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MECHANISM-BASED
ENZYME
INACTIVATION:
CHEMISTRY
and
ENZYMOLGY
Volume I

Richard B. Silverman

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Mechanism-Based Enzyme Inactivation: Chemistry and Enzymology

Volume I

Author

Richard B. Silverman

Professor of Chemistry and of
Biochemistry, Molecular Biology, and Cell Biology
Northwestern University
Evanston, Illinois



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PREFACE

This book is intended to be used as a reference text by those in the field interested in applying mechanism-based inactivation approaches to studies of a particular enzyme or by those with an interest in this exciting area of enzyme inactivation in order to gain an overview of the field and to learn the fundamentals of the method. The text also can be used in a graduate-level course concerned with mechanism-based enzyme inactivation or as one of several texts in an advanced undergraduate or graduate course on enzyme inhibition in general. Since it is assumed in this text that the reader is familiar with enzyme mechanisms, it may be helpful to precede a course that utilizes this text by a course on enzyme mechanisms. At least, the students should be familiar with writing organic chemical mechanisms.

It may be useful to the reader to know how the information in this text was collected. It was observed that a computer search was not very useful, since most of the papers in the field do not have the words "mechanism-based," "enzyme-activated," or "suicide" in their titles or abstracts (and I did not have the inclination to peruse every paper that mentioned "enzyme inhibition or inactivation"). The approach taken was a more direct one, namely, that letters were sent requesting reprints (or publication lists) from 146 different principal authors of papers published in the field. Of the 146 requests, all but six were answered (I have restrained myself from revealing the names of those six individuals). These references were used as primary sources from which other relevant references were extracted. This process continued, i.e., obtaining references from within the references, until all possibilities were exhausted. I am indebted to the 140 individuals who responded to my request; much time in collecting references was saved by their assistance. When these sources were expended, the references in available reviews were checked to be certain that no obvious omissions were made. The literature through the first half of 1987 is covered here (the work cited from mid-1986 and references therein were added to the galley proofs). These endeavors should have been sufficient to uncover most of the relevant references. If I missed your contribution to this field, please accept my apology. Rather than sending me a nasty note regarding my oversight, kindly send me copies of your relevant publications; maybe, some day an addendum will be published.

Richard B. Silverman
Evanston, IL
August, 1986

THE AUTHOR

Richard B. Silverman, Ph.D., is Professor of Chemistry and Professor of Biochemistry, Molecular Biology, and Cell Biology at Northwestern University.

Dr. Silverman received his B.S. degree in chemistry at the Pennsylvania State University in 1968, then spent two years in the U.S. Army as a medicinal chemist at the Walter Reed Army Institute of Research in Washington, D.C. He obtained his M.A. degree in 1972 and Ph.D. degree in 1974 in chemistry from Harvard University. Prior to joining the faculty of Northwestern University in 1976, Dr. Silverman was a National Institutes of Health post-doctoral research fellow in the Graduate Department of Biochemistry at Brandeis University.

Dr. Silverman's current research interests are the design and synthesis of mechanism-based enzyme inactivators and their mechanisms of enzyme inactivation, the elucidation of enzyme mechanisms, and the design of potential new pharmaceutical agents.

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*To loving Barbara for her devotion, her understanding, and her radiance, to
Matt and Marggie for their love, their wit and their exuberance, and to Philly
for his giant smiles, his hugs, and his belly laughs.*

MECHANISM-BASED
ENZYME INACTIVATION:
CHEMISTRY
AND
ENZYMOLGY

Volume I

Introduction
Protonation and Deprotonation Reactions
Phosphorylation Reactions
Addition Reactions
Acylation Reactions
Elimination Reactions

Volume II

Isomerization Reactions
Decarboxylation Reactions
Oxidation Reactions
Oxygenation Reactions
Polymerization Reactions

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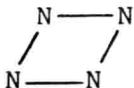
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ABBREVIATIONS AND SHORTHAND NOTATIONS USED IN THE BOOK

Because of the myriad of abbreviations commonly used, particularly in synthetic organic chemistry, this alphabetized compilation of abbreviations is included for easy referral while reading the book.

ACC	1-aminocyclopropane-1-carboxylate
Ad	adenine
Ado	adenosine
$\uparrow$	
B:	active site base
BHT	butylated hydroxytoluene (2,6,-di- <i>tert</i> -butyl-4-methylphenol)
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bz	benzoyl
Cbz	carbobenzoxyl
CH ₂ H ₄ folate	5,10-methylenetetrahydrofolate
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
Cy	cyclohexyl
Dabco	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDEP	3,5-dicarbethoxy-2,6-dimethyl-4-ethyl-1,4-dihydropyridine
DEAD	diethyl azodicarboxylate
Dibal	diisobutyl aluminum hydride
DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulfoxide
DON	6-diazo-5-oxo- <i>L</i> -norleucine
DONV	5-diazo-4-oxo- <i>L</i> -norvaline
dR	deoxyribosyl
dRP	deoxyribose phosphate
DTNB	5,5'-dithiobis(2-nitrobenzoate)
DTT	dithiothreitol
EDTA	ethylenediaminetetraacetic acid
EPR	electron paramagnetic resonance
ESR	electron spin resonance
FdUMP	5-fluoro-2'-deoxyuridine monophosphate
Fl	oxidized flavin
FlH [•] or Fl ^{•-}	flavin semiquinone
FlH ⁻ or FlH ₂	reduced flavin
GABA	γ -aminobutyric acid
GTP	guanosine triphosphate
HPLC	high performance liquid chromatography
Im	imidazole
IR	infrared
LDA	lithium diisopropylamide
MAO	monoamine oxidase
MPDP ⁺	1-methyl-4-phenyl-2,3-dihydropyridinium ion
MPP ⁺	1-methyl-4-phenylpyridinium ion

MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
Ms	mesyl (methanesulfonyl)
NAC	<i>N</i> -acetylcysteamine
NAD ⁺	nicotinamide adenine dinucleotide
NADH	reduce form of NAD ⁺
NaDodSO ₄	sodium dodecyl sulfate
NBS	<i>N</i> -bromosuccinimide
NMR	nuclear magnetic resonance
	porphyrin ring system (usually protoporphyrin IX)
Np	naphthyl
NXS	<i>N</i> -halosuccinimide
ORD	optical rotatory dispersion
PAGE	polyacrylamide gel electrophoresis
Pant	pantetheine
PhthN	phthalimido
P _i	phosphate ion
PLP	pyridoxal 5'-phosphate
PMP	pyridoxamine 5'-phosphate
PPA	polyphosphoric acid
PQQ	pyrroloquinoline quinone
Pyr	the substituted pyridine nucleus of PLP or PMP
RBL	rat basophilic leukemia
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl
TPCK	<i>L</i> -1-chloro-3-tosylamido-4-phenyl-2-butanone
TPP	thiamin pyrophosphate
Ts	tosyl (<i>p</i> -toluenesulfonyl)
	
X:	active site nucleophile