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CHAPTER 2

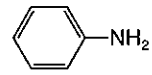
Principles of Coordination Chemistry Related to Bioinorganic Research

This chapter presents aspects of inorganic coordination chemistry that are of particular relevance to the roles of metal ions in biology. The special properties of metal ions distinguish them from surrounding organic functional groups in a biological milieu. In order to understand the functions of metal centers, a minimal knowledge of these special properties is required. This chapter provides information about the chemical reactions and electronic structural features of metal ions; the measurement of physical properties is treated separately, in Chapter 4.

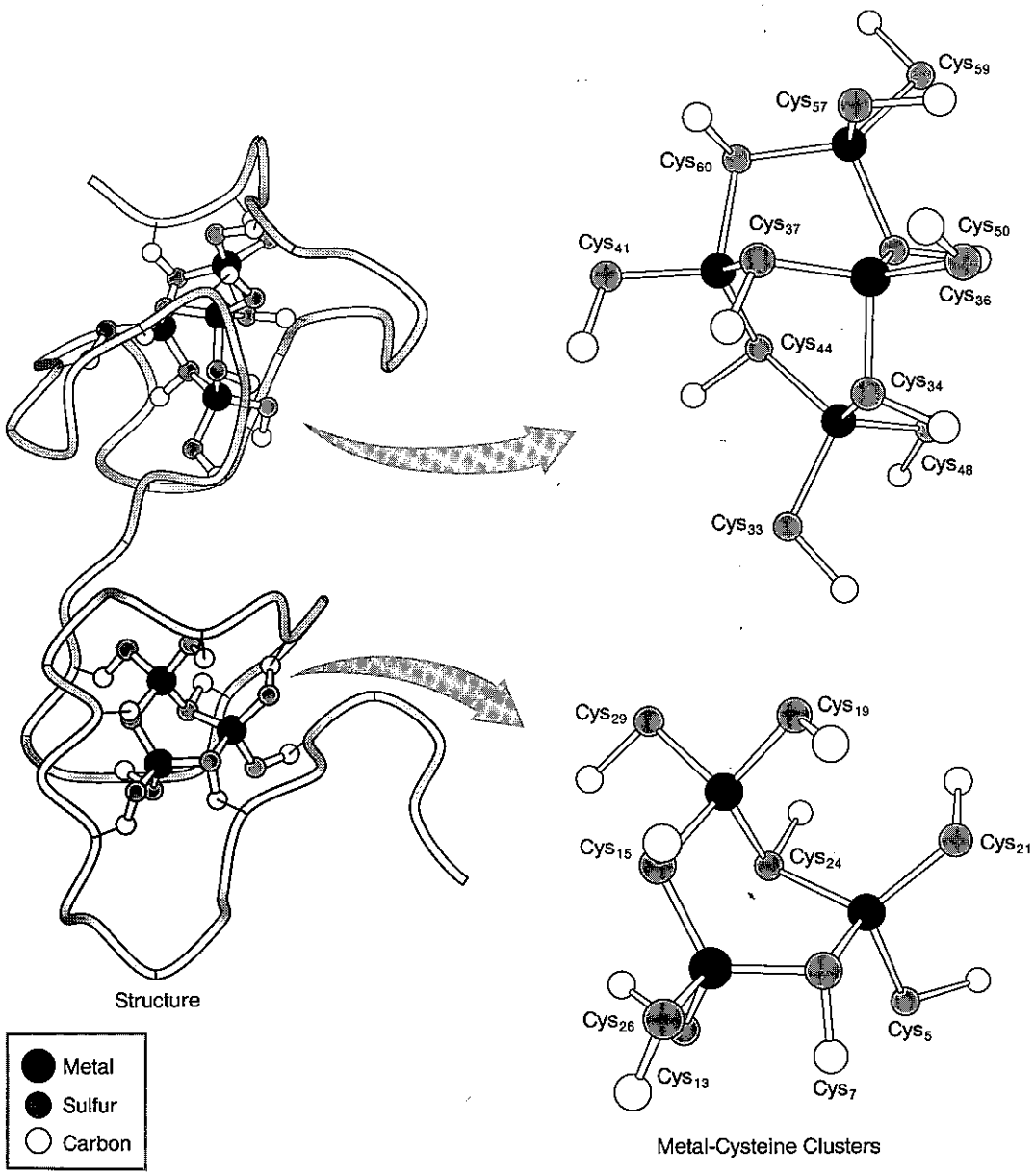
2.1. Thermodynamic Aspects

2.1.a. The Hard-Soft Acid-Base Concept. Metal ions in biology most frequently bind to donor ligands according to preferences dictated by the hard-soft theory of acids and bases. Table 2.1 lists the hard-soft character of essential metal ions listed previously (Table 1.1) and several of those used as biological probes and pharmaceuticals. In this classification scheme, the term "soft" refers to species that are large and fairly polarizable, whereas "hard" species are small and less easily polarized. Metal ions are considered to be Lewis acids. Also listed in the table are the hard-soft preferences of Lewis bases, ligand atoms that coordinate to the metal centers. In a biological medium, these ligands are provided by protein side chains, the bases of the nucleic acids, small cellular cytoplasmic constituents, organic cofactors (see Figure 1.3), and, of course, water. Although exceptions exist, the general rule is that hard acids bind preferentially to hard bases and soft acids to soft bases. For example, when a crystal of a protein is soaked in a solution of K_2PtCl_4 in

Table 2.1
Hard-soft acid-base classification of metal ions and ligands important to bioinorganic chemistry

Metals			Ligands		
Hard					
H^+	Mn^{2+}	Cr^{3+}	H_2O	CO_3^{2-}	NH_3
Na^+	Al^{3+}	Co^{3+}	OH^-	NO_3^-	RNH_2
K^+	Ga^{3+}	Fe^{3+}	$CH_3CO_2^-$	ROH	N_2H_4
Mg^{2+}	Ca^{2+}	Tl^{3+}	PO_4^{3-}	R_2O	RO^-
			$ROPO_3^{2-}$	$(RO)_2PO_2^-$	Cl^-
Borderline					
Fe^{2+}	Ni^{2+}	Zn^{2+}	NO_2^-		
Co^{2+}	Cu^{2+}		N_2		
			SO_3^{2-}		
			Br^-		
			N_3^-		
Soft					
Cu^+	Pt^{2+}	Pt^{4+}	R_2S	R_3P	
Au^+	Tl^+	Hg^{2+}	RS^-	CN^-	
Cd^{2+}	Pb^{2+}		RSH	RNC	
			$(RS)_2PO_2^-$	$(RO)_2P(O)S^-$	
			SCN^-	CO	
			H^-	R^-	

order to prepare a heavy-atom derivative to help provide phasing in an X-ray structure determination, the soft Pt(II) ion will bind most avidly to the exposed soft ligands, most commonly cysteine sulfhydryl groups or methionine thioether linkages. Binding to exposed glutamate or aspartate carboxylate groups is far less likely. Alkali and alkaline earth metals like Ca^{2+} are most commonly coordinated by carboxylate oxygen atoms, Fe^{3+} by carboxylate and phenoxide oxygen donors, and Cu^{2+} by histidine nitrogen atoms (Table 2.1). One of the best illustrations of the hard-soft acid-base principle in bioinorganic chemistry is provided by the metallothionein proteins (Figure 2.1). Nearly 30–35 percent of the amino acids of this class of small proteins are cysteine residues, the sulfhydryl groups of which bind avidly to soft metal ions such as Cd^{2+}, Hg^{2+}, Pb^{2+}, and Tl^+. One of the biological functions of metallothionein is to protect cells against the toxic effects of these metal ions.



Amino acid sequence

CH_3CONH–Met Asp Pro Asn **Cys** Ser **Cys** Ala Thr Asp Gly Ser **Cys** Ser **Cys** Ala Gly Ser **Cys** Lys **Cys** Lys Gln **Cys** Lys **Cys** Thr Ser Cys Lys-Lys Ser **Cys Cys** Ser **Cys Cys** Pro Val Gly **Cys** Ala Lys **Cys** Ser Gln Gly **Cys** Ile **Cys** Lys Glu Ala Ser Asp Lys **Cys** Ser **Cys Cys** Ala-COO^-

Figure 2.1
Amino acid sequence and three-dimensional structure of metallothionein and its tetrametallic (top) and trimetallic (bottom) clusters.

2.1.b. The Chelate Effect and the Irving-Williams Series. Chelation refers to coordination of two or more donor atoms from a single ligand to a central metal atom. The resulting metal-chelate complex has unusual stability derived in part from the favorable entropic factor accompanying the release of nonchelating ligands, usually water, from the coordination sphere. This phenomenon is illustrated in Equation 2.1 for the chelation of nickel(II) in

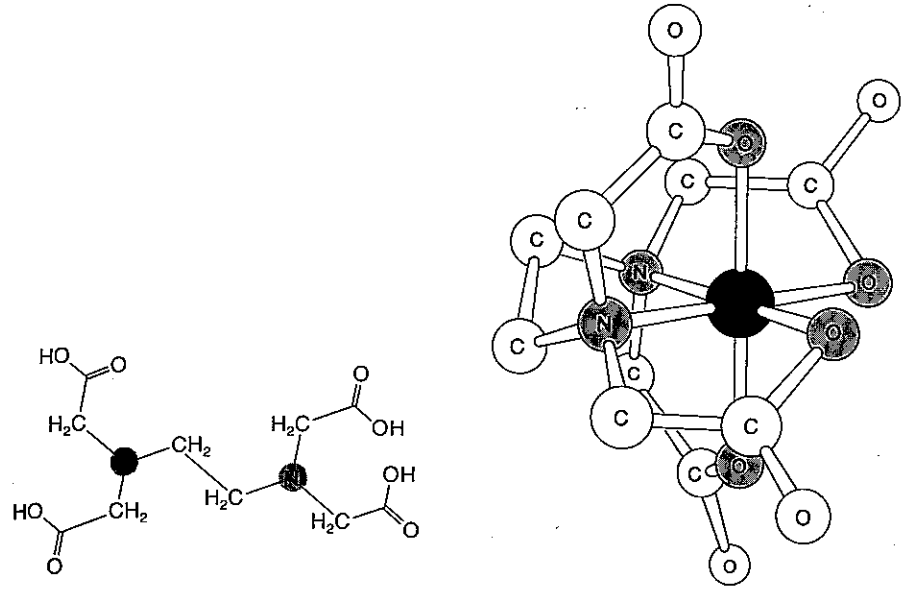
$$[Ni(OH_2)_6]^{2+} + H_2edta^{2-} \rightarrow [Ni(edta)]^{2-} + 4H_2O + 2H_3O^+ \quad (2.1)$$

aqueous solution by the hexadentate ligand ethylenediaminetetraacetate (H_2edta^{2-}; shown in its protonated form in Figure 2.2). Ligands such as H_2edta^{2-}, hereafter referred to for simplicity as EDTA in this book, are used in medicine to chelate metal ions that might be present in toxic excess and as food additives to limit the availability of essential metals to harmful bacteria, thereby preventing spoilage. The ligand EDTA itself is commonly added to buffer solutions in biological research to reduce the concentration of free metal ions that could promote undesired reactions.

An important example of the chelate effect in bioinorganic chemistry is afforded by the porphyrin and corrin ligands, illustrated in Figure 1.3. These macrocyclic molecules have four nearly coplanar pyrrole rings with their nitrogen donor atoms directed toward a central metal ion. The resulting metalloporphyrin or -corrin units are thermodynamically very stable, accommodating a variety of metal ions in different oxidation states. As a consequence, these chelating units provide bioinorganic functional groups of widespread occurrence and utility in biology, being found in cytochromes (Fe), chlorophyll (Mg), and vitamin B-12 (Co), to mention but a few examples.

Another useful principle of inorganic chemistry is the binding preference, for a given ligand, of divalent first-row transition-metal ions. These preferences typically follow the stability series $Ca^{2+} < Mg^{2+} < Mn^{2+} < Fe^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+} > Zn^{2+}$, as first delineated by Irving and Williams. This order, known as the Irving-Williams series, is related to the decrease in ionic radii across the series, an effect that leads to stronger metal-ligand bonds.

2.1.c. pK_a Values of Coordinated Ligands. The positive charge on most metal ions in biology stabilizes the acid anion (conjugate base) of protic ligands bound in the coordination sphere. This effect is best exemplified by coordinated water, but occurs for many other biological ligands, including thiols, imidazole, phenols, alcohols, phosphoric and carboxylic acids, and their derivatives. Table 2.2 lists the pK_a values of selected examples from among these ligand groups in the presence and absence of various metal ions. Tri-

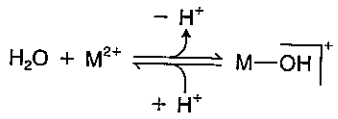
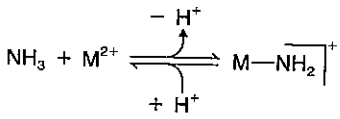
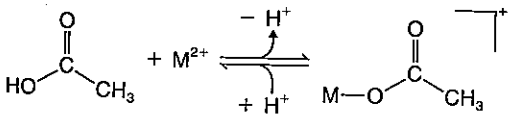
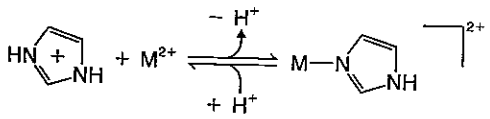


(a) Ethylenediaminetetraacetic acid (H_4EDTA)

(b) $[Co(EDTA)]^-$ complex

Figure 2.2
(a) The metal chelating agent ethylenediaminetetraacetic acid (EDTA).
(b) Structure of a Co^{3+} complex of EDTA.

Table 2.2
pK_a values for selected ligands with and without metal ions

Ligand and reaction	Metal ion	pK_a (25°C, 0.1 M)
	None	14.0
	Ca^{2+}	13.4
	Mn^{2+}	11.1
	Cu^{2+}	10.7
	Zn^{2+}	10.0
	None	35.0
	Co^{2+}	32.9
	Cu^{2+}	30.7
	Ni^{2+}	32.2
	None	4.7
	Mg^{2+}	4.2
	Ca^{2+}	4.2
	Ni^{2+}	4.0
	Cu^{2+}	3.0
	None	7.0
	Co^{2+}	4.6
	Ni^{2+}	4.0
	Cu^{2+}	3.8

valent metal ions are better able to lower the pK_a values of protic ligands than their divalent analogs, as expected on the basis of charge considerations.

Deprotonation of coordinated water to form a hydroxo ligand is a step postulated in several hydrolytic mechanisms to explain metalloenzyme catalysis. Coordination of two or more metal ions to a protic ligand produces an even more dramatic lowering of the pK_a. This effect is illustrated for the hydrolysis of iron(III) in Table 2.3. In $[Fe(OH_2)_6]^{3+}$, water can

Table 2.3
Hydrolysis reactions of Fe(III), 25°[a]

Reaction	pK_a
$Fe^{3+} + H_2O \rightarrow Fe(OH)^{2+} + H^+$	2.2
$2Fe^{3+} + 2H_2O \rightarrow Fe_2(OH)_2{}^{4+} + 2H^+$	2.9
$Fe(OH)^{2+} + H_2O \rightarrow Fe(OH)_2{}^{+} + H^+$	3.5
$Fe(OH)_2{}^{+} + H_2O \rightarrow Fe(OH)_3\downarrow + H^+$	6
$Fe(OH)_3 + H_2O \rightarrow Fe(OH)_4{}^{-} + H^+$	10

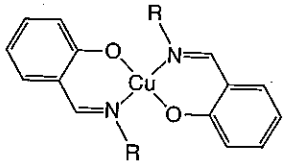
[a] Additional water molecules coordinated to the iron atoms are not shown.

be deprotonated with a pK_a of 2.2, whereas the hydroxide ligand in $[Fe(H_2O)_4(OH)_2]^+$ is deprotonated with $pK_a \sim 6$ owing to the formation of (μ-hydroxo)- and μ-(oxo)diiron(III) units. These results illustrate that aquated iron(III) and many other metal-ion complexes cannot exist at physiological pH values ~ 7 in the absence of supporting ligands. Di- or polymetallation of other protic biological ligands is a fairly common occurrence, examples being the triply bridged (μ_3-sulfido) triiron cluster units found in iron-sulfur proteins (deprotonation of H_2S) and the bridged (μ_2-imidazolato) copper(II)-zinc(II) moiety in bovine erythrocyte superoxide dismutase (deprotonation of imidazole side chain of histidine).

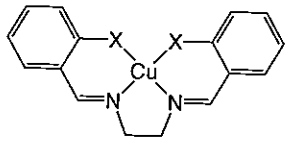
2.1.d. Tuning of Redox Potentials. Alterations in the ligand donor atom and stereochemistry at the metal center can produce great differences in the potential at which electron-transfer reactions will occur. The potentials listed for the aqua ions in Table 1.2 can be altered by more than 1.0 V by these factors. The data in Table 2.4 illustrate the ability of various ligands to tune the Cu(I)/Cu(II) redox potential, one of the best-studied examples in both inorganic and bioinorganic chemistry. Copper(I), a closed shell, d^{10} ion (see Section 2.4), prefers tetrahedral four-coordinate or trigonal three-coordinate

Table 2.4
Effect of ligands on Cu(I)/Cu(II) reduction potential in DMF solution

Compound name	$E_{1/2}$, V[a]
Cu(*O*-sal)$_2$en	−1.21
Cu(Me-sal)$_2$	−0.90
Cu(Et-sal)$_2$	−0.86
Cu(*S*-sal)$_2$en	−0.83
Cu(*i*-Pr-sal)$_2$	−0.74
Cu(*t*-Bu-sal)$_2$	−0.66



Cu(*R*-sal)$_2$



Cu(*X*-sal)$_2$en
X = *O* or *S*

[a] Potential at which the complex is half-oxidized and half-reduced.

geometries. Divalent copper(II) complexes, on the other hand, are typically square-planar with perhaps one or two additional, weakly bonded axial ligands. Thus, a ligand environment that produces a tetrahedral geometry will usually stabilize Cu(I) over Cu(II), rendering the latter a more powerful oxidizing agent by raising the redox potential. As can be seen in Table 2.4, addition of bulky R groups in the Cu(*R*-sal)$_2$ complexes distorts the geometry from planar toward tetrahedral, making it easier to reduce the copper and raising the potential. In addition, Cu(I) is a soft acid, preferring to bind to soft donors such as RS^- or R_2S ligands. The placement of soft ligands in the coordination sphere also increases the Cu(I)/Cu(II) reduction potential.

These effects of ligand donor type and stereochemistry on the Cu(I)/Cu(II) potential are manifest not only in the inorganic complexes listed in Table 2.4, but also in several copper-containing proteins. Here, high redox potentials are achieved by the proteins through distortion of the coordination geometry toward trigonal planar and the use of two histidine-imidazole and one cysteine-thiolate side chains as donor ligands. Many other important examples of redox-potential tuning by the local protein environment are encountered in bioinorganic chemistry, including the iron-sulfur clusters and the cytochromes. Sometimes the potential is influenced by the local dielectric

constant provided by residues in the vicinity of, but not necessarily coordinated to, the metal atom. This phenomenon is analogous to the influence of solvent on the redox potentials of simple coordination complexes.

2.1.e. Biopolymer Effects. As the previous discussion has already illustrated, the thermodynamic stability of a metal center in a biological environment is determined not only by the inherent preferences of the metal for a particular oxidation state, ligand donor set, and coordination geometry, but also by the ability of the biopolymer to control, through its three-dimensional structure, the stereochemistry and ligands available for coordination. Noncoordinating residues also contribute such factors as local hydrophilicity or hydrophobicity, steric blockage of coordination sites, and hydrogen-bonding groups that can interact with bonded and nonbonded atoms in the coordination sphere of the metal to increase or reduce stability. These factors, which occur for metals bound to nucleic acids as well as to proteins, must be elucidated in any serious attempt to understand how metals function in biology.

Some of the most dramatic manifestations of the chelate effect in bioinorganic chemistry are the occurrences in many metalloprotein cores of strong and specific metal-binding sites. Nature has possibly the most effective chelating ligands at its disposal in the form of protein chains that can fold (see Chapter 3), orienting amino-acid residue donors to provide virtually any desired stereochemistry at a metal center. A nice example of this phenomenon is the zinc-binding site in bovine erythrocyte superoxide dismutase (Cu_2Zn_2SOD). The zinc-coordinating environment at this site is so favorable that the metal-free (or apo) protein (E_2E_2SOD; E = empty) can remove traces of zinc from phosphate buffer upon dialysis. The binding site is sufficiently specific that when Cu_2Cu_2SOD, in which Cu^{2+} ion occupies the Zn^{2+} site, is treated with excess divalent zinc, the copper in the Zn^{2+} site is displaced. This chemistry is unusual, since it violates the usual preferences of the Irving-Williams series (see Section 2.1.b). Clearly, zinc must be functionally important in this site, which has evolved in a manner that assures the requisite metal-ion specificity.

2.2. Kinetic Aspects

2.2.a. Ligand Exchange Rates. Table 2.5 lists the water-exchange rates for many essential metal ions. From these values, it is clear that $M-OH_2$ bonds are very labile, breaking and reforming as fast as a billion times per second. The labilities of metal-ligand bonds typically follow the trends for the

Table 2.5
Exchange rates for water molecules from the first coordination sphere of metal ions at 25°C

Ion	k_1, sec^{-1}	Ion	k_1, sec^{-1}	Ion	k_1, sec^{-1}
Li^+	4×10^8	V^{2+}	8×10^1	Sn^{2+}	$>10^4$
Na^+	7×10^8	Cr^{2+}	1×10^9	Hg^{2+}	4×10^8
K^+	1×10^9	Mn^{2+}	2×10^7	Al^{3+}	1
Be^{2+}	8×10^2	Fe^{2+}	4×10^6	Fe^{3+}	2×10^2
Mg^{2+}	6×10^5	Co^{2+}	3×10^6	Ga^{3+}	4×10^2
Ca^{2+}	3×10^8	Ni^{2+}	4×10^4	Gd^{3+}	2×10^9
Ba^{2+}	2×10^9	Cu^{2+}	1×10^9	Bi^{3+}	$>10^4$
		Zn^{2+}	2×10^7	Cr^{3+}	2×10^{-6}
				Co^{3+}	$<10^{-6}$
				Rh^{3+}	6×10^{-9}

aqua complexes in Table 2.5. In general, ligand exchange rates are faster for the less highly charged M^{2+} than for the M^{3+} metal ions. Very inert first-row transition-metal ions such as Cr^{3+} and Co^{3+} are only rarely encountered in bioinorganic chemistry. Second- and third-row transition-metal complexes are much more kinetically inert than their first-row counterparts. For example, once the anticancer drug *cis*-$[Pt(NH_3)_2Cl_2]$ binds to DNA through loss of chloride ligands, the platinum cannot be exchanged out even upon prolonged dialysis of the platinated biopolymer. Only strong platinum-binding ligands such as cyanide can displace the Pt-DNA adduct. A similar situation occurs for ruthenium bound to amino-acid residues, as encountered in studies of protein electron-transfer reaction kinetics.

→ is cisplatin DNA specific?

The fast metal-ligand exchange rates of first-row transition-metal ions such as Fe^{2+} are markedly diminished when they are bound by multidentate chelating ligands. Metalloporphyrins (Figure 1.3), for example, are kinetically rather inert. The axial ligands, which are not part of the chelate ring, can undergo exchange at the usual fast rates, however. Ligands such as CO, RS^-, and CN^- form more inert M–L bonds. Many metalloproteins contain tightly bound metal ions that cannot be exchanged with free metal ions even during prolonged dialysis against good chelating ligands. The kinetic inertness of these protein cores often results from solvent inaccessibility to the metal coordination sphere owing to steric shielding by the protein. If the protein is denatured, for example by heating or adding a solvent such as dimethyl sulfoxide, the metal can usually be released.

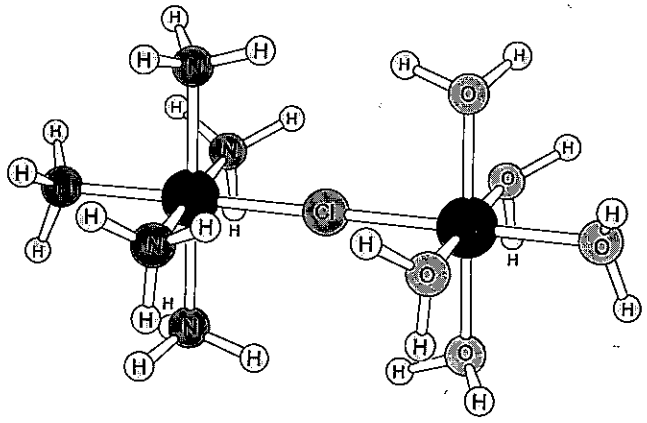
2.2.b. Substitution Reactions. Displacement of one ligand by another in the coordination sphere of a metal ion can occur by either associative (second-order) or dissociative (first-order) pathways, with kinetic and mechanistic features quite analogous to S_N2 and S_N1 substitution reactions in organic chemistry, respectively. Metals with lower coordination numbers (≤ 4) tend to undergo associative ligand displacement reactions, whereas higher-coordinate metals (coordination number ≥ 6) use dissociative pathways. Substitution reactions occurring at metal centers bound to proteins or nucleic acids can be far more complex, owing to interactions of the incoming ligand with other nearby groups and to coupling of these reactions to conformational changes in the macromolecule.

2.2.c. Electron Transfer Reactions. Two major pathways, designated as inner-sphere and outer-sphere, have been elucidated for transfer of electrons to or from transition metal ions. Inner-sphere electron transfer reactions are characterized by the presence of one or more bridging ligands directly bonded to the coordination spheres of the reactants. A classic example of this reaction pathway is illustrated in Equation 2.2, in which the labile Cr(II) complex transfers an electron to an inert Co(III) receptor to form a labile,

$$[Co(NH_3)_5Cl]^{2+} + [Cr(H_2O)_6]^{2+} \xrightarrow{5H^+} [Co(H_2O)_6]^{2+} + [Cr(H_2O)_5Cl]^{2+} + 5NH_4^+ \qquad (2.2)$$

reduced Co(II) complex and an inert Cr(III) species. The specific transfer of the chloride ion from the Co(III) to the Cr(II) center in this reaction proves that the transition state for the electron-transfer step consists of the bridged binuclear complex illustrated in Figure 2.3. Since electron transfer in this bridged complex is fast compared to atom transfer, the chloride ion remains in the coordination sphere of the kinetically inert chromium(III) product. In the outer-sphere electron-transfer reaction mechanism, the two redox partners approach one another with their associated solvent molecules to form a so-called "precursor complex." Electron transfer then occurs without any accompanying exchange of ligands between coordination spheres of the oxidant and reductant.

We do not now know of any inner-sphere electron-transfer reactions that involve a pair of metalloproteins. Although such a mechanism cannot be ruled out *a priori*, the steric barrier to formation of the requisite ligand-bridged transition state would appear to be formidable. Electron-transfer reactions between metal centers within and between metalloprotein mole-



$[(NH_3)_5\,Co—Cl—Cr(OH_2)_5]^{4+}$

Figure 2.3
Structure of the chloride-bridged binuclear intermediate formed in the inner-sphere electron transfer reaction between $[Co(NH_3)_5Cl]^{2+}$ and $[Cr(H_2O)_6]^{2+}$.

cules is a subject of great current interest. Long-range electron transfer occurs over distances up to ~ 30 Å at reasonable rates ($> 10\ sec^{-1}$).

Useful theoretical relationships between the equilibrium and rate constants have been derived by Marcus for outer-sphere electron-transfer reactions. The correlation between second-order rate constants predicted by this theory with those obtained experimentally is remarkably good for small molecules. Among the predictions of this theory is that electron-transfer reactions should have an optimal driving force. Making the free energy of a reaction more favorable than this value decreases rather than increases the rate. This so-called "inverted region" has been observed experimentally for small-molecule reactions and, more recently, for electron-transfer reactions involving metalloproteins as well.

MARCUS THEORY

2.3. Electronic and Geometric Structures of Metal Ions in Biology

Table 2.6 lists the common oxidation states of metal ions in biology and, for the transition metal ions, the corresponding d-electron configuration. The latter values are obtained by subtracting the formal oxidation state of the metal from its atomic number (Z) and calculating how many electrons must be added to the preceding noble-gas element (usually Ar, Z = 18) to achieve

Table 2.6
Common oxidation states of important elements in bioinorganic chemistry

Metal	Redox state	Number of d electrons
Na	(I)	
K	(I)	
Mg	(II)	
Ca	(II)	
V	(III)	2
	(V)	0
Cr	(III)	3
Mo	(II)	4
	(III)	3
	(IV)	2
	(V)	1
	(VI)	0
Mn	(II)	5
	(III)	4
	(IV)	3
Tc	(I)	6
Fe	(II)	6
	(III)	5
Co	(I)	8
	(II)	7
	(III)	6
Ni	(II)	8
Cu	(II)	9
	(I)	10
Zn	(II)	10

the resulting number. For example, Fe(III) has a d^5 electron count ($26 - 3 - 18 = 5$), Mo(IV) is a d^2 ion ($42 - 4 - 36 = 2$), Cu(I) is d^{10} ($29 - 1 - 18 = 10$), and so forth. In Figure 2.4 are illustrated the most common coordination geometries, for coordination numbers 3 to 6, for metals encountered in bioinorganic chemistry. As previously mentioned, substantial distortions from these idealized structures can and do occur. When a metal ion in a given formal oxidation state is placed at the center of a coordination polyhedron defined by a set of ligands, the energy levels of the d-orbitals housing the metal electrons are altered from those found in the free

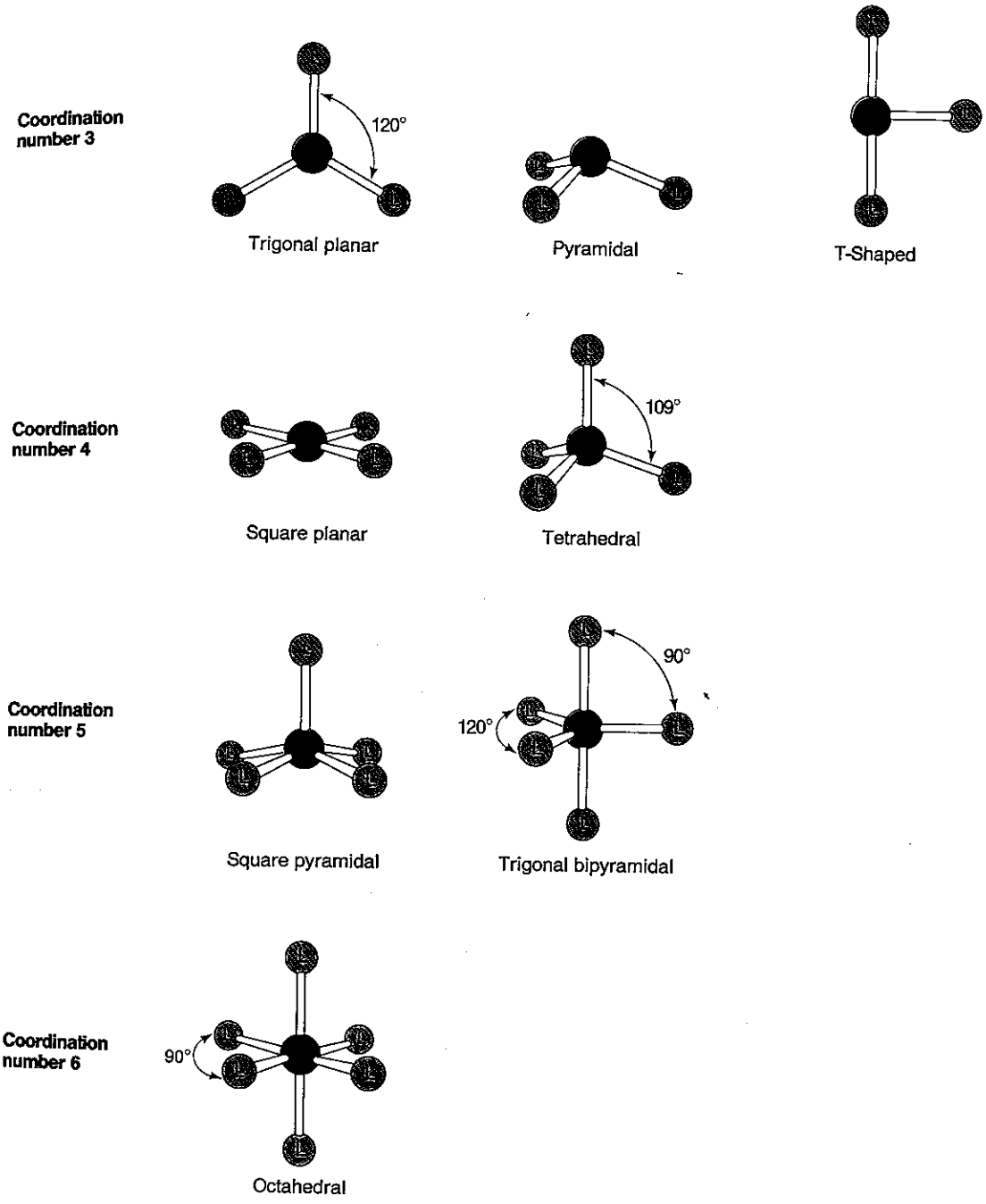


Figure 2.4
Common geometries for coordination numbers 3–6.

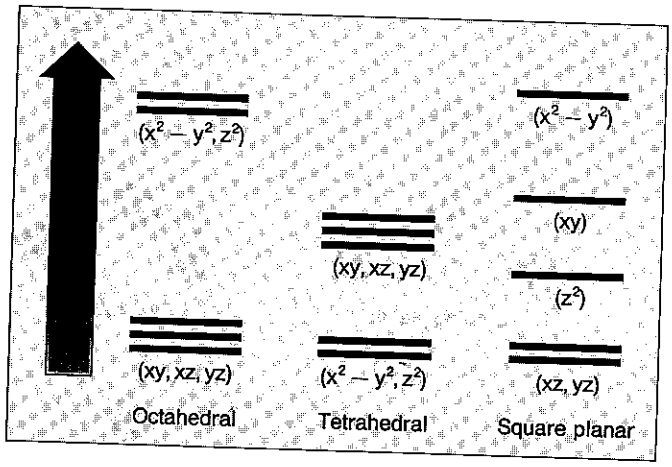


Figure 2.5
Ligand-field splitting diagrams for d orbitals in octahedral, tetrahedral, and square-planar transition metal complexes. The energy separation between the lower and upper sets of orbitals is designated Δ_o for octahedral complexes and Δ_t for tetrahedral complexes.

metal ion. This phenomenon, referred to as ligand-field splitting, is best described in terms of an energy-level diagram that reveals the one-electron orbital energies as a function of the strength of the ligand field.

Ligand-field splitting diagrams for the more important structures adopted by bioinorganic metal centers are provided in Figure 2.5. These diagrams are extremely useful when attempting to correlate the physical properties of metal centers in proteins, such as their optical spectra, magnetism, and electron-spin resonance spectra, with their structures or reactivity. If, for example, one were to encounter a diamagnetic (no unpaired electrons) Ni(II) center in a protein, it most probably would have a square-planar geometry, since both tetrahedral and octahedral d^8 complexes would be expected to have two unpaired electrons and be paramagnetic, as shown in Figure 2.6. The strength of the ligand field at a metal center is largely determined by the set of ligand donor atoms to which it is bonded. The ability of ligands to split the d-orbitals varies according to the "spectrochemical series" in the following order:

Spectrochemical series

$$I^- < Br^- < S^{2-} < Cl^- < NO_3^- < OH^-$$
$$\approx RCOO^- < H_2O \approx RS^- < NH_3$$
$$\approx \text{Im (imidazole)} < \text{en (1,2-diaminoethane)}$$
$$< \text{bpy (2,2'-bipyridine)} < CN^- < CO.$$

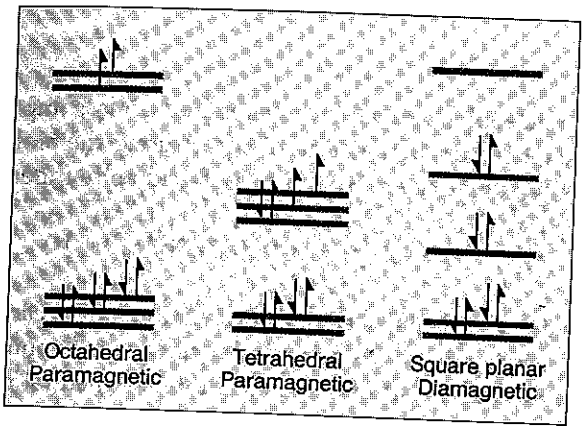


Figure 2.6
Ligand-field splitting diagrams, orbital occupancies, and magnetic properties for d^8 Ni(II) complexes having octahedral, tetrahedral, and square planar geometries.

This list is valuable for deciding whether a high-spin or low-spin electronic configuration will occur in the several situations in which such a dichotomy can exist.

Apart from their characteristic electronic features, many of the metal ions in bioinorganic chemistry possess nuclear properties that greatly facilitate their spectroscopic investigation. The experimental methods employed in such studies will be discussed in Chapter 4. Thus it is possible to highlight a very localized region of a metalloprotein by measuring the magnetic and spectroscopic properties of the metal center, which is a unique functional group embedded in a sea of organic residues that are more difficult to distinguish.

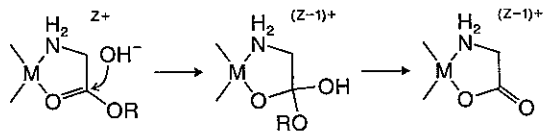
2.4. Reactions of Coordinated Ligands

The ability of metal ions to alter the reactivity of ligands toward external substrates is at the heart of their role as catalytic centers in biology. One such reaction is the enhancement of the acidity of coordinated ligands. As shown in Table 2.2 and discussed in Section 2.1.c, the pK_a values of coordinated water and other molecules are lower than those of the free ligands, because the positively charged metal center can stabilize the conjugate base, in this case, hydroxide (Equation 2.3). Increasing the susceptibility of substrate mole-

cules toward nucleophilic attack is a related and no less important biological function of metal centers in metalloproteins. Among the biological processes that fall into this category are hydrolyses of acid anhydrides, esters, amides,

$$M(H_2O)_n^{z+} \longrightarrow M(H_2O)_{n-1}(OH)^{(z-1)+} + H^+ \qquad (2.3)$$

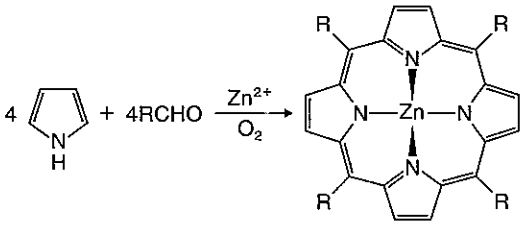
phosphate esters, and Schiff's bases, carboxylation and decarboxylation reactions, and transaminations. An example of how metal centers can serve as Lewis acids is the hydrolysis of amino-acid esters at neutral pH. As indicated in Equation 2.4, nucleophilic attack on the carbonyl group is facilitated by coordination to the positively charged metal ion. The rates for this reaction



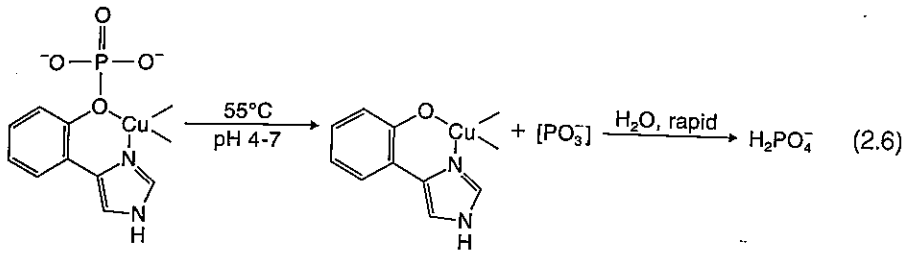
(2.4)

vary as $M = Cu^{2+} > Co^{2+} > Mn^{2+} > Ca^{2+} \sim Mg^{2+}$, a trend that follows the Irving-Williams series. The uncatalyzed reaction at neutral pH is essentially unobservable.

Additional reactions facilitated by metal centers include the template effect, enhancement of leaving group reactivity, the activation of small molecules such as N_2 and O_2, and the masking of chemical reactivity by coordination. The template effect is a phenomenon by which the metal serves to organize reactive units in condensation reactions, as illustrated in Equation 2.5 for the laboratory synthesis of porphyrin rings. The use of zinc, which prefers tetrahedral stereochemistry, in this reaction facilitates removal of the metal and generation of the porphyrin free base. Equation 2.6 depicts a reaction in which phosphate ester hydrolysis is promoted by coordination of cupric ion to the leaving group. In this biomimetic chemistry, hydrolysis of 2-(imidazol-4-yl)phenyl phosphate is accelerated 10^3 to 10^4 times in the pH 4–7 range by the metal center.



(2.5)



(2.6)

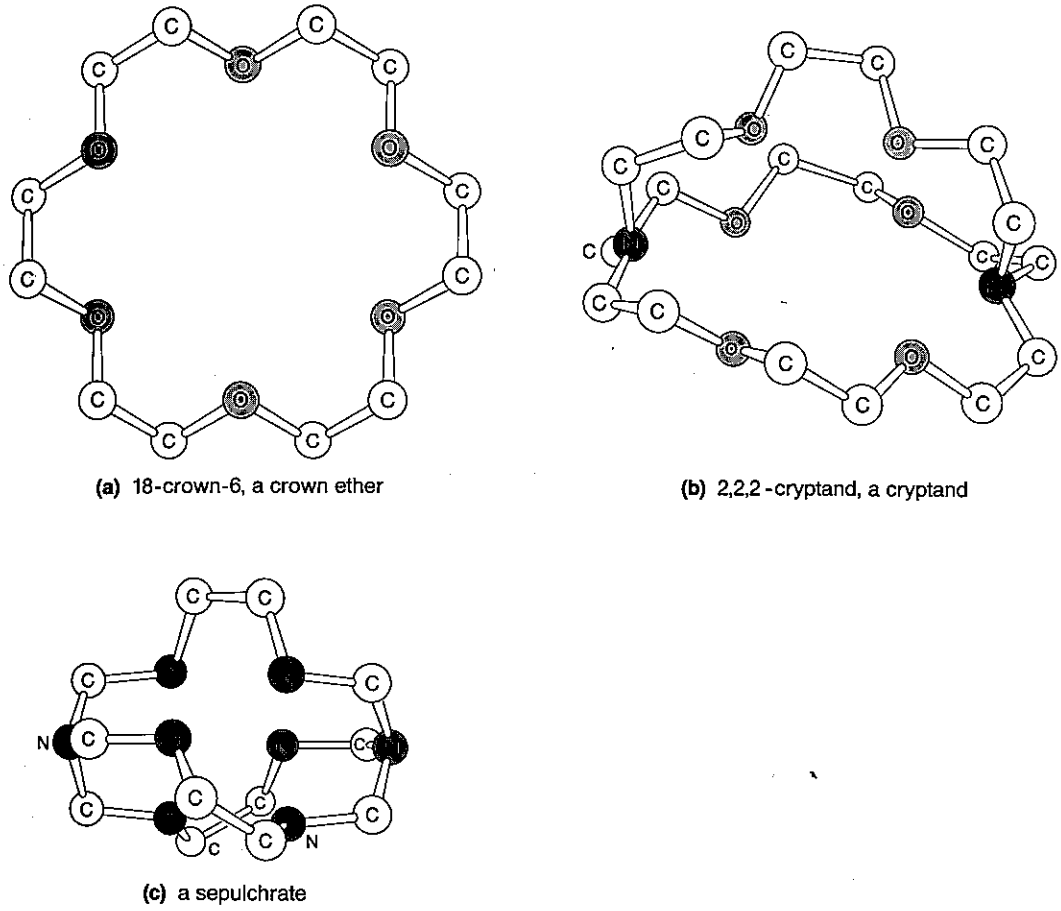
2.5. Model Complexes and the Concept of Spontaneous Self-Assembly

Because of the large size of metallobiopolymers, it is usually difficult to obtain high-resolution structural information about the metal coordination sphere. Other physical properties are sometimes also difficult to measure because of the complexity of the molecule, as is true for the redox potential of a particular metal center in a metalloprotein that has several different metal sites. Investigating the chemical reactivity of a metal ion in a biopolymer can present a similar challenge, since it is difficult to modify the coordinated ligands in a systematic manner to test features of a postulated reaction mechanism, although this objective can now be approached by using site-directed mutagenesis. For these reasons, bioinorganic chemists frequently synthesize and study model complexes designed to replicate as faithfully as possible the physical and chemical properties of the metal center in a biopolymer. If the structure of the latter is known, for example, through an X-ray crystal structure determination, it is possible to design an exact replica of the coordination environment in a model complex. These complexes have been termed *replicative models*. If the environment is unknown, the model approach affords bioinorganic chemists a chance to test postulated structures in what may be called *speculative models*. In both approaches, good judgment must prevail to prevent overinterpretation of information from a model compound in attempting to explain the physical or chemical properties of the biological molecule. It is essential that the structure of the model complex be known, preferably by single-crystal X-ray diffraction work. The model approach has provided many valuable insights into structural and mechanistic metallobiochemistry, including assignment or verification of the charges, and hence the metal-oxidation states, of metal clusters in proteins, the effects of distance and medium on electron-transfer rates, the roles of steric and electronic factors in promoting reversible dioxygen binding to heme iron centers, and the identi-

fication of likely intermediates in a variety of enzyme-catalyzed reactions. It should be pointed out, however, that the discovery and characterization of metal centers in biology have had a similar impact on the development of the field of coordination chemistry. In other words, the effects have been symbiotic, and both have been essential parts of the growth of the field of bioinorganic chemistry.

In the design of model complexes, a variety of strategies is available. One of these, which has come to be known as "spontaneous self-assembly," involves reaction of the metal and the simplest ligands containing the known or suspected biological donor atoms to form the desired replica molecule. The rationale behind this approach is that nature may have adopted a similar strategy in assembling such a metal center, borrowing available chemistry from the geosphere during evolution of the biosphere. The spontaneous self-assembly approach has been successful in replicating known metalloprotein core structures, such as the $\{Fe_nS_n\}^{m-}$ clusters in iron-sulfur proteins and the $\{Fe_2O(O_2CR)_2\}^{2+}$ cores in diiron-carboxylate proteins. These successes have inspired some to rephrase "spontaneous self-assembly" as "dumb luck," but such critics have missed an important point. As already discussed, metal-ligand bonds in most bioinorganic centers are labile. Thus, the synthetic model chemistry is nearly always under thermodynamic, rather than kinetic, control. The molecules that are obtained, usually as crystalline solids, often become major components of the mixture of compounds formed between metal and ligands only because of the tactical skills of the synthetic inorganic chemist at the laboratory bench. Undesired side products must be avoided by judicious choice of solvents, counter-ions, ligand steric properties, and temperature. The use of such tactics to assemble the desired model complex from simple ligands as the thermodynamically most stable entity among a potentially complex mixture of products contrasts with the synthetic approach to most organic and organometallic compounds, where reactions are usually under kinetic control owing to the more inert character of carbon-carbon and metal-carbon bonds.

Although spontaneous self-assembly has produced good models for the structural and spectroscopic properties of metalloprotein cores, duplicating the functional chemistry usually requires more complex ligands. The development of compartmentalized ligands such as crown ethers, cryptands, sepulchrates (Fig. 2.7), and other macropolycyclic molecules has afforded a variety of new strategies for mimicking metalloprotein core chemistry. The construction of synthetic peptides is another rapidly developing field that is likely to have important effects on bioinorganic model chemistry. At some point,



(a) 18-crown-6, a crown ether

(b) 2,2,2-cryptand, a cryptand

(c) a sepulchrate

Figure 2.7
Macrocyclic ligands.

however, the limitations of the model approach will be reached, because the subtleties of metalloprotein core chemistry cannot fully be duplicated, no matter how good the designer ligand. Nature did, after all, develop complicated molecules to achieve such specific functions as those listed in Table 1.1. Ultimately, there is no substitute for direct studies of the biomolecules.