pertinent questions developed within the chapter. In brief, we hope that this approach will stimulate curiosity.

Professor B. Belleau from McGill University acted as a "catalyst" in promoting the idea to write this book. Most of the material was originally inspired from his notes. The authors would like to express their most sincere appreciation for giving us the opportunity of teaching, transforming, and expanding *his* course into a book. It is Dr. Belleau's influence and remarkable dynamism that gave us consant inspiration and strength throughout the writing.

The references are by no means exhaustive, but are, like the topics chosen, selective. The reader can easily find additional references since many of the citations are of books and review articles. The instructor should have a good knowledge of individual references and be able to offer to the students the possibility of discussing a particular subject in more detail. Often we give the name of the main author concerning the subject presented and the year the work was done. This way the students have the opportunity to know the leader in that particular field and can more readily find appropriate references. However, we apologize to all those who have not been mentioned because of space limitation.

The book includes more material than can be handled in a single course of three hours a week in one semester. However, in every chapter, sections of material may be omitted without loss of continuity. This flexibility allows the instructor to emphasize certain aspects of the book, depending if the course is presented to an audience of chemists or biochemists.

We are indebted to the following friends and colleagues for providing us with expert suggestions and comments regarding the presentation of certain parts of the book: P. Brownbridge, P. Deslongchamps, P. Guthrie, J.B. Jones, R. Kluger, and C. Lipsey. And many thanks to Miss C. Potvin, from the Université de Montréal, for her excellent typing assistance throughout the preparation of this manuscript.

Finally, criticisms and suggestions toward improvement of the content of the text are welcome.

Montréal, Canada
January 1981

Hermann Dugas
Christopher Penney

Contents

Chapter 1

Introduction to Bioorganic Chemistry

"It might be helpful to remind ourselves regularly of the sizeable incompleteness of our understanding, not only of ourselves as individuals and as a group, but also of Nature and the world around us."

N. Hackerman
Science **183**, 907 (1974)

1.1 Basic Considerations

Among the first persons to develop biooriented organic projects was F.H. Westheimer, in the 1950s. He was probably the first physical organic chemist to do serious studies of biochemical reactions. However, it was only twenty years later that the field blossomed to what is now accepted as bioorganic chemistry.

Bioorganic chemistry is a discipline that is essentially concerned with the application of the tools of chemistry to the understanding of biochemical processes. Such an understanding is often achieved with the aid of *molecular models* chemically synthesized in the laboratory. This allows a "sorting out" of the many variable parameters simultaneously operative within the biological system.

For example, how does a biological membrane work? One builds a simple model of known compositions and studies a single behavior, such as an ion transport property. How does the brain work? This is by far a more complicated system than the previous example. Again one studies single synapses and single synaptic constituents and then uses the observations to construct a model.