PROGRESS IN INORGANIC CHEMISTRY

Edited by

KENNETH D. KARLIN

DEPARTMENT OF CHEMISTRY
JOHNS HOPKINS UNIVERSITY
BALTIMORE, MARYLAND

VOLUME 45

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Contents

Progress in Inorganic Chemistry

Volume 45

Selective Recognition of Organic Molecules by Metallohosts

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CONTENTS

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I. INTRODUCTION

Many of the studies in the 1970s and 1980s that provided impetus for the rapid evolution of supramolecular chemistry were concerned with the use of highly structured organic molecules as receptors for inorganic ions such as the alkali metal cations. Notable examples include Pedersen's crown ethers (1, 2), Cram's spherands (3), and Lehn's cryptands (4), each of which formed stable complexes with alkali metal cations. Part of the elegance of this work included the *designed architecture* of the receptors: consideration of size and shape of the receptor site in comparison with the guest were used to rationalize observed binding data and to design new systems with unique properties. Meanwhile, classic coordination chemistry has continued to develop, and during the past several years much exciting work on inorganic and metalloorganic hosts has been reported (5). Indeed, as we will see in this chapter, the employment of metal ions in the design of new host architectures has opened the way for complexation of many structurally sophisticated guests. This chapter will focus on the development of *metalloorganic* hosts for the selective recognition of *organic* substrates. For a discussion of a new class of inorganic hosts, see V Pecoraro et al. (6) (Chapter 2 in this volume).

A. Definitions

We will use Cram's original definitions (7) of host and guest: A host is a component of a molecular complex whose binding interactions converge in the complex. A guest is the component in a molecular complex with divergent binding interactions. In this chapter, the host is itself a coordination complex composed of one or more metal atoms together with organic scaffolding and functional groups that form a binding site for an organic guest.

Several detailed discussions of the influence and significance of host structure on host–guest complex stability are available (5, 8–10). We find it convenient to summarize this substantial body of information with three statements (11). First, the selectivity of a host to bind a particular guest is determined by the complementarity of the host to the guest. If discrimination between two very similar guests is desired (e.g., recognition of a single enantiomer), then a large number of specific interactions between the host and the guest will be required.

Second, the stability of the host–guest complex will be greatest when both partners are preorganized for binding (i.e., need not undergo conformational change in order to form a complex). Finally, the stability of the host–guest complex will depend on the relative solvation of the host, the guest, and the host–guest complex. For example, if host and guest form a complex via hydrogen bonds, the complex will be more stable in nonpolar solvents due to their reduced ability to solvate the individual hydrogen-bond donor and acceptor sites of the host and the guest.

Several of the papers discussed in the chapter draw analogies to allosteric behavior. An allosteric molecule (e.g., hemoglobin) (12) contains a binding site that is regulated by interactions with one or more separate, nonadjacent sites (13). Allosteric interactions are crucial in many physiologic processes such as enzyme regulation. Several host–guest complexes have been studied in an effort to model allosteric biomolecules (14–19). One common strategy has been to design hosts with binding sites for both a metal ion and an organic molecule. Nearly every host discussed is an example of an allosteric molecule, since the binding sites for organic guests are somehow "regulated" by metal ions present in the host scaffold. In most cases, positive allosteric (cooperative) interactions are observed, since the binding of metal and guest mutually increases the binding of each partner. In some cases, negative allosteric interactions may be observed; that is, the binding of a particular metal may decrease the binding constant of the organic guest. From the perspective of this chapter, the concepts of "allosterism" and "preorganization" are difficult to distinguish. We consider allosterism to be a special case of preorganization requiring relatively labile metal ions. An example of an allosteric, metal ion–ligand–guest ternary complex would be one in which the metal preorganizes the ligand for guest binding, and in which the guest preorganizes the ligand for metal ion binding.

B. Why Metal-Organized Hosts?

One of the problems of supramolecular chemistry is that of obtaining suitable scaffolds. If the desired compound is to be a receptor, it will often need to be sufficiently larger than the targeted guest so that functional groups may be directed from the scaffold to form an array that is complementary to the guest; thus, the molecular weight of the target compound may be an order of magnitude larger than that of the guest. Furthermore, large organic molecules require built-in elements of rigidity in order to assure that the conformation taken by the receptor is the desired one. For such systems, it is generally found that the larger and more rigid a molecular receptor, the longer the synthesis. One common solution to the synthetic problem has been to choose targets with high degrees of symmetry, so that syntheses can be designed in which several bonds may be formed in each step. The trade-off here is that highly symmetrical receptor sites are most suitable for highly symmetrical guests. Hence, this strat-

egy has worked extremely well for designed hosts for alkali metal cations, which are spherical. However, if one is interested in selective complexation of organic guests, large receptors with complex (i.e., non-symmetrical) binding sites are required. Of course, nature has solved this problem with protein receptor binding sites, and many of the goals of molecular recognition chemists can be achieved with the development of such binding sites by protein engineering (20). Another recent strategy has been to find recognition units from large pools of compounds using efficient screening techniques (21–23). In the long run, however, it would still be desirable to be able to rationally design and synthesize hosts from first principles and abiotic materials because of the greater potential to control factors such as environmental stability.

Construction of hosts with metal ions in the scaffold offers a solution to these problems due to increased synthetic flexibility. If the "glue" that holds a scaffold together is expanded from the standard set of covalent bonds commonly used in organic chemistry to the vast array of bonds available in inorganic complexes, many new building blocks can be used, and receptors with many different sizes and shapes become available. The metalloscaffold may be put together by self-assembly, by organometallic synthesis, or by using classic coordination chemistry techniques. For example, the backbone of the host may be a flexible polyamine ligand that becomes rigid upon addition of a metal ion.

Another benefit made available by the presence of a metal ion in the host architecture is the potential for using the chemistry of the metal for catalysis or as a reporter (e.g., in the development of a sensor). Indeed, metal ions were first appended to organic binding units for these purposes long ago (24), but building the receptor around the metal has been less common until recently.

C. Scope

This chapter highlights chemistry at the interface between classical inorganic coordination chemistry and host–guest or supramolecular chemistry. It will cover studies of the binding of organic substrates by receptors whose structure is in some way affected by a metal ion, with the metal-forming part of the structural backbone of the host or the host being built up from a coordination complex. We have taken the host descriptor "convergent" literally in limiting the scope of this chapter: metallosupramolecular complexes designed to bind to macromolecules (25) and self-assembling materials lacking binding sites (26, 27) have not been included. "Hosts" that have not been shown to form host–guest complexes have also not been discussed.

Each subsection begins with simple coordination complexes in which interligand noncovalent interactions play a role in molecular recognition. Subsequent examples demonstrate increasing architectural complexity, from clefts to macrocyclic hosts to bowl-shaped receptors. Although it can be argued that

porphyrins are not strictly "preorganized" by their central metal atom, examples of metalloporphyrin-guest chemistry are included because they represent such a significant contribution to the field (28). Several examples of catalytic hosts have also been included where appropriate. For catalysts, the substrate selectivity is determined by the complementarity of the host to a reaction transition state rather than to a particular compound in its ground state (29).

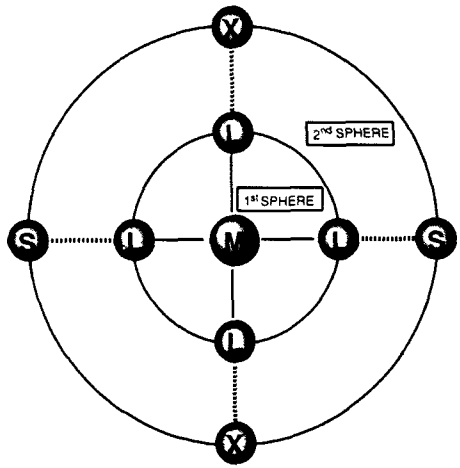
D. First and Second Sphere Coordination

In the examples that follow, the metal ion(s) preorganize the host for guest complexation. However, whether or not the guest coordinates to the metal ion is dependent on the architecture of the system. We will use "first sphere coordination" to refer to ligation of the metal ion, and "second sphere coordination" to refer to noncovalent interactions with the organic part of the host (30, 31). These terms were discussed in an excellent chemical and historical perspective by Stoddart and Zarzycki (32). Alfred Werner coined the term "second sphere coordination" in 1893 (33, 34). The general concept is illustrated in Fig. 1(*a*). In this chapter, host–guest complexes have been grouped according to whether the guest is bound through a combination of first- and second-coordination sphere interactions [Fig. 1(*b*)] or through only second coordination sphere interactions [Fig. 1(*c*)].

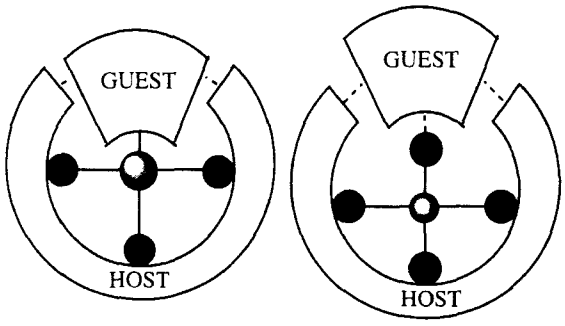
II. "LIPOPHILIC" GUESTS

In reviewing recent work in this field, it is convenient to divide the guests that have been studied into two major categories: lipophilic guests and hydrogen-bonding guests. Division of the field in this manner also has the effect of largely categorizing the studies according to the media in which the complexation experiments were performed; many of the studies of lipophilic guests have been carried out in aqueous solution, while nearly all of the hydrogen-bonding guest studies utilized nonpolar solvents.

Lipophilic interactions can involve many different types of noncovalent forces, such as dipole–dipole interactions, dipole-induced dipole interactions, π-stacking interactions (35–37), charge-transfer interactions, and solvation, especially in aqueous solution. The importance of these interactions in nature is well known (29, 38). Recently, the interplay between these interactions and the coordination of a metal ion has become a subject of great interest (39, 40). Relatively weak (1 kcal mol^{-1}) noncovalent interactions can often be observed between ligands that are coordinated to a metal, since the ligation compensates for entropy losses that would otherwise prohibit experimental observation of the interaction. Thus, some coordination complexes have served as excellent plat-



(*a*)



(*b*) (*c*)

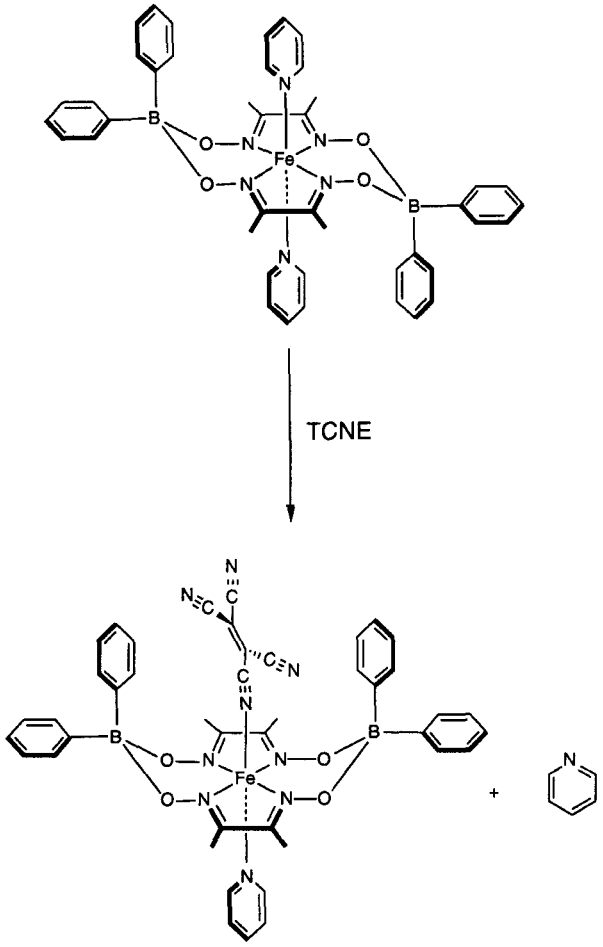
Figure 1. Illustration of first and second sphere coordination to a metal ion. (*a*) General concept as previously described (32). (*b*) Host–guest complex in which guest is bound by both first- and second-coordination sphere interactions. (*c*) Complex in which guest is bound by only second coordination sphere interactions.

forms on which to study these weak forces. Indeed, such interactions can play a role in determining chemo- and stereoselectivity in synthetic chemistry (41). This area has been reviewed (41, 42), so this chapter will focus on studies in which selective organic molecule complexation was observed, either with purely lipophilic interactions or with cooperative inner-sphere binding to the metal in combination with lipophilic host–guest interactions. A physical organic chemistry study of stacking and ionic contributions to ligand–metalloporphyrin complexes has been reported (43).

A. Guest Binding with Both First and Second Sphere Coordination

1. Clefts

A series of host–guest chemisty studies using a conformationally flexible macrocyclic receptor, bis[(dimethylglyoximato)diphenylborato]iron(II) [Fe-$(dmgBPh_2)_2$, where dmg = dimethylglyoximato, Scheme 1], has been reported (44, 45). Amines and nitriles form complexes with the receptor by coordination to one of two available metal sites in the octahedral Fe(II) complex. The relative



Scheme 1. Ligand exchange of tetracyanoethylene (TCNE) for pyridine in a conformationally flexible macrocyclic receptor, $Fe(dmgBPh_2)_2$ (44).

stability of various complexes was found to be strongly influenced by repulsive or attractive $\pi-\pi$ interactions. Study of a series of nitrile guests showed that electron-deficient guests were strongly preferred; a range of 10^6 in association constants was observed. A listing of free energies of formation for [Fe(dmgX)$_2$LT] (X = BPh_2 or BF_2) appears in Table I. The values in the table

TABLE I
$\Delta\Delta G_{298}$ for [Fe(dmgX)$_2$LT] in CH_2Cl_2 (kcal/mol)[a]

		$-\Delta G$[c]		
L	T[b]	X = BF_2	X = BPh_2	$\Delta\Delta G$
2-MeIm	2-MeIm	5.73	1.95	3.8
py	py	9.07	6.38	2.7
py	PhCN	6.02	4.06	2.0
py	2-CNpy	(6.1)	4.52	1.6
t-$BuNH_2$	*t*-$BuNH_2$	3.6	1.96	1.6
PhCN	PhCN	0.56	−0.68	1.2
MeCN	2-MeIm	4.37	3.30	1.1
py	9-CNanth	6.2	5.1	1.1
py	$BuNH_2$	12.1	11.2	0.9
i-$PrNH_2$	*i*-$PrNH_2$	10.30	9.65	0.6
MeCN	*t*-$BuNH_2$	2.4	1.90	0.5
MeCN	$BuNH_2$	8.05	7.64	0.4
$BuNH_2$	$BuNH_2$	14.46	7.64	0.4
MeCN	*i*-$PrNH_2$	5.86	5.45	0.4
MeCN	py	5.8	5.56	0.2
py	3,4-DNB	(6.1)	6.0	0.1
MeCN	MeCN	0	0	0
py	3,5-DNB	(6.1)	6.3	−0.2
py	CO	12.6	12.9	−0.3
py	H_2DDQ	(6.1)	7.3	−0.3
py	PT	6.1	7.0	−0.8
py	2-CNpyMe$^+$	(6.1)	7.47	−1.4
py	$MePz^+$	7.7	9.57	−1.9
py	4-NPT	6.1	8.2	−2.1
TCNE	TCNE	2.7	5.0	−2.3
py	TNFM	(6.1)	8.6	−2.5
MeCN	TCNE	1.6	5.3	−3.7
py	DDQ	7.1	10.9	−3.8
py	TCNE	7.9	12.5	−4.6

[a]See (44).

[b]Benzonitrile = PhCN; dinitrobenzonitrile = DNB; phthalonitrile = PT; 2,3-dichloro-5,6-dicyano-1,4-benzoquinone = DDQ; 2,3-dichloro-5,6-dicyano-1,4-dihydroxybenzene = H_2DDQ; (2,4,7-trinitrofluorenylidene)malononitrile = TNFM; methylpyrazinium = $MePz^+$; tetracyanoethylene = TCNE; 2-cyanopyridine = 2-CNpy; 2-cyanomethylpyridinium = 2-CNpyMe$^+$; 9-cyanoanthracene = 9-CNanth; imidazole = IM; pyridine = py.

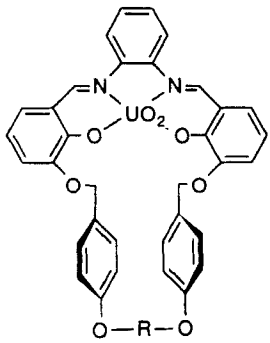
[c]Values in parentheses were not measured but are assumed similar to those for PT.

were obtained via a thermodynamic cycle using equilibrium data for ligand-exchange reactions, and assigning $\Delta G = 0$ for the complexes, where L = T = MeCN. A difference in free energy of binding of 7.3 kcal mol^{-1} was observed for the exchange of pyridine for TCNE, which is accompanied by a conformational change in the coordination complex (Scheme 1). This energy results from the combination of 2.7 kcal mol^{-1} of repulsive energy between the pyridine and phenyl substituents and -4.6 kcal mol^{-1} for attraction between the highly electron-deficient TCNE and the electron-rich phenyl group (46). Amine guests also bound to the hosts, but with a different geometry of coordination to the electrophilic metal sites, resulting in lower complementarity to the cleft of the host. Amine binding constants were therefore differentiated mainly by the presence or absence of repulsive steric interactions.

Recent flash photolysis studies provided interesting kinetic data on the [Fe(dmgBR$_2$)$_2$RR'] system (47). For example, the complex [Fe(dmgBPh$_2$)$_2$(py)(TCNE)] was found to be much more inert to dissociation than the complex [Fe(dmgBF$_2$)$_2$(py)(TCNE)]. This result was attributed to the Coulombic attraction occurring between the bound TCNE and the peripheral phenyl groups of the former complex. It was noted that the kinetic off-rate (expressed in terms of free energy of activation) is the best measure of the metal–ligand bond energy, which takes into account all effects that accompany coordinate bond dissociation, including the phenyl group/TCNE Coulombic attraction. Thus, the situation arises in which the Fe—N bond length may be similar in the two complexes [Fe(dmgBPh$_2$)$_2$(py)(TCNE)] and [Fe(dmgBF$_2$)$_2$(py)(TCNE)], but the bond dissociation energy is quite different (47). On-rate effects produced by sterically bulky groups such as phenyl were compared with those for hemoproteins and superstructured hemes.

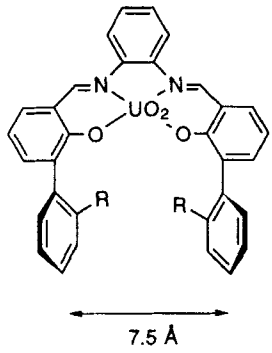
Reinhoudt and co-workers have been exceptionally active in host–guest chemistry studies of metalloclefts (48, 49) and metallomacrocycles (50). Metalloclefts such as **1** and **2** are derived from a salen complex of uranyl ion (UO_2^{2+}) (51). The uranyl moiety prefers a pentagonal-bipyramidal coordination with the two oxygens at the apical positions and with equatorial sites occupied by the salen/salophen moiety, leaving an available equatorial Lewis acidic coordination site. The appended aromatic substituents form a cleft with walls positioned for π–π interactions with bound guests. Thus, guests such as substituted pyridines are bound that can both coordinate to the metal and favorably interact with the aromatic walls of the cleft. Polarography in acetonitrile with TEAP (Et_4NClO_4) as the supporting electrolyte was used to measure the stability constants of host–guest complexes. The results obtained by this method were corroborated by a ^{1}H NMR titration of benzylamine with compound **1** (R = $CH_2CH_2OCH_2CH_2$). Binding constants for the other host–guest complexes could not be obtained by ^{1}H NMR due to overlapping signals and other practical limitations. The guests studied included pyridines, pyridine *N*-oxide, isoqui-

noline, benzylamine, and benzamide; free energies of complexation up to more than 6.3 kcal mol^{-1} were observed. Less basic or more hindered amines such as aniline and 2,6-dimethylpyridine gave complexes of low stability. In some cases, the polarographic data indicated that the interaction between the guest and the uranyl was unfavorable but a complex was still formed due to the π–π stacking driving force. A relative increase in binding free energy of approximately 1.5–2.2 kcal mol^{-1} specifically due to the π–π stacking contribution was observed. Host **1** gave the best overall binding, possibly due to an optimal distance between the aromatic rings of the host (6.8–6.9 Å as suggested by molecular modeling). Partially refined X-ray crystallographic data were obtained for the complex of **2** (R = OMe) with *p*-(*tert*-butyl)pyridine which were consistent with the proposed structure of the complexes. Molecular mechanics calculations also supported the proposed structures of the complexes (51).



O-R-O = $O(CH_2)_{3\text{-}4}O$
$O(CH_2CH_2O)_2$

1

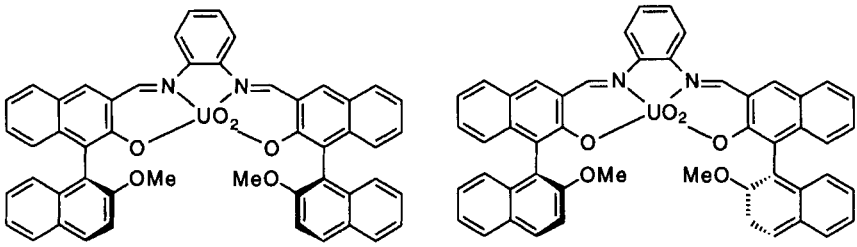


R = H, OMe

2

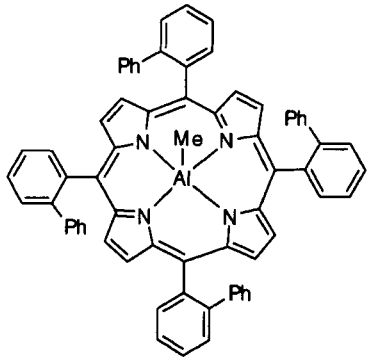
This approach has been extended to potentially chiral systems. Diastereomers of Compound **3** were prepared, affording both meso- and racemic stereoisomers (52). The compounds form stable complexes with pyridine, quinoline, isoquinoline, and 1-naphthalenemethanamine. A $\Delta\Delta G°$ of -2.4 kcal mol^{-1} was observed for meso-**3**•isoquinoline versus racemic-**3**•isoquinoline. The direction and magnitude of the difference was consistent with steric complementarity as suggested by molecular mechanics modeling studies.

A study of the conformational behavior of a metalloporphyrin provided interesting data on lipophilic host–guest interactions. Rates of isomerization of



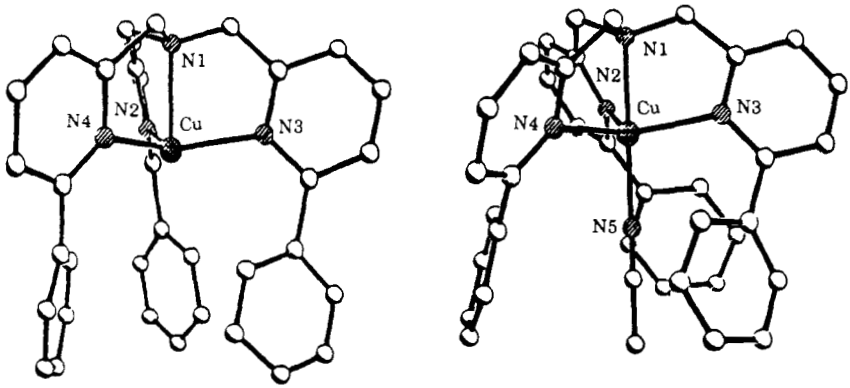
meso-3 and racemic-3

methyl [α^4-5,10,15,20-tetrakis(2'-phenylphenyl)porphyrinato]aluminum (**4**) atropisomers and related compounds were interpreted as a consequence of favorable CH–π interactions between the methyl and phenyl substituents (53). The ligand tended to adopt a conformation such that the methyl substituent could come into close contact with the π electrons from a maximum number of phenyl substituents.



4

The synthesis and characterization of the ligand, tris(6-phenyl-2-pyridylmethyl)amine (TPPA) and some of its copper complexes were described (54, 55). The complexes [Cu^{I}(TPPA)]BPh_4 (**5**) and [Cu^{II}(TPPA)MeCN)]$(ClO_4)_2$ (**6**) (Fig. 2) were prepared and their X-ray crystal structures and redox potentials were determined. Contacts were observed between the bound MeCN and the phenyl substituents in the Cu(II) complex **6** that were considerably shorter than the sum of the van der Waals radii; the observed distances were close to those previously reported for stacked aromatic rings engaged in favorable π–π interactions (56). Figure 3 shows that in the Cu(I) complex **5,** two phenyl rings stack in a "T" configuration as observed in solid benzene and protein aromatic side chains (35). The space-filling models indicate that the Cu(I) is completely



5 **6**

Figure 2. X-ray structures of $[Cu^{I}(TPPA)]BPh_4$ (**5**) and $[Cu^{II}(TPPA)(MeCN)](ClO_4)_2$ (**6**). [Adapted from (54).]

encapsulated by the TPPA ligand. In **6**, the ligand contains a cavity in which a MeCN solvent molecule is bound [Fig. 3(*c*)]. To create the cavity, the ligand undergoes a helical "twist." The average angle between the best axis of the 6-phenylpyridine "arms" and the Cu—N1 bond in **5** is 14.8°; in **6** it is 36.6°. These angles are achieved solely by rotation about the 2-pyridyl—CH_2 bond. Thus, the conformational change in the ligand that would be required to create the cavity for the MeCN in **6** resembles the motion of a flower undergoing anthesis. Recently, conformational control of the direction of the helical twist in related coordination complexes was reported (57). A single asymmetric center in one arm of the tripod biases the molecule to adopt a helical twist in a single direction.

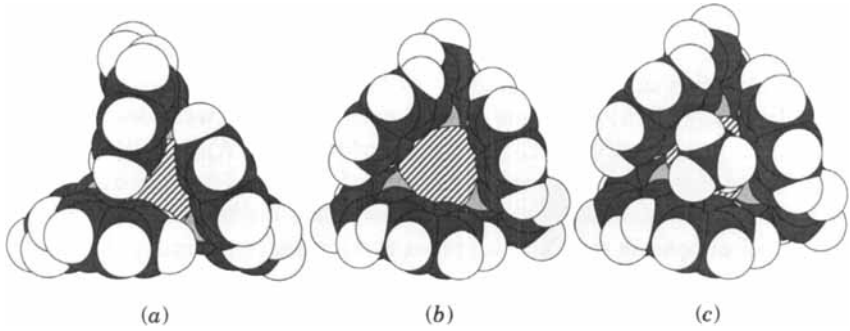
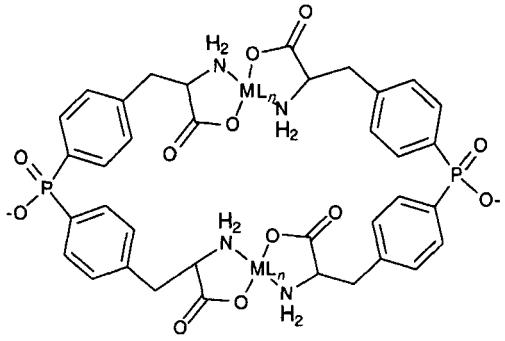


Figure 3. Space-filling models generated from X-ray coordinates of compounds listed in Fig. 2: (*a*) Compound 5; (*b*) Compound **6** with MeCN guest omitted to emphasize positional change of phenyl substituents compared to **5**; (*c*) compound **6**. [Adapted from (54)]

2. *Macrocycles*

Schwabacher et al. (58) reported metal-assembled metallomacrocycles that bind aromatic substrates in aqueous solution. Compound **7** typifies the approach in which a metal ion orients two or more phenyl substituents so that the surface forms a hydrophobic cavity. Compound **7** transported aromatic hydrocarbons through an aqueous membrane; the rate of transport depended on the metal ion used. Nickel(II) or cobalt(II) complexes of the host displayed cooperative binding of naphthalene and tryptophan derivatives that both fill the hydrophobic cavity and coordinate to the metal (59). Dissociation constants were determined by ^{1}H NMR titration methods for 16 guests; strong correlations with host–guest electronic and geometric complementarity were observed. In the case of a difunctional guest A—B (e.g., 3-indolylpropionate, **8**), the "effective molarity" (EM = K_aK_b/K_{ab}) represents the increased binding efficiency gained from concomitant binding at both sites of the host compared with simple binding of monofunctional guests A (**9a**) or B (**9b**). The EM for ditopic binding of 3-indolylpropionate to **7** assembled with Co^{2+} was found to be 17 *M*. This relatively significant EM was observed in spite of the electrostatic repulsion between the anionic host and guest.



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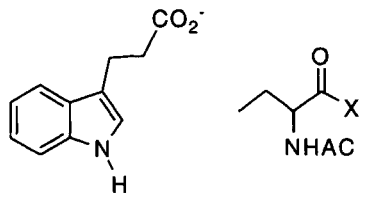
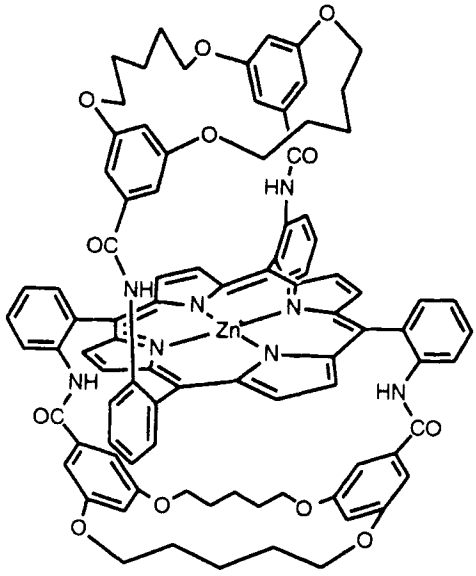


8 **9a** X = NH_2
9b X = OH

One interesting system (**10**) was reported by Imai et al. (60, 61) that showed selectivity for alkyl amines that coordinate and fill a lipophilic cavity formed by the macrobicyclic structure. Comparative binding studies in the organic solvents toluene and chloroform showed that amine guests that are complementary to the hydrophobic cavity of **10** formed complexes that were stabilized compared to porphyrins lacking hydrophobic cavities (61, 62). The selectivity was defined as shown in Eq. 1, where P_x represents a porphyrin host and L_x refers to an amine guest. By defining the selectivity in this way (as a ratio of ratios), differences in substrate binding due to the pK_a of L are canceled, as is the influence of solvation of the binding sites or ligation of water (61). The parameter K_{recog} was 20-fold for the binding of azetidine **11** [referenced to butylamine



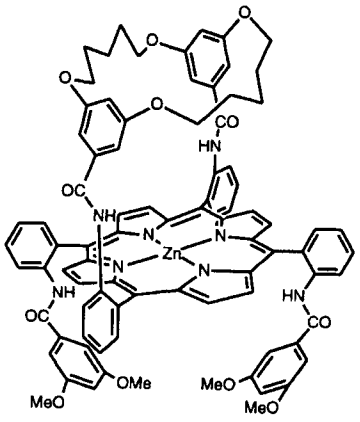
10

11

and tetrakis(*p*-methylphenyl)porphyrinatozinc], which is reasonably large to be observed in nonpolar solvents. The selectivity was attributed to CH–π interactions (63).

$$K_{recog} = \left[\frac{K(P_1L_1)/K(P_1L_2)}{K(P_2L_1)/K(P_2L_2)}\right] \quad (1)$$

Similar studies with compounds **12** and **13** showed that the selectivity disappeared (60); this result was attributed to the lower degree of preorganization of the host.



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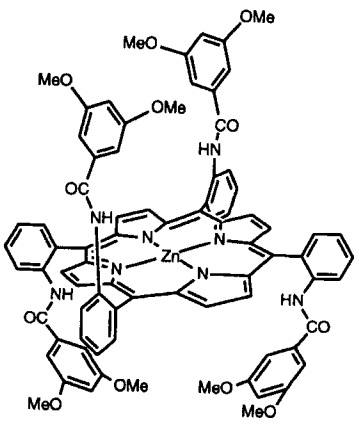
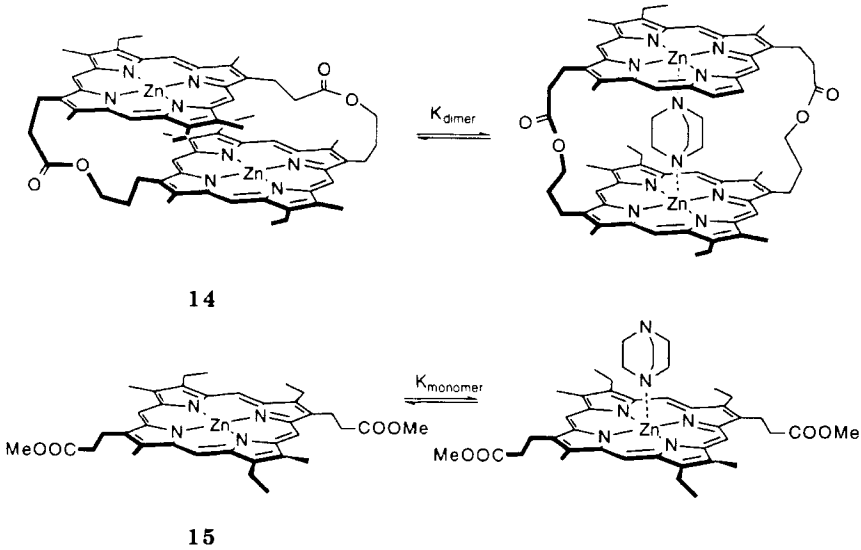


13

The study by Imai and Kyuno (62) included careful control experiments, and brings up a general point that should be emphasized. A problem with hosts that bind guests by simultaneous metal ion coordination and weak physical forces is that one must be very careful in comparing binding affinities to take into account differences in metal ion coordination. Because the metal ion ligation is often the largest driving force, small changes in metal–ligand binding (e.g., due to inductive effects on nucleophilicity or electrophilicity of the guest) can be as large or larger than the entire effect ascribable to π stacking or other weak interactions. Thus, the selection of valid control experiments is critical to any study in this field.

It should be noted that selectivity for the binding of metal-coordinated guests via nonpolar interactions was previously noted in metalloporphyrin studies such as those with ruthenium picnic-basket porphyrins (64, 65). The selectivity was attributed to solvation (66) as well as to dipolar effects (67).

An interesting study of dimeric zinc porphyrin molecules provided insight into the thermodynamics of π–π interactions (36). The porphyrin dimer host (**14**) shown in Scheme 2 was originally designed as an artificial enzyme. The host was found to bind difunctional bases such as 1,4-diazabicyclooctane (DABCO) by ligation to two zinc ions. In the absence of guest, however, the host collapses due to strong π–π interactions between the faces of the two zinc porphyrins. Advantage was taken of this situation to determine the thermodynamics of this interaction. The intrinsic binding energy of the zinc–ligand interaction was determined using the zinc porphyrin monomer **15** shown in Scheme 2. The data from the two experiments was used to determine the π–π interaction to be 48 $\pm$ 10 kJ mol^{-1} (68, 69). These and related studies have been reviewed



Scheme 2. (*a*) A macrocyclic porphyrin dimer forms a cavity for binding a bifunctional ligand, breaking $\pi-\pi$ interactions in the process. (*b*) The control experiment used to determine the intrinsic binding energy associated with the zinc–ligand interaction (36).

(36, 56). Expansion of the distance between the porphyrin rings led to several interesting coordination chemistry studies (70–74), but these are beyond the scope of this chapter.

3. Bowls

A number of metallohosts have been studied in which a cyclodextrin forms part of the receptor site. The α-, β-, and γ-cyclodextrins are six-, seven-, and eight-membered α-1,4-linked cyclic oligomers of D-glucopyranose. The structure of β-cyclodextrin is shown in Fig. 4. The compounds present a toroidal shape containing a hydrophobic cavity, the size of which increases with the number of monomer units (75). Cyclodextrins and their derivatives have been widely studied for their complexation and selective catalysis properties (76–79). In many of the reported cyclodextrin-coordination complex conjugates, the metal ion has been appended primarily to generate a functional host whose substrate selectivity would be determined primarily by the binding properties of the cyclodextrin moiety (80–84). For example, several studies of electron transfer between guests bound in cyclodextrin cavities and metal ions appended to the periphery of the cyclodextrin have provided information on the mechanism of energy and electron transfer in molecular assemblies (85, 86).

Several years ago, Tabushi (87) studied cyclodextrin–polyamine conjugates

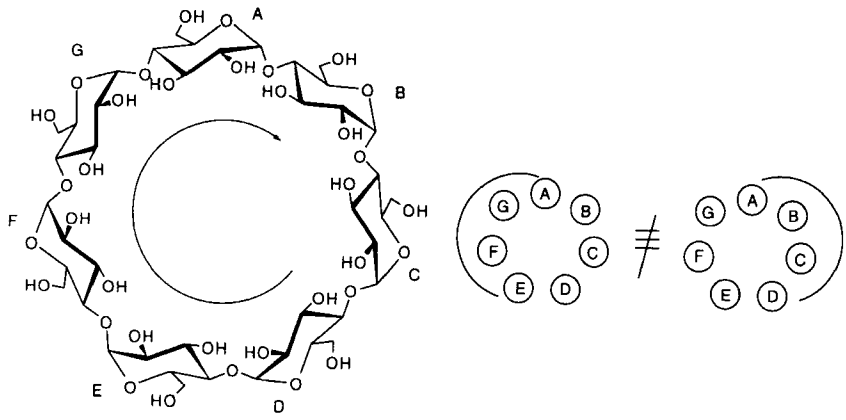
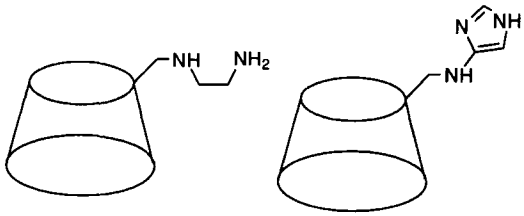


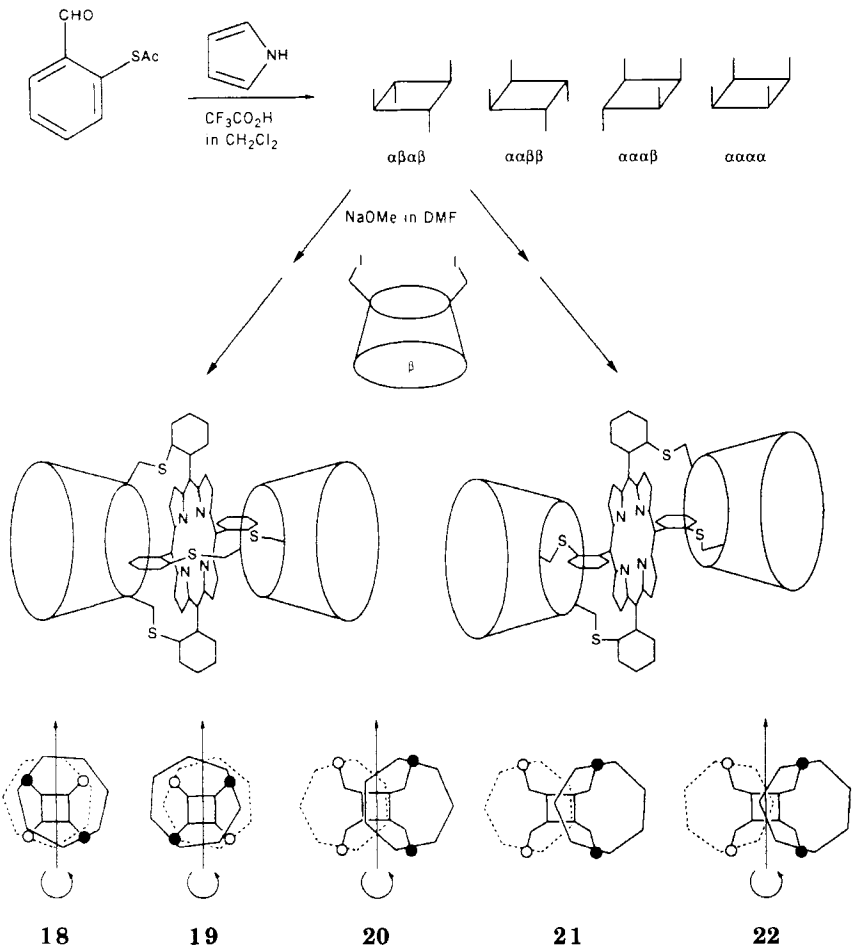
Figure 4. Directionality of β-cyclodextrin double attachments.

(e.g., **16**) as hosts for anionic substrates, observing significant enhancement of stability constants when the modified cyclodextrin, Zn(II) ion, and guest were all present. Absence of any one component resulted in significantly reduced binding. A recently reported extension of this work determined the thermodynamic parameters associated with amino acid binding to a Cu(II) complex of histamine monofunctionalized β-cyclodextrin **17** (88). The data indicated weak differences in binding between the enantiomers of amino acids; nevertheless, high-performance liquid chromatography (HPLC) separation of the enantiomers was achieved (Phe, Trp, and Tyr) using an achiral C_{18} column by adding the complex to the eluent.



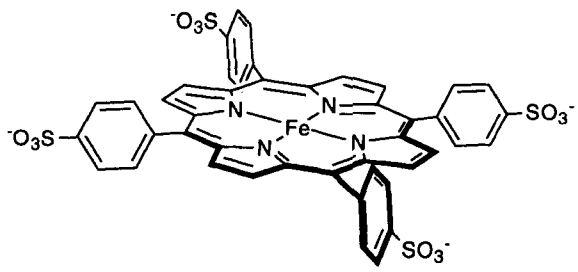
16 **17**

A porphyrin has been synthesized that is covalently sandwiched between two cyclodextrin molecules (89, 90). As shown in Scheme 3, the compound may be formed as any of a number of stereochemical isomers. Two of four atropisomers ($\alpha\beta\alpha\beta$ and $\alpha\alpha\beta\beta$) of a tetra(thiophenyl)porphyrin react with A,D-diiodo-β-cyclodextrin to form two sets of isomers. One set possesses cyclodextrins attached to diagonal thiophenyl substituents (**18** and **19** in Scheme 3)



Scheme 3. Synthesis and stereoisomers of cyclodextrin-sandwiched porphyrins (89).

and another set has the cyclodextrins attached to adjacent thiophenyl substituents (**20, 21,** and **22** in Scheme 3). The additional level of isomerism (e.g., **18** vs. **19**) results from the stereochemical properties of the A,D-disubstituted-β-cyclodextrin, pictured in Fig. 4. The Fe(III) and Zn(II) metalated porphyrins formed mixed complexes with benzylmercaptan and adamantanecarboxylate (89). It was subsequently shown that a mixture of compounds **18** and **19** facilitated oxygen-atom transfer from iodosobenzene to certain olefins. The yield of epoxide formed from cyclohexene was enhanced relative to reaction with por-



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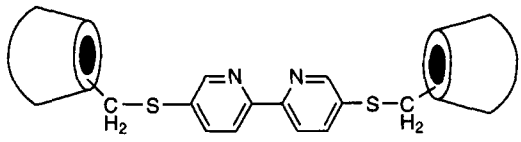
phyrin (**23**) and compared to olefins that would be expected to be less complementary to the cyclodextrin cavities. It was postulated that the better yield for reaction with **18/19** was due to effective binding of the alkenes in the cyclodextrin cavities, or alternatively, that the oxene reactive intermediate generated in aqueous media is stabilized by the bulky and hydrophobic cyclodextrin groups. In a direct competition experiment, cyclohexene was found to react five times faster than 2,3-dimethylbut-2-ene, whereas the inherent reactivity was seven times lower, as determined for reaction with **23** (91).

Host–guest and catalytic studies have been carried out with dimers of cyclodextrins (92). Very stable complexes are formed with substrates that can simultaneously bind to both binding sites. Binding constants as large as 10^{11} M^{-1} have been observed, more than the square of those observed for typical monocyclodextrin/substrate complexes ($\sim 10^4$ M^{-1}) (93). While part of the extra binding strength in the dimeric host–guest complexes might be expected to derive from entropic driving forces, calorimetric measurements show the binding to be entropically disfavored compared to the monomeric systems, apparently due to the flexibility of the systems and solvation changes that can lead to entropy–enthalpy compensation (94). Cyclodextrin dimers containing ligands for metal ions between them (e.g., **24**) have been studied. A metal ion such as Zn^{2+}, Cu^{2+}, or Ni^{2+} binds to the bipyridyl unit and catalyzes the hydrolysis of esters that bind to the two cyclodextrin units. In a solution containing **24** and Cu^{2+}, the substrate **25** was hydrolyzed 2.2 m $\times$ 10^5 times faster than uncatalyzed hydrolysis at pH 7.0 and 37°C (95). Hydrolysis of the same substrate in



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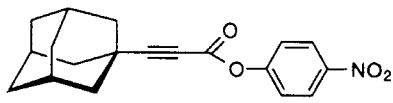
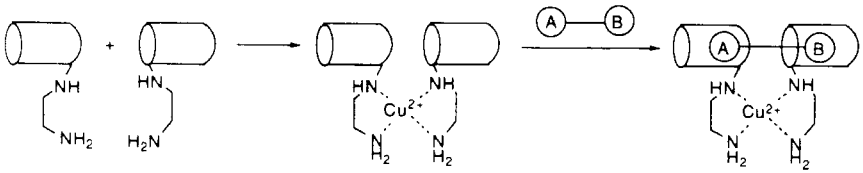


25

the presence of **24,** Cu^{2+} and pyridine-2-carboxaldoxime gives a rate acceleration of 1.7×10^6 over the background rate at pH 7.0 (96). Besides excellent rate enhancement and specificity, this system also showed significant turnover, thus displaying several properties of natural enzymes. More recently, compound **24** was shown to facilitate the hydrolysis of bis(*p*-nitrophenyl)phosphate and methyl bis(*p*-nitrophenyl)phosphate in the presence of La^{3+} and H_2O_2 (96).

A pertinent cyclodextrin dimer study was reported in which 6-(2-aminoethyl)amino-6-deoxy-β-cyclodextrin **26** was prepared (Fig. 5) (97). The compound forms a 2 : 1 complex with Cu^{2+}, forming a metal-assembled cyclodextrin dimer **28.** The dimeric material showed enhanced binding of substrates large enough to bind to both cyclodextrin cavities. Catalytic rates of ester hydrolysis were also measured. The relatively low binding and catalytic rate enhancements for the metal-assembled compound were rationalized as due to nonideal geometry between the assembled host and the guest.

A number of recent studies reported metal ion complexation by calixarenes and related compounds (98–102). An interesting crystallographic structure was reported of an oxomolybdenum(VI) calix[4]arene in which a nitrobenzene was included in the cavity formed by the metallocalixarene associated in clam-shell fashion with a free calixarene (Fig. 6) (103). Mononuclear W(VI) complexes of calix[4]arenes have also been studied. The oxotungsten complex shown in Fig. 7(*a*) presents an electrophilic metal coordination site (trans to the oxo group) to potential guests (e.g., acetate) that coordinate within the cavity. The *cis*-dichlorotungsten complex shown in Fig. 7(*b*) displays a distorted cavity, since the four-coordinated calixarene oxygen atoms are no longer defined by an equatorial plane (104). Recently, oxotungsten calix[4]arenes **29** and **30** were shown to form a new type of columnar liquid crystal (Scheme 4). The mesomorphic



26 **27** **28**

Figure 5. A metal-assembled cyclodextrin dimer (97).

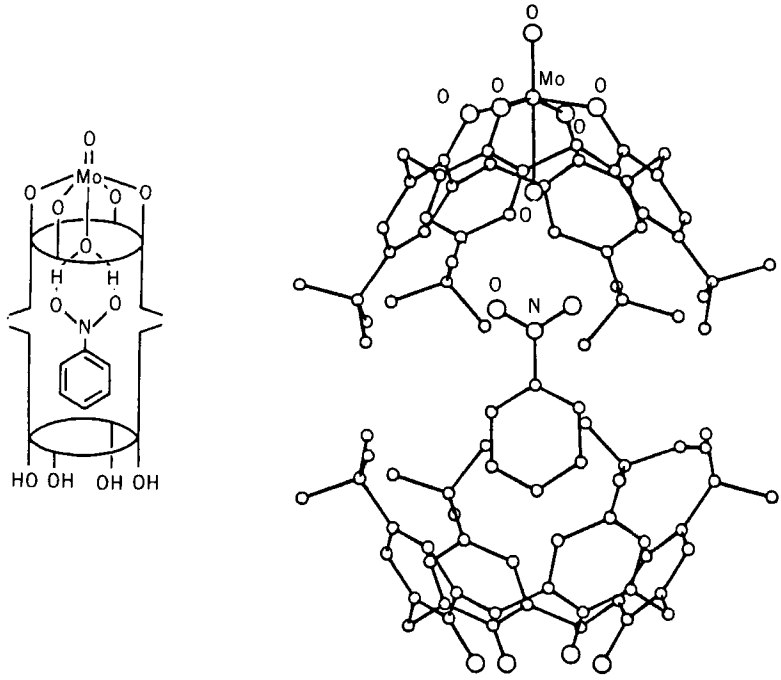
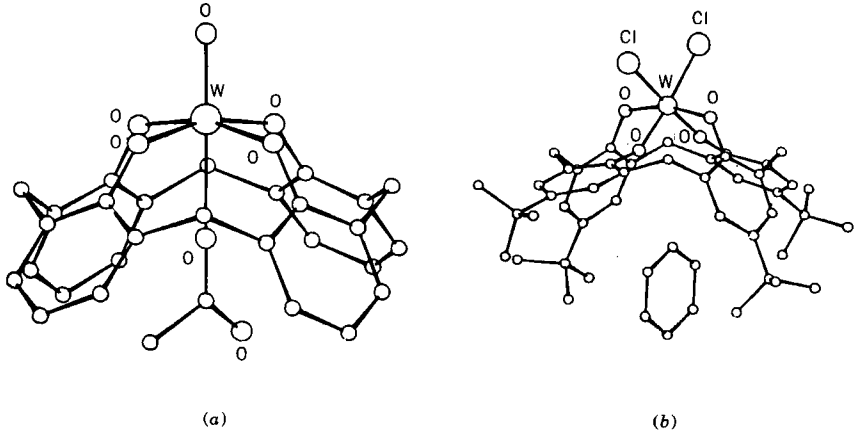
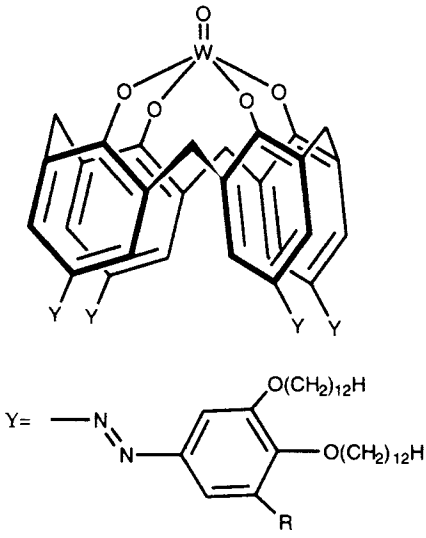


Figure 6. A sandwich complex of a nitrobenzene between an oxomolybdenum(VI) calix[4]arene and calix[4]arene. [Adapted from (103).]



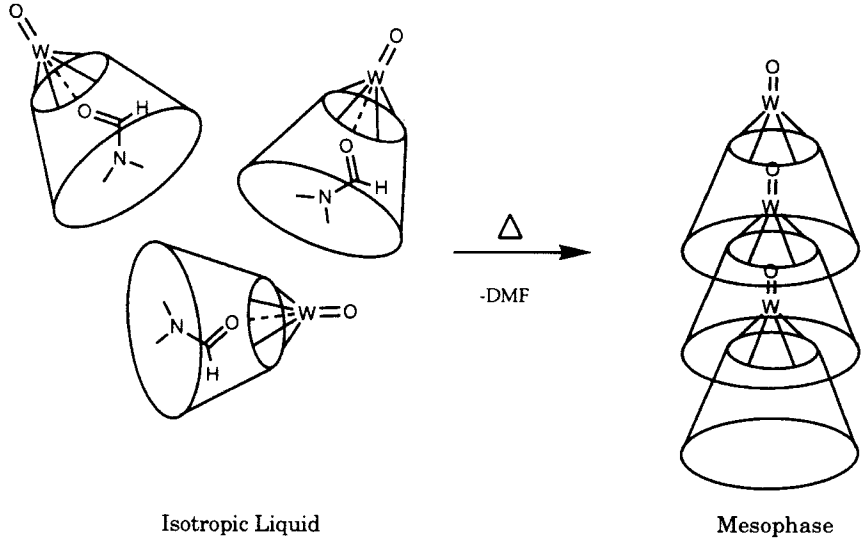
(*a*) (*b*)

Figure 7. Tungsten complexes of calix[4]arenes. [Adapted from (104).]



29 R = H

30 R = $O(CH_2)_{12}H$



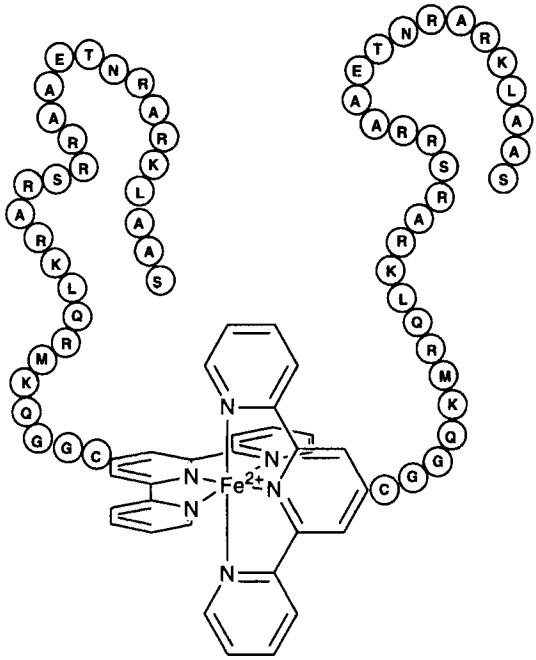
Scheme 4. Guest-dependent isotropic-mesophase transition in tungsten-oxo calix[4]arenes (105).

behavior of the complexes was observed to depend strongly on the presence and character of Lewis base guests such as DMF or pyridine (105).

A. Guest Binding With Second Sphere Coordination Only

1. Clefts

Coordination complexes may also be used in the architectural control of biomolecular structure (106). The metallopeptide $[G_{29}T_s]_2Fe$ (**31**) consists of two strands of DNA recognition peptide of the yeast bZIP protein GCN4. The peptides were attached via the C-terminus to terpyridyl moieties. The binding properties of the 2 : 1 coordination complex with Fe(II) differed from the yeast protein in that it selectively recognized one target site over another when there was only one base pair difference between the two sites. Analysis indicated that this discrimination was a result of the sterically demanding scaffold inducing changes to the peptide strand's ability to bind with particular areas of the DNA surface. The overall host–guest assembly might be pictured as a pair of scissors (**31,** the host) in which the hinge is the iron atom (probably 12 Å away from



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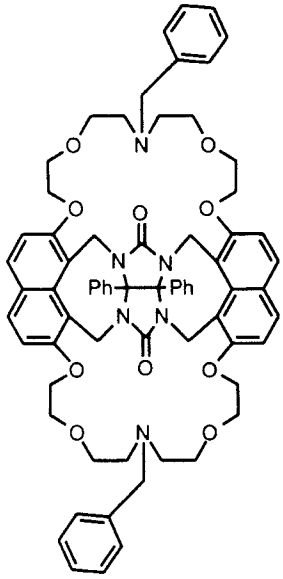
the DNA), while the peptides reach out to form a concave binding site for the DNA (the guest). The geometrical requirements of the coordination complex are therefore propagated down the length of the chain. Other interesting examples of assembling biomolecular structure with coordination complexes (107–112) are beyond the scope of this chapter.

2. *Macrocycles*

Receptor **32,** derived from glycoluril **33** (113) shows cooperative binding of potassium and lipophilic substrates (16). In the absence of a metal ion, the host lacks a preorganized receptor site. Upon addition of K^+, one arm of the host moves into position (Scheme 5), creating a cleft suitable for binding 1,3-dinitrobenzene; the K_a increases by a factor of 2–6, depending on the solvent. The Na^+ binds to **32,** but does not increase the binding of lipophilic substrate since the geometry of $[Na(\mathbf{32})]^+$ is not complementary to the guest.



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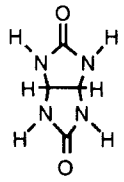

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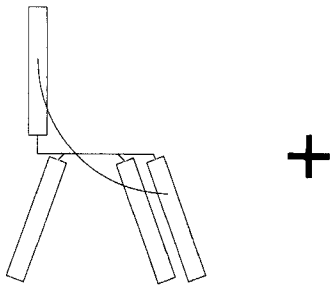
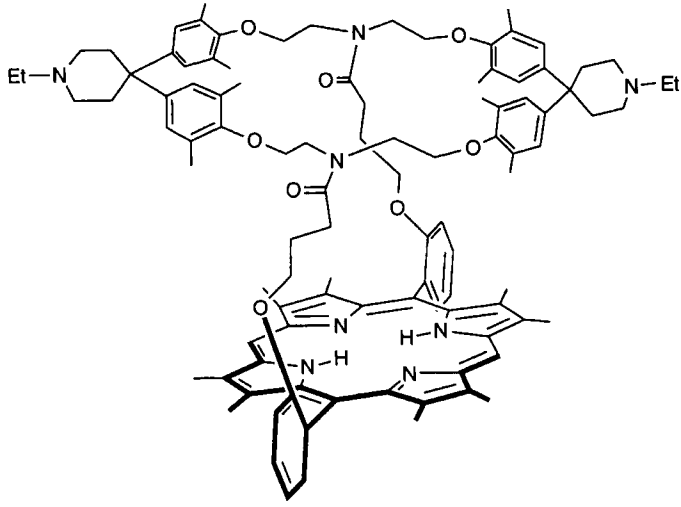
Diederich and co-workers (114) reported an elegant model of the enzyme cytochrome P450. In the model, a cyclophane moiety, known from previous studies (115, 116) to form stable complexes with nonpolar guests, was positioned over the reactive center of a porphyrin unit. Compound **34** was shown to form very stable complexes with phenanthrene (**37**) and acenaphthylene (**38**),



Scheme 5. Induced binding of 1,3-dinitrobenzene by addition of potassium ion (16).

with K_a larger than 10^5 M^{-1} (114). Upon metalation, the Zn(II) and Fe(III) derivatives **35** and **36** were obtained in good yields. Upon treatment of **36** with base, a μ-oxo dimer (**39**) formed. Both **36** and **39** were active as catalysts in the oxidation of acenaphthylene to acenaphthen-1-one (**40**) (with acenaphthylene epoxide as intermediate) using iodosobenzene as the oxidant (117, 118). Phenanthrene was a competitive inhibitor of the reaction due to strong binding in a geometry unsuitable for oxidation.

The transition metal lacunar cyclidenes (**41, 42,** and **43,** Fig. 8) of Busch and co-workers demonstrated lipophilic guest complexation, and were already



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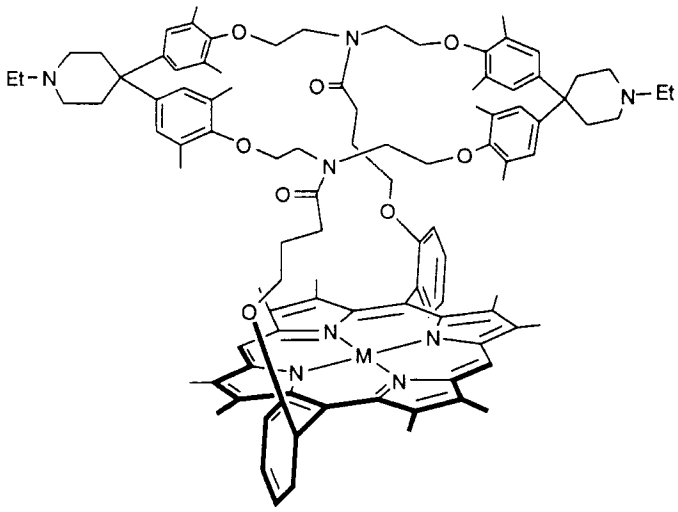
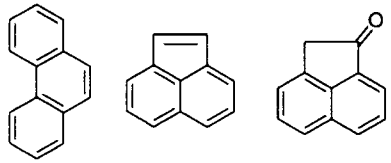


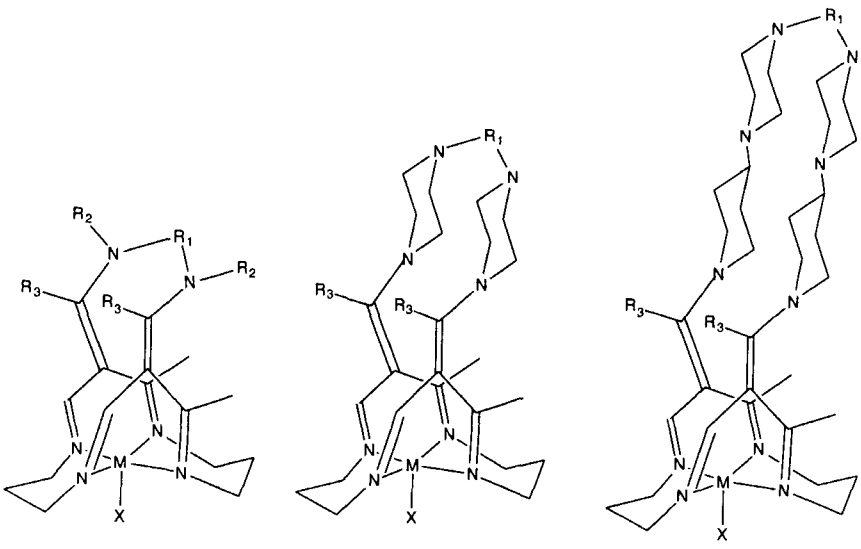
35 M = Zn

36 M = FeBr



37 **38** **40**

reviewed (119–122). The term "cyclidene" refers to the N_4-macrocycle that binds the metal ion, and the term "lacunar" refers to the cavity created by a second macrocyclic bridge built across one face of the cyclidene (123). Like many of the superstructured metalloporphyrins (124), part of the interest in these compounds relates to dioxygen binding and activation (122, 125), but several interesting studies of organic guest binding have been reported. The binding site for an organic guest is formed by the lacunar bridge, which may be varied to tailor the binding site for a particular guest. Binding studies of lipophilic alcohol guests in aqueous media have been reported (126). Relaxation experiments (^{1}H NMR) were used to determine the structure of paramagnetic host–guest complexes in solution (127, 128). Most interestingly, the relaxation method provided evidence for the formation of a ternary complex involving a Co(II) cyclidene host, dioxygen, and n-butanol (129). The experimental studies have been accompanied by molecular mechanics calculations (130). The structure of $[Co(\mathbf{44})(MeIm)(O_2)]^{2+}$ (MeIm = *N*-methylimidazole) is shown in Fig. 9 so that the geometry of the compounds may be appreciated.



41 42 43

Figure 8. Cyclidene ligands with cavities or clefts of various sizes (5).

The cyclidene complexes of iron, manganese, and chromium are competent catalysts for the oxygenation of substrates oxidized by cytochrome P450 and porphyrin-based mimics. Oxidation of organic substrates with hydrogen peroxide in aqueous solution gave results consistent with participation by the hydrophobic cavity in the reaction (123). However, several practical problems

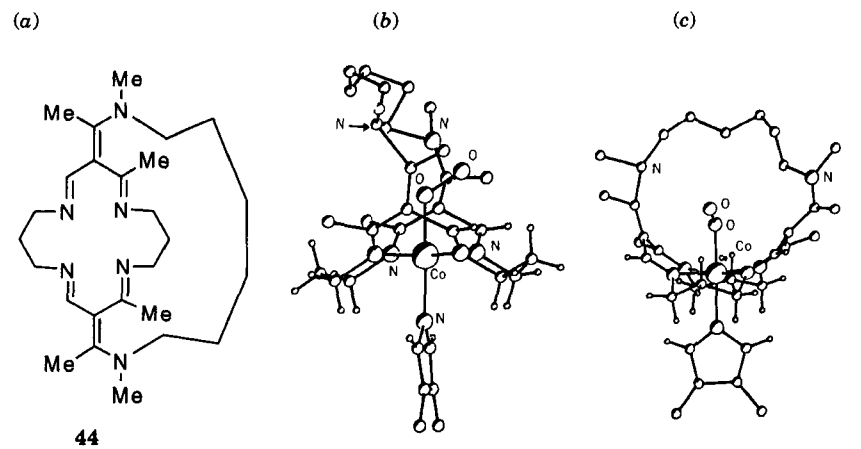


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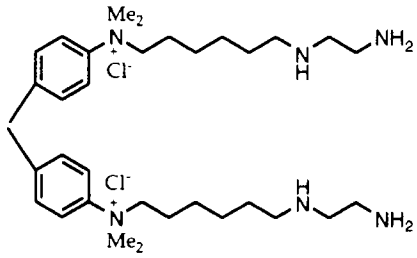
Figure 9. X-ray crystallographic structure of $[Co(\mathbf{44})(MeIm)(O_2)]^{2+}$. (*a*) Diagram of **44**. (*b*) Side view. (*c*) Front view. [Adapted from (125).]

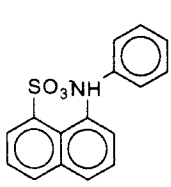
have been encountered in organic substrate oxidations, including oxidation of the host and solubility (123). Cobalt–cyclidene dioxygen adducts also catalyze the oxygenation of 2,6-di-*tert*-butylphenol (123).

One metal-organized lipophilic receptor utilized the Cu^{2+} complex of compound **45**, which contains two ethylenediamine units (17). Upon binding a metal

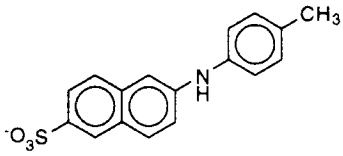


45

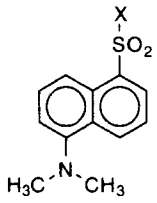
ion (Scheme 6), a lipophilic binding site assembles that is capable of forming a stable complex with naphthalene or dansylamide (**49**). Fluroescent compounds **46–49** are convenient guests for spectroscopic determination of asso-



46 (ANS)

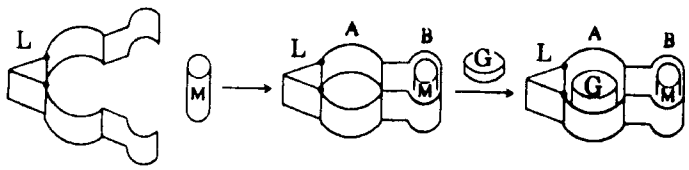


47 (TNS)



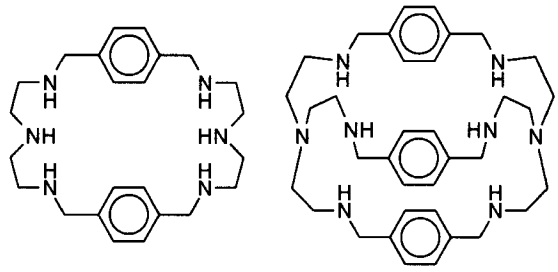
48 (X = OH, DNSA)
49 (X = NH_2, DNS)

ciation constants in water. At least 10- to 100-fold stronger complexation of **45** with the organic guests was observed when the Cu^{2+} ions were present as judged



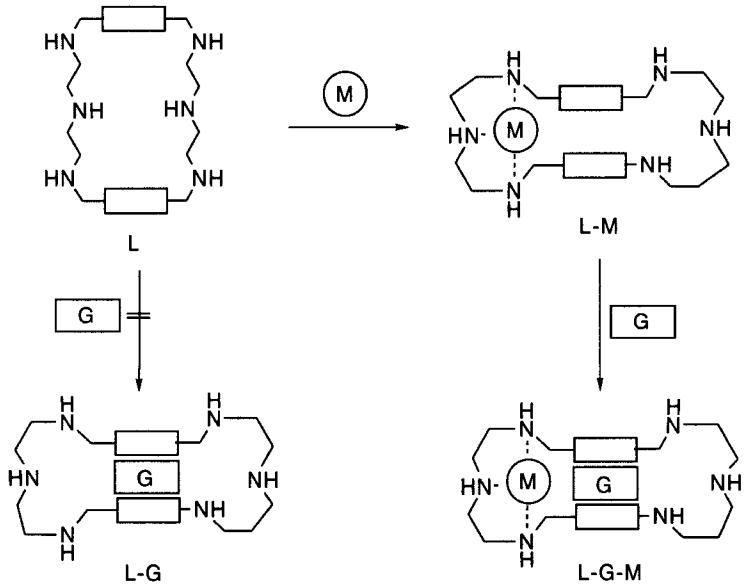
Scheme 6. Schematic outline of the cooperative formation of binding sites by **45**. L = **45**, M = metal ion, A = hydrophobic binding site, B = polar binding site, G = lipophilic guest molecule. [Adapted from (17).]

by NMR and fluorescence measurements. Another study reported the use of a related dinuclear complex for the hydrolysis of complementary *p*-nitrophenyl esters (131). Recently, an example of allosterism was provided by studies of compounds **50** and **51** (132). In this study, the host binds lipophilic guests



50 **51**

poorly in the absence of metal ion; binding of Zn(II) ion preorganizes the lipophilic cavity by reducing and rigidifying the cavity size (Scheme 7) (133). The presence of Zn(II) ions increased the binding of DNSA (dimethylaminonaphthylsulfonic acid, **48**) by a factor of 100 by preorganizing the aromatic rings to form a cavity more complementary to the guest than the cavity present

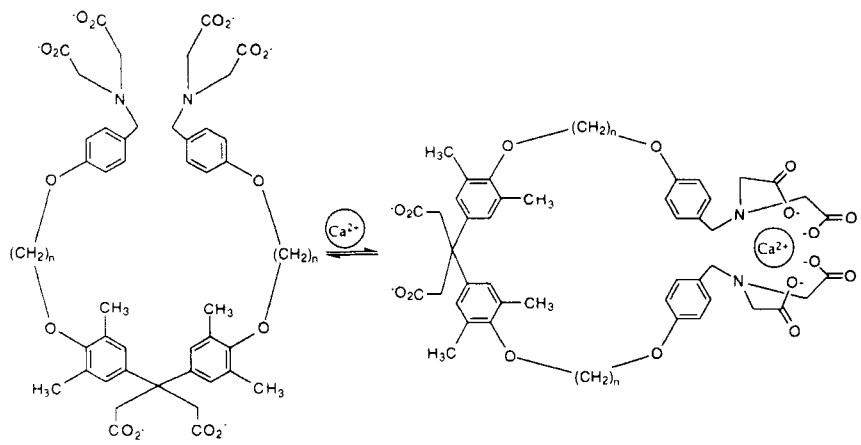


Scheme 7. Allosteric control of a hydrophobic cleft by metal ion binding (133).

in the uncomplexed macrocycle. A possible application of such phenomena lies in the development of high sensitivity fluorescence spectroscopic methods for the determination of the concentration of metal ions, as the fluorescence intensity in the **50/48** system was directly proportional to the Zn(II) concentration in the region 10^{-6} to 10^{-4} *M*.

Scheme 8 shows a Ca^{2+} organized receptor (**52**) that binds TNS (*N*-tolylaminonaphthylsulfonate, **47**) with $K_a = 5.0 \times 10^3\ M^{-1}$, determined by fluorescence titration experiments (134). The concentration of the Ca^{2+} was critical for strong binding: At very low calcium concentration, little fluorescence intensity was observed because the host required preorganization by calcium for binding TNS. At very high calcium concentration, the fluorescence intensity of TNS began to decrease, possibly due to formation of a different mode of calcium binding, such as a bis-calcium complex. Maximal fluorescence intensity was observed with calcium concentration around 10 m*M*.

The self-assembly of cationic, box-like metallomacrocycles was reported recently (135, 136). The compounds possess a receptor site reminiscent of compounds studied extensively by Stoddart (137). Fujita et al. (135) reported that the complex $[(en)Pd(4,4'\text{-bipyridyl})]_4(NO_3)_8$ (**53**) forms a 1 : 1 complex with 1,3,5-trimethoxybenzene ($K_a = 750\ M^{-1}$). A variety of other neutral and anionic substrates were also shown to form complexes with **53** as well as with the Pt(II) analogue in aqueous solution (138). Introduction of longer spacer units between the metal ions resulted in larger cavities and better binding of electron-rich guests, especially when the spacer contained an electron-deficient moiety as in **54** ($K_a = 2500\ M^{-1}$ for 1,3,5-trimethoxy benzene, D_2O) (139). Cage-like



52

Scheme 8. Calcium-organized hydrophobic receptor (n = 3 or 4) (134).