The Compleat Coordination Chemistry—One Practioner's Perspective

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Contents

Daryle H. Busch received the B.A. from Southern Illinois University in 1951 and the M.S. (1952) and Ph.D. (1954) from the University of Illinois (Urbana) in Inorganic Chemistry. From 1988 until the present he has held the position Roy A. Roberts Distinguished Professor of Chemistry at the University of Kansas. From 1954 through 1988 he was a member of the chemistry faculty at The Ohio State University, his last title being Presidential Professor. Appropos of this volume, as a graduate student he received the only Bersworth Fellowship in Chelate Chemistry and co-edited and co-authored, with his preceptor, John C. Bailar, Jr., the classic American Chemical Society monograph entitled *Coordination Chemistry*. Working on opposite sides of the world, Busch and Neil Curtis (New Zealand) brought the subject of synthetic macrocyclic ligands into being. The coordination template was a product of his research in this area. Recognitions have included the Bailar Medal (University of Illinois), the Dwyer Medal (Chemical Society of New South Wales), the American Chemical Society awards for research in Inorganic Chemistry and for Distinguished Service in the Advancement of Inorganic Chemistry. He has served as consultant to Dupont, 3M, Monsanto, Air Products, and others, and he has served the professional societies and journals in many ways. He chaired the IUPAC Commission on Inorganic Nomenclature while the 1990 recommendations were being brought to publication. He is author of over 300 publications and 6 patents. His research interests proceed from transition metal coordination chemistry, featuring original synthesis, to the control of chemical reactions by metal atoms including functional biomimics and catalysis, and the general subject of molecular organization and its subfields, such as inclusion chemistry, template reactions, and design of extended structures.

1. Introduction

Coordination chemistry first found expression in order to explain chemical substances that we view today as extremely simple, yet they were labeled "complex compounds" because of the consternation their existence generated in the minds of early chemists. These materials are substantially stable, stoichiometrically reliable compounds, but they are combinations of other chemical compounds that are independently stable. Further, those "other chemical compounds" formed the basis of the previously accepted rules of valency, so that the uniting of the independently stable substances violated the cherished rules of chemical valence.

The 1992 International Conference on Coordination Chemistry (Lausanne, August 19–24)[1] celebrated the centennial of the publication of the paper in which Professor Alfred Werner launched the field.[2] In addition to his many primary publications, Werner, the founder of coordination chemistry, presented his concepts in his book *Neuere Anschauungen auf dem Gebiete der Anorganischen Chemie* in 1905; a second edition appeared in 1908; and the book was translated into English by E. P. Hedley in 1911.[3] The translated word "coordination", and other phrasings in his writings, convey the concept of molecular organization. According to Webster, and in the appropriate context, the transitive verb "coordinate" means to bring into proper and relative order. In writing about "addition compounds" Werner wrote of "explaining the formation of all possible compounds of higher order". *The major purpose of this introductory essay is to focus on the realization that "coordination chemistry", the seminal, but highly augmented, legacy to science of Alfred Werner, is foundational to the understanding of the global issue of the organization of molecules in whatever sample of matter such a process may occur, be it natural or synthetic.*

Whereas Werner's contribution is generally stated to be explaining the "molecular addition compounds, such as $PtCl_2 \cdot (NH_3)_2$, $PtCl_2 \cdot (NH_3)_3$, $PtCl_2 \cdot (NH_3)_4$, $CoCl_3 \cdot (NH_3)_3$, $CoCl_3 \cdot (NH_3)_4$, $CoCl_3 \cdot (NH_3)_5$, and $CoCl_3 \cdot (NH_3)_6$, and double salts, such as $PtCl_2 \cdot KCl$ and $PtCl_2 \cdot 2KCl$, he devoted considerable attention at least to the theory of derivatives of the nonmetals, including the polyhalogen compounds, and he treated oxoanions extensively. Ethylenediamine, carbonate, and oxalate were treated as chelating ligands, requiring two coordination sites on a single metal ion. He was aware of the polymeric nature of many binary compounds, and it is clear that

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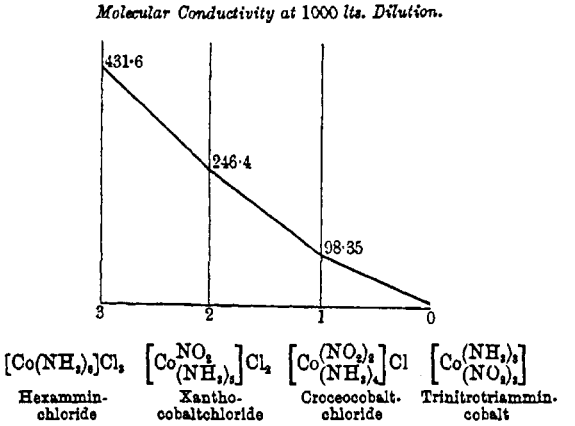


Figure 1. Werner's use of molar conductance to prove coordination formulas. (Reprinted from Werner, A. *New Ideas on Inorganic Chemistry*; Longmans, Green & Co.: Copyright 1911.)

he saw global significance in his theory, as evidenced by the statement: "Almost all compounds of the first order (saturated hydrocarbons form the sole exception) possess the property of combining with other compounds of like nature". These words are prophetic of the modern fields of molecular recognition and inclusion chemistry; *a second purpose of this paper is to emphasize the oneness of these fields with the traditional coordination chemistry of Werner.*

The enormous insight required in the formulation of the original coordination model is remarkable when one thinks in terms of the tools available to the researcher at the beginning of the 20th century. Spectroscopy and X-ray diffraction were not available for deducing structure. The most important accessible information included stoichiometry, color stoichiometry correlations, numbers and nature of isomers, and a very few physical measurements, especially molar conductance in aqueous solution (Figure 1) and molecular weight determination. Stereochemistry and isomerism provided the most subtle and most powerful experimental tool at Werner's disposal. It is a signal fact that stereochemistry is at the heart of the greatly extended compleat coordination chemistry.

The growth of coordination chemistry has been three dimensional, encompassing breadth, depth, and applications. The ongoing respect for the evolving science is apparent in the 5 Nobel prizes that have impinged heavily on the subject (A. Werner, 1913; M. Eigen, 1967; Wilkinson and Fischer, 1973; H. Taube, 1983, Cram, Lehn, and Pedersen, 1987. The first (Werner) and last (Cram, Lehn, and Pedersen) in the preceding list recognized the old and the new realms of coordination chemistry specifically. While both the old and the new coordination chemistries were soon recognized at this highest level, the activities within the established and traditional field have continued to define the frontiers of knowledge, producing giant subfields wherein developments stand shoulder to shoulder in quality and significance to those creating the subject. The Nobel prizes for reaction chemistry and for organometallic chemistry dramatize this fact; further, the subject of bioinorganic chemistry is a peerage in all respects.

In a very real sense, coordination chemistry is a field that spawns fields; noteable examples being transition metal organometallic chemistry, homogeneous catalysis, and bioinorganic chemistry. And equally important, it is foundational to other burgeoning fields, for example solid-state chemistry, extended and mesoscopic materials, photonic materials, models for solid surfaces, separations science, and molecular electronics, machines and devices. The enormous extensions of the field reflect its fundamental nature; the principles are so basic that they have immediate application as undreamed of new substances serendipitously appear in chemistry (e.g., dihydrogen complexes, metal derivatives of fullerenes, metal-containing liquid crystals). The spawning of, or key roles in, new fields is an inevitable consequence of the foundational position of coordination chemistry in the chemical sciences.

2. Growth of Classic Coordination Chemistry

During the greater part of its first 100 years, coordination chemistry focused on the concept of a monatomic, cationic, central atom bound to Lewis bases as ligands. It has been a *cation core-focused model.* If one were concerned with defining still more confining boundaries for the field, then reference would be made to "Werner complexes", a phrase that conjures up colored transition metal cation complexes with nitrogen, oxygen, and, possibly, sulfur donor atoms in their ligands, the most common examples being the cobalt(III) ammines and similar platinum(II) complexes.[4] The cation core focus and emphasis on metal ions as central atoms provide the point of departure from which to view the expansion of coordination chemistry into its current natural and compleat form. The discussion in this and following sections will attempt to justify this concept of completeness that derives from pulling the totality of the field together.

Over the years, the *coordination polyhedron* had come to be recognized as the unifying concept of coordination chemistry and the species of significance is best phrased as the *coordination entity.* The traditional coordination entity has each of the following attributes: a central (metal) atom, a number of ligands, a coordination number, and a polyhedral structure. Early on, the central atom was expected to be a cation, but such long-known species as $Ni(CO)_4$ and $Fe(CO)_4^{2-}$ opened the way for neutral and anionic central atoms, and of course, nonmetallic central atoms have, in principle, always been included. The notion that the coordination entity is constructed of separately definable chemical entities has remained a viable conceptual relationship, but it is secondary in generality to the coordination entity itself. Indeed such common ligands as O^{2-}, N^{3-}, CH_3^-, $C_6H_5^-$, and O_2^{2-} are high-energy species with little independent existence outside of a crystal lattice or coordination sphere.

In a broad context, the science of chemistry may be viewed as comprised of (1) a conceptual foundation of principles and theoretical, often hypothetical, relationships, (2) an experimental base of currently available methods and techniques for manipulating and evaluating matter, and (3) the chemical content, an enormous data base of specific information about individual chemicals, chemical systems, and chemical reactions. Whereas all parts of the experimental capability are available to any subfield of chemistry that can make use of them, coordination chemistry uniquely provides and effectively maintains a stew-

ardship over certain parts of the conceptual foundations and the chemical content of chemistry. Because coordination chemistry was the home of the chemistry of transition metal compounds, certain conceptual topics were largely developed by the followers of that discipline; for example, stereochemistry of higher coordination numbers (5 and above), bonding in systems having d orbitals, and mechanisms of reactions of the metallic elements. The conceptual base of structure and bonding in coordination chemistry has evolved from simple Lewis acid–base ideas and hard and shoft acids and bases, sequentially through valence bond theory, crystal field theory, ligand field theory, the angular overlap model, and onward through a diversity of molecular orbital models, both semiempirical and ab initio. Study of the reactions of coordination compounds has been manifested in magnificent contributions to the understanding of their mechanisms, outstanding examples being the elucidation of electron-transfer processes by Taube and Marcus and their contemporaries and associates, the unfolding of the velocity spectrum of substitution reactions of the total collection of metal ions by the fast-reaction school of Eigen and associated contemporaries, the early elaboration of substitution mechanisms in transition metal complexes led by Basolo and Pearson and their associates and contemporaries, and the initiation of the photochemistry of metal complexes and organometallic compounds by Adamson and its expansion by a number of outstanding investigators. Mechanistic understanding has been united with organometallic chemistry to provide the foundations for the fruitful field of homogeneous catalysis. Modern electrochemistry has brought sound thermodynamic measurements to the redox processes that are uniquely abundant in the coordination chemistry of transition metal compounds, and speciation and equilibrium constant measurement in labile systems is a mature field. The chemical content of the total data base of coordination chemistry has been greatly increased by the evolution of subdisciplines such as transition metal organometallic chemistry with the π-complexes with alkenes, alkynes, and aromatic molecules, including ferrocene and its relatives; multiple aspects of systems having extended structures ranging over polynuclear complexes, metal–metal bonds, and the related areas of clusters, coordination polymers, and fractal-like oligomers; complexes of the small molecules O_2, N_2, H_2, NO, CO, CS, CO_2, SO_2, alkyls, and others; complexes of polydentate chelates, including macrocycles, compartmental ligands, and the metalloporphyrins; and many biomimics.

It is humbly and with sincere apologies that the content of modern traditional coordination chemistry is treated so briefly and inadequately here. For example, from among the various offspring of classical coordination chemistry, the family resemblance is perhaps greatest in organometallic chemistry. The conceptual framework of organometallic chemistry is among the most simple, the most beautiful, and the most generally applicable in all of chemistry. It pulls coordination chemistry closer to organic chemistry than any other of the progeny fields of coordination chemistry. This and many of the other subjects listed above deserve lengthy treatment, but space and the primary goals of this presentation leave no alternative but to stop at this point. Again, major goals are to call for the unification of all of those realms that are naturally a part of a complete coordination chemistry and to examine how they share in providing fundamental principles of molecular organization.

3. Expansion of the Boundaries of Coordination Chemistry

The compleat coordination chemistry exists today because all of the binding interactions that yield distinct molecular species, i.e., *coordination entities*, by the union of two, or more, lesser molecular species, i.e., complex formations, can now be included within the expanded field. Quoting from Lehn[5] "the chemistry of artificial receptor molecules may be considered a generalized coordination chemistry, not limited to transition metal ions but extending to all types of substrates (receptees): cationic, anionic, or neutral species of organic, inorganic or biological nature". A comment on nomenclature here is highly appropriate. A most general term that encompasses both ligands and hosts is receptor, and its use is to be strongly encouraged. In contradistinction, the word "substrate" is not a suitable conjugate term for truly wide ranging applications. Substrate is appropriate when the receptor is part of an enzyme; however, the term already has two meanings (also the underlying or supporting substance in certain materials useages). It is recommended that the obvious conjugate, "receptee" be used. That new term is not otherwise burdened with context and its conjugate relationship is obvious.

The compleat coordination chemistry as more broadly defined here requires only that *distinct molecular species be formed by the binding interaction.* The coordination polyhedron has lost its pivotal position in the broad definition of coordination chemistry, but the centrality of the coordination entity remains. Cram's host/guest complexation[7] is recognizable as a generalization from macrocyclic coordination chemistry that includes all manner of intermolecular interactions and interacting pairs, and a variety of host (ligand, receptor) shapes in addition to a single ring. This focus on formation of a molecular coordination entity suggests a possible distinction between coordination chemistry and Lehn's supramolecular chemistry,[5,6] the latter being more broadly concerned with intermolecular interactions. A strong temptation arises to disinclude the endless molecular arrays, such as those in membranes, films, dendritic structures, and continuous solids, whether the repeat units are atoms, ions, or molecules, but this is not justifiable. The binding interactions may be the same on both sides of such a distinction, and the same principles of coordination chemistry are applied.

It is suggested here, with apology if necessary, that the coordination chemistry need not exclude covalent bond formation, as indicated in host/guest complexation and supramolecular chemistry. A position of compromise, that well serves both traditional coordination chemistry and those subjects, demands only that the molecular entities, which unite (either in reality, or in concept) to form the complex, still be recognizable substructures within the complex. Consider the following three situations: the H_2 molecule is (a) bound as H_2 to a metal atom, (b) oxidatively adds and is bound

as two hydride ligands to a metal atom, and (c) is trapped in the cavity of an encapsulating molecule. All represent coordination compounds and a and c involve the same moiety, H_2 as a ligand in a and as a receptee in c. As has been true since the early years of coordination chemistry, in b the conceived ligand is hydride.

Four developments provide the basis for the expansion of the boundaries of coordination chemistry to their natural limits: (1) the expansion of the domain for complexation by macrocyclic, macrobicyclic, and macropolycyclic ligands, first to alkali metal ions and then to complex cations, complex anions, and neutral molecule central moieties in so-called host/guest complexes; (2) utilization of the receptor qualities of the individual genetic bases, and their analogs, to form hydrogen-bonded complexes; (3) the development of superstructures on polydentate ligands to perform a range of additional functions beyond the role of the parent structure, which is, itself, a specialized receptor; (4) the emerging use of multiple receptors of various kinds within a single coordination compound. These developments rest largely on the design and synthesis of organic ligands having special stereochemical relationships, many of which can be identified with molecular organization.

The greatest importance of coordination chemistry in the future will almost certainly be in bringing higher levels of molecular organization into the design of molecules and complicated molecular systems. The key intellectual tools for the design of remarkably complicated, highly ordered molecular systems exist today, and those concepts provide reason for great excitement for the present and following generations of chemists.

3.1. Molecular Organization

Increased emphasis on the subject of *complementarity* between receptee, guest, or central atom and receptor, host, or ligand has entered coordination chemistry naturally as attention to the metal ion selectivity of ligands grew, as host/guest chemistry developed, and as studies on *molecular recognition* directed attention toward capturing the interactions of the genetic bases for small molecule interactions. The fit of metal ions into low-energy conformations of macrocycles, a subject that has been much discussed, exemplifies complementarity. Further, the necessity for a favorable binding force requires an additional complementarity which may be exemplified by charges of opposite sign or by the hard and soft donor and acceptor atoms. Rebek[8] states "the principle of molecular recognition: identification is most effective with surfaces of complementary shape, size, and functionality". Expanding on this and on the words of Lehn,[5] *complementarity is a congruence of shape and size factors and energetic or electronic compatibility between receptor and receptee, host and guest, or central atom and ligand.*

It is particularly fascinating to realize how the most fundamental structural elements of molecular organization, including complementarity, have entered into coordination chemistry.[9] For polydentate ligands, the role of molecular organization is strikingly evident in the various so-called "effects" that have been found to give stronger metal complexes: the chelate effect, the macrocyclic effect, and preorganization or multiple-juxtapositional fixedness.

The four general structural factors that underlie molecular organization are specified at this point,[9] and a few words of explanation are offered. The factors are size, shape, or geometry, connectedness or topology, and rigidity (the constrained converse of flexibility). No stereochemical relationships are more obvious to the modern chemist than those dependent on size and shape, but they do require constant consideration in complex formation; in fact, from among the four general structural factors, only these two are involved in stereochemical complementarity. More subtle are the contributions of the topological and rigidity factors. The word topology is used here in the limited sense that reflects connectedness of the system. Obviously a macrocycle has a different topology than does an acyclic tetradentate ligand; a fused-ring macrobicycle has a still more constrained topology, etc. A major result to be kept in mind is that, given a high level of complementarity (size and shape), *an additional stereochemical contribution to the complexation affinity of receptor and receptee (for each other) is determined by topological and rigidity constraints.* Complementarity provides the minimal requirements for strong affinity; topological and rigidity constraints are the design factors available for arbitrarily enhancing affinity. This will be illustrated by using well-known examples in this highly useful unifying context.

Figure 2 displays the general observation that the affinity between ligands of a particular kind, amines in the example, and a given metal ion increases with the increasing topological constraint of the ligand system. Contained in the example are the *chelate effect*, which increases with the number of donors linked together through the series ethylenediamine (en), diethylenetriamine, and *N,N'*-bis(2-aminoethyl)-1,3-diaminopropane (abbreviated 2,3,2), the *macrocycle effect* for the case of the tetraazacyclotetradecane, and the *cryptate effect* for the last structure. These topological effects are displayed in both kinetic and thermodynamic properties. Table I recalls equilibrium constants for the binding to nickel(II) of 4 nitrogen donors, successively 4 NH_3, 2 en, 1 trien (triethylenetetramine), and 1 tetradentate "2,3,2" ligand.[10] This measured indication of affinity increases with the number of fused chelate rings so long as exceptional strain energy is not encountered; the latter is the case for the trien complex. The trien example illustrates the need for good complementarity in order to observe enhanced affinity due to an increase in topological constraint. The kinetic data of Figure 3 show a characteristic of the chelate effect.[11] For the complex of a polydentate ligand, the rate constants for dissociation from an Ni–N bond may be comparable to, or even faster than (for strained chelate rings), that from the related monodentate group, but the overall rate of ligand dissociation will still be very slow because of the topological constraint. The relatively rapid individual steps typically begin with donor groups at the ends of the ligand.

The topological difference that arises for a flexible macrocyclic ligand is the absence of "end" donor groups because a ring has no end. This has profound effects on ligand dissociation rates (Figure 4)[12,13] as first

Topology and the Chelate, Macrocycle and Cryptate Effects

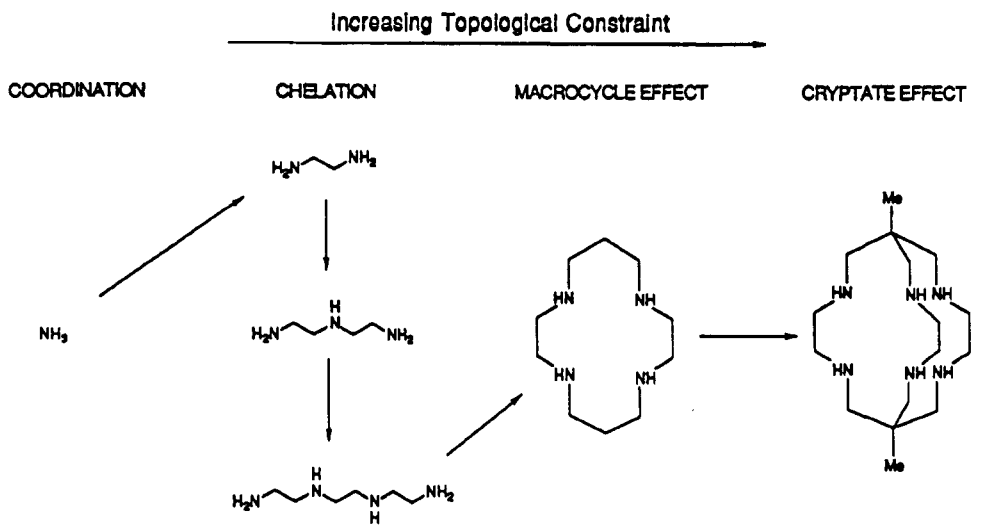


Figure 2. Topology and the chelate, macrocycle, and cryptate effects. (Reprinted from *Superstructured Transition Metal Complexes—A Basis for Functioning Molecules*; DHB, Battelle: Richland, WA. Copyright 1992.)

Table I. Chelate Effect and Complementarity

$$Ni(H_2O)_6^{2+} + nL \leftrightarrow Ni(L)_n(H_2O)_2^{2+} + 4H_2O$$

L =	NH_3	en	trien	2,3,2
n =	4	2	1	1
$\log \beta_n$ =	8.12	13.5	13.8	14.6

$Ni(H_2O)_6^{2+} + H_2{}^*O \longrightarrow Ni(H_2O)_5H_2{}^*O^{2+} + H_2O$ $\quad k_{25} = 3 \times 10^4 s^{-1}$

$Ni(NH_3)(H_2O)_5^{2+} + H_2O \longrightarrow Ni(H_2O)_6^{2+} + NH_3$ $\quad k_{25} = 5.7 s^{-1}$

$Ni(trien)(H_2O)_2^{2+} + 4H_2O \longrightarrow Ni(H_2O)_6^{2+} + trien$ $\quad k_{calc.} = 1.4 \times 10^{-9} s^{-1}$

$Ni(trien)(H_2O)_2^{2+} \xrightarrow[H^+]{15 s^{-1}} Ni(Htrien)(H_2O)_3^{3+} \xrightarrow[H^+]{4 s^{-1}} Ni(H_2trien)(H_2O)_4^{4+} \xrightarrow[H^+]{2 s^{-1}}$

$Ni(tren)(H_2O)_2^{2+} \xrightarrow[H^+]{66 s^{-1}} Ni(Htren)(H_2O)_3^{3+} \xrightarrow[H^+]{0.22 s^{-1}}$

Figure 3. Chelate effect and rates of ligand dissociation.

TETRADENTATE TETRAAZA MACROCYCLES

" $Cu(tet\ a)^{2+}$ (red) $\longrightarrow Cu^{2+} + (tet\ a)H_n^{n+}$

$k_d = 3.6 \times 10^{-7}\ s^{-1}$ in 6.1M HCl at 25°C

$Cu(2,3,2)^{2+} \longrightarrow Cu^{2+} + (2,3,2)H_n^{n+}$

$k_d = 4.1\ s^{-1}$ in 6.1M HCl at 25°C

"teta = 5, 5, 7, 12, 12, 14 - hexamethyl - 1, 4, 8, 11 - tetraaza cyclotetradecane

TETRADENTATE, TETRATHIA MACROCYCLES

$Cu(MAC)^{2+} \longrightarrow Cu^{2+} + (MAC)H_n^{n+}$

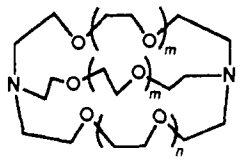
MAC	K_{eq}	k_d, s^{-1}	$lc_f\ M^{-1}s^{-1}$
[12]aneS4	3.0×10^2	4.4	1.2×10^3
[13]aneS4	2.7×10^2	51.	1.4×10^4
[14]aneS4	3.1×10^3	9.	2.8×10^4
[15]aneS4	2.3×10^2	1.9×10^2	4.3×10^4
[16]andS4	9.	3.2×10^3	2.9×10^4
Et_2TTU	13.	3.0×10^4	4.1×10^5

Figure 4. Kinetic and thermodynamic observation of the macrocyclic effect.

quantitated by Cabbiness and Margerum many years ago.[12] Since the effect is greater on dissociation than on association, the kinetic manifestation of the macrocyclic effect also generates a thermodynamic effect. The ligand in the top part of Figure 4 is racemic 5,5,7,-12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane. The relatively systematic abbreviations in the Table II represent tetrathiamacrocycles with the ring sizes indicated in brackets. The early data of Lehn and Sauvage[14] (Table II) showed the advantage of the cryptate effect on the affinities for the hard alkali and alkaline earth metal ions. The equilibrium data show that the greatly constrained macrobicycle binds much more strongly than does the monocyclic crown ether, if complementarity has been achieved. The general lesson of the chelate, macrocyclic, and cryptate effects is that *increasing topological constraint leads to increases in binding affinities, so long as there are no problems with complementarity.*

Figure 5 dramatizes the effect of increasing the rigidity of the ligand framework on the labilities of transition metal complexes with amine ligands;[11,15,16] the overall rate effect is of the order of 10^7–10^8. Long ago, this relationship was whimsically labeled *multiple juxtapositional fixedness* (MJF).[16] A similar dramatization of the benefit of increasingly rigid structures, this time called *preorganization*,[17] is shown in Figure 6, where estimated free energies of binding to a metal ion are given for families of cyclic ethers having differing levels of flexibility.[7] Despite its bicyclic structure, the flexible cryptand binds lithium cation less strongly than does the single rigid spherand ring. A more dramatic difference due to preorganization of the ligand is seen by comparing the values for the rigid cyclic spherand and its acyclic counterpart, the podand. The constraint of receptor (host, ligand) conformation to a shape closely approximating that required for complementary re-

Table II. Equilibrium Data on the Cryptate Effect, log K_{EQ}



1. $m = 0, n = 1$ [2.1.1]
2. $m = 1, n = 0$ [2.2.1]
3. $m = n = 1$ [2.2.2]
4. $m = 1, n = 2$ [3.2.2]
5. $m = 2, n = 1$ [3.3.2]
6. $m = n = 2$ [3.3.3]

M^{n+}	[2.1.1]	[2.2.1]	[2.2.2]	[3.2.2]	[3.3.2]	18-cr	EDTA
Ca^{2+}	2.5	6.95	4.4	~2	~2	0.4	11
Sr^{2+}		7.35	8.0	3.4	~2	3.24	8.80
Ba^{2+}		6.3	9.5	6.0	3.6		7.78
Li^{+}	5.5	2.50				0.6	2.85
Na^{+}	3.2	5.40	3.9	1.65		1.7	1.79
K^{+}		3.95	5.4	2.2		2.2	0.96
Rb^{+}		2.55	4.35	2.05		1.5	0.59
Cs^{+}				2.0		1.2	0.15

ceptee (guest, central moiety) binding leads to substantial stabilization of the complex.

The recurrence of the word "constraint" is central to this analysis of the structural factors contributing to the affinities of the bound pairs in coordination entities. *Size* and *shape* lead to *optimized complementarity* when the receptor and receptee enjoy the best fit; in terms of classic stereochemistry, nothing more can be done to enhance the binding affinity when this optimized mutual compatibility has been achieved. However, the addition of topological and flexibility constraints can enhance affinity a great deal more, so long as their addition does not interfere with complementarity. These conclusions elaborate slightly on Cram's statement: "Just as preorganization is the central determinant of binding power, complementarity is the central determinant of structural recognition."[7] The relationships among the structural factors of molecular organization are summarized in Figure 7.

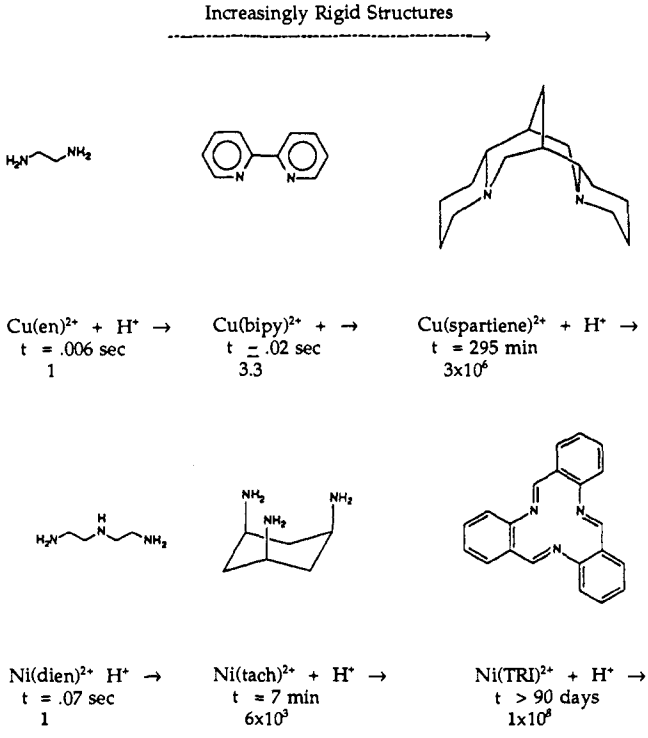


Figure 5. Host/ligand preorganization—multiple juxtapositional fixedness.

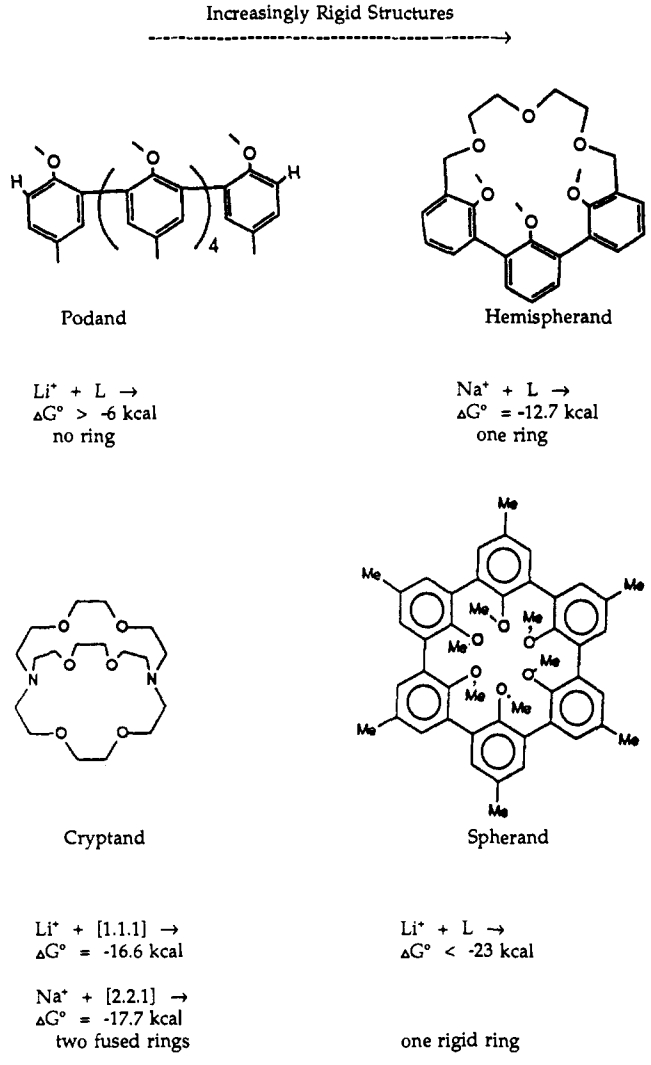


Figure 6. Ligand preorganization—multiple juxtapositional fixedness.

3.2. Macrocyclic Ligands for Alkali Cations, Complex Cations, Anions, and Neutral Molecules

In the new testament for coordination chemistry, the monograph published in 1956 by Bailar,[18] it was possible to indicate only a few examples of reasonably well-characterized complexes for the alkali metal ions, especially the larger ones. That situation prevailed until those previously ignored elements were brought into coordination chemistry by the discovery of the ionophores[19] and by the demonstration that cyclic polyglycol

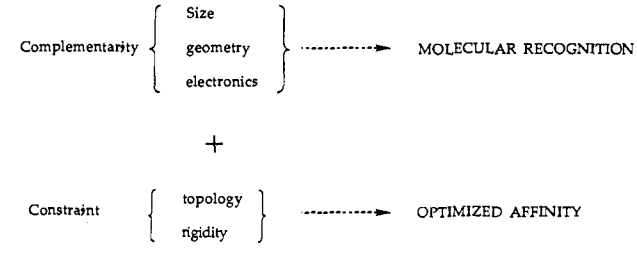


Figure 7. Molecular organization in complex formation.

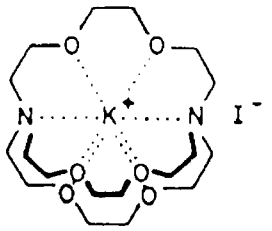


Figure 8. Potassium ion bound to a cryptate ligand. (Reprinted from Prog. Inorg. Chem. **1985**, *33*, 59–126. Copyright 1985 John Wiley & Sons.)

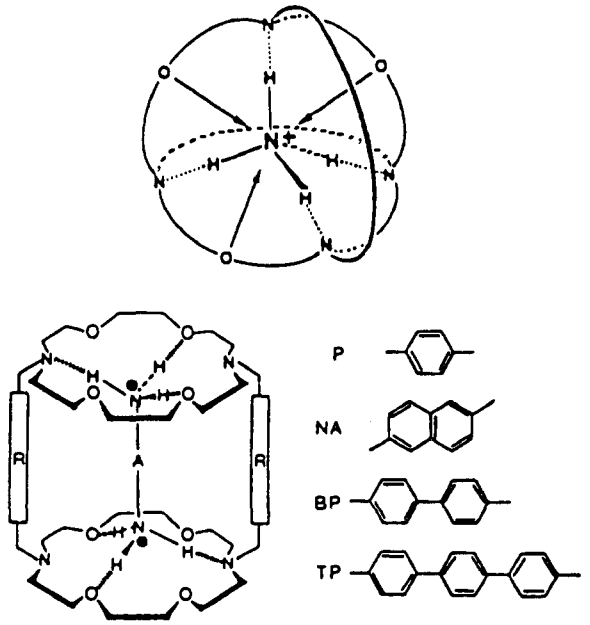


Figure 9. Complexes of complex cations with hydrogen bonding receptors. (Reprinted from Figure 26, lower part, p 365, Lehn, J.-M. Supramolecular Chemistry—Scope and Perspectives: Molecules—Supermolecules—Molecular Devices. *J. Inclusion Phenom.* **1988**, *6*, 351–396. Copyright 1988 Dordrecht.)

ethers and cyclic polyglycol-like ethers of appropriate ring size can bind to alkali metal ions.[20] Optimized alkali metal ion and, to a lesser extent, alkaline earth metal ion ligands were then developed using both the more constraining macrobicyclic topology[5,14] (Figure 8), first produced by Rose,[21] Holm,[22] and Goedken,[23] and increasingly rigid ligand structures.[7] Variants of the cryptates yielded early examples of receptors for such complex cationic species as NH_4^+ and $^+NH_3(CH_2)_nNH_3^+$ (Figure 9),[24] simple halide anions,[25] and carboxylates and phosphates.[26]

Still more complicated receptees, for example $[Co(NH_3)_6]^{3+}$, $[Co(NH_2CH_2CH_2NH_2)_3]^{3+}$, and even [Co(1,3,6,8,10,13,16,19-octaazabicyclo[6.6.6]eicosane)]$^{3+}$, have been incorporated as central moieties in coordination entities; the ligand in this case was lasalocid A, LAS, Figure 10.[27] The X-ray crystal structure of $[Co(NH_3)_6](LAS)_3$ shows a hydrogen-bonding network similar to those formed in host/guest complexes between metal ammines and crown ethers.[28] Similar examples are also provided by complexation of ferri- and ferrocyanide with macrocyclic polyammonium hosts.[29] These complexes of complexes are illustrative of a general principle that will become increasingly important in the coordination chemistry of extended structures. The use of complexes as receptors or receptees is, in

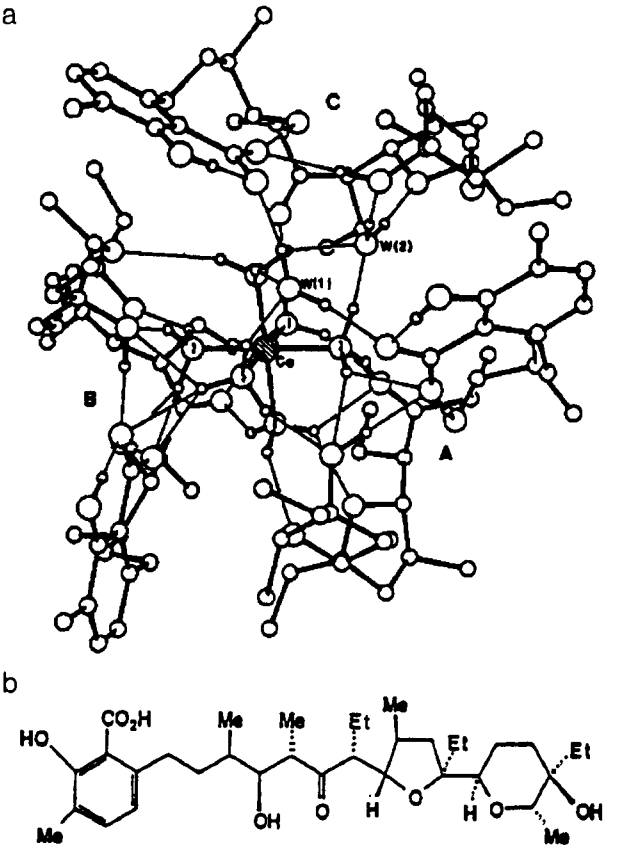


Figure 10. X-ray crystal structure of (a) $2[Co(NH_3)_6]^{3+}\cdot 3LAS$ and (b) LAS is lasalocid A. (Reprinted from (a) Takusagawa; Shaw; Everett. *Inorg. Chem.* **1988**, *27*, 3107–3112 and (b) Chia; Lindoy; Walker; Everett. *J. Am. Chem. Soc.* **1991**, *113*, 2533–2537. (Copyright 1988 and 1991 American Chemical Society.)

principle, indefinitely extendable. Indeed, NH_3 is a complex molecule that is a ligand in the hexaammine complex that is the receptee in the lasalocid complex. Placement of $[Co(NH_3)_6](LAS)_3$ in a membrane, as receptor, is like a fourth level of complexation. Similar, but enjoying interesting contrasts, is the notion of building up three-dimensional clusters by the addition of layers, which, in turn, is rather like the growth of crystals. The fractal-like buildup of polynuclear complexes, using chelating binucleating ligands,[30] is a highly innovative, totally different approach to extended structures that augment three dimensionally (Figure 11); the fractal character is shown in Figure 12.

The receptor for $^+NH_3CH_2CH_2NH_3^+$ (Figure 9) is the ditopic topological equivalent of the face-to-face porphyrins;[31] both are illustrative of the growing importance in coordination chemistry of compartmental ligands. In principle there is no limit to the number and relative orientations of the receptee sites of polytopic compartmental ligands.

While the voluminous research in the area of macrocyclic, macrobicyclic, and macropolycyclic ligands rests on precedents from earlier research with the traditional metal ions of coordination chemistry (e.g., Busch[31] and Curtis[32] to Pedersen[20] to Cram[7] and Lehn[5]) and, in many cases, exploits topologically equivalent ligands, at least two additional beginnings can be found for the expansion of the boundaries of coordination chemistry to include other central species than the usual metal and nonmetal ions (complex cations, anions,

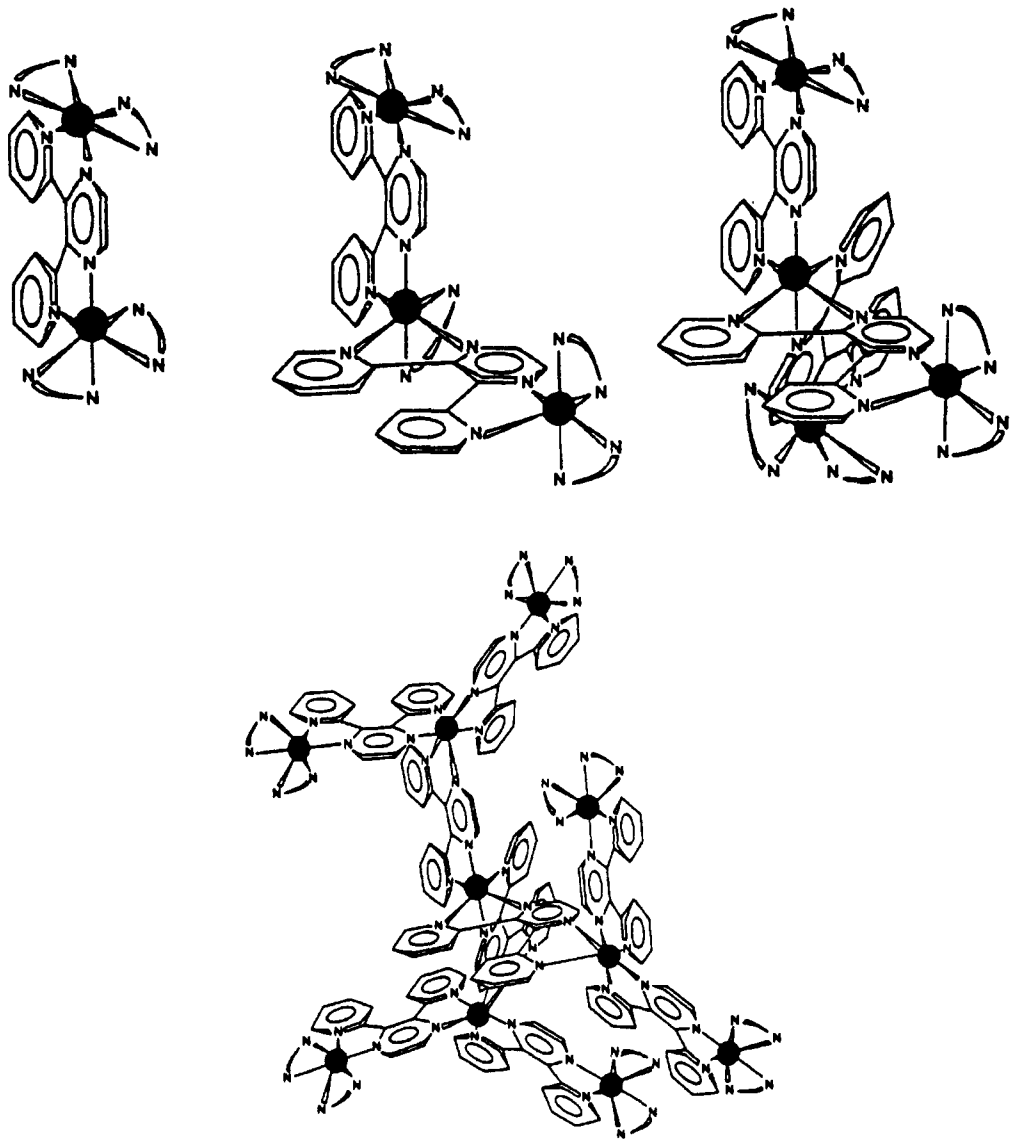


Figure 11. Extended structures based on fractal-like growth. (Reprinted from Figure 4, p 156. *Perspectives in Coordination Chemistry*; Williams, A. F., Floriani, C., Merbach, A. E., Eds.; Verlag Helvetica Chimica Acta: Basel, 1992. Copyright 1992 Verlag.)

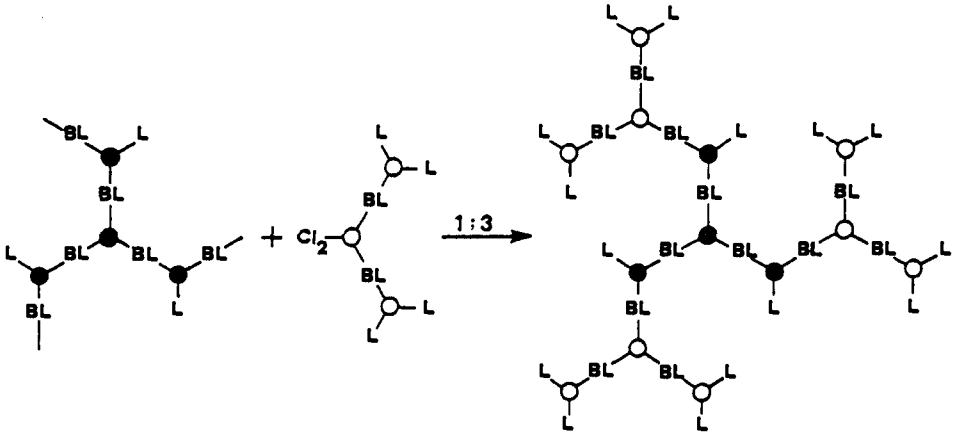


Figure 12. Synthesis of a fractal-like tetradecanuclear compound. (Reprinted from Figure 3, p 155. *Perspectives in Coordination Chemistry*; Williams, A. F., Floriani, C., Merbach, A. E., Eds.; Verlag Helvetica Chimica Acta: Basel, 1992. Copyright 1992 Verlag.)

neutral molecules)—the cyclodextrins and the cyclophanes.

The cyclodextrins[34] are cyclic oligosaccharides consisting of six or more α-1,4-linked D-glucose units (Figure 13). These "lampshade"-shaped molecules contain hydrophobic cavities in the shape of truncated cones (with the top removed); their ability to form complexes with various molecular substrates is the subject of many

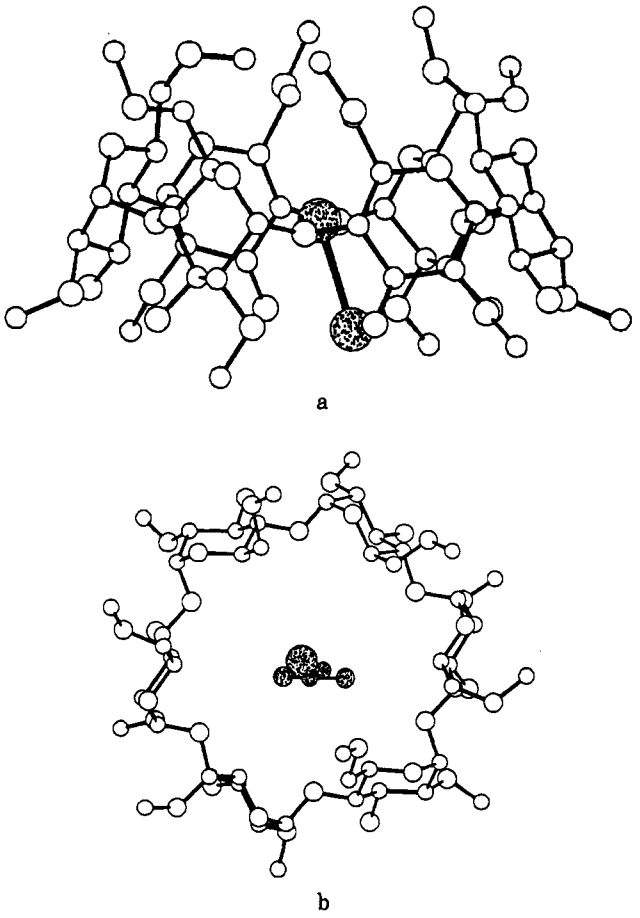


Figure 13. The complex with iodine of dimethyl-α-cyclodextrin. (Reprinted from Harata, K. Recent Advances in the X-ray Analysis of Cyclodextrin Complexes. *Inclusion Compounds*; Atwood, Davies, MacNicol, Eds.; Oxford University Press: Oxford, 1991; Vol. 5. Copyright 1991 Oxford.)

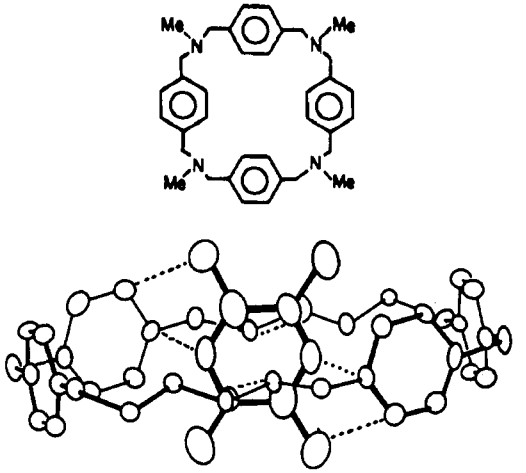


Figure 14. Neutral molecule complexation with cyclophane host. (Reprinted from Meade; Busch. Inclusion Complexes of Molecular Transition Metal Hosts. *Prog. Inorg. Chem.* **1985**, *33*, 59–126. Copyright 1985 John Wiley & Sons, Inc.)

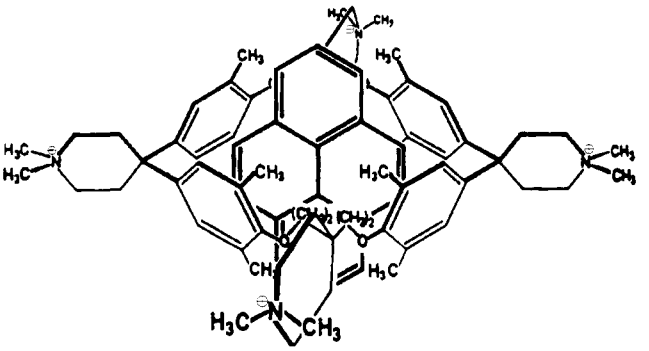


Figure 15. Pyrene complex of a cationic cyclophane. (Reprinted from ref 37. Copyright 1984 American Chemical Society.)

earlier and on-going studies, has generated books, and established a continuing international symposium series. Both entries into the hydrophobic cavities of a cyclodextrin are lined with hydroxyl groups, and the net effect of the hydrophobic interior and polar periphery is good affinity for neutral and anionic guests. These systems alone would have extended the boundaries of coordination chemistry to include anionic and neutral molecules as the core moieties within the coordination entities, but as pointed out in the preceding and following paragraphs, they were not alone in this capability.

Pioneering studies by Tabushi,[35] Murakami,[36] and their associates introduced cyclophanes as a new family of receptor, especially suited for hydrophobically binding aromatic molecules in aqueous solutions (Figure 14). In order to meet the minimum requirements for hydrophobic receptee binding, the receptor molecule must be water soluble and contain a hydrophobic domain in which a guest can reside.[35,36] The main structural features have been incorporated to provide a balance between hydrophobic and hydrophilic qualities. With cationic cyclophane hosts (Figure 15), both hydrophobic and electrostatic forces come into play and not only aromatic molecules but their anionic derivatives are also bound.[37] Studies on these systems are providing insight into the nature of $\pi-\pi$ interactions,[38] an old but evolving subject[39] that is naturally a part of the new and compleat coordination chemistry.

3.3. Small Molecule Complexes with Hydrogen-Bonding Receptors

The incorporation of the base pairing, so well known in genetic materials, into small molecule complexation has been a target of research in molecular recognition.[40] These developments have brought specific hydrogen-bonding patterns into coordination chemistry. Hydrogen bonding has also been heavily used in anion, molecule, and complex cation coordination by studies with macrocyclic receptors, as mentioned earlier. Studies on base-pair emulative receptors have often been augmented by stacking interactions between aromatic groups in addition to specific hydrogen bonding, a design feature that has also been borrowed from the natural systems. Rebek's genetic base receptor[41] and its complex with adenine are shown in Figure 16, along with Hamilton's receptor,[42] the latter being derived from a macrocyclic parent structure. Rebek's message of the virtue of converging binding units in nonmacrocyclic receptors is also heeded in designs by others. Zimmerman[43] and Lehn[44] and their associates have developed receptors capable of strong stacking interactions, and Wilcox,[45] Schmidtchen,[46] Bell,[47] Kelly,[48] Gokel,[49] and Fenton[50] have focused on hydrogen-bonding interactions. Examples are given in Figure 17.

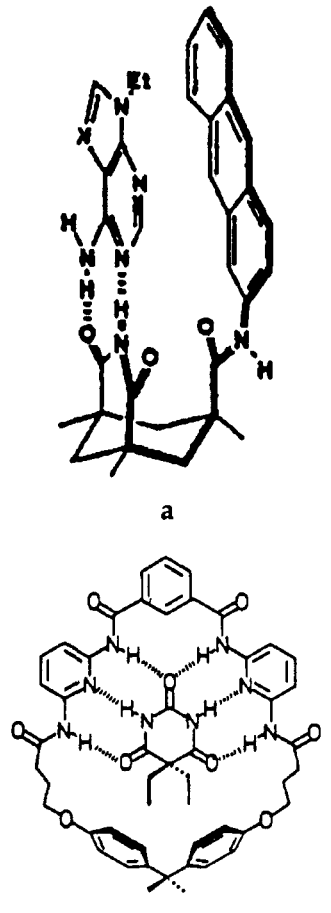


Figure 16. Hydrogen-bonded complexes: (a) adenine complex with Rebek receptor and (b) barbitrate complex with Hamilton receptor. (Part a is reprinted from the second citation of ref 40. Copyright 1990 VCH. Part b is reprinted from the third citation of ref 42. Copyright 1988 American Chemical Society.)

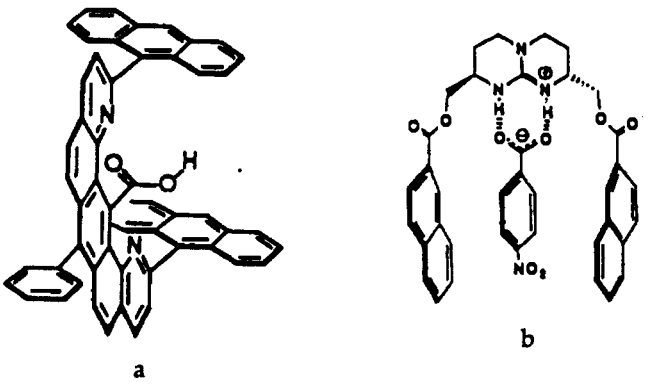


Figure 17. Complexation using combined stacking and hydrogen bonding. (Part a is reprinted from the first citation of ref 43. Copyright 1991 American Chemical Society. Part b is reprinted from the second citation of ref 40. Copyright 1990 (VCH.)

3.4. Superstructures on Polydentate Ligands

The concept of a superstructure[51] in a molecular system follows an analogy to the design of ships. The same sea frame could accommodate a variety of applications, and the outfitting of that sea frame with a superstructure specializes its function. The great stability and minute lability, which is achievable upon complexation by incorporating favorable structural

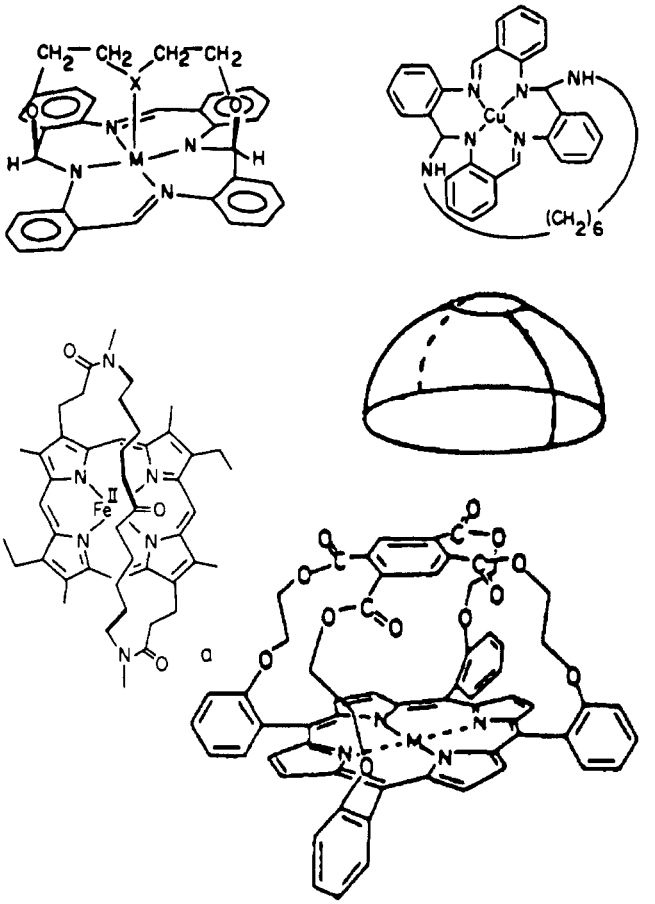


Figure 18. Early examples of superstructured macrocyclic complexes. (Reprinted from Meade; Busch. Inclusion Complexes of Molecular Transition Metal Hosts. *Prog. Inorg. Chem.* **1985**, *33*, 59–126. Copyright 1985 John Wiley & Sons, Inc.)

features (chelate effect, macrocyclic effect, cryptate effect, MJF), lead to the realization that certain complexes are suitable chemical entities for use in further synthetic elaboration by the appending of superstructure to the parent component, or *platform*. The superstructure may play many roles: an enclosed site may be created to provide a particular kind of environment (e.g., polar or apolar), to facilitate the binding of some species, or to prevent access to the site by some particular species; specific groups may be appropriately built into the superstructure to contribute to the function (proton donors or acceptors, hydrogen bonders, redox centers, spectrally active groups); the shape of the superstructure and the orientation of groups within it may be critical to function (selective binding, synergism in catalysis); the general nature of the site may be equally important, i.e., completely enclosed cages, cavities with large openings and clefts that are fully open on one side. Because of the benefit of the macrocyclic effect and ease with which rigidity can be imposed on them, many macrocyclic complexes are ideal platforms. The earliest superstructures were extremely simple, being merely straps, caps or pillars attached to macrocyclic structures[52] (Figure 18), with more complicated superstructures following. Porphyrins have provided the platforms for the largest number of the studies that have added superstructures to macrocycles. Applications have included fixing the axial base to the larger ligand[53] (Figure 19), providing a protected area within which O_2 can bind, generating

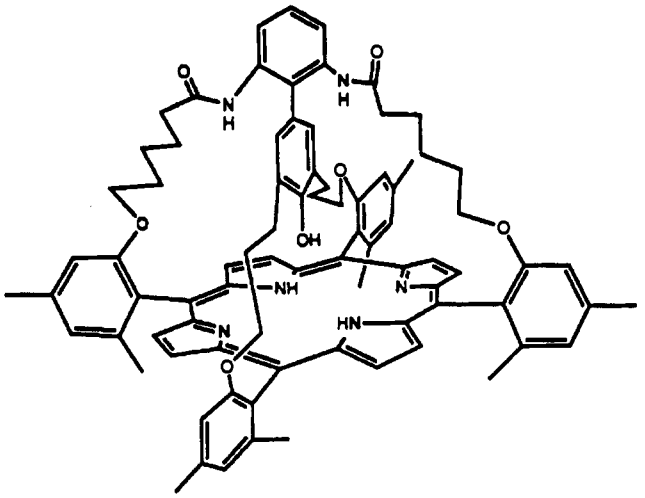


Figure 19. Uniquely superstructured axial ligand. (Reprinted from the first citation of ref 53. Copyright 1990 American Chemical Society.)

a particular environment near an O_2 or H_2O_2 binding site,[54] and accommodating a potential substrate.[55]

The transition metal cyclidenes have generalized the concept by incorporating essentially all of the above superstructure applications on a different platform, a nonplanar macrocyclic ligand with certain structural advantages (Figure 20).[56] The functional groups shown as vinyl amines are not accurately represented by that structure. They display about the same reactivity as carboxamide groups and are derived from vinyl ethers that display reactivities very similar to esters. The deep cleft resulting from the saddle shape of the coordinated cyclidene macrocycle directs the two equivalent functional groups to the same side of the N4-coordination plane and facilitates closure of a fused second ring. Fused macrobicycles have been used to produce other simple superstructured macrocycles, including the Goedken macrocycle[57] and BF_2^+-bridged α-dioximes.[58] Similar simple superstructures have been incorporated into modifications of the long-known Schiff bases, salen,[59] and acacen.[60] Pillared and other very bulky structures have also been incorporated into Schiff bases and synthetic macrocycles.[61]

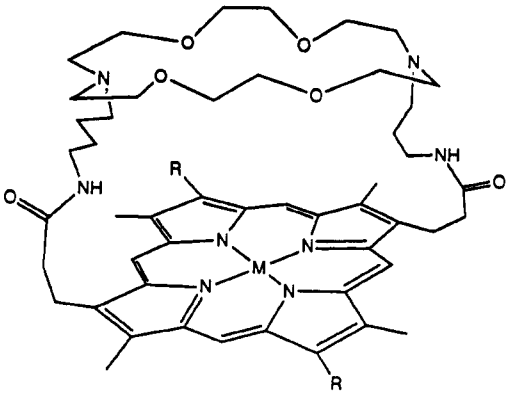


Figure 21. Multiple varied receptors: face-to-face prophyrin/crown ether. (Reprinted from Meade; Busch. Inclusion Complexes of Molecular Transition Metal Hosts. *Prog. Inorg. Chem.* **1985**, *33*, 59–126. Copyright 1985 John Wiley & Sons, Inc.)

3.5. Multiple Varied Receptors within a Single Coordination Compound

In the simplest case, ditopic, tritopic, or polytopic receptors would repeat identical receptor sites along a chain, sheet, or three-dimensional matrix after the fashion of functionalized polymers, especially ion-exchange resins. Compartmental ligands continue to be of great interest for such functions as receptee separations, conducting polymers, ferromagnetically coupled molecules, and the like, but far more intricate levels of molecular organization now exist among the ambitions of coordination chemists. The inventory of receptor sites includes the following, and examples of any or all might be incorporated into the design of a single multireceptor supramolecular system: macrocycles, macrobicycles, macropolycycles, fixed but open cleft structures, and flat platforms, whose binding is based on (a) donor atoms, (b) hydrogen bonds, (c) charged groups, (d) hydrophobic interactions, and (e) stacking interactions. Many examples of the pairing of disparate receptors exist. A few early examples are crown ether face to face with a porphyrin[62] (Figure 21) to provide an alkali metal site near a transition metal site; porphyrin appended to a cyclodextrin[63] (Figure 22), a picnic basket porphyrin[55] (Figure 23), and a vaulted cyclidene[64] (Figure 24) to locate an oxidizing

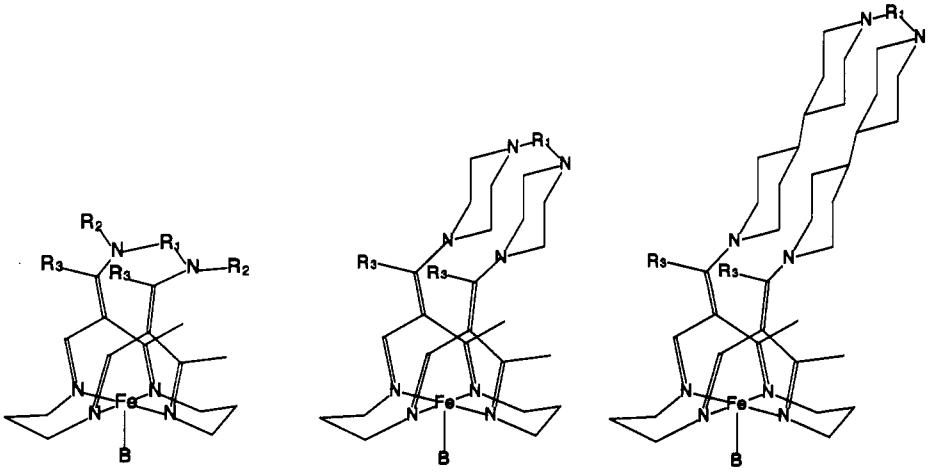


Figure 20. Cyclidene ligands with cavities of various sizes. (Reprinted from *Superstructured Transition Metal Complexes—A Basis for Functioning Molecules*; D4B, Battelle: Richland, WA. Copyright 1992.)

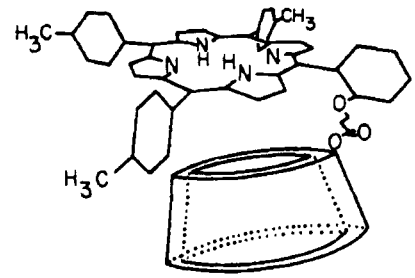


Figure 22. Multiple varied receptors: porphyrin/cyclodextrin. (Reprinted from Meade; Busch. Inclusion Complexes of Molecular Transition Metal Hosts. *Prog. Inorg. Chem.* **1985**, *33*, 59–126. Copyright 1985 John Wiley & Sons, Inc.)

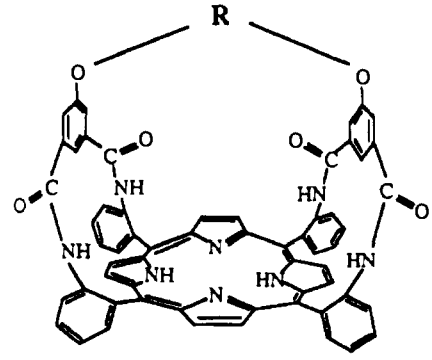


Figure 23. Multiple varied receptors: macrobicycle with sites for metal ion and substrate. (Reprinted from ref 55. Copyright 1990 American Chemical Society.)

center near a receptor site for an organic molecule; and Rebek hydrogen bonding receptors on porphyrins[65] (Figure 25) to bind complementary molecules near metal site.

Enzymes, especially metalloenzymes, provide an exhilarating view of the potential for multiple receptor site systems; a typical set of receptors and their roles might be (a) metal ion site (all ligands except substrates and cofactors), (b) substrate binding site (hydrophobic, hydrogen binding, stacking), (c) active-site environmental control (polar, apolar), (d) nucleophilic or electrophilic cofactor, (e) proton-transfer system, and (f) electron-transfer system. Certainly, not all of these functions would be needed for most systems and not all would require specific receptors; i.e., substituent groups might be used instead. However, even in those cases where the functioning unit might be provided as a substituent, maximum flexibility would probably be achieved by incorporating the factor in question into its own special receptor site.

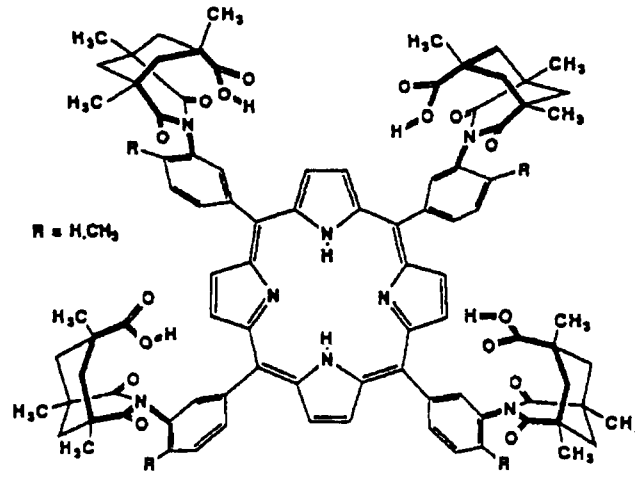


Figure 25. Multiple varied receptors: porphyrin/Rebek receptor. (Reprinted from the second citation of ref 40. Copyright 1990 VCH.)

4. Expectations for Coordination Chemistry in the Future

A major discrepancy exists between the complexity of the total universe in which the practitioners of chemistry exist and that of the science that they practice. The extent to which systematic organization occurs in many natural microcosms, particularly in vivo, is overwhelmingly complicated compared to that generally achievable in chemical laboratories. The complete coordination chemistry has revealed ways of closing this intimidating gap, to move toward the organization of molecular systems of substantial complexity—one of those giant steps that mankind must take in the eternal struggle to control his destiny. Intrepid inorganic chemists, notably Francis P. Dwyer, Gunther Eichhorn, and possibly others, took bold steps in this direction when their scholarship conceived the field of bioinorganic chemistry many years ago. That and the companion field of bioorganic chemistry have burgeoned and created enormous understanding, but the limitation can still justifiably be leveled that the fields tend to fluorish by isolating phenomena and subsystems and, thereby, simplifying to the point of manageability, but at the expense of begging the real issue—the ultimate complexity of truly functional natural systems. Please do not misunderstand, this is in no way a criticism of the marvelous research that has been done—the astrolabe had to precede the satellite. This is a call to arms!

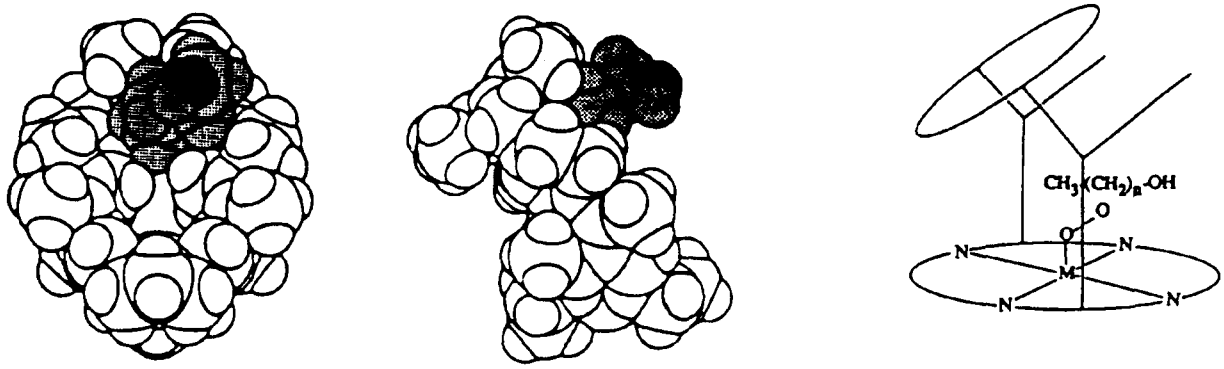


Figure 24. Multiple varied receptors: macrobycyclic cyclidene with sites for metal and substrate (shown as ternary complex). (Reprinted from Busch; Stephenson. Inclusion Chemistry for the Modeling of Heme Proteins. *Inclusion Phenom. Mol. Recogn. Chem.* **1989**, *7*, 137–153. Copyright 1989 Kluwer Academic Publishers.)

Those trained as traditional coordination chemists who read this might share the view that it was a truly remarkable experience to watch exceptionally creative organic chemists discover chemistry beyond the molecule. The experience is illustrative of the compartmentalization of knowledge in today's world. It takes no challenging analysis to conclude that those new aspects of the compleat coordination chemistry constitute a replay, in a different realm, of the thesis of Werner's work of an even 100 years ago. From this time forward, the important mission is not just chemistry beyond one molecule, it is the increasingly complete control over multimolecular systems, regardless of their complexity. The mission is control over the organization of molecules in systems of relevance throughout the total zone of man's needs. If chemistry is to justify its continued existence as a science, progress in this realm must be a major theme. Not only bioinorganic and bioorganic chemistry, but other areas such as molecular prostheses, environmental remediation, new materials of unimagined (or barely imagined) capability, electronic and mechanical molecular devices, and environmentally favorable industrial processes, for example, must profit from constantly growing levels of molecular organization and control in the understanding and design of functional systems.

Generalizing is easy, but clarity comes from real examples. Despite enormous commitments of resources and the involvement of astounding talents, contemporary bioinorganic models bring to the problem at hand only two or three simultaneously implemented favorable influences. Cytochrome P450 mimics illustrate the situation very well. It is generally agreed that the ternary enzyme/dioxygen/substrate complex is at the center of the problem of the unique capabilities observed in the functioning of this enzyme. The word ternary hardly does justice to the complexity of the system: ligand, metal ion, axial ligand, substrate, cofactor, reaction environment, selective site for substrate. Nonetheless, that ternary complex can be modeled. Further, it is generally believed that reduction of the dioxygen adduct by a cofactor, with the substrate in place, initiates the highly selective oxygenation process. Then, marvelously, the O–O bond cleaves, the high-valent species blossoms briefly, and passes along an oxygen atom to the entrapped substrate.

The limitations of today's model systems are ultimately traceable to the second law of thermodynamics and are highly instructive. Before proceeding it must be emphasized that this is no way a criticism of those present models; they are excellent and their evolution was essential. The point to be made is that there is a next generation of model toward which we should begin to look. The specifics are manifold, but the fact is that organic substrates can be bound simultaneously with dioxygen, in a fashion paralleling that in P450;[55,64] further, dioxygen can be activated (maybe even to a hypervalent iron species)[66,67]—this requires a reducing agent—and, maybe, an electrophile. Certainly, hypervalent iron species can be generated using other oxidizing agents, and most important, they can oxidize substrates.[66,68]

Despite the fact that each of the steps in the catalytic cycle of cytochrome P450 has been mimicked, it has not been possible to do them all in concert at any pleasing level of efficiency.[66] In the second law-disorganized laboratory systems, the cofactor, that is supposed to reduce and activate the dioxygen adduct, competes with the substrate for the activated species. Any "axial base" that might determine the coordinating properties of the metal ion competes with dioxygen for the metal ion site and, maybe, competes as a substrate. The problem is an organizational one—that of getting the right species to the right place at the right time. Today's bioinorganic chemistry has brilliantly provided the foundations for what needs to be done next, but it differs from that realm of biomimicry in just the way the sounds made by a group of individual musicians, each practicing separately, differ from the performance of a symphony; clearly the difference is a matter of organization.

Among the chemical motifs of the era, a most embarassing phrase expresses the situation; the phrase is "self-assembly". Unless someone invents a molecular tweezer more generally controllable than those of Zimmerman,[43] *at the molecular level there is only self-assembly*. The chemists' job is to learn to facilitate those kinds of self-assemblies that are intricately and multiply organized at the molecular level. There are those self-assemblies that are purely random and then there are those that participate in the evanescence of ultimate subtlety. Molecular design and chemical templates will help provide the species and processes that create order. It is as it has always been that the enemy is the second law of thermodynamics. The job of coordination chemists is, within the systems that are their focus, to confound the second law. That is the essence of molecular organization, and, within limits specified in the concept of a coordination entity, the broad mission of the compleat coordination chemistry.

Acknowledgments

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