Contents

Preface \textit{xv}

1 Water Runs Deep 1  
\textit{Nicholas E. Ernst and Bruce C. Gibb}

1.1 The Control of Water 1
1.2 The Shape of Water 2
1.3 The Matrix of Life as a Solvent 4
1.4 Solvation Thermodynamics 6
1.5 The Three Effects 9
1.5.1 The Hydrophobic Effect 11
1.5.2 The Hofmeister Effect 19
1.5.3 The Reverse Hofmeister Effect 23
1.6 Conclusions and Future Work 24
Acknowledgments 25
References 25

2 Water-Compatible Host Systems 35  
Frank Biedermann

2.1 General Overview 35
2.2 Acyclic Systems 36
2.2.1 Acyclic Molecular Recognition Units 36
2.2.2 Molecular Tweezers 38
2.2.3 Foldamers 39
2.2.4 Compartmentalized Structures Formed by Surfactant-Like Molecules 40
2.3 Macrocyclic Receptors that Bind Charged Guests 42
2.3.1 Crown Ethers, Cryptands, and Spherands 42
2.3.2 Bambus\textit{[n]}urils 44
2.3.3 Calix\textit{[n]}arenes 45
2.3.4 Pillar\textit{[n]}arenes 48
2.4 Macrocyclic Receptors that (also) Bind Non-charged Organic Guests 50
2.4.1 Cyclodextrins 50
2.4.2 Cucurbit\textit{[n]}urils 54
2.4.3 Deep Cavitands 58
## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.4.4</td>
<td>Molecular Tubes</td>
<td>62</td>
</tr>
<tr>
<td>2.5</td>
<td>Practitioner’s Guidelines for Choosing a Water-Compatible Host</td>
<td>64</td>
</tr>
<tr>
<td>2.5.1</td>
<td>Guest Binding Affinity and Selectivity</td>
<td>64</td>
</tr>
<tr>
<td>2.5.2</td>
<td>Availability/Scalability</td>
<td>65</td>
</tr>
<tr>
<td>2.5.3</td>
<td>Functionality</td>
<td>65</td>
</tr>
<tr>
<td>2.5.4</td>
<td>Solubility</td>
<td>66</td>
</tr>
<tr>
<td>2.5.5</td>
<td>Biocompatibility/Toxicity</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>67</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Artificial Peptide and Protein Receptors</td>
<td>79</td>
</tr>
<tr>
<td>3.1</td>
<td>Introduction</td>
<td>79</td>
</tr>
<tr>
<td>3.2</td>
<td>Peptide Recognition</td>
<td>79</td>
</tr>
<tr>
<td>3.2.1</td>
<td>Calixarenes</td>
<td>80</td>
</tr>
<tr>
<td>3.2.2</td>
<td>Guanidiniocarbonyl Pyrroles</td>
<td>80</td>
</tr>
<tr>
<td>3.2.3</td>
<td>Cucurbiturils</td>
<td>82</td>
</tr>
<tr>
<td>3.2.4</td>
<td>Metal Complexes</td>
<td>84</td>
</tr>
<tr>
<td>3.2.5</td>
<td>Phosphonates</td>
<td>86</td>
</tr>
<tr>
<td>3.2.6</td>
<td>Thiourea-Containing Copolymers</td>
<td>87</td>
</tr>
<tr>
<td>3.3</td>
<td>Protein Recognition</td>
<td>88</td>
</tr>
<tr>
<td>3.3.1</td>
<td>Molecular Tweezer: Huntingtin Protein (htt)</td>
<td>89</td>
</tr>
<tr>
<td>3.3.2</td>
<td>Foldamer: Human Carbonic Anhydrase</td>
<td>89</td>
</tr>
<tr>
<td>3.3.3</td>
<td>Tetravalent Peptide: $\beta$-Tryptase</td>
<td>90</td>
</tr>
<tr>
<td>3.3.4</td>
<td>Semisynthetic Fusicoccin Derivative: 14-3-3/Gab2 Protein</td>
<td>91</td>
</tr>
<tr>
<td>3.3.5</td>
<td>Ruthenium Complex: Cytochrome C</td>
<td>92</td>
</tr>
<tr>
<td>3.3.6</td>
<td>Nitrilotriacetic Acid–Peptide Conjugate: His-Tag Calmodulin</td>
<td>93</td>
</tr>
<tr>
<td>3.3.7</td>
<td>Cucurbit[7]uril: Native Insulin and Human Growth Hormone</td>
<td>95</td>
</tr>
<tr>
<td>3.3.8</td>
<td>Phosphonated Calix[6]arene: Cytochrome C</td>
<td>96</td>
</tr>
<tr>
<td>3.3.9</td>
<td>$p$-Sulfonatocalixarene: Human Insulin A</td>
<td>96</td>
</tr>
<tr>
<td>3.3.10</td>
<td>Multivalent Calixarene: Platelet-Derived Growth Factor</td>
<td>97</td>
</tr>
<tr>
<td>3.4</td>
<td>Sensor Arrays for Proteins</td>
<td>99</td>
</tr>
<tr>
<td>3.4.1</td>
<td>Tripodal Peptide-Containing Receptors: Proteins and Glycoproteins</td>
<td>99</td>
</tr>
<tr>
<td>3.4.2</td>
<td>Substituted Porphyrins: Proteins and Metalloproteins</td>
<td>100</td>
</tr>
<tr>
<td>3.4.3</td>
<td>Poly($p$-phenyleneethynylene)s: Proteins</td>
<td>101</td>
</tr>
<tr>
<td>3.4.4</td>
<td>Chemiluminescent Nanomaterials: Proteins and Cells</td>
<td>103</td>
</tr>
<tr>
<td>3.5</td>
<td>Combinatorial Fluorescent Molecular Sensors for Proteins</td>
<td>104</td>
</tr>
<tr>
<td>3.5.1</td>
<td>Probe for MMP, GST, and PDGF Protein Families</td>
<td>104</td>
</tr>
<tr>
<td>3.5.2</td>
<td>Probe for Amyloid Beta Proteins</td>
<td>107</td>
</tr>
<tr>
<td>3.6</td>
<td>Conclusions and Future Directions</td>
<td>108</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>109</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Recognition, Transformation, Detection of Nucleotides and Aqueous</td>
<td>115</td>
</tr>
<tr>
<td></td>
<td>Nucleotide-Based Materials</td>
<td></td>
</tr>
<tr>
<td>4.1</td>
<td>Introduction</td>
<td>115</td>
</tr>
<tr>
<td>4.2</td>
<td>Nucleotide Structures</td>
<td>118</td>
</tr>
</tbody>
</table>

---

3 Artificial Peptide and Protein Receptors

Joydev Hatai and Carsten Schmuck

3.1 Introduction

3.2 Peptide Recognition

3.2.1 Calixarenes

3.2.2 Guanidiniocarbonyl Pyrroles

3.2.3 Cucurbiturils

3.2.4 Metal Complexes

3.2.5 Phosphonates

3.2.6 Thiourea-Containing Copolymers

3.3 Protein Recognition

3.3.1 Molecular Tweezer: Huntingtin Protein (htt)

3.3.2 Foldamer: Human Carbonic Anhydrase

3.3.3 Tetravalent Peptide: $\beta$-Tryptase

3.3.4 Semisynthetic Fusicoccin Derivative: 14-3-3/Gab2 Protein

3.3.5 Ruthenium Complex: Cytochrome C

3.3.6 Nitrilotriacetic Acid–Peptide Conjugate: His-Tag Calmodulin

3.3.7 Cucurbit[7]uril: Native Insulin and Human Growth Hormone

3.3.8 Phosphonated Calix[6]arene: Cytochrome C

3.3.9 $p$-Sulfonatocalixarene: Human Insulin A

3.3.10 Multivalent Calixarene: Platelet-Derived Growth Factor

3.4 Sensor Arrays for Proteins

3.4.1 Tripodal Peptide-Containing Receptors: Proteins and Glycoproteins

3.4.2 Substituted Porphyrins: Proteins and Metalloproteins

3.4.3 Poly($p$-phenyleneethynylene)s: Proteins

3.4.4 Chemiluminescent Nanomaterials: Proteins and Cells

3.5 Combinatorial Fluorescent Molecular Sensors for Proteins

3.5.1 Probe for MMP, GST, and PDGF Protein Families

3.5.2 Probe for Amyloid Beta Proteins

3.6 Conclusions and Future Directions

References

4 Recognition, Transformation, Detection of Nucleotides and Aqueous Nucleotide-Based Materials

Isabel Pont, Cristina Galiana-Rosello, Alberto Lopera, Jorge González-Garcia, and Enrique García-España

4.1 Introduction

4.2 Nucleotide Structures
### Contents

4.3 Nucleotide Receptors 119  
4.3.1 Receptors Without Aromatic Units 119  
4.3.2 Receptors with Aromatic Units 123  
4.3.3 Metal Complexes as Nucleotide Receptors 131  
4.3.4 Catalytic Aspects 134  
4.4 Nucleotide Sensing 140  
4.4.1 General Aspects 140  
4.4.2 UV–vis Sensing 140  
4.4.3 Fluorescence Sensing 142  
4.5 Soft Materials Incorporating Nucleotides, Nucleosides, and Nucleobases 147  
4.6 Biomedical Applications 150  
4.7 Challenges and Future Perspectives 151  
Acknowledgment 152  
References 153  

5 Carbohydrate Receptors 161  
Anthony P. Davis  
5.1 Introduction 161  
5.2 Organic Molecular Receptors 163  
5.2.1 Acyclic Receptors 164  
5.2.2 Macrocyclic Receptors 167  
5.2.3 Macropolycyclic Cage Receptors 171  
5.3 Metal Complexes as Carbohydrate Receptors 178  
5.4 Boron-Based Receptors 180  
5.5 Conclusions 184  
References 186  

6 Ion Receptors 193  
Luca Leoni, Antonella Dalla Cort, Frank Biedermann, and Stefan Kubik  
6.1 Introduction 193  
6.1.1 Potential Applications for Ion Receptors 194  
6.1.2 Binding Modes of Ion Receptors 194  
6.2 Cation Receptors 197  
6.2.1 Neutral Receptors 197  
6.2.1.1 Crown Ethers and Cryptands 197  
6.2.1.2 Cyclodextrins 198  
6.2.1.3 Cucurbiturils 199  
6.2.1.4 Cavitands 201  
6.2.2 Negatively Charged Receptors 202  
6.2.2.1 Cyclophanes 202  
6.2.2.2 Cryptophanes 204  
6.2.2.3 Calixarenes 204  
6.2.2.4 Pillararenes 205  
6.2.2.5 Molecular Tweezers 206  
6.2.2.6 Acyclic Cucurbiturils 208  
6.2.3 Metal-Containing Receptors 209
## Contents

6.2.3.1 Metallacycles 209  
6.2.3.2 Coordination Cages 210  
6.3 Anion Receptors 211  
6.3.1 Metal-Containing Receptors 211  
6.3.1.1 Coordination Cages 212  
6.3.1.2 Tetraazaamacrocyle-Based Receptors 214  
6.3.1.3 Diethylenetriamine- and Bis(2-pyridylmethyl)amine-Based Receptors 215  
6.3.1.4 Tris(2-aminomethyl)amine and Tris(2-pyridylmethyl)amine-Based Receptors 218  
6.3.1.5 Miscellaneous 220  
6.3.2 Positively Charged Receptors 221  
6.3.2.1 Receptors with Quaternary Ammonium Groups 221  
6.3.2.2 Amine-Based Receptors 223  
6.3.2.3 Guanidine-Based Receptors 225  
6.3.2.4 Imidazolium-Based Receptors 227  
6.3.3 Negatively Charged Receptors 228  
6.3.4 Neutral Receptors 231  
6.4 Zwitterion Receptors 236  
6.5 Conclusion and Future Challenges 238  
References 239  

7 Coordination Compounds 249  
Anna J. McConnell and Marc Lehr  
7.1 Introduction 249  
7.2 Organometallic Compounds 249  
7.2.1 Macrocycles 251  
7.2.2 Cages 252  
7.3 Metallomacrocycles 253  
7.4 Metallosupramolecular Helicates 255  
7.4.1 Transition Metal Helicates 255  
7.4.2 Lanthanide Helicates 257  
7.5 Metallosupramolecular Bowls and Tubes 260  
7.6 Metallosupramolecular Cages 262  
7.6.1 Design Considerations 263  
7.6.2 Thermodynamics of Guest Binding 263  
7.6.3 Cage and Guest Dynamics upon Encapsulation 265  
7.6.4 Chiral Recognition 266  
7.6.5 Encapsulation of Biorelevant Molecules 266  
7.6.6 Stabilization of Encapsulated Species 269  
7.6.7 Controlling Reactivity 269  
7.6.8 Catalysis 270  
7.7 Metal–Organic Frameworks 272  
7.8 Challenges and Future Directions 273  
References 274
8 Aqueous Supramolecular Polymers and Hydrogels 285
Daniel Spitzer and Pol Besenius
8.1 Introduction 285
8.2 Hydrogen-Bonded Supramolecular Systems 287
8.3 Host–Guest Induced Supramolecular Polymers and Hydrogels 292
8.4 Metal–Ligand Coordinated Systems 296
8.5 π-Conjugated Systems 301
8.6 Low Molecular Weight Hydrogelator Systems 307
8.7 Peptide-Based Molecular Amphiphiles and Their Supramolecular Systems 314
8.8 Bioinspired Systems 321
8.9 Challenges and Future Directions 326
References 326

9 Foldamers 337
Morgane Pasco, Christel Dolain, and Gilles Guichard
9.1 Introduction 337
9.2 Discrete Protein-Like Architectures by Lateral Assemblies of Helical Foldamers 338
9.2.1 Bioinspired Helix Assemblies: Top-Down Approaches 340
9.2.2 Bioinspired Helix Assemblies: Bottom-Up Approaches 344
9.3 Helix Duplexes in Aqueous Solution 350
9.4 Assemblies of Extended Chains 355
9.5 Elongated Nanostructures by Self-Assembly 357
9.6 Applications 359
9.6.1 Host–Guest Interactions With and Within Helix Bundles 359
9.6.2 Self-Assembling Foldamers Targeting Heparin 362
9.6.3 Catalysis with Self-Assembled Foldamers 363
9.6.4 Foldamer-Mediated Protein Oligomerization 364
9.6.5 Nanopores by Insertion of Foldamers into Phospholipid Membranes 366
9.7 Challenges and Future Directions 366
Acknowledgments 367
References 367

10 Vesicles and Micelles 375
Wilke C. de Vries and Bart Jan Ravoo
10.1 Introduction 375
10.2 Building Blocks and Structure of Vesicles and Micelles 376
10.2.1 Conventional Building Blocks and Packing Parameter 376
10.2.2 Driving Forces and Dynamics 379
10.2.3 Nonconventional Building Blocks 382
10.3 Stimulus-Responsive Vesicles and Micelles 387
10.3.1 Endogenous Stimuli: Redox and pH 387
10.3.1.1 Redox 387
Contents

10.3.1.2 pH 389
10.3.2 Exogenous Stimuli: Light and Temperature 391
10.3.2.1 Light 391
10.3.2.2 Temperature 392
10.4 Vesicles and Micelles as Template Structures for Nanomaterials 393
10.4.1 Condensation and Polymerization Reactions Using Template Structures 393
10.4.2 Stabilization of Vesicle and Micelle Structures by Cross-Linking 394
10.4.3 Polymer Shells Enclosing Vesicle Templates 395
10.5 Molecular Recognition of Vesicles and Micelles in Biomimetic Systems and Nanomaterials 397
10.5.1 Macrocyclic Amphiphiles 397
10.5.2 Carbohydrate and Peptide-Based Recognition 399
10.5.3 DNA-Based Recognition 402
10.6 Challenges and Future Directions 404
References 405

11 Monolayer-Protected Gold Nanoparticles for Molecular Sensing and Catalysis 413
Fabrizio Mancin, Leonard J. Prins, Federico Rastrelli, and Paolo Scrimin
11.1 Introduction 413
11.2 Analytical Techniques 414
11.2.1 Nuclear Magnetic Resonance Spectroscopy 414
11.2.2 Electron Paramagnetic Resonance Spectroscopy 416
11.2.3 Fluorescence Spectroscopy 417
11.2.4 Isothermal Titration Calorimetry 417
11.2.5 Surface-Enhanced Raman Scattering 418
11.3 Molecular Recognition and Chemosensing of Small Molecules 418
11.3.1 Multivalent Binding Interactions at the Monolayer Surface 419
11.3.2 Binding Pockets in the Monolayer 420
11.3.3 Gold Nanoparticle-Based Chemosensors 426
11.3.3.1 Indicator Displacement Assays 426
11.3.3.2 NMR Chemosensing 428
11.4 Catalysis by Nanozymes 430
11.5 Controlling Molecular Recognition Processes at the Monolayer 435
11.5.1 Regulatory Mechanisms 435
11.5.2 Adaptive Multivalent Surfaces 438
11.6 Challenges and Future Directions 442
References 442

12 Optical Probes and Sensors 449
Pavel Anzenbacher, Jr and Lorenzo M. Mosca
12.1 Introduction and Lexicon 449
12.2 Brief Fundamentals of Molecular Photoprocesses 451
12.3 Some Comments on the Design of Probes and Sensors 455
12.3.1 General Aspects 455
### Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.3.2</td>
<td>Fighting with Water</td>
<td>457</td>
</tr>
<tr>
<td>12.4</td>
<td>Probes and Sensors for Electroneutral Species</td>
<td>459</td>
</tr>
<tr>
<td>12.4.1</td>
<td>Carbohydrates</td>
<td>459</td>
</tr>
<tr>
<td>12.5</td>
<td>Probes and Sensor for Cations</td>
<td>462</td>
</tr>
<tr>
<td>12.5.1</td>
<td>Alkali and Alkali-Earth Cations</td>
<td>462</td>
</tr>
<tr>
<td>12.5.2</td>
<td>First-Row Transition Metal Ions</td>
<td>464</td>
</tr>
<tr>
<td>12.5.3</td>
<td>Heavy Metal Ions, Particularly Cadmium and Mercury</td>
<td>467</td>
</tr>
<tr>
<td>12.6</td>
<td>Probes and Sensors for Anions</td>
<td>469</td>
</tr>
<tr>
<td>12.6.1</td>
<td>Fluoride</td>
<td>469</td>
</tr>
<tr>
<td>12.6.2</td>
<td>Cyanide</td>
<td>472</td>
</tr>
<tr>
<td>12.6.3</td>
<td>Inorganic and Organic Phosphates</td>
<td>473</td>
</tr>
<tr>
<td>12.6.4</td>
<td>Carboxylates</td>
<td>482</td>
</tr>
<tr>
<td>12.6.5</td>
<td>Other Anions of Interest</td>
<td>487</td>
</tr>
<tr>
<td>12.6.6</td>
<td>Sensors for Multiple Anions</td>
<td>487</td>
</tr>
<tr>
<td>12.7</td>
<td>Sensing of Biomacromolecules</td>
<td>489</td>
</tr>
<tr>
<td>12.8</td>
<td>Challenges and Future Directions</td>
<td>491</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>492</td>
</tr>
</tbody>
</table>

### 13 Probes for Medical Imaging  501

*Felicia M. Roland and Bradley D. Smith*

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.1</td>
<td>Medical Imaging</td>
<td>501</td>
</tr>
<tr>
<td>13.2</td>
<td>Structure and Supramolecular Properties of Molecular Probes</td>
<td>503</td>
</tr>
<tr>
<td>13.2.1</td>
<td>Structure</td>
<td>503</td>
</tr>
<tr>
<td>13.2.2</td>
<td>Linkers</td>
<td>503</td>
</tr>
<tr>
<td>13.2.3</td>
<td>Reporter Groups</td>
<td>504</td>
</tr>
<tr>
<td>13.2.4</td>
<td>Design Aspects</td>
<td>504</td>
</tr>
<tr>
<td>13.3</td>
<td>Targeting Groups for Receptors</td>
<td>506</td>
</tr>
<tr>
<td>13.3.1</td>
<td>Drug-Like Molecules</td>
<td>506</td>
</tr>
<tr>
<td>13.3.2</td>
<td>Vitamins</td>
<td>507</td>
</tr>
<tr>
<td>13.3.3</td>
<td>Peptides</td>
<td>508</td>
</tr>
<tr>
<td>13.3.4</td>
<td>Antibodies</td>
<td>508</td>
</tr>
<tr>
<td>13.3.5</td>
<td>Aptamers</td>
<td>510</td>
</tr>
<tr>
<td>13.4</td>
<td>Signal Enhancement Strategies</td>
<td>511</td>
</tr>
<tr>
<td>13.4.1</td>
<td>Intracellular Accumulation</td>
<td>511</td>
</tr>
<tr>
<td>13.4.2</td>
<td>Signal Activation by Enzymes</td>
<td>512</td>
</tr>
<tr>
<td>13.5</td>
<td>Targeting Cell Surface Biomolecules</td>
<td>513</td>
</tr>
<tr>
<td>13.5.1</td>
<td>Anionic Phospholipids</td>
<td>513</td>
</tr>
<tr>
<td>13.5.2</td>
<td>Glycans</td>
<td>514</td>
</tr>
<tr>
<td>13.5.3</td>
<td>Antigens</td>
<td>515</td>
</tr>
<tr>
<td>13.6</td>
<td>Clinical Development</td>
<td>516</td>
</tr>
<tr>
<td>13.6.1</td>
<td>Government Approval</td>
<td>516</td>
</tr>
<tr>
<td>13.6.2</td>
<td>Multimodal Approaches</td>
<td>518</td>
</tr>
<tr>
<td>13.6.3</td>
<td>Theranostic Approaches</td>
<td>519</td>
</tr>
<tr>
<td>13.7</td>
<td>Future Role of Supramolecular Chemistry</td>
<td>520</td>
</tr>
<tr>
<td></td>
<td>Acknowledgments</td>
<td>521</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>521</td>
</tr>
</tbody>
</table>
14 Supramolecular Catalysis in Water 525
Piet W. N. M. van Leeuwen and Matthieu Raynal

14.1 Introduction 525
14.2 Classification of Supramolecular Catalysts Operating in Water 527
14.2.1 Mass Transfer Promotion Through Substrate Sequestration (S1) 529
14.2.2 Catalysis by Confinement (S2) 529
14.2.3 Directed Substrate Reactivity (S3) 531
14.2.4 Construction and Modulation of the Catalytic Structure (S4) 532
14.3 Synthetic Hosts for Catalysis in Water 533
14.3.1 Cyclodextrins (CDs) 536
14.3.2 Cucurbit[n]urils (CBn) 536
14.3.3 Hosts with Aromatic Walls 537
14.3.4 Velcrands 538
14.3.5 Octa-acid 538
14.3.6 Metallocages 538
14.3.7 Hyperbranched Polymers 539
14.3.8 Dendrimers 539
14.3.9 Micelles 540
14.3.10 Vesicles 541
14.4 Supramolecular Catalysts for the Aqueous Biphasic Hydroformylation Reaction 542
14.5 Supramolecular Catalysts for Other Organometallic Reactions in Water 547
14.6 Future Directions 550
References 551

Index 567