

Preface

The Biological Chemistry of the Elements

The Inorganic Chemistry of Life

J. J. R. FRAÚSTO da SILVA

*Professor of Analytical Chemistry, Instituto Superior Técnico,
Universidade Técnica de Lisboa*

and

R. J. P. WILLIAMS

*Royal Society Napier Research Professor,
University of Oxford*

CLARENDON PRESS · OXFORD

Oxford University Press, Walton Street, Oxford OX2 6DP

Oxford New York Toronto

Delhi Bombay Calcutta Madras Karachi

Kuala Lumpur Singapore Hong Kong Tokyo

Nairobi Dar es Salaam Cape Town

Melbourne Auckland Madrid

and associated companies in

Berlin Ibadan

Oxford is a trade mark of Oxford University Press

Published in the United States

by Oxford University Press Inc, New York

© J. J. R. Frausto da Silva and R. J. P. Williams, 1991

First published 1991

Reprinted with corrections 1993

First published in paperback 1993

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, or otherwise, without the prior permission of Oxford University Press.

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

Library of Congress Cataloging in Publication Data

da Silva, J. J. R. Frausto.

The biological chemistry of the elements: the inorganic chemistry of life/J. J. R. Frausto da Silva and R. J. P. Williams.

1. Bioinorganic chemistry. I. Williams, R. J. P. [Robert Joseph Paton]

II. Title.

QP531.S54 1991 574.19'214—dc20 91-11585 CIP

✓ ISBN 0-19-855598-9 (h/b)

0-19-855802-3 (p/b)

Printed in Great Britain by

Butler & Tanner Ltd, Frome, Somerset

0055024

THE BIOLOGICAL CHEMISTRY OF THE ELEMENTS

The Biological Chemistry of the Elements

The Inorganic Chemistry of Life

J. J. R. PRAYSTO da SILVA

Professor of Chemistry, Federal University of Rio de Janeiro,
Rio de Janeiro, Brazil

R. J. P. WILLIAMS

Senior Lecturer in
Chemistry at the

CURRENT

Preface

The majority of present-day living organisms require rather strict environmental conditions: temperature from 0 to about 40°C, pressure of the order of 1 atm., salinity up to about 4 per cent, pH in the range 4 to 9, redox potential in the region of stability of water (-0.4 to $+0.8$ V at pH=7 versus the standard H^+/H_2 electrode), water activity between 0.7 and 1.0 mole fraction. In a few cases these limits can be greatly exceeded and it is known that, in the earth's past, conditions existed which were quite different from the present ones but did not hinder the development of life, although they did impose constraints upon the *forms* of life that could exist. Indeed, this is an essential feature of life itself: the continuous adaptation of living organisms to changing environmental conditions through the development of defence devices and mechanisms against those changes, while sometimes turning new (adverse) factors into favourable ones. The result was, and still is, the survival and predominant proliferation of the fittest, and the history of evolution, which started as development under constraints of fixed conditions, became the history of the continuous adaptation of living organisms to changing conditions. In fact, and as we shall see, organisms themselves have caused much of the chemical environmental change.

Although ideas concerning the evolution of species and forms are well accepted, they are less recognized when transferred to the small molecule chemistry scale, even though it has become customary to call 'chemical evolution' the series of events which is thought to have taken place between the beginnings of prebiotic synthesis of large organic molecules and the appearance of the first vesicles ('protocells') to which one might assign some 'vital' properties. Throughout the (unfinished) biological evolution there has been, in addition, a continual selection toward the best chemical components for the necessary functions and a continuous improvement in the conditions of their utilization, leading to the formation of separate compartments in cells, to the functional separation of cells, to the specialization of different multicellular organisms and to their diversification and development. As the species became more complex, so did their chemistry, as evidenced by the increased complexity of the materials used and the manipulation of dynamic factors. The development of materials is again well recognized in the evolution of biological polymers but it can only be thoroughly appreciated, we believe, in terms of the structures and patterns of the flow of elements and chemicals, of ionic and electronic charge, and of energy directed in biological space. The strict environmental conditions that are required today by living organisms also point to the necessity of strict internal control and regulation of these processes, and this again means time and space organization of the biological substances, both large and small, and of their reactions. Much of this control is included in the now well-known classical treatment of the organic chemistry of

life but, diverging from the classical tradition, we shall regard it in this book as the interplay of not just the great number of small and very large organic molecules but also of a group of about 25 chemical elements, free as ions, combined as complexes, or as precipitates, organized in biological space and time. Most of these elements are classified as 'inorganic'. We shall go on to insist that a proper appreciation of living systems and their evolution cannot be obtained without reference to these elements.

Central to this group of elements is a series of metals, each one of them used in many ways within a given biological system. The position of each metal element in space and the variation of this position in time, as well as the exact chemical partners with which it interacts, have been selected and perfected by the demands of evolution seemingly in such a way that the element's function has become virtually optimal and its role separate and distinct. Hence, several such elements are essential for life. In order to fully appreciate the subtleties of the function that Nature makes of these *ca.* 15 metal elements, it is necessary to understand how they are selected, in terms of uptake, and how they are combined, transported, stored, and tuned to their specific functions. Evolution refined function by acting on the interaction of the metals with their partners (usually proteins) or by abandoning some in favour of others more appropriate to conditions. Much of this chemistry involves ionic interactions.

Of course, in the description of the way in which the chemical elements are involved in life we cannot concentrate on metal ions alone. Some non-metals actually function in ways not too different from those of the metals, but as anions not cations, e.g. Cl^- . Others, the major elements of life, C, N, O, and S, to which we refer to rather a small degree since their biological chemistry is well described elsewhere, behave very differently, much as their chemistry is also very different, being loosely called covalent rather than ionic. Between the extremes lies the chemistry of phosphorus, as phosphate in biology, and hydrogen, which have both ionic and covalent chemistry. Our point will be that all the elements we find in biology are used in some optimal manner developed from their chemical possibilities. Biological chemistry is concerned, therefore, with this intricate, interwoven, 'designed', and sometimes symbiotic use of organic (non-metal) molecules and inorganic (metal) chemical elements in cells and tissues and cannot be restricted or related to so-called organic chemistry rather than to so-called inorganic chemistry. This book is then about biological chemistry seen from a particular inorganic perspective where a certain inorganic *bias* is inevitable to compensate for the traditional approach which leans heavily on organic chemistry. Accordingly, we have named it *The biological chemistry of the elements*.

Before entering the main body of the text, the reader is warned that every biological device is unlikely to be the best of all possible devices. Not only has biology general chemical limitations, but it is also evolving in changing conditions, many of which are created by life itself. A consequence of this slow progression is that now and then a less than perfect feature will survive, which has evolved from a committed route earlier in evolution and then found a new semi-effective use. It also follows that, should environmental conditions, the air, the sea, or the land, change very rapidly, complex life forms are at risk. There is a very general warning here, as man's activities saturate the ability of the environment to buffer the chemical changes he makes.

The book is organized in the following manner. In Chapter 1 we analyse the occurrence of the chemical elements in biology showing that of the 92 elements in the periodic table some 25–30 are especially important in biology. Much of the reason behind this selection lies in the limitations imposed by the abundance of the elements (even in the universe) and their availability on earth. Availability is further constrained by the concentration in waters and in the air and depends on local conditions. In the absence of organic chemicals most elements are bound in simple oxygen- or sulphur-containing compounds, as hydrates or precipitates. On entering biology the elements undergo special combinations with organic molecules. In the next five chapters we shall be considering this chemical speciation in a great variety of compounds in biology. We shall describe in the first instance in Chapter 2 how the biological uptake of the elements from natural sources can be controlled by selective (energized) chemistry of the elements and leads on to selective chemical combinations, e.g. of metals, M, with organic ligands, L. In Chapter 3 we extend the discussion to physical transfer and separation of M, L, or ML across membranes into compartments. Only at this stage will it be possible to start to explore function. Function is dependent upon the ability of elements to undergo chemical change (within compounds). The kinetics of activity will therefore be analysed in Chapter 4. Chapter 5 will illustrate how energy is put into compounds within biology. This is an obvious necessity both in synthesis and in transfer. We shall then turn in Chapter 6 to one major concern of this book—the functionally necessary requirement for life of a variety of elements. Chapter 7 will be a rather lengthy but necessary interjection concerning the biopolymers of life. The second part of the book, Chapters 8 to 19, will consider the essential functions of individual inorganic elements in life's processes in detail and especially in relation to the principles we outline in the first part, before we attempt to pull all the (inorganic) chemistry of life together, in the last part of the book.

We begin the difficult final analysis with an enquiry into the nature of minerals in biology (Chapter 20), since this allows us to look at a peculiar biological problem, the relationship between chemical activity and morphology. Shape is so clearly an essential feature of living things. Having established some simple principles, we move in Chapter 21 to a consideration of the simultaneous homeostasis of shape and chemistry. It is here that the interactive feedback relationships between the functions of elements become so intriguing. It almost goes without saying at this stage that the balance of elements in life is related to the elements available and it follows that changing the availability must affect life. We look at problems of man's interference with the natural supply of elements in Chapter 22.

Each chapter has only a limited number of references and most of them are to reviews. We realize that this approach may offend some but we found it impossible to be sure that we could give proper priority amongst the vast number of primary sources we have used.

Lisbon and Oxford
January 1991

JJRFdS
RJJPW

Acknowledgements

Our special thanks go to Mrs S. Compton and Mrs J. Edwards who typed the manuscript and to Oxford University Press for their assistance in its final preparation.

The work reviewed here reflects in large part the efforts of a now very distinguished group of research scientists from all over the world, who have been with us. We wish to thank them for all that they brought to the research. We trust that the integrated view in this book will be seen as the result of an international effort to examine a further part of the wonders of chemistry within biology.

J. J. R. Fraústo da Silva acknowledges a travel grant for the preparation of this book from the Junta Nacional de Investigação Científica e Tecnológica (JNICT)—Portugal. Acknowledgements are also due to the Instituto Nacional de Investigação Científica (INIC)—Portugal for general support of research activities, to Mrs Teresa Maria Carreiras da Silva and Mrs Maria Idalisa Figueiredo dos Santos for secretarial help and to Mrs Ilda Proença for typing parts of the preliminary versions of the manuscript.

R. J. P. Williams acknowledges the generous support of Wadham College, Oxford, of Oxford University, of two British Research Councils (the Medical Research Council and the Science and Engineering Research Council), and of The Royal Society over some forty years.

Contents

PART I • The chemical and physical factors controlling the elements of life

1	The chemical elements in biology	3
1.1	The natural selection of the elements	3
1.1.1	Abundance in living systems	3
1.1.2	Chemical speciation: limitations of life chemistry and physics	6
1.2	An aside: some biological chemistry of hydrogen	7
1.3	The economical use of resources: abundance and availability	8
1.4	Biological environment and element availability	11
1.4.1	pH and redox potential considerations	11
1.4.2	Element concentrations in aerobic environments and in some organisms	14
1.4.3	Solubility products	18
1.5	Sulphide chemistry in water (anaerobes)	18
1.6	A note on homeostasis	20
1.7	Conclusion	22
2	The principles of the uptake and chemical speciation of the elements in biology	23
2.1	General aspects	24
2.2	The separations that biology can achieve	26
2.3	The selective uptake of metal ions	28
2.4	Effective stability constants	31
2.5	Element uptake at 'equilibrium'—the selectivity of the uptake	33
2.5.1	Selection by charge type	36
2.5.2	Selection by ion size	37
2.5.3	Combination of radius and charge effect	40
2.5.4	Selection by liganding atom	40
2.5.5	Selection by preferential co-ordination geometry	41
2.5.6	Selection by spin-pairing stabilization	43
2.5.7	Selection by binding in clusters	44
2.6	Hydrolysis	45
2.7	Selective control of oxidation states of metals	47
2.8	Selection by control of concentration by buffering	48
2.9	Selection by transfer coefficients from water to proteins	50
2.10	Soft and hard acids, solvents, and extraction	52

2.11	The selectivity of channels	53
2.12	Kinetic effects and control	54
2.12.1	The distribution coefficient D for ML_1	54
2.12.2	Kinetics of transport	54
2.12.3	Insertion in pre-formed holes or chelating rings	55
2.12.4	Energy coupling to the selective movement of M (gates and pumps)	56
2.12.5	A summary of the kinetics of uptake of metal ions	57
2.13	Rejection of metal ions	58
2.14	General aspects of the uptake of non-metals	58
2.15	Mechanisms of selection of anions based on thermodynamic properties	60
2.15.1	Selection by charge and size; the hydration of anions and their binding to proteins	60
2.15.2	Selection of anions by differences in binding affinity for different types of cationic centres	62
2.15.3	Kinetic binding traps for anions with or without accompanying redox reactions	63
2.16	Redox incorporation of anions	64
2.17	Coenzymes	65
2.18	Concluding remarks: element handling in biological systems	67
2.19	Precipitates in compartments	68
3	Physical separations of elements: compartments and zones in biology	71
3.1	General aspects	71
3.2	The nature of compartments	73
3.3	The chemical solutions and physical states of compartments	73
3.4	The role and nature of membranes	76
3.5	Different types of membrane	77
3.5.1	Internal and external particles and their relationship to membranes	78
3.5.2	Lateral membrane organization and in-membrane flow	79
3.5.3	Transmembrane organization and flow	82
3.5.4	Flow of vesicles in cells	83
3.6	Special solution conditions in vesicles	86
3.7	Co-operativity of separations and localizations	87
3.8	Summary of metal ion positioning	87
3.9	Symbiosis and multicellular systems	88
3.10	Spatial distribution of non-metals	89
3.11	The spatial transfer of H , C , N , S : mobile and fixed coenzymes	90
3.11.1	H (and O) transport	90
3.11.2	Phosphate transport	91
3.11.3	Carbon transport	92
3.11.4	Nitrogen transport	92
3.11.5	Sulphur transport	93
3.12	Summary of non-metal transport	93

4	Kinetic considerations of chemical reactions, catalysis, and control	95
4.1	Introduction	95
4.2	Chemical transformations	96
4.3	The nature of acid–base reactions: hydrolysis and condensation	97
4.4	The hydrolysis of proteins, RNA, DNA, and other polymers	99
4.5	The nature of ion flow	100
4.5.1	Signals and controls	100
4.5.2	Ion migration rates: electrolytics	101
4.6	On/off reactions: control systems	103
4.7	Electron transfer reactions: electronics	105
4.8	Redox potentials of complexes	108
4.9	Atom transfer reactions	109
4.10	Group transfer	111
4.11	The nature of transition-metal centres in catalysis	112
4.12	Free radical reactions	114
4.13	Sizes of atoms, stereochemistry, and reaction paths	115
4.14	The creation of local small spaces: mechanical devices for transfer reactions	116
4.15	Summary	118
5	Energy in biological systems and hydrogen biochemistry	120
5.1	Introduction	120
5.2	Biological systems and light	122
5.3	Oxidative energy: mitochondria	124
5.4	Proton migration coupled to redox reaction	126
5.5	The coupling of gradients to ATP formation	126
5.6	Anaerobes in the dark	128
5.7	Compartments, energy, and metabolism	131
5.8	Organization and tension	132
5.9	Motion of organisms	133
5.10	Local storage of elements	134
5.11	The evolution of the compartments for energy generation	135
5.12	Early sources of energy	135
5.13	Sulphur compounds	136
5.14	Feedback	136
5.15	Flow of material	136
5.16	The role of the proton in homeostasis	137
5.17	The proton and redox potentials	138
6	The functional value of the chemical elements in biological systems	140
6.1	Introduction	140
6.2	Major chemical properties of elements in aqueous solutions	141

6.3	Biochemical functions of the chemical elements	143
6.4	The living process	146
6.5	The chemical flow in biology	149
6.5.1	The synthesis and degradation of the polymers of life	149
6.5.2	Synthesis and degradation of monomers	151
6.5.3	The uptake and loss of elements	154
6.5.4	The flow of energy in compounds	154
6.5.5	Self-organization and flow patterns	155
6.6	Organization and flow	156
6.6.1	Patterns of electron flow: electrical potentials	156
6.6.2	Patterns of proton gradients and flow electrolytic potentials	157
6.6.3	Patterns of ion gradients and flow: communication	158
6.6.4	Tension patterns and flow	159
6.7	The integration of activity	160
6.8	Conclusion	160
6.8.1	The biological selection of elements	160
6.8.2	The evolution of the chemistry of life	161
7	The role of biological macromolecules and polymers	163
A	Proteins and nucleic acids	163
7.1	Introduction	163
7.2	Protein composition and basic structure	164
7.3	The protein fold and the internal motions in solution	171
7.4	The amino-acid composition of specific proteins	173
7.5	Structural proteins and mechanical devices	178
7.6	Matching of proteins and organic and inorganic ions	178
7.7	Enzymes	180
7.8	States of metal ions in proteins	182
7.8.1	General aspects	182
7.8.2	The copper blue centres	182
7.8.3	Protein/protein assemblies and metal ions	184
7.9	Summary of proteins	185
7.10	Nucleic-acid composition and outline structure	185
7.11	Metal-ion binding to polynucleotides	188
7.11.1	Cavities and metal-ion binding in DNA	188
7.11.2	DNA sequences and mutation	190
7.12	Nucleic acids and proteins	190
7.13	Polymer synthesis and degradation	191
B	Polysaccharides and lipids	193
7.14	Introduction to polysaccharides	193
7.15	Backbones of biological polymers	195
7.15.1	Proteins	195
7.15.2	Nucleic acids	195
7.15.3	Polysaccharides	195
7.16	Sidechains: physical properties	197
7.16.1	Proteins	197

7.16.2	Nucleic acids	197
7.16.3	Polysaccharides	197
7.17	The information content of biopolymers	198
7.18	Space-filling	199
7.18.1	Proteins	199
7.18.2	Nucleic acids	199
7.18.3	Polysaccharides	200
7.19	Chain branching in polysaccharides	201
7.20	Polysaccharide sidechains: chemical nature	201
7.21	Functions of biological polymers and oligomers	202
7.21.1	General notes	202
7.21.2	Roles of polysaccharides: relatively rigid structures	202
7.21.3	Recognizability of short mobile polysaccharide structures	203
7.22	Larger random polysaccharides	204
7.22.1	Non-interactive polysaccharides	204
7.22.2	Random extensions of glycoproteins: cell surface packing	205
7.22.3	Polysaccharides showing chain-chain repulsion or attraction	206
7.22.4	Anionic linear polymers	206
7.23	The cation interactions	210
7.24	Conclusions about polysaccharides	210
7.25	Properties of lipids	210
7.25.1	Lipids in membranes as macromolecular assemblies	210
7.25.2	Composition and general functions of lipids	211
7.25.3	Membrane functions and their lateral anisotropic organization	214
7.25.4	Ion association with lipid surfaces	215
7.25.5	The influences of selected inorganic elements	216
7.25.6	Potentials on membrane surfaces	216
7.26	The connection between lipids, hormones, and coenzymes	216
7.26.1	Cholesterol	216
7.26.2	Essential fatty acids	217
7.27	Summary of biopolymers	217

PART II · The roles of individual elements in biology

8	Sodium, potassium, and chlorine: osmotic control, electrolytic equilibria, and currents	223
8.1	Introduction	223
8.2	Passive diffusion	225
8.3	Gated channels	230
8.4	Channel selectivity and possible constructions	230
8.5	Active transport: pumps	232
8.6	The nature of selective pumps	236
8.7	Building electrolytic circuits	236

8.7.1	The positions of pumps and channels	236
8.7.2	The ATPase pumps: some general comments	236
8.7.3	Exchangers	237
8.7.4	Organic anions and cations as current carriers	238
8.7.5	Currents of ions and morphogenic patterns: growth	239
8.8	Simple salts and the conditions of polyelectrolytes	239
8.9	Enzymes requiring potassium	240
8.10	Ion energies: summary	240
8.11	Conclusions	241
9	The biological chemistry of magnesium: phosphate metabolism	243
9.1	Introduction	243
9.2	The spatial distribution of magnesium	244
9.3	Magnesium chemistry	245
9.4	Magnesium pumping in biology	248
9.5	Very strong binding of magnesium	249
9.6	Magnesium in walls and membranes	250
9.7	Magnesium enzymes: magnesium and phosphates	250
9.8	Magnesium and muscle cells	255
9.8.1	Activation of tension	255
9.8.2	Magnesium and muscle relaxation: calcium buffering	255
9.9	Magnesium and polynucleotides	256
9.9.1	Structures of DNA and RNA particles	256
9.9.2	Ribozymes	257
9.10	Competition with polyamines	257
9.11	Polymeric equilibria: tubulins, DNA, and the cell cycle	260
9.12	Sol/gel equilibria and magnesium	261
9.13	Magnesium and lipids	261
9.14	Magnesium and chlorophyll	262
9.14.1	Chlorophyll binding in proteins	262
9.14.2	Magnesium insertion in chlorophyll	263
9.15	The use of manganese as a magnesium probe	265
9.16	Pollution and Mg^{2+} biochemistry	266
9.17	Lithium and magnesium	266
9.18	Conclusion	266
10	Calcium: controls and triggers	268
10.1	Introduction	268
10.2	Free calcium ion levels	270
10.3	The calcium ion	271
10.4	Protein ligands for calcium	272
10.5	Magnesium/calcium competition	275
10.6	The resting state of calcium in cells	276
10.7	Calcium triggering: calmodulins	276
10.8	The calcium trigger proteins	278
10.9	S-100 proteins	280

10.10	Other triggering modes	281
10.10.1	Vesicular contents and their release: exocytosis	281
10.10.2	Calcium, filaments, and cell shape	282
10.11	Calcium and protein phosphorylation	283
10.12	Calcium buffering and calcium transport in cells	283
10.13	Calcium currents: movement through membranes, channels, gates, and pumps	284
10.14	Internal calcium-induced proteases	286
10.15	General remarks concerning control systems in cells	287
10.16	Extracytoplasmic calcium	288
10.16.1	Vesicular calcium: exchangers	288
10.16.2	Organelle calcium	289
10.16.3	Calcium in circulating fluids	289
10.17	Extracellular enzymes and calcium: digestion and blood clotting	289
10.18	Calcium proteins of biominerals	292
10.19	Calcium biominerals	293
10.20	Intra- and extracytoplasmic calcium balances	294
10.20.1	Multiple sites for calcium	294
10.20.2	Cell shape	295
10.20.3	Cell-cell interaction	295
10.20.4	Cell morphogenesis	295
10.21	Summary	296
11	Zinc: Lewis acid catalysis and regulation	299
11.1	Introduction to Lewis acids	299
11.2	Zinc in biological space	302
11.3	Availability and concentration of free Zn^{2+} ions	303
11.4	Types of protein associated with zinc	303
11.5	Zinc exchange rates	307
11.6	The number and selectivity of ligands to zinc	307
11.7	Zinc as a catalytic group in enzymes	308
11.7.1	Zinc as a Lewis acid	308
11.7.2	Zinc and redox reactions	311
11.7.3	The entatic state and probes	311
11.8	The use of zinc in biological space and time	312
11.9	Regulatory roles of zinc	312
11.10	Zinc and peptide hormones	314
11.11	Summary of intracellular zinc: is zinc a master hormone?	314
11.12	Extracellular zinc	315
11.12.1	The export of zinc enzymes: digestion	315
11.12.2	Cross-linking and hardening of extracellular matrices	316
11.12.3	Zinc in solid-state devices	317
11.13	Conclusion	317
	Note. Probes of metal sites by isomorphous substitution	318

12	Non-haem iron: redox reactions and controls	319
12.1	General introduction to transition metals in biology	319
12.2	Introduction to iron biological chemistry	322
12.3	Iron uptake	323
12.4	The non-haem iron proteins	326
12.5	The iron/sulphur proteins	326
12.6	Fe/S centres active as enzymes	329
12.7	Location of Fe/S proteins	330
12.8	Why are there Fe_nS_n clusters in biology?	331
12.9	The organization and synthesis of ferredoxins	332
12.10	The Fe–O–Fe cluster	333
12.11	Mononuclear non-haem/non-Fe/S iron and oxidative enzymes	335
12.12	Iron and secondary metabolism	337
12.13	Binding ligands in non-haem/non-Fe/S proteins	338
12.14	Iron as an acid catalyst	338
12.15	Summary of non-haem iron functions	339
12.16	Iron regulation and homeostasis	339
12.17	Iron buffering	340
	Note. The discovery of Fe/S centres	341
13	Haem iron: coupled redox reactions	343
13.1	Iron in porphyrins	343
13.2	Properties of isolated haem units	344
13.3	Classification of haem proteins by iron properties	347
13.4	Classification of haem proteins by secondary structure	348
13.5	Where are haem proteins in cells?	352
13.6	Haem-protein functions I: electron transfer	353
13.6.1	Simple electron transfer proteins	353
13.6.2	Multahaem electron transfer proteins	354
13.6.3	Electron transfer/proton transfer coupling: models	354
13.6.4	The membrane electron transfer proteins: protein coupling	356
13.7	The surfaces of haem proteins	357
13.8	Haem-protein functions II: storage and transport	358
13.8.1	Dioxygen: storage, transport, and signalling	358
13.8.2	Nitric oxide and haem receptors	359
13.8.3	Cytochrome <i>c</i> and cyanide	360
13.9	Haem-protein functions III: oxidases and dioxygenases	361
13.9.1	Cytochrome oxidase	362
13.9.2	Cytochrome P-450	363
13.9.3	Peroxidases and catalases	364
13.10	Substrates of haem enzymes and secondary metabolism	365
13.11	Haem in controls	366
13.12	The synthesis of haem	367
13.13	Summary of haem-iron functions	367
13.14	Control of cell activity and iron	368

14	Manganese: dioxygen evolution and glycosylation	370
14.1	Introduction	370
14.2	Manganese chemistry	372
14.2.1	Oxidation states	372
14.2.2	Structures of Mn(II) complexes with organic ligands	372
14.2.3	Manganese(II) equilibria and biochemistry	373
14.2.4	The kinetics of Mn(II) complexes	375
14.3	Monomeric Mn(III) and Mn(IV) chemistry	376
14.3.1	Structures	376
14.3.2	Thermodynamics	376
14.3.3	Kinetics of Mn(III) and Mn(IV) reactions	377
14.3.4	Manganese cluster chemistry	377
14.4	The biological chemistry of manganese	379
14.4.1	The occurrence and availability to biology of manganese	379
14.4.2	The uptake of manganese	379
14.4.3	Pumping of manganese gradients	379
14.4.4	The distribution of Mn in biological systems	380
14.5	Manganese control systems	380
14.6	The production of dioxygen	381
14.7	Manganese and dioxygen metabolism	382
14.8	Manganese precipitates	383
14.9	The evolution of manganese functions	385
14.10	Summary	386
15	Copper: extracytoplasmic oxidases and matrix formation	388
15.1	Introduction	388
15.2	Copper and electron transfer	389
15.3	Copper and dioxygen	391
15.3.1	Haemocyanin	391
15.3.2	A comment on copper of cytochrome oxidase	391
15.3.3	Copper and extracellular oxidases	392
15.3.4	Substrates of copper oxidases	393
15.3.5	Copper proteins and coenzyme PQQ	394
15.4	Copper enzymes and nitrogen oxides	394
15.5	Superoxide dismutase	395
15.5.1	The location	395
15.5.2	The reactions of superoxide dismutases	395
15.6	The transport and homeostasis of copper	396
15.6.1	The binding proteins	396
15.6.2	Copper exchange rates	396
15.6.3	Regulatory copper proteins	397
15.7	The overall functions of copper	397
16	Nickel and cobalt: remnants of early life?	400
16.1	Introduction	400
16.2	The chemistry of cobalt and nickel	402
16.3	Hydrogenases	405