

# *Metal Complexes in Aqueous Solutions*

*Arthur E. Martell*

*Texas A&M University  
College Station, Texas*

*Robert D. Hancock*

*IBC Advanced Technologies  
American Fork, Utah*

**PLENUM PRESS • NEW YORK AND LONDON**

## Contents

### Chapter 1 Introductory Overview

1.1	Background of the Study of Complex-Formation in Aqueous Solution.....	1
1.2	Metal Ions in Solution, and Metal Complexes.....	5
1.2.1	Metal ions in aqueous solution.....	6
1.2.2	Trends in the periodic table.....	9
1.3	Steric Strain in Complex Formation .....	12

### Chapter 2 Factors Governing the Formation of Complexes with Unidentate Ligands in Aqueous Solution. Some General Considerations

2.1	The Role of the Solvent .....	15
2.1.1	Protonation reactions in the gas-phase.....	15
2.1.2	Complex-formation reactions of metal ions in the gas-phase.....	21
2.1.3	Reaction rates in the gas-phase .....	24
2.2	Linear Free Energy Relationships (LFER) .....	26
2.3	Ligand Field Theory and Metal to Ligand Bonding .....	28
2.4	Patterns in Lewis Acid-Base Behavior in Aqueous Solution .....	34
2.5	The Coordinating Tendencies of Different Donor Groups .....	40
2.5.1	The neutral oxygen donor .....	40
2.5.2	The negatively charged oxygen donor .....	44
2.5.3	The neutral saturated nitrogen donor .....	49
2.5.4	Unsaturated nitrogen donors .....	55
2.5.5	Ligands with heavier donor atoms S, Se, P, As .....	55

### Chapter 3 Chelating Ligands

3.1	The Chelate Effect .....	63
3.2	The Standard Reference State and the Chelate Effect .....	64
3.3	Equations for Predicting the Stability of Complexes of Chelating Ligands.....	65
3.4	Rule of Average Environment for Chelating Ligands .....	70
3.5	The Size of the Chelate Ring and Complex Stability .....	73
3.6	The Geometry of the Chelate Ring, and Preferred Metal Ion Sizes.....	77
3.7	Chelate Rings of Other Sizes .....	82
3.7.1	Chelate rings larger than six membered.....	82
3.8	More Highly Preorganized Chelating Ligands .....	87
3.9	The Effect of Mixtures of Chelate Rings of Different Sizes on Complex Stability .....	92
3.10	Steric and Inductive Effects in Chelating Ligands.....	93

## **Chapter 4 Complexes of Macrocycles and Other More Highly Preorganized Ligands**

4.1	The Thermodynamics of the Macrocyclic and Cryptate Effects .....	98
4.2	The Preferred Geometry of Chelate Rings Containing Neutral Oxygen and Nitrogen Donors.....	101
4.3	The Origin of the Macrocyclic Effect.....	105
4.4	Inductive Effects in Complexes of Macrocyclic Ligands.....	108
4.5	The Macrocyclic Effect in Mixed Donor Macrocycles.....	111
4.6	The Selectivity of Macrocyclic Ligands for Metal Ions .....	112
4.6.1	The metal ion selectivities of the tetraaza macrocycles .....	113
4.6.2	The metal ion selectivities of the crown ethers.....	120
4.6.3	The selectivity patterns of triaza and pentaaza macrocycles.....	125
4.7	Macrocycles with Pendent Donor Groups .....	127
4.7.1	Triaza macrocycles with pendent donor groups.....	127
4.7.2	Ligands based on cyclen, that have pendent donors .....	131
4.7.3	Ligands based on hexadentate macrocycles, that have pendent donor groups.....	132
4.8	The Cryptands.....	134
4.9	Macrocycles with Pendent Donor Groups Attached via the Carbon Atoms of the Bridging Groups .....	137
4.10	More Highly Preorganized Macrocycles .....	138
4.11	Binucleating Macrocycles.....	140
4.12	Conclusions.....	142

## **Chapter 5 Medical Applications of Metal Complexes**

5.1	Applications of Ligand Design Principles .....	151
5.1.1	Hard metal ions of biomedical interest ( $\text{Li}^+$ , $\text{Rb}^+$ , $\text{Sr}^{2+}$ , $\text{Y}^{3+}$ , $\text{Sm}^{3+}$ , $\text{Gd}^{3+}$ , $\text{Dy}^{3+}$ , $\text{Ho}^{3+}$ , $\text{Yb}^{3+}$ , $\text{Fe}^{3+}$ , $\text{Pu}^{4+}$ , $\text{Al}^{3+}$ , $\text{Ga}^{3+}$ ).....	151
5.1.2	Metal ions of biomedical interest, that are intermediate in HSAB ( $\text{Ni}^{2+}$ , $\text{Cu}^{2+}$ , $\text{In}^{3+}$ , $\text{Pb}^{2+}$ , $\text{Bi}^{2+}$ ).....	154
5.1.3	Soft metal ions of biomedical interest ( $\text{Cd}(\text{II})$ , $\text{Hg}(\text{II})$ , $\text{Tl}(\text{I})$ , $\text{Pt}(\text{II})$ , $\text{Au}(\text{I})$ , $\text{Au}(\text{III})$ , and possibly $\text{Tc}$ in its +1 to +7 oxidation states)....	154
5.2	Iron Overload .....	155
5.2.1	The hydroxypyridinones .....	159
5.3	Aluminum .....	160
5.4	Nickel.....	160
5.5	Copper.....	161
5.6	Plutonium and the Actinides.....	161
5.7	Uranium .....	162
5.8	Toxic Heavy Metal Ions.....	163
5.9	Cadmium.....	163
5.10	Lead.....	164

5.11	Arsenic .....	165
5.12	Mercury .....	165
5.13	General Summary .....	165
5.14	Diagnostic Radiopharmaceuticals Based on Ga(III) and In(III) Complexes .....	166
5.14.1	Synthesis and evaluation of new low molecular weight ligands .....	168
5.14.2	Hydroxypyridinones .....	174
5.14.3	Bifunctional chelates of Ga(III) and In(III) .....	175
5.15	Technetium .....	177
5.15.1	Technetium(VII) .....	178
5.15.2	Technetium(VI) .....	178
5.15.3	Technetium(V) .....	180
5.15.4	Technetium(IV) .....	181
5.15.5	Technetium(III) .....	182
5.15.6	Technetium(II) .....	184
5.15.7	Technetium(I) .....	184
5.16	Rhenium .....	185
5.16.1	Development of rhenium-radiopharmaceuticals of therapeutic value .....	185
5.17	Magnetic Resonance Imaging (MRI) .....	186
5.17.1	Factors influencing the water-relaxation ability of paramagnetic complexes .....	187
5.17.2	Concentration of the paramagnetic complex .....	188
5.17.3	Magnetic moment of the paramagnetic complex .....	188
5.17.4	Modulation of magnetic interactions between unpaired electrons and nuclei .....	188
5.17.5	Number of coordinated water molecules .....	188
5.17.6	Rate of water exchange .....	188
5.17.7	Metal-to-nucleus distance .....	189
5.17.8	Metal chelates recently investigated for magnetic resonance imaging .....	189
5.17.9	Hepatobiliary MRI contrast agents .....	191
5.17.10	New MRI contrast agents .....	191

## **Chapter 6 The Selectivity of Ligands of Biological Interest for Metal Ions in Aqueous Solution. Some Implications for Biology**

6.1	Significance of HSAB Ideas for Zinc-Containing Metalloenzymes .....	199
6.2	Chelate Ring Size and Metal Ion Selectivity .....	203
6.3	The Neutral Oxygen Donor .....	207
6.4	The Negative Oxygen Donor .....	210
6.5	The Neutral Nitrogen Donor .....	212
6.6	Sulfur Donors .....	213

## Chapter 7 Stability Constants and Their Measurement

7.1	Introduction.....	217
7.2	Early Work.....	217
7.3	Recent Work .....	218
7.4	The Stability Constant .....	220
7.5	pH and p[H] .....	222
7.6	Ca(II)-EDTA Complexes.....	223
	7.6.1 Stability constants for Ca(II)-EDTA.....	223
7.7	Species Distribution Diagrams .....	225
7.8	Experimental Methods for Measuring Complex Equilibria.....	226
	7.8.1 Absorbance methods .....	228
7.9	Specific Metal Ion Electrodes.....	229
7.10	Polarography and the Study of Solution Equilibria .....	231
7.11	Other Methods .....	236
7.12	Competition Methods .....	236
	7.12.1 Ligand-ligand competition by potentiometric methods.....	236
	7.12.2 Spectrophotometric determinations of competition constants .....	237
7.13	Amphoteric Metal Ions .....	238
7.14	Critical Stability Constants and Their Selection.....	238
	7.14.1 Minimum requirements for equilibrium data.....	239
7.15	Development of a Complete Metal Complex Database.....	240
	<b>Index.....</b>	<b>245</b>