

METAL IONS IN LIFE SCIENCES

edited by

Astrid Sigel,⁽¹⁾ Helmut Sigel,⁽¹⁾ and Roland K. O. Sigel⁽²⁾

⁽¹⁾ *Department of Chemistry
Inorganic Chemistry
University of Basel
Spitalstrasse 51
CH-4056 Basel, Switzerland*

⁽²⁾ *Institute of Inorganic Chemistry
University of Zürich
Winterthurerstrasse 190
CH-8057 Zürich, Switzerland*

VOLUME 3

The Ubiquitous Roles of Cytochrome P450 Proteins



John Wiley & Sons, Ltd

METAL IONS IN LIFE SCIENCES

VOLUME 3

**The Ubiquitous Roles
of Cytochrome P450 Proteins**

METAL IONS IN LIFE SCIENCES

edited by

Astrid Sigel,⁽¹⁾ Helmut Sigel,⁽¹⁾ and Roland K. O. Sigel⁽²⁾

⁽¹⁾ *Department of Chemistry
Inorganic Chemistry
University of Basel
Spitalstrasse 51
CH-4056 Basel, Switzerland*

⁽²⁾ *Institute of Inorganic Chemistry
University of Zürich
Winterthurerstrasse 190
CH-8057 Zürich, Switzerland*

VOLUME 3

The Ubiquitous Roles of Cytochrome P450 Proteins



John Wiley & Sons, Ltd

Copyright © 2007

John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester,
West Sussex PO19 8SQ, England

Telephone (+44) 1243 779777

Email (for orders and customer service enquiries): cs-books@wiley.co.uk

Visit our Home Page on www.wiley.com

All Rights Reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning or otherwise, except under the terms of the Copyright, Designs and Patents Act 1988 or under the terms of a licence issued by the Copyright Licensing Agency Ltd, 90 Tottenham Court Road, London W1T 4LP, UK, without the permission in writing of the Publisher. Requests to the Publisher should be addressed to the Permissions Department, John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, England, or emailed to permreq@wiley.co.uk, or faxed to (+44) 1243 770620.

Designations used by companies to distinguish their products are often claimed as trademarks. All brand names and product names used in this book are trade names, service marks, trademarks or registered trademarks of their respective owners. The Publisher is not associated with any product or vendor mentioned in this book.

This publication is designed to provide accurate and authoritative information in regard to the subject matter covered. It is sold on the understanding that the Publisher is not engaged in rendering professional services. If professional advice or other expert assistance is required, the services of a competent professional should be sought.

The Publisher, the Editors and the Authors make no representations or warranties with respect to the accuracy or completeness of the contents of this work and specifically disclaim all warranties, including without limitation any implied warranties of fitness for a particular purpose. This work is sold with the understanding that the Publisher is not engaged in rendering professional services. The advice and strategies contained herein may not be suitable for every situation. In view of ongoing research, equipment modifications, changes in governmental regulations, and the constant flow of information relating to the use of experimental reagents, equipment, and devices, the reader is urged to review and evaluate the information provided in the package insert or instructions for each chemical, piece of equipment, reagent, or device for, among other things, any changes in the instructions or indication of usage and for added warnings and precautions. The fact that an organization or Website is referred to in this work as a citation and/or a potential source of further information does not mean that the Authors, the Editors, or the Publisher endorse the information the organization or Website may provide or recommendations it may make. Further, readers should be aware that Internet Websites listed in this work may have changed or disappeared between when this work was written and when it is read. No warranty may be created or extended by any promotional statements for this work. Neither the Publisher nor the Editors nor the Authors shall be liable for any damages arising herefrom.

Other Wiley Editorial Offices

John Wiley & Sons Inc., 111 River Street, Hoboken, NJ 07030, USA

Jossey-Bass, 989 Market Street, San Francisco, CA 94103-1741, USA

Wiley-VCH Verlag GmbH, Boschstr. 12, D-69469 Weinheim, Germany

John Wiley & Sons Australia Ltd, 42 McDougall Street, Milton, Queensland 4064, Australia

John Wiley & Sons (Asia) Pte Ltd, 2 Clementi Loop #02-01, Jin Xing Distripark, Singapore 129809

John Wiley & Sons Ltd, 6045 Freemont Blvd, Mississauga, Ontario L5R 4J3, Canada

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Anniversary Logo Design: Richard J. Pacifico

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

ISBN 978-0-470-01672-5

Typeset in 10/12pt Times by Integra Software Services Pvt. Ltd, Pondicherry, India

Printed and bound in Spain by Grafos S.A., Barcelona

This book is printed on acid-free paper responsibly manufactured from sustainable forestry in which at least two trees are planted for each one used for paper production.

The figure on the dustcover is part of Figure 2 of Chapter 6 by Andrew K. Udit, Stephen M. Contakes, and Harry B. Gray.

Historical Development and Perspectives of the Series

Metal Ions in Life Sciences

It is an old wisdom that metals are indispensable for life. Indeed, several of them, like sodium, potassium, and calcium, are easily discovered in living matter. However, the role of metals and their impact on life remained largely hidden until inorganic chemistry and coordination chemistry experienced a pronounced revival in the 1950s. The experimental and theoretical tools created in this period and their application to biochemical problems led to the development of the field or discipline now known as *Bioinorganic Chemistry*, *Inorganic Biochemistry*, or more recently also often addressed as *Biological Inorganic Chemistry*.

By 1970 *Bioinorganic Chemistry* was established and further promoted by the book series *Metal Ions in Biological Systems* founded in 1973 (edited by H.S., who was soon joined by A.S.) and published by Marcel Dekker, Inc., New York, for more than 30 years. After this company ceased to be a family endeavor and its acquisition by another company, we decided, after having edited 44 volumes of the *MIBS* series (the last two together with R.K.O.S.) to launch a new and broader minded series to cover today's needs in the *Life Sciences*. Therefore, the Sigels' new series is entitled

Metal Ions in Life Sciences

and we are happy to join forces in this new endeavor with a most experienced Publisher in the *Sciences*, John Wiley & Sons, Ltd, Chichester, UK.

The development of *Biological Inorganic Chemistry* during the past 40 years was and still is driven by several factors; among these are (i) the attempts to reveal the interplay between metal ions and peptides, nucleotides, hormones or vitamins, etc.; (ii) the efforts regarding the understanding of accumulation, transport, metabolism and toxicity of metal ions; (iii) the development and application of metal-based drugs; (iv) biomimetic syntheses with the aim to understand biological processes as well as to create efficient catalysts; (v) the determination of high-resolution structures of proteins, nucleic acids, and other biomolecules; (vi) the utilization of powerful spectroscopic tools allowing studies of structures and dynamics; and (vii), more recently, the widespread use of

macromolecular engineering to create new biologically relevant structures at will. All this and more is and will be reflected in the volumes of the series *Metal Ions in Life Sciences*.

The importance of metal ions to the vital functions of living organisms, hence, to their health and well-being, is nowadays well accepted. However, in spite of all the progress made, we are still only at the brink of understanding these processes. Therefore, the series *Metal Ions in Life Sciences* will endeavor to link coordination chemistry and biochemistry in their widest sense. Despite the evident expectation that a great deal of future outstanding discoveries will be made in the interdisciplinary areas of science, there are still ‘language’ barriers between the historically separate spheres of chemistry, biology, medicine, and physics. Thus, it is one of the aims of this series to catalyze mutual ‘understanding’.

It is our hope that *Metal Ions in Life Sciences* proves a stimulus for new activities in the fascinating ‘field’ of *Biological Inorganic Chemistry*. If so, it will well serve its purpose and be a rewarding result for the efforts spent by the authors.

Astrid Sigel, Helmut Sigel
Department of Chemistry
Inorganic Chemistry
University of Basel
CH-4056 Basel
Switzerland

Roland K. O. Sigel
Institute of Inorganic Chemistry
University of Zürich
CH-8057 Zürich
Switzerland

October 2005

Preface to Volume 3

The Ubiquitous Roles of Cytochrome P450 Proteins

Cytochrome P450 monooxygenases (P450s) own a dual functionality and are often referred to as ‘mixed-function oxidases’ because they possess both ‘oxygenase’ and ‘oxidase’ reactivities, meaning that they incorporate an oxygen atom from atmospheric dioxygen into a substrate molecule oxidizing it. The electron transfer functionalities of P450s also earned them the label of ‘cytochrome’. The signature of all P450s is the heme Soret band at about 450 nm in the absorption spectrum of the Fe(II)-CO complex; this spectroscopic feature is diagnostic of a cysteinate residue bound *trans* to the carbon monoxide ligand.

This volume encompasses the breadth of research efforts focused on P450s from structure to function, including an appreciation of the diversity and complexity of the biotransformations they catalyze. The introductory Chapter 1, setting the scene, explores the many different levels at which these P450 enzymes (and their respective genes) have diverged in the process of evolution to yield the plethora of enzymes that are now termed ‘P450 monooxygenases’. This broad and unprecedented reactivity of P450 enzymes which contain a heme iron center (most commonly iron(III)protoporphyrin IX) with a deprotonated cysteine side chain providing the fifth ligand to iron, has challenged the ‘biomimetic community’. Indeed, much has been accomplished over the past five decades, e.g., regarding the understanding of the unusual activation of paramagnetic dioxygen by reductive oxygen cleavage, as is evident from Chapter 2 which provides an in-depth overview of structural and functional mimics of P450s.

The structures of P450 proteins and their molecular phylogeny are detailed in Chapter 3, together with the P450 nomenclature and classification. It is made clear in this account that the P450 protein fold is unique and highly conserved independent of the organism; astonishingly, the same fold is also used by some enzymes that catalyze non-P450 redox transformations. It is worthwhile to note that some P450s function at extremes of pH and heat, as was recently discovered with archaeans. The diversity of P450s is also reflected in aquatic species as

outlined in Chapter 4 where especially P450 activities in invertebrates are in the focus.

Chapter 5 examines the ability of electrochemical techniques to unravel fundamental aspects of the electron transfer process of P450 enzymes. This process is central to P450 catalysis and thus, in Chapter 6 extensive studies are summarized which have shown that interprotein electron transfer is facilitated by proper positioning, e.g., of the flavin mononucleotide- and heme-containing domains. Clearly, generation of a truly catalytic system that utilizes non-native redox cofactors in place of the reductase proteins is a 'holy grail' of P450 research.

The next four chapters center on mechanistic considerations. At first leakage reactions are considered which occur during the P450 catalytic cycle, followed by detailed evaluations of the structural basis for substrate recognition and catalysis, including the architecture of the active site. Roles of the secondary coordination sphere, i.e., at the proximal (thiolate) and the distal side (where activation of dioxygen and substrate binding occurs) are described next, as is the coordination to the heme iron of several small-molecule inhibitors, such as nitrogen monoxide (nitric oxide), carbon monoxide, cyanide, and imidazole.

P450-catalyzed hydroxylations and epoxidations, the biosynthesis of steroid hormones, and the catalyzed carbon-carbon bond cleavage are discussed in Chapters 11-13. The design and engineering of cytochrome P450 systems is detailed in Chapter 14 regarding the oxidation of non-natural substrates. Evidently, potential applications of altered P450s in the environmentally benign synthesis of chemical products and intermediates are expected in this research area.

In the terminating three chapters of *The Ubiquitous Roles of Cytochrome P450 Proteins* first the biotransformation of xenobiotics is comprehensively dealt with, i.e., the 'chemical defense' or response of an organism to foreign chemicals. Thereafter the metabolism of drugs by human P450 systems is described, an area of particular significance for drug development and finally also for daily life in the clinic, as is emphasized by a clinical pharmacist.

Astrid Sigel
Helmut Sigel
Roland K. O. Sigel

Contents

HISTORICAL DEVELOPMENT AND PERSPECTIVES OF THE SERIES	v
PREFACE TO VOLUME 3	vii
CONTRIBUTORS TO VOLUME 3	xvii
TITLES OF VOLUMES 1–44 IN THE <i>METAL IONS IN BIOLOGICAL SYSTEMS</i> SERIES	xxi
CONTENTS OF VOLUMES IN THE <i>METAL IONS IN LIFE SCIENCES</i> SERIES	xxiii
1 DIVERSITIES AND SIMILARITIES IN P450 SYSTEMS: AN INTRODUCTION	1
<i>Mary A. Schuler and Stephen G. Sligar</i>	
1. Oxygenases: Mediators of Biochemical Diversity	2
2. P450 Superfamily: Diversity at the Sequence Level	3
3. Diversity of P450 Structures: Folds and Conformations for Functions	5
4. Diversity in P450 Mechanisms	6
5. Diversity in Regulation Across the Superfamily	13
6. Diversity in the Evolution of Common Metabolic Functions	16
7. Summary and Outlook	18
Acknowledgments	19
Abbreviations	19
References	19
2 STRUCTURAL AND FUNCTIONAL MIMICS OF CYTOCHROMES P450	27
<i>Wolf-D. Woggon</i>	
1. Introduction	27
2. Iron Porphyrins Carrying a Thiolate or Modified Thiolate Ligand	31

3. Structurally Remote P450 Mimics	40
4. Concluding Remarks	52
Acknowledgments	52
Abbreviations	53
References	53
3 STRUCTURES OF P450 PROTEINS AND THEIR MOLECULAR PHYLOGENY	57
<i>Thomas L. Poulos and Yergalem T. Meharena</i>	
1. Introduction	58
2. P450 Evolution	59
3. P450 Families and Subfamilies	60
4. P450 Structures	62
5. Variation in P450 Function and Fold	81
6. Archaeon P450s	86
7. Summary and Conclusions	90
Acknowledgments	91
Abbreviations	91
References	91
4 AQUATIC P450 SPECIES	97
<i>Mark J. Snyder</i>	
1. Introduction. 'P450s Under the Surface'	98
2. Diversity of Aquatic Species	100
3. P450 Activities in Aquatic Invertebrates	101
4. Aquatic P450 Gene Families Identified	108
5. How Can We Use Information About P450s in Aquatic Species?	116
6. Conclusions and Outlook	120
Acknowledgments	121
Abbreviations	121
References	122
5 THE ELECTROCHEMISTRY OF CYTOCHROME P450	127
<i>Alan M. Bond, Barry D. Fleming, and Lisandra L. Martin</i>	
1. Introduction	127
2. Redox Titration (Potentiometric Equilibrium) Measurements	131
3. Voltammetric (Dynamic) Measurements	139
4. Conclusions	150
Acknowledgments	151
Abbreviations	151
References	152

6	P450 ELECTRON TRANSFER REACTIONS	157
	<i>Andrew K. Udit, Stephen M. Contakes, and Harry B. Gray</i>	
1.	Introduction	158
2.	Catalytic Cycles	158
3.	Electron Tunneling Wires	171
4.	Concluding Remarks	180
	Acknowledgments	181
	Abbreviations	181
	References	181
7	LEAKAGE IN CYTOCHROME P450 REACTIONS IN RELATION TO PROTEIN STRUCTURAL PROPERTIES	187
	<i>Christiane Jung</i>	
1.	Introduction	188
2.	Protein Structural Parameters	191
3.	The Reaction Cycle of Cytochrome P450	195
4.	Protein Structural Parameters and Extent of Competitive Reactions	222
5.	Concluding Remarks	225
	Acknowledgments	226
	Abbreviations	226
	References	227
8	CYTOCHROMES P450 – STRUCTURAL BASIS FOR BINDING AND CATALYSIS	235
	<i>Konstanze von König and Ilme Schlichting</i>	
1.	Introduction	236
2.	Ligand Binding: Substrate Recognition and Access to the Distal Pocket	237
3.	Architecture of the Active Site of CYP101	239
4.	The Distal Acid-Alcohol Pair	242
5.	Experimental Characterization of Reaction Intermediates. Radiolysis as a Tool to Study Redox Reactions	250
6.	Crystal Structures of Oxy-Ferrous Complexes	253
7.	Mechanism: Summary, Conclusions, Speculations	258
	Acknowledgments	260
	Abbreviations	260
	References	261

9	BEYOND HEME-THIOLATE INTERACTIONS: ROLES OF THE SECONDARY COORDINATION SPHERE IN CYTOCHROME P450 SYSTEMS	267
	<i>Yi Lu and Thomas D. Pfister</i>	
1.	Overview of Cytochrome P450 Active Site Structure	268
2.	Secondary Coordination Sphere on the Proximal Side	269
3.	Secondary Coordination Sphere on the Distal Side	275
4.	Summary and Outlook	280
	Acknowledgments	281
	Abbreviations	281
	References	281
10	INTERACTIONS OF CYTOCHROME P450 WITH NITRIC OXIDE AND RELATED LIGANDS	285
	<i>Andrew W. Munro, Kirsty J. McLean, and Hazel M. Girvan</i>	
1.	Introduction. Interactions of Ligands and Substrates with P450 Enzymes: General Features	286
2.	Nitric Oxide and Its Interactions with P450s	289
3.	Interactions of Imidazoles and Substituted Imidazoles with P450s	300
4.	Other Ligands and Inhibitors of P450 Function	305
5.	Conclusions and Future Prospects	310
	Acknowledgments	310
	Abbreviations	311
	References	311
11	CYTOCHROME P450-CATALYZED HYDROXYLATIONS AND EPOXIDATIONS	319
	<i>Roshan Perera, Shengxi Jin, Masanori Sono, and John H. Dawson</i>	
1.	Introduction	320
2.	The Cytochrome P450 Enzymes	322
3.	Three-Dimensional Structures of the Active Sites of Cytochrome P450 Enzymes	327
4.	Role of the Cys Ligand: the Proximal Thiolate 'Push' and Distal Proton-Delivery	333
5.	Multiple Mechanisms of P450 Catalysis	337
6.	Multiple Oxidants in P450 Catalysis	343
7.	Two States Theory	347
8.	Influence of Substrate on the Spectral Properties and Reactivity of P450 Intermediates	348
9.	Formation and Reactivity of Transient P450 Oxygen Intermediates	351

10. Summary and Future Prospective	352
Acknowledgments	353
Abbreviations	353
References	354
12 CYTOCHROME P450 AND STEROID HORMONE BIOSYNTHESIS	361
<i>Rita Bernhardt and Michael R. Waterman</i>	
1. Introduction	362
2. Steroidogenic P450s	363
3. Steroid Hormone Biosynthesis in the Adrenal Cortex	374
4. Steroid Hormone Biosynthesis in the Gonads	379
5. Extraadrenal and Extragonadal Steroidogenesis	382
6. Outlook for the Future	385
Acknowledgments	386
Abbreviations	387
References	387
13 CARBON-CARBON BOND CLEAVAGE BY P450 SYSTEMS	397
<i>James J. De Voss and Max J. Cryle</i>	
1. Introduction	398
2. Cleavage Between Oxygenated Carbons	398
3. Cleavage Alpha to Oxygenated Carbons	408
4. Cleavage Alpha to Carbon Bearing Nitrogen	422
5. Carbon-Carbon Bond Cleavage Involving Peroxides	423
6. General Conclusions	429
Acknowledgments	430
Abbreviations	430
References	430
14 DESIGN AND ENGINEERING OF CYTOCHROME P450 SYSTEMS	437
<i>Stephen G. Bell, Nicola Hoskins, Christopher J. C. Whitehouse, and Luet L. Wong</i>	
1. Introduction	438
2. Engineering Bacterial Cytochrome P450 Systems	444
3. Engineering Mammalian Cytochrome P450 Enzymes	462
4. Engineering Plant P450 Enzymes	467
5. Conclusions and Outlook	468
Abbreviations	469
References	469

15	CHEMICAL DEFENSE AND EXPLOITATION. BIOTRANSFORMATION OF XENOBIOTICS BY CYTOCHROME P450 ENZYMES	477
	<i>Elizabeth M. J. Gillam and Dominic J. B. Hunter</i>	
1.	Introduction. Chemical Defense	478
2.	P450 Systems Involved in Chemical Defense	481
3.	Common Themes	529
4.	Industrial Applications of P450 Systems for Xenobiotic Decomposition	530
5.	Conclusions and Future Prospects	534
	Acknowledgments	535
	Abbreviations	535
	References	537
16	DRUG METABOLISM AS CATALYZED BY HUMAN CYTOCHROME P450 SYSTEMS	561
	<i>F. Peter Guengerich</i>	
1.	Introduction	562
2.	Importance of P450 Enzymes in Drug Metabolism	563
3.	Approaches to Predicting P450 Activity in Humans	565
4.	P450s Involved in Drug Metabolism	570
5.	Examples of Major Issues Involving Drug Metabolism by P450	576
6.	Summary	582
	Acknowledgments	583
	Abbreviations	583
	References	584
17	CYTOCHROME P450 ENZYMES: OBSERVATIONS FROM THE CLINIC	591
	<i>Peggy L. Carver</i>	
1.	Introduction	592
2.	Drug Interactions	593
3.	Drug Metabolism by Cytochrome P450 Enzymes	594
4.	Alterations in P450 Enzymes	596
5.	Active Transport of Drugs	603
6.	Enzyme-Transporter Cooperativity	603
7.	Use of Probes to Quantitate CYP Activity in Humans	604
8.	Prodrugs	604
9.	The Effect of Intravenous Versus Oral Administration on Drug Interactions	605
10.	Additional Factors Affecting Drug Interactions	606
11.	Herbal and Dietary Effects on CYP	608

CONTENTS

xv

12. Interactions with Commonly Used Medications	610
13. Beneficial Effects of Drug Interactions	611
14. FDA Regulations Regarding CYP450-Mediated Drug Interactions	612
15. Clinical Significance of Drug Interactions	613
16. Summary	614
Acknowledgment	615
Abbreviations	615
References	615

SUBJECT INDEX

619

Contributors

Numbers in parentheses indicate the pages on which the authors' contributions begin.

Stephen G. Bell Department of Chemistry, Inorganic Chemistry Laboratory, Oxford University, South Parks Road, Oxford, OX1 3QR, UK, <stephen.bell@chem.ox.ac.uk> (437)

Rita Bernhardt Institut für Biochemie, Universität des Saarlandes, P. O. Box 151150, D-66041 Saarbrücken, Germany, <ritabern@mx.uni-saarland.de> (361)

Alan M. Bond School of Chemistry, Monash University, Clayton, Victoria 3800, Australia, <alan.bond@sci.monash.edu.au> (127)

Peggy L. Carver University of Michigan College of Pharmacy, Clinical Sciences Department, 428 Church St., Ann Arbor, MI 48109-1065, USA, <peg@umich.edu> (591)

Stephen M. Contakes The Beckman Institute, California Institute of Technology, Pasadena, CA 91125, USA, <contakes@caltech.edu> (157)

Max J. Cryle School of Molecular and Microbial Sciences, University of Queensland, Brisbane, QLD 4072, Australia (397)

John H. Dawson Department of Chemistry and Biochemistry, and School of Medicine, University of South Carolina, Columbia, SC 29208, USA, <dawson@sc.edu> (319)

James J. De Voss School of Molecular and Microbial Sciences, University of Queensland, Brisbane, QLD 4072, Australia, <j.devoss@uq.edu.au> (397)

Barry D. Fleming School of Chemistry, Monash University, Clayton, Victoria 3800, Australia, <barry.fleming@sci.monash.edu.au> (127)

Elizabeth M. J. Gillam School of Biomedical Sciences, The University of Queensland, St. Lucia, Brisbane, Qld 4072, Australia, <e.gillam@uq.edu.au> (477)

Hazel M. Girvan Manchester Interdisciplinary Biocentre, School of Chemical Engineering and Analytical Science, University of Manchester, 131 Princess Street, Manchester M1 7DN, UK (285)

Harry B. Gray The Beckman Institute, California Institute of Technology, Pasadena, CA 91125, USA, <hbgray@caltech.edu> (157)

F. Peter Guengerich Department of Biochemistry and Center in Molecular Toxicology, Vanderbilt University School of Medicine, 638 Robinson Research Building, 23rd & Pierce Avenues, Nashville, TN 37232-0146, USA, <f.guengerich@vanderbilt.edu> (561)

Nicola Hoskins Department of Chemistry, Inorganic Chemistry Laboratory, Oxford University, South Parks Road, Oxford, OX1 3QR, UK (437)

Dominic J. B. Hunter School of Biomedical Sciences, The University of Queensland, St. Lucia, Brisbane, Qld 4072, Australia, <d.hunter1@uq.edu.au> (477)

Shengxi Jin Department of Chemistry and Biochemistry, University of South Carolina, Columbia, SC 29208, USA, <jinshengxi@gmail.com> (319)

Christiane Jung Max-Delbrück Center for Molecular Medicine, Research Group Protein Dynamics, D-13125 Berlin, Germany. Present address: KKS Ultraschall AG, Surface Treatment Division, Frauholzring 29, CH-6422 Steinen, Switzerland, <christiane_jung@hotmail.com> (187)

Yi Lu Department of Biochemistry and Department of Chemistry, University of Illinois at Urbana-Champaign, A322 Chemical and Life Science Building, Box 8-6, 600 S. Matthews Avenue, Urbana, IL 61801, USA, <yi-lu@uiuc.edu> (267)

Lisandra L. Martin School of Chemistry, Monash University, Clayton, Victoria 3800, Australia, <lisa.martin@sci.monash.edu.au> (127)

Kirsty J. McLean Manchester Interdisciplinary Biocentre, School of Chemical Engineering and Analytical Science, University of Manchester, 131 Princess Street, Manchester M1 7DN, UK (285)

Yergalem T. Meharennia Department of Biochemistry and Molecular Biology, Physiology and Biophysics, and Chemistry, University of California, Irvine, CA 92697-3900, USA, <ymeharen@uci.edu> (57)

Andrew W. Munro Manchester Interdisciplinary Biocentre, School of Chemical Engineering and Analytical Science, University of Manchester, 131 Princess Street, Manchester M1 7DN, UK, <andrew.munro@manchester.ac.uk> (285)

Roshan Perera Department of Chemistry and Biochemistry, University of South Carolina, Columbia, SC 29208, USA, <perera@scripps.edu> (319)

Thomas D. Pfister Department of Biochemistry, University of Illinois at Urbana-Champaign, A322 Chemical and Life Science Building, Box 8-6, 600 S. Matthews Avenue, Urbana, IL 61801, USA (267)

Thomas L. Poulos Department of Biochemistry and Molecular Biology, Physiology and Biophysics, and Chemistry, University of California, Irvine, CA 92697-3900, USA, <poulos@uci.edu> (57)

Ilme Schlichting Department of Biomolecular Mechanisms, Max Planck Institute for Medical Research, Jahnstrasse 29, D-69120 Heidelberg, Germany, <ilme.schlichting@mpimf-heidelberg.mpg.de> (235)

Mary A. Schuler Departments of Cell and Developmental Biology, Biochemistry and Plant Biology, 190ERML, 1201 W. Gregory Drive, University of Illinois, Urbana, IL 61801, USA, <maryschu@uiuc.edu> (1)

Stephen G. Sligar Departments of Biochemistry, Chemistry and the College of Medicine, 116 Morrill Hall, MC-119, 505 S. Goodwin Avenue, Urbana, IL 61801, USA, <s-sligar@uiuc.edu> (1)

Mark J. Snyder Department of Clinical Pharmacology, University of California at San Francisco, Kenwood, CA 95452, USA. Contact address: P. O. Box 609, Kenwood, CA 95452, USA, <snyder181@comcast.net> (97)

Masanori Sono Department of Chemistry and Biochemistry, University of South Carolina, Columbia, SC 29208, USA, <sono@mail.chem.sc.edu> (319)

Andrew K. Udit Department of Chemistry, Occidental College, Los Angeles, CA 90041, USA, <udit@oxy.edu> (157)

Konstanze von K nig Department of Biomolecular Mechanisms, Max Planck Institute for Medical Research, Jahnstrasse 29, D-69120 Heidelberg, Germany, <konstanze.von.koenig@mpimf-heidelberg.mpg.de> (235)

Michael R. Waterman Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, TN 37232-0146, USA, <michael.waterman@vanderbilt.edu> (361)

Christopher J. C. Whitehouse Department of Chemistry, Inorganic Chemistry Laboratory, Oxford University, South Parks Road, Oxford, OX1 3QR, UK (437)

Wolf-D. Woggon Department of Chemistry, Organic Chemistry, University of Basel, St. Johannisring 19, CH-4056 Basel, Switzerland, <wolf-d.woggon@unibas.ch> (27)

Luet L. Wong Department of Chemistry, Inorganic Chemistry Laboratory, Oxford University, South Parks Road, Oxford, OX1 3QR, UK, <luet.wong@chem.ox.ac.uk> (437)

Titles of Volumes 1–44 in the *Metal Ions in Biological Systems Series*

*edited by the SIGELs
and published by Dekker/Taylor & Francis*

- Volume 1: **Simple Complexes**
- Volume 2: **Mixed-Ligand Complexes**
- Volume 3: **High Molecular Complexes**
- Volume 4: **Metal Ions as Probes**
- Volume 5: **Reactivity of Coordination Compounds**
- Volume 6: **Biological Action of Metal Ions**
- Volume 7: **Iron in Model and Natural Compounds**
- Volume 8: **Nucleotides and Derivatives: Their Ligating Ambivalency**
- Volume 9: **Amino Acids and Derivatives as Ambivalent Ligands**
- Volume 10: **Carcinogenicity and Metal Ions**
- Volume 11: **Metal Complexes as Anticancer Agents**
- Volume 12: **Properties of Copper**
- Volume 13: **Copper Proteins**
- Volume 14: **Inorganic Drugs in Deficiency and Disease**
- Volume 15: **Zinc and Its Role in Biology and Nutrition**
- Volume 16: **Methods Involving Metal Ions and Complexes in
Clinical Chemistry**
- Volume 17: **Calcium and Its Role in Biology**
- Volume 18: **Circulation of Metals in the Environment**
- Volume 19: **Antibiotics and Their Complexes**
- Volume 20: **Concepts on Metal Ion Toxicity**
- Volume 21: **Applications of Nuclear Magnetic Resonance to
Paramagnetic Species**
- Volume 22: **ENDOR, EPR, and Electron Spin Echo for Probing
Coordination Spheres**
- Volume 23: **Nickel and Its Role in Biology**
- Volume 24: **Aluminum and Its Role in Biology**
- Volume 25: **Interrelations Among Metal Ions, Enzymes, and
Gene Expression**
- Volume 26: **Compendium on Magnesium and Its Role in Biology,
Nutrition, and Physiology**

- Volume 27: **Electron Transfer Reactions in Metalloproteins**
- Volume 28: **Degradation of Environmental Pollutants by Microorganisms and Their Metalloenzymes**
- Volume 29: **Biological Properties of Metal Alkyl Derivatives**
- Volume 30: **Metalloenzymes Involving Amino Acid-Residue and Related Radicals**
- Volume 31: **Vanadium and Its Role for Life**
- Volume 32: **Interactions of Metal Ions with Nucleotides, Nucleic Acids, and Their Constituents**
- Volume 33: **Probing Nucleic Acids by Metal Ion Complexes of Small Molecules**
- Volume 34: **Mercury and Its Effects on Environment and Biology**
- Volume 35: **Iron Transport and Storage in Microorganisms, Plants, and Animals**
- Volume 36: **Interrelations Between Free Radicals and Metal Ions in Life Processes**
- Volume 37: **Manganese and Its Role in Biological Processes**
- Volume 38: **Probing of Proteins by Metal Ions and Their Low-Molecular-Weight Complexes**
- Volume 39: **Molybdenum and Tungsten. Their Roles in Biological Processes**
- Volume 40: **The Lanthanides and Their Interrelations with Biosystems**
- Volume 41: **Metal Ions and Their Complexes in Medication**
- Volume 42: **Metal Complexes in Tumor Diagnosis and as Anticancer Agents**
- Volume 43: **Biogeochemical Cycles of Elements**
- Volume 44: **Biogeochemistry, Availability, and Transport of Metals in the Environment**

Contents of Volumes in the *Metal Ions in Life Sciences Series*

edited by the SIGELs

and published by John Wiley & Sons, Ltd, Chichester, UK

<<http://www.wiley.com/go/mils>>

Volume 1: Neurodegenerative Diseases and Metal Ions

1. The Role of Metal Ions in Neurology. An Introduction
Dorothea Strozyk and Ashley I. Bush
2. Protein Folding, Misfolding, and Disease
*Jennifer C. Lee, Judy E. Kim, Ekaterina V. Pletneva,
Jasmin Faraone-Mennella, Harry B. Gray, and Jay R. Winkler*
3. Metal Ion Binding Properties of Proteins Related to Neurodegeneration
*Henryk Kozłowski, Marek Luczkowski, Daniela Valensin, and
Gianni Valensin*
4. Metallic Prions: Mining the Core of Transmissible Spongiform
Encephalopathies
David R. Brown
5. The Role of Metal Ions in the Amyloid Precursor Protein and in
Alzheimer's Disease
Thomas A. Bayer and Gerd Multhaup
6. The Role of Iron in the Pathogenesis of Parkinson's Disease
*Manfred Gerlach, Kay L. Double, Mario E. Götz, Moussa B. H. Youdim,
and Peter Riederer*
7. *In Vivo* Assessment of Iron in Huntington's Disease and Other Age-Related
Neurodegenerative Brain Diseases
George Bartzokis, Po H. Lu, Todd A. Tishler, and Susan Perlman
8. Copper-Zinc Superoxide Dismutase and Familial Amyotrophic Lateral
Sclerosis
Lisa J. Whitson and P. John Hart
9. The Malfunctioning of Copper Transport in Wilson and Menkes Diseases
Bibudhendra Sarkar
10. Iron and Its Role in Neurodegenerative Diseases
Roberta J. Ward and Robert R. Crichton

11. The Chemical Interplay between Catecholamines and Metal Ions in Neurological Diseases
Wolfgang Linert, Guy N. L. Jameson, Reginald F. Jameson, and Kurt A. Jellinger
 12. Zinc Metalloneurochemistry: Physiology, Pathology, and Probes
Christopher J. Chang and Stephen J. Lippard
 13. The Role of Aluminum in Neurotoxic and Neurodegenerative Processes
Tamás Kiss, Krisztina Gajda-Schranz, and Paolo F. Zatta
 14. Neurotoxicity of Cadmium, Lead, and Mercury
Hana R. Pohl, Henry G. Abadin, and John F. Risher
 15. Neurodegenerative Diseases and Metal Ions. A Concluding Overview
Dorothea Strozyk and Ashley I. Bush
- Subject Index

Volume 2: Nickel and Its Surprising Impact in Nature

1. Biogeochemistry of Nickel and Its Release into the Environment
Tiina M. Nieminen, Liisa Ukonmaanaho, Nicole Rausch, and William Shotyk
2. Nickel in the Environment and Its Role in the Metabolism of Plants and Cyanobacteria
Hendrik Küpper and Peter M. H. Kroneck
3. Nickel Ion Complexes of Amino Acids and Peptides
Teresa Kowalik-Jankowska, Henryk Kozłowski, Etelka Farkas, and Imre Sóvágó
4. Complex Formation of Nickel(II) with Sugar Residues, Nucleobases, Phosphates, Nucleotides, and Nucleic Acids
Roland K. O. Sigel and Helmut Sigel
5. Synthetic Models for the Active Sites of Nickel-Containing Enzymes
Jarl Ivar van der Vlugt and Franc Meyer
6. Urease. Recent Insights on the Role of Nickel
Stefano Ciurli
7. Nickel Iron Hydrogenases
Wolfgang Lubitz, Maurice van Gastel, and Wolfgang Gärtner
8. Methyl-Coenzyme M Reductase and Its Nickel Corphin Coenzyme F₄₃₀ in Methanogenic Archaea
Bernhard Jaun and Rudolf K. Thauer
9. Acetyl-Coenzyme A Synthases and Nickel-Containing Carbon Monoxide Dehydrogenases
Paul A. Lindahl and David E. Graham
10. Nickel Superoxide Dismutase
Peter A. Bryngelson and Michael J. Maroney
11. Biochemistry of the Nickel-Dependent Glyoxylase I Enzymes
Nicole Sukdeo, Elisabeth Daub, and John F. Honek

12. Nickel in Acireductone Dioxygenase
Thomas C. Pochapsky, Tingting Ju, Marina Dang, Rachel Beaulieu, Gina Pagani, and Bo Ouyang
 13. The Nickel-Regulated Peptidyl-Prolyl *cis/trans* Isomerase SlyD
Frank Erdmann and Gunter Fischer
 14. Chaperones of Nickel Metabolism
Soledad Quiroz, Jong K. Kim, Scott B. Mulrooney, and Robert P. Hausinger
 15. The Role of Nickel in Environmental Adaptation of the Gastric Pathogen *Helicobacter pylori*
Florian D. Ernst, Arnoud H. M. van Vliet, Manfred Kist, Johannes G. Kusters, and Stefan Bereswill
 16. Nickel-Dependent Gene Expression
Konstantin Salnikow and Kazimierz S. Kasprzak
 17. Nickel Toxicity and Carcinogenesis
Kazimierz S. Kasprzak and Konstantin Salnikow
- Subject Index

Volume 3: The Ubiquitous Roles of Cytochrome P450 Proteins
(this book)

Volume 4: Biomineralization. From Nature to Application
(tentative contents)

1. Crystals and Life. An Introduction
Arthur Veis
2. Gene-Directed Crystal Growth Exemplified by the Biomineralization of Calcium Carbonate
Fred H. Wilt and Christopher E. Killian
3. The Role of Enzymes in Biomineralization Processes
Ingrid M. Weiss and Frédéric Marin
4. Metal-Bacteria Interactions at Both the Planktonic Cell and Biofilm Levels
Ryan C. Hunter and Terry J. Beveridge
5. Biomineralization of Calcium Carbonate. The Interplay with Biosubstrates
Amir Berman and Yael Levi-Kalisman
6. Sulfate-Containing Biominerals
Fabienne Bosselmann and Matthias Epple
7. Oxalate Biominerals
Enrique J. Baran and Paula V. Monje
8. Structural Control, Molecular Components, and Multi-Level Regulation of Biosilification in Diatoms
Aubrey K. Davis, Kim Thamtrakoln, and Mark Hildebrand
9. Dynamics of Biomineralization and Biodemineralization
Lijun Wang and George H. Nancollas
10. Mechanism of Mineralization of Collagen Based Connective Tissues
Adele J. Boskey

11. Mammalian Enamel Formation
Janet Moradian-Oldak and Michael Paine
 12. Heavy Metals in the Jaws of Invertebrates
Helga C. Lichtenegger
 13. Ferritin. Biomineralization of Iron
Elizabeth C. Theil
 14. Molecular Biology and Magnetism of Magnetic Iron Minerals in Bacteria
Richard B. Frankel, Sabrina Schuebbe, and Dennis Bazylinski
 15. Mechanical Design of Biomineralized Tissues
Peter Fratzl
 16. Biominerals. Records of the Past
Danielle Fortin, Susan Glasauer, and Sean Langley
 17. Bio-Inspired Growth of Mineralized Tissue
Darilis Suarez and William L. Murphy
 18. Biomineralization of Novel Inorganic Materials for Application
Helmut Cölfen and Markus Antonietti
 19. Crystal Tectonics. Chemical Construction and Self-Organization
Annie K. Powell
- Subject Index

Comments and suggestions with regard to contents, topics, and the like for future volumes of the series are welcome.

1

Diversities and Similarities in P450 Systems: An Introduction

*Mary A. Schuler*¹ and *Stephen G. Sligar*²

¹Department of Cell and Developmental Biology, University of Illinois,
Urbana, IL 61801, USA
<maryschu@uiuc.edu>

²Department of Biochemistry, University of Illinois,
Urbana, IL 61801, USA
<s-sligar@uiuc.edu>

1. OXYGENASES: MEDIATORS OF BIOCHEMICAL DIVERSITY	2
2. P450 SUPERFAMILY: DIVERSITY AT THE SEQUENCE LEVEL	3
3. DIVERSITY OF P450 STRUCTURES: FOLDS AND CONFORMATIONS FOR FUNCTIONS	5
4. DIVERSITY IN P450 MECHANISMS	6
4.1. Diversity of Redox Partners	6
4.2. The Heme-Oxygen Catalytic Landscape	9
4.3. The Oxy and Peroxo Iron Intermediates	10
4.4. High-Valent Metal-Oxo Complexes	11
4.5. Uncoupling: Nature's Leakage Pathways	12
4.6. Other Heme-Thiolate Systems: Needs from a Mechanistic Viewpoint	12
5. DIVERSITY IN REGULATION ACROSS THE SUPERFAMILY	13
5.1. Transcriptional Regulation	13
5.2. Post-translational Regulation	15
6. DIVERSITY IN THE EVOLUTION OF COMMON METABOLIC FUNCTIONS	16
6.1. Hormone Biosynthesis	16
6.2. Xenobiotic Catabolism	17
6.3. Fatty Acid Hydroxylases: Bacteria to Mammals to Plants	17

7. SUMMARY AND OUTLOOK	18
ACKNOWLEDGMENTS	19
ABBREVIATIONS	19
REFERENCES	19

1. OXYGENASES: MEDIATORS OF BIOCHEMICAL DIVERSITY

The introduction of oxygen into biochemical processes has had a profound effect on the evolution of life. An appreciation for this traumatic event was presented in a beautiful recent review on the linkages of gene development that occurred at this juncture [1]. Although the first important utilization of atmospheric dioxygen was perhaps through its use as a terminal electron acceptor in metabolic energy conversion, an equally important leap in complexity and diversity was appreciated when, in the mid-1950s, Osamu Hayaishi and Howard Mason discovered the oxygenases [2,3]. This advance changed the simplistic view of how Nature uses atmospheric dioxygen from that of a simple electron acceptor and pointed to the rich metabolic diversity allowed by the incorporation of atmospheric dioxygen into substrate molecules. The discovery, naming and mechanistic understanding of the first ‘oxygenase’ enzymes have provided wonderful opportunities and scientific impetus to understand the great diversity of these systems in the synthesis and catabolism of organic molecules.

Before describing their various levels of diversity, one must consider the prime biochemical similarity that categorizes nearly all of them within the class of ‘oxidases’ that use atmospheric dioxygen as a terminal electron acceptor and, hence, yield an oxidized substrate molecule. In technical terms, the ‘oxygenases’ that exist within this broader oxidase category are classed as ‘mono-’ or ‘di-’, depending on whether one or both atoms of atmospheric dioxygen are incorporated into their respective substrates. In their reaction cycles, the classic stoichiometry of monooxygenases represents a sort of ‘half-way’ point on the pathway for the full four-electron reduction of dioxygen to generate two molecules of water as is typical of the redox counting of cytochrome ‘oxidases’. Positioned midstream in this pathway, monooxygenases require only two electrons and two protons to reductively cleave atmospheric dioxygen, producing only a single water molecule in the process while saving the second atom for the incorporation and formal oxidation of the organic substrate molecule. As a result of their dual functionality, cytochrome P450 monooxygenases (P450s) are often referred to as ‘mixed-function oxidases’ since they possess both ‘oxygenase’ and ‘oxidase’ reactivities. The electron transfer functionalities of P450s also earned them the label of ‘cytochrome’.