

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 Macrocyclic 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 (Li^+ , Rb^+ , Sr^{2+} , Y^{3+} , Sm^{3+} , Gd^{3+} , Dy^{3+} , Ho^{3+} , Yb^{3+} , Fe^{3+} , Pu^{4+} , Al^{3+} , Ga^{3+}).....	151
5.1.2	Metal ions of biomedical interest, that are intermediate in HSAB (Ni^{2+} , Cu^{2+} , In^{3+} , Pb^{2+} , Bi^{2+}).....	154
5.1.3	Soft metal ions of biomedical interest (Cd(II) , Hg(II) , Tl(I) , Pt(II) , Au(I) , Au(III) , and possibly 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
	Index.....	245