Contents

About the Editor xiii
List of Contributors xv
Preface xix
Acknowledgements xxi

1. New Applications of Immobilized Metal Ion Affinity Chromatography in Chemical Biology **1**
Rachel Codd, Jiesi Gu, Najwa Ejje and Tulip Lifa

1.1 Introduction 1
1.2 Principles and Traditional Use 2
1.3 A Brief History 4
1.4 New Application 1: Non-protein Based Low Molecular Weight Compounds 5
1.4.1 Siderophores 6
1.4.2 Anticancer Agent: Trichostatin A 10
1.4.3 Anticancer Agent: Bleomycin 12
1.4.4 Anti-infective Agents 13
1.4.5 Other Agents 14
1.4.6 Selecting a Viable Target 15
1.5 New Application 2: Multi-dimensional Immobilized Metal Ion Affinity Chromatography 17
1.6 New Application 3: Metabolomics 20
1.7 New Application 4: Coordinate-bond Dependent Solid-phase Organic Synthesis 20
1.8 Green Chemistry Technology 21
1.9 Conclusion 23
Acknowledgments 24
References 24

2. Metal Complexes as Tools for Structural Biology **37**
Michael D. Lee, Bim Graham and James D. Swarbrick

2.1 Structural Biological Studies and the Major Techniques Employed 37
2.2 What do Metal Complexes have to Offer the Field of Structural Biology? 38
2.3 Metal Complexes for Phasing in X-ray Crystallography 39

2.4 Metal Complexes for Derivation of Structural Restraints via Paramagnetic NMR Spectroscopy 41
2.4.1 Paramagnetic Relaxation Enhancement (PRE) 42
2.4.2 Residual Dipolar Coupling (RDC) 43
2.4.3 Pseudo-Contact Shifts (PCS) 43
2.4.4 Strategies for Introducing Lanthanide Ions into Bio-Macromolecules 44
2.5 Metal Complexes as Spin Labels for Distance Measurements via EPR Spectroscopy 53
2.6 Metal Complexes as Donors for Distance Measurements via Luminescence Resonance Energy Transfer (LRET) 54
2.7 Concluding Statements and Future Outlook 56
References 56

3. AAS, XRF, and MS Methods in Chemical Biology of Metal Complexes 63
Ingo Ott, Christophe Biot and Christian Hartinger

3.1 Introduction 63
3.2 Atomic Absorption Spectroscopy (AAS) 64
3.2.1 Fundamentals and Basic Principles of AAS 64
3.2.2 Instrumental and Technical Aspects of AAS 65
3.2.3 Method Development and Aspects of Practical Application 67
3.2.4 Selected Application Examples 69
3.3 Total Reflection X-Ray Fluorescence Spectroscopy (TXRF) 72
3.3.1 Fundamentals and Basic Principles of TXRF 72
3.3.2 Instrumental/Methodical Aspects of TXRF and Applications 73
3.4 Subcellular X-ray Fluorescence Imaging of a Ruthenium Analogue of the Malaria Drug Candidate Ferroquine Using Synchrotron Radiation 74
3.4.1 Application of X-ray Fluorescence in Drug Development Using Ferroquine as an Example 75
3.5 Mass Spectrometric Methods in Inorganic Chemical Biology 80
3.5.1 Mass Spectrometry and Inorganic Chemical Biology: Selected Applications 83
3.6 Conclusions 90
Acknowledgements 90
References 90

4. Metal Complexes for Cell and Organism Imaging 99
Kenneth Yin Zhang and Kenneth Kam-Wing Lo

4.1 Introduction 99
4.2 Photophysical Properties 100
4.2.1 Fluorescence and Phosphorescence 100
4.2.2 Two-photon Absorption 101
4.2.3 Upconversion Luminescence 102

4.3 Detection of Luminescent Metal Complexes in an Intracellular Environment 104
4.3.1 Confocal Laser-scanning Microscopy 104
4.3.2 Fluorescence Lifetime Imaging Microscopy 105
4.3.3 Flow Cytometry 106
4.4 Cell and Organism Imaging 107
4.4.1 Factors Affecting Cellular Uptake 107
4.4.2 Organelle Imaging 116
4.4.3 Two-photon and Upconversion Emission Imaging for Cells and Organisms 133
4.4.4 Intracellular Sensing and Labeling 136
4.5 Conclusion 143
Acknowledgements 143
References 143

5. Cellular Imaging with Metal Carbonyl Complexes 149
Luca Quaroni and Fabio Zobi

5.1 Introduction 149
5.2 Vibrational Spectroscopy of Metal Carbonyl Complexes 151
5.3 Microscopy and Imaging of Cellular Systems 154
5.3.1 Techniques of Vibrational Microscopy 155
5.4 Infrared Microscopy 155
5.4.1 Concentration Measurements with IR Spectroscopy and Spectromicroscopy 157
5.4.2 Water Absorption 158
5.4.3 Metal Carbonyls as IR Probes for Cellular Imaging 158
5.4.4 *In Vivo* Uptake and Reactivity of Metal Carbonyl Complexes 162
5.5 Raman Microscopy 167
5.5.1 Concentration Measurements with Raman Spectroscopy and Spectromicroscopy 169
5.5.2 Metal Carbonyls as Raman Probes for Cellular Imaging 169
5.6 Near-field Techniques 171
5.6.1 Concentration Measurements with Near-field Techniques 172
5.6.2 High-resolution Measurement of Intracellular Metal–Carbonyl Accumulation by Photothermal Induced Resonance 173
5.7 Comparison of Techniques 175
5.8 Conclusions and Outlook 176
Acknowledgements 177
References 178

6. Probing DNA Using Metal Complexes 183
Lionel Marcélis, Willem Vanderlinden and Andrée Kirsch-De Mesmaeker

6.1 General Introduction 183
6.2 Photophysics of Ru(II) Complexes 184
6.2.1 The First Ru(II) Complex Studied in the Literature: $[Ru(bpy)_3]^{2+}$ 184

6.2.2 Homoleptic Complexes 186
6.2.3 Heteroleptic Complexes 186
6.2.4 Photoinduced Electron Transfer (PET) and Energy Transfer Processes 188
6.3 State-of-the-art on the Interactions of Mononuclear Ru(II) Complexes with Simple Double-stranded DNA 190
6.3.1 Studies on Simple Double-stranded DNAs 191
6.3.2 Influence of DNA on the Emission Properties 193
6.4 Structural Diversity of the Genetic Material 194
6.4.1 Mechanical Properties of DNA 195
6.4.2 DNA Topology 195
6.4.3 SMF Study with $[Ru(phen)_2(PHEHAT)]^{2+}$ and $[Ru(TAP)_2(PHEHAT)]^{2+}$ 198
6.5 Unusual Interaction of Dinuclear Ru(II) Complexes with Different DNA Types 200
6.5.1 Reversible Interaction of $[\{(Ru(phen)_2\}_2HAT]^{4+}$ with Denatured DNA 201
6.5.2 Targeting G-quadruplexes with Photoreactive $[\{Ru(TAP)_2\}_2TPAC]^{4+}$ 204
6.5.3 Threading Intercalation 205
6.6 Conclusions 207
Acknowledgement 208
References 208

7. Visualization of Proteins and Cells Using Dithiol-reactive Metal Complexes 215
Danielle Park, Ivan Ho Shon, Minh Hua, Vivien M. Chen and Philip J. Hogg

7.1 The Chemistry of As(III) and Sb(III) 215
7.2 Cysteine Dithiols in Protein Function 217
7.3 Visualization of Dithiols in Isolated Proteins with As(III) 218
7.4 Visualization of Dithiols on the Mammalian Cell Surface with As(III) 218
7.5 Visualization of Dithiols in Intracellular Proteins with As(III) 219
7.6 Visualization of Tetracysteine-tagged Recombinant Proteins in Cells with As(III) 219
7.7 Visualization of Cell Death in the Mouse with Optically Labelled As(III) 220
7.7.1 Cell Death in Health and Disease 220
7.7.2 Cell Death Imaging Agents 222
7.7.3 Visualization of Cell Death in Mouse Tumours, Brain and Thrombi with Optically Labelled As(III) 223
7.8 Visualization of Cell Death in Mouse Tumours with Radio-labelled As(III) 225
7.9 Summary and Perspectives 227
References 227

8. Detection of Metal Ions, Anions and Small Molecules Using Metal Complexes **233**
Qin Wang and Katherine J. Franz

8.1 How Do We See What's in a Cell? 233
8.1.1 Why Metal Complexes as Sensors? 234
8.1.2 Design Strategies for Sensors Built with Metal Complexes 234
8.1.3 General Criteria of Metal-based Sensors for Bioimaging 236
8.2 Metal Complexes for Detection of Metal Ions 236
8.2.1 Tethered Sensors for Detecting Metal Ions 237
8.2.2 Displacement Sensors for Detecting Metal Ions 240
8.2.3 MRI Contrast Agents for Detecting Metal Ions 240
8.2.4 Chemodosimeters for Metal Ions 249
8.3 Metal Complexes for Detection of Anions and Neutral Molecules 252
8.3.1 Tethered Approach: Metal Complex as Recognition Unit 255
8.3.2 Displacement Approach: Metal Complex as Quencher 258
8.3.3 Dosimeter Approach 262
8.4 Conclusions 268
Acknowledgements 268
Abbreviations 268
References 269

9. Photo-release of Metal Ions in Living Cells **275**
Celina Gwizdala and Shawn C. Burdette

9.1 Introduction to Photochemical Tools Including Photocaged Complexes 275
9.2 Calcium Biochemistry and Photocaged Complexes 278
9.2.1 Strategies for Designing Photocaged Complexes for Ca^{2+} 278
9.2.2 Biological Applications of Photocaged Ca^{2+} Complexes 282
9.3 Zinc Biochemistry and Photocaged Complexes 284
9.3.1 Biochemical Targets for Photocaged Zn^{2+} Complexes 284
9.3.2 Strategies for Designing Photocaged Complexes for Zn^{2+} 286
9.4 Photocaged Complexes for Other Metal Ions 291
9.4.1 Photocaged Complexes for Copper 291
9.4.2 Photocaged Complexes for Iron 295
9.4.3 Photocaged Complexes for Other Metal Ions 297
9.5 Conclusions 298
Acknowledgment 298
References 298

10. Release of Bioactive Molecules Using Metal Complexes **309**
Peter V. Simpson and Ulrich Schatzschneider

10.1 Introduction 309
10.2 Small-molecule Messengers 310
10.2.1 Biological Generation and Delivery of CO, NO, and H_2S 310

10.2.2 Metal–Nitrosyl Complexes for the Cellular Delivery of Nitric Oxide 311
10.2.3 CO-releasing Molecules (CORMs) 314
10.3 "Photouncaging" of Neurotransmitters from Metal Complexes 321
10.3.1 "Caged" Compounds 321
10.3.2 "Uncaging" of Bioactive Molecules 322
10.4 Hypoxia Activated Cobalt Complexes 324
10.4.1 Bioreductive Activation of Cobalt Complexes 324
10.4.2 Hypoxia-activated Cobalt Prodrugs of DNA Alkylators 326
10.4.3 Hypoxia-activated Cobalt Prodrugs of MMP Inhibitors 329
10.5 Summary 333
Acknowledgments 333
References 323

11. Metal Complexes as Enzyme Inhibitors and Catalysts in Living Cells 341
Julien Furrer, Gregory S. Smith and Bruno Therrien

11.1 Introduction 341
11.2 Metal-based Inhibitors: From Serendipity to Rational Design 342
11.2.1 Mimicking the Structure of Known Enzyme Binders 342
11.2.2 Coordinating Known Enzymatic Inhibitors to Metal Complexes 343
11.2.3 Exchanging Ligands to Inhibit Enzymes 344
11.2.4 Controlling Conformation by Metal Coordination 344
11.2.5 Competing with Known Metallo-Enzymatic Processes 345
11.3 The Next Generation: Polynuclear Metal Complexes as Enzyme Inhibitors 346
11.3.1 Polyoxometalates: Broad Spectrum Enzymatic Inhibitory Effects 347
11.3.2 Polynuclear G-quadruplex DNA Stabilizers: Potential Inhibitors of Telomerase 349
11.3.3 Polynuclear Polypyridyl Ruthenium Complexes: DNA Topoisomerase II Inhibitors 352
11.4 Metal Complexes as Catalysts in Living Cells 355
11.4.1 Catalysis of NAD^+/NADH 355
11.4.2 Oxidation of the Thiols Cysteine and Glutathione 357
11.4.3 Cytotoxicity Controlled by Oxidation 361
11.5 Catalytic Conversion and Removal of Functional Groups 361
11.6 Catalytically Controlled Carbon–Carbon Bond Formation 362
11.7 Conclusion 364
References 364

12. Other Applications of Metal Complexes in Chemical Biology 373
Tanmaya Joshi, Malay Patra and Gilles Gasser

12.1 Introduction 373
12.2 Surface Immobilization of Proteins and Enzymes 373

12.3 Metal Complexes as Artificial Nucleases 378
12.3.1 Mono- and Multinuclear Cu(II) and Zn(II) Complexes 380
12.3.2 Lanthanide Complexes 388
12.4 Cellular Uptake Enhancement Using Metal Complexes 390
12.5 Conclusions 394
Acknowledgments 394
References 394

Index **403**