Formation of Artificial Receptors by Metal-Templated Self-Assembly

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Brian Linton was born in western Pennsylvania in 1969. He received a B.A. in music and chemistry from Allegheny College, under the supervision of Martin Serra. Currently he is pursuing his Ph.D. at the University of Pittsburgh, working with Andrew Hamilton on the creation of molecular receptors through rational design and combinatorial synthesis. After completing his degree in the Fall of 1997, he plans to pursue postdoctoral research with Alanna Schepartz at Yale University.

Andrew D. Hamilton is currently Professor and Chair of Chemistry at the University of Pittsburgh. His research interests lie at the interface of organic and biological chemistry with particular focus on the understanding and mimicry of enzyme activity. A central theme of his work is molecular recognition and the development of both synthetic receptors and novel antitumor agents based selective binding to biological receptors, such as Ras farnesyltransferase. He received his undergraduate education at the University of Exeter, U.K. In 1974 he moved to the University of British Columbia where he worked with Professor David Dolphin and then to Cambridge University where he received his Ph.D. in 1980 for work on porphyrin chemistry with Sir Alan Battersby. He was awarded a NATO postdoctoral fellowship which he held at the Université of Louis Pasteur, Strasbourg, under the supervision of Professor Jean-Marie Lehn. In 1981 he was appointed to an Assistant Professorship in Chemistry at Princeton University. He stayed at Princeton until 1988 when he moved to Pittsburgh. In the Fall of 1997 he will move to Yale University to become the Irénée duPont Professor of Chemistry.

I. Introduction

Nature provides many examples of proteins that form their substrate binding sites by bringing together the component pieces in a process of self-assembly. The important aspartate proteinase HIV protease is a homodimer in which half of the enzyme recognition site and one of the two catalytically essential aspartate carboxylate groups comes from each monomer.[1] Self-assembly is driven by the interdigitation of two peptide strands on each subunit and the formation of an extended β-sheet structure between the two halves of the protein (Figure 1).

A related example is seen in the formation of the antigen recognition site in antibodies. The essential structure of the key Fab fragment of all antibodies involves the interaction of two proteins, a light chain and a heavy chain (Figure 2). Each protein is divided into two domains; a constant region with few changes in amino acid sequence among different antibodies, and a variable region with many residue modifications. The heavy chain and light chain are linked by a disulfide bond, and the two constant and variable regions interact with each other through many hydrophobic contacts on two four-stranded β-sheet regions, forcing a close association of the two variable domains. At the end of each variable domain are three hypervariable loops which interact with the antigen and whose variability leads in large measure to the diversity of antibodies. The complementary determining region formed by the six hypervariable loops can change its shape depending on the antigen. For small antigens an enclosed cavity with a solvent exposed area of approximately 300 Å^2 is formed. In the case of protein antigens, a more open and flat recognition site with a larger surface area (>600 Å^2) is created.[2] As a result of this self-assembling combination of monomer units, the immune system is able to generate an immense number of different antibody complementarities. This enormous diversity derives from changes in the length,

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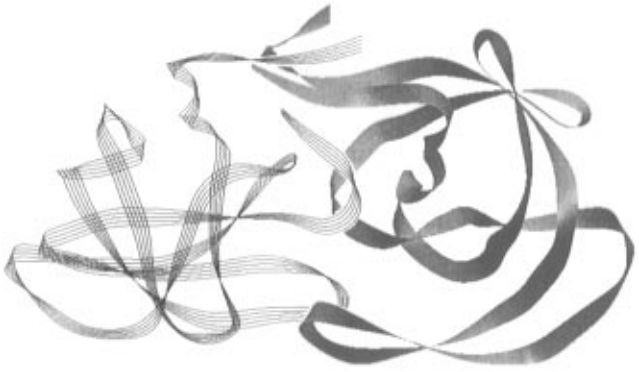


Figure 1. X-ray structure of HIV protease.

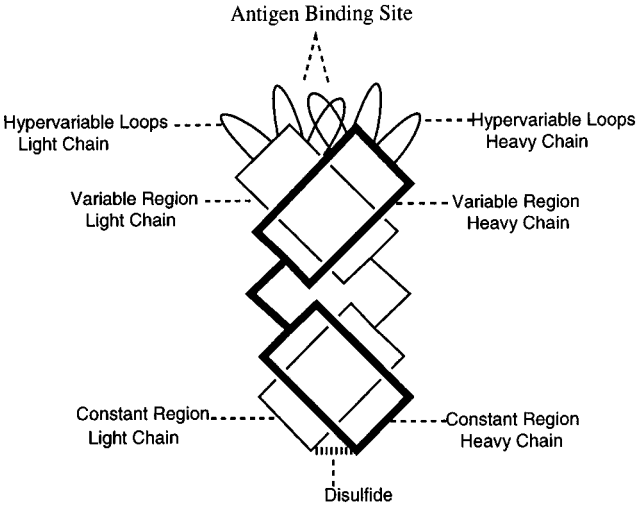
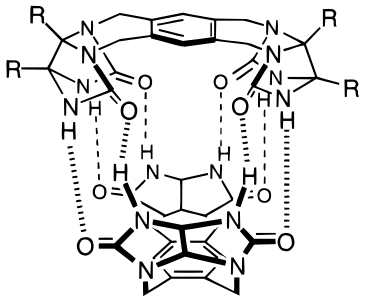


Figure 2. A generalized structure for the Fab fragment of immunoglobulins.

sequence, and conformation of the hypervariable loops as well as the combination of different light and heavy chain partners.

The strategy of receptor site self-assembly is one that has only been exploited in synthetic chemistry in recent years. A range of different approaches can be envisioned for the association of two or more components in the formation of new recognition sites. For example, Rebek has shown that complementary lactam subunits positioned on a concave framework can dimerize to form spherical structures (**1**). These



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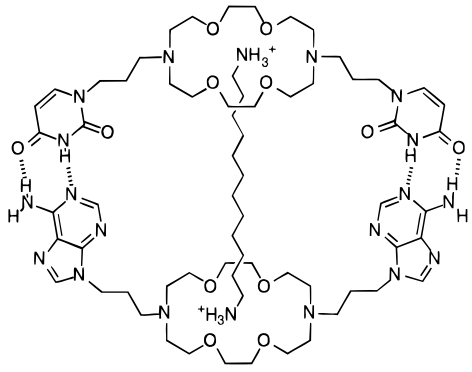
self-assembled cavities have been shown to bind small organic guests in nonpolar solvents.[3] The complementarity between adenine and thymine bases has been exploited by Gokel[4] in the formation of two hydrogen-bonded base pair units linked by crown ethers. The resulting box structure is able to coordinate alkyl bis-ammonium ions inside the self-assembled bis-crown ether cavity (**2**).



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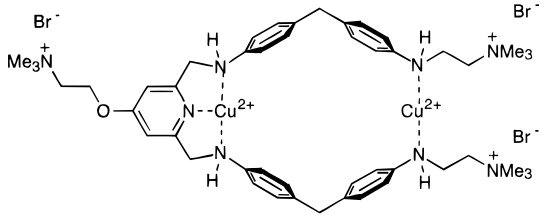
These two examples represent systems where hydrogen bonding is used as the primary interaction to generate the recognition site. Among other approaches, the hydrophobic self-assembly of membranes and monolayers should also be considered. For example, Kunataki[5] has positioned hydrogen-bonding groups on amphiphiles and shown excellent recognition properties for complementary hydrogen-bonding guests at the air−water interface of Langmuir−Blodgett films. However, the primary focus of this paper will be the use of metal ions as the means for self-assembling recognition sites. The paper will be divided into an initial discussion of intramolecular organization of binding sites followed by a consideration of intermolecular assembly based on one, two, and more metal ion centers.

II. Intramolecular Assembly of Recognition Sites by Metal Ion Complexation

The ability of a metal ion to organize a flexible ligand around its coordination sphere has led to the design of several intramolecularly organized recognition sites. This concept is exemplified in Figure 3 where coordination of one part of a molecule to a metal center results in the allosteric organization of a second distant binding site. For example, the flexible bis(aminomethyl)pyridine derivative (**3**), developed by Scrimin, is organized by Cu^{2+} binding to the tridentate binding site. This leads to enhanced



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complexation of a second Cu^{2+} ion at the distal amine site. The resulting bis Cu^{2+} complex shows selective catalysis of the hydrolysis of β-amino acid esters due to the cooperative effect of the two metal ions, a process which is inhibited by α-amino acids.[6] Schneider[7] has developed another allosteric two-binding domain system. This involves a hexaamine molecule that has binding sites for a metal ion and a

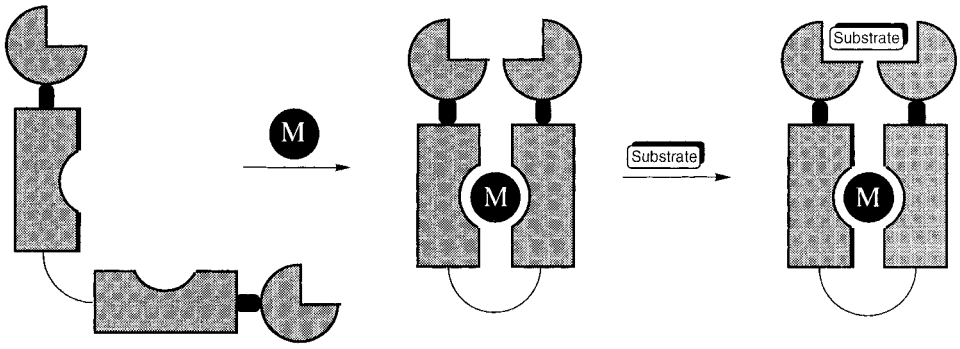


Figure 3. Schematic of intramolecular binding site organization by a metal.

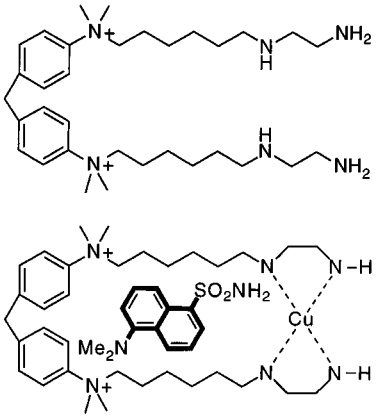
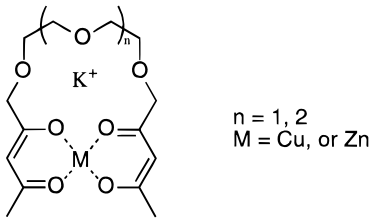


Figure 4. Copper ion preorganization of lipophilic binding site.

lipophilic substrate. Initial binding of copper ions preorganizes the lipophilic binding site and results in a 10−100-fold increase of substrate binding into the lipophilic center (Figure 4).

Strong ligand-to-metal coordination has also been used by Kobuke to close the macrocyclic ring of crown ether derivatives. A flexible bis-acetylacetone derivative forms a 4-coordinate complex with Zn or Cu (as in **4**) and in doing so closes the oligoether



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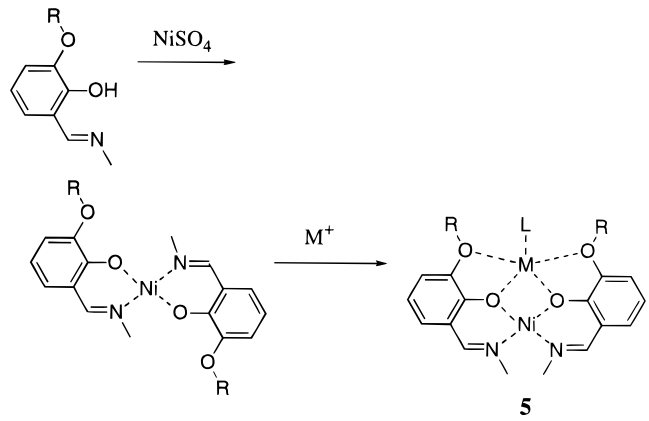
macrocycle. The advantages of the macrocyclic effect in the presence of transition metal ions was seen by selective binding and partition of alkali metal ions into the crown ether-like cavity, with some selectivity being shown for K^+.[8] A related but intermolecular version of this strategy has been reported by Scheppartz[9] who linked polyether chains of different lengths onto salicylaldimine groups. Complexation of the hydroxyimine units by Ni(II) brings two ether substituents into proximity and able to cooperate in the binding of alkali metal ions, as in **5**. Particularly effective transport of alkali metals across a chloroform membrane was seen with cation selectivity depending upon the length of the polyether unit.



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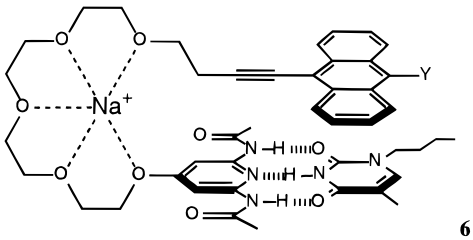
R = CH_3 or $CH_2CH_2OCH_3$

or $CH_2CH_2OCH_2CH_2OCH_3$

In a reverse of these strategies, Shinkai has exploited oligoether complexation of alkali metals to organize multiple binding interactions for a nucleotide substrate.[10] Anthracene and (diacylamino)-pyridine units were positioned at opposite ends of an oligo(ethyleneoxy) chain. Addition of Na^+ ions positioned the two termini to bind in a cooperative manner with an alkyl thymine derivatives by simultaneous hydrogen bonding and π-stacking interaction, as in **6**. A significant increase in the association



6

constant was seen between the salt free (1000 M^{-1}) and sodium containing (7000 M^{-1}) solutions. The metal ion is not a mere spectator in this system as molecules containing only the (diacylamino)pyridine unit showed significant increases in association to thymine on addition of Na^+, suggesting a possible ionic strength effect.

In a strategy that exploits tripodal coordination to a transition metal, Scrimin has developed a metal templated transacylase mimic.[11] The key ligand was based on a Tren derivative [tris(aminoethyl)amine] functionalized with three *m*-hydroxyphenyl groups. Addition of Zn(II) ions leads to tripodal coordination

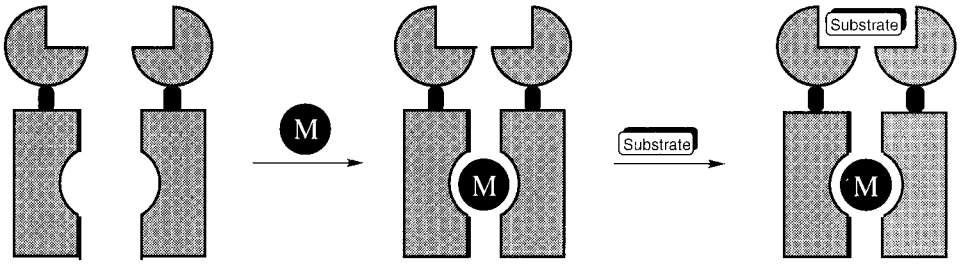
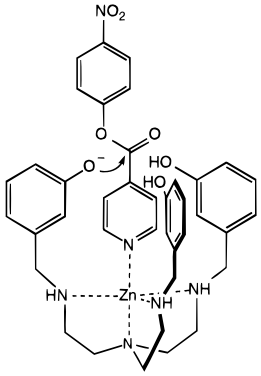


Figure 5. Schematic of binding site organization by metal template effects.

and organization of the three hydroxy groups in a region above the metal center. In this position they are able to interact with the *p*-nitrophenyl ester of 4-pyridinecarboxylic acid, which is simultaneously coordinated to the open site on the Zn(II). One of the three phenol groups was shown to be more acidic than the others and thus more easily deprotonated to form the nucleophilic phenoxide shown in **7**. Large



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rate accelerations were seen for the transacylation reaction only in the presence of templating Zn(II) and unfunctionalized hydroxyl groups. A similar strategy for tripodal organization of chiral environments has been reported by Canary.[12]

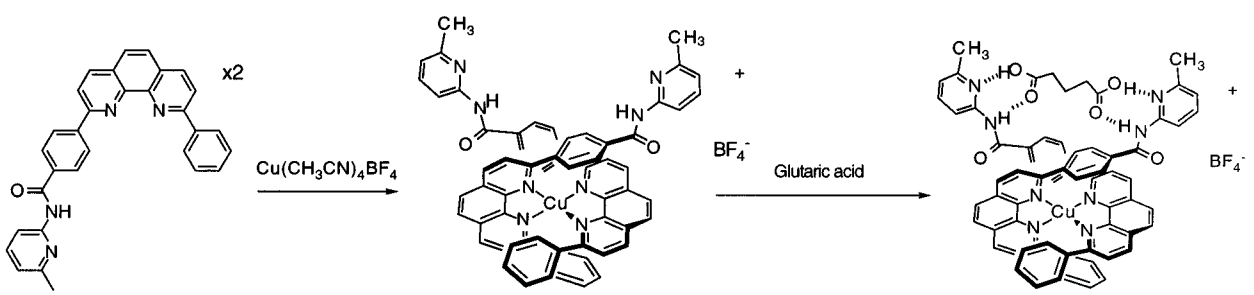
III. Intermolecular Binding Site Organization by One Metal Center

The intermolecular recruitment of different binding groups can be readily achieved by metal templates. The basic concept shown in Figure 5 requires that individual subunits contain both a metal binding region and a substrate binding region. Addition of a metal ion will then cause the coordination of two or more metal binding regions and as a result organize the substrate binding groups for complexation. A critical design requirement is that the metal and substrate binding regions should be independent of one another and that metal ion coordination should not influence the substrate binding region.

We have established the effectiveness of this approach by using diarylphenanthroline derivatives as the metal binding unit. Attachment of a potential substrate binding site, for example one or two aminopyridine groups in **8** and **9**, respectively, leads to the formation of dual function subunits. Addition of Cu(I) salts to a CH_2Cl_2 solution of **8** results in the recruitment of two phenanthrolines around the metal center and the resulting formation of two bis(acylamino)pyridine binding sites as in **10**[13] (Scheme 1). This arrangement is ideally suited for the strong hydrogen bonding complexation of dicarboxylic acids, as in **11**.[14] Subunit **8** is well designed for this purpose as the Cu(I) ion does not interact with the aminopyridine region but binds preferentially to the bidentate phenanthroline group. In this way the metal template and substrate binding functions are separated. Dicarboxylic acid binding to **10** can be followed readily by the large downfield shifts of the NH resonances, as would be expected on the formation of intermolecular hydrogen bonding. Strong complexation is seen (for example $K_a = 4.9 \times 10^4\ M^{-1}$ for glutaric acid), consistent with a complex containing four hydrogen bonds as shown in **11**.

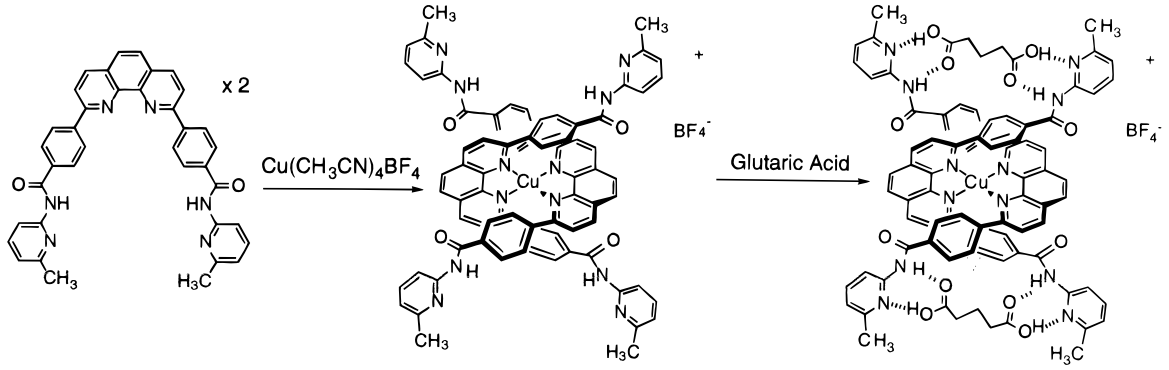
In these cases the metal ion is not just a template for receptor self-assembly but also a spectroscopic reporter group detecting substrate binding. On addition of glutaric acid to **10** a blue shift in λ_{max} of 9 nm is seen as well as an increase in intensity of a shoulder at 550 nm. This effect is seen more dramatically with the bis functionalized subunit **9**. Addition of Cu(I) ions to this derivative results in the formation of a metal templated receptor containing two dicarboxylic acid binding sites (**12**) which can form 2:1 complexes, as shown in **13** (Scheme 2). Proton NMR analysis of **12** shows very similar binding affinity for glutaric acid and other dicarboxy-

Scheme 1



8 **10** **11**

Scheme 2



9 **12** **13**

lic acids as compared to **10**. However, significant changes in the UV absorption of **12** take place on addition of glutaric acid in CH_2Cl_2. In particular, there is a large increase (>100%) in the intensity of the shoulder at 550 nm resulting in a distinct change in the color of solution from orange to dark red (Figure 6).[15] The origin of this chromogenic effect is unclear but presumably comes from a change in the conjugation of the (benzoylamino)pyridyl side arms with the phenanthroline metal system, due to conformational changes on substrate binding. A calculated structure for this complex (Figure 7) shows how well positioned the two aminopyridine units are on each side of the metal center for dicarboxylic acid binding. The corresponding intraphenanthroline binding mode is disfavored due to steric effects of the 9,10-positions of the second phenanthroline ring. It should be noted that both **11** and **13** are chiral. As a consequence, binding of chiral substrates leads to the formation of diastereomeric complex mixtures. For example, addition of *N*-CBZ-L-glutamic acid to a racemic mixture of **10** leads to the observation of two sets of receptor peaks from the respective diastereomeric complexes.

Cu(I) is limited as a template for receptor self-assembly due to its relatively fast ligand exchange properties. This would complicate not only the formation of unsymmetrical receptors (containing two different substrate binding regions) but also the

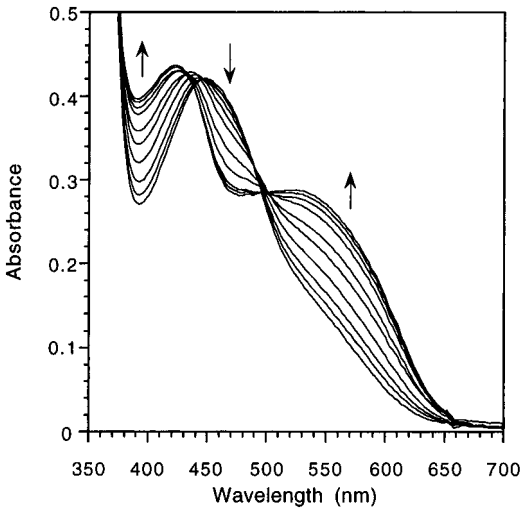


Figure 6. UV−vis changes for **12**:glutaric acid.

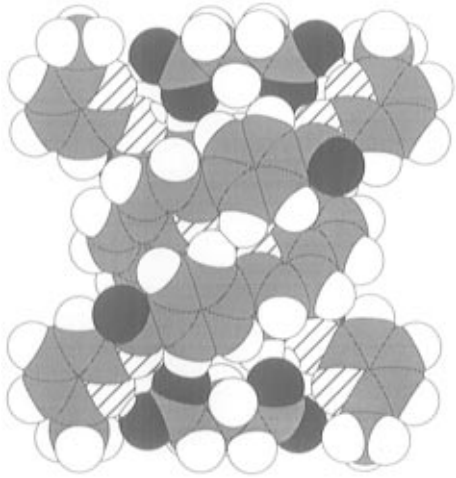
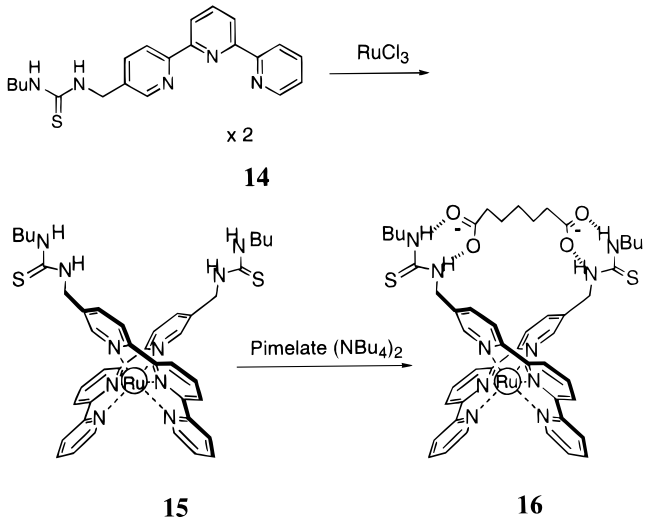


Figure 7. Calculated structure for **13**.

binding to substrates containing potential metal-chelating groups (such as amines or carboxylates). A better alternative would be second or third row transition metals with much slower ligand exchange kinetics. We have begun investigations in this area with the synthesis of a family of subunits containing terpyridine as the metal ligation site. For example, the terpyridinethiourea derivative **14** will react with half an equivalent of $RuCl_3$ to give the bis(terpyridine)ruthenium(II) receptor **15**. As in the case



14

15 **16**

of the phenanthroline derivatives, this receptor con-

Table 1. Binding Constants for 15·2PF_6^- with Tetrabutylammonium Dicarboxylates in 5% D_2O/DMSO-d_6

dicarboxylate	binding constant (K_a), M^{-1}
glutarate	8.3×10^3
adipate	2.9×10^3
pimelate	6.0×10^3
isophthalate	3.5×10^3
1,3-phenylenediacetate	6.2×10^3

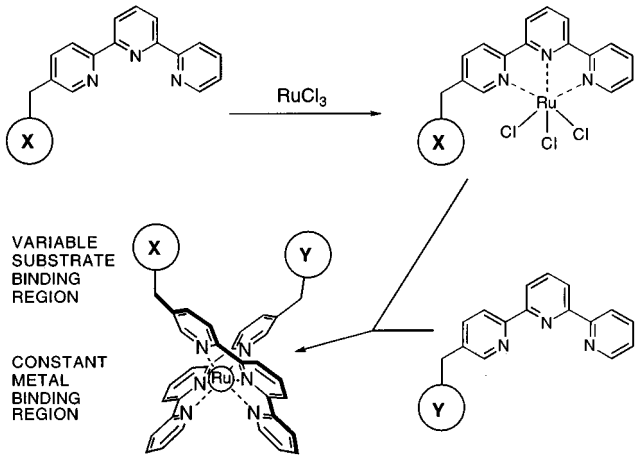


Figure 8. Metal-templated approach to formation of unsymmetrical receptors.

tains two proximally positioned substrate binding sites, now able to complex carboxylate derivatives.

Addition of dicarboxylate salts to a DMSO-d_6 solution of **15** results in large downfield shifts of the thiourea NH protons ($\Delta\delta$ > 3 ppm).[16] These shifts are similar to those seen in related covalently linked bis-thiourea receptors[17] and are consistent with the formation of a complex containing four hydrogen bonds between receptor and dicarboxylate, as shown in **16**. Binding constants of this complex were too high (K_a > 10^4 M^{-1}) to be measured accurately in pure DMSO by NMR. The binding strength comes from both the hydrogen-bond donor effects of the thioureas and also presumably from additional electrostatic contributions from the doubly cationic ruthenium ion. In 5% D_2O−DMSO-d_6 more accurate K_a values could be measured and are shown in Table 1. Strong binding was observed for most substrates studied, suggesting a flexible binding cavity able to accommodate dicarboxylate substrates of different lengths.

The slow ligand exchange kinetics for ruthenium terpyridine complexes permits the facile formation of unsymmetrical receptors. We have exploited this property in the synthesis of a small library of ruthenium templated receptors. The stepwise synthesis of unsymmetrical ruthenium complexes is shown in Figure 8. To test this strategy we have prepared a series of terpyridine derivatives with different binding regions (alkyl, thiourea, hydroxyl, diphenylmethane, and crown ether) linked to the 5-position, as in **17**, **14**, **18**, **19**, and **20**. Reaction of the terpyridine derivatives in refluxing ethanol gave the corresponding monoterpyridine·$RuCl_3$ complexes. These were divided into five portions which were reacted with one equivalent of the five terpyridine derivatives, respectively. The resulting symmetrical

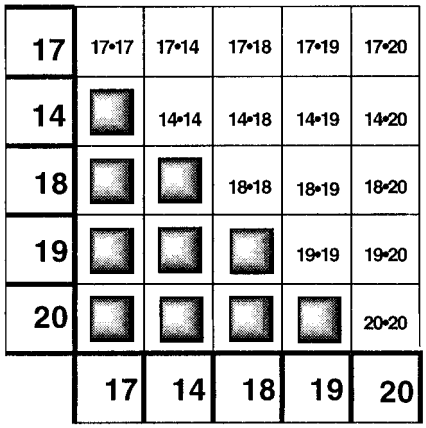


Figure 9. Combinatorial grid of receptors from five subunits.

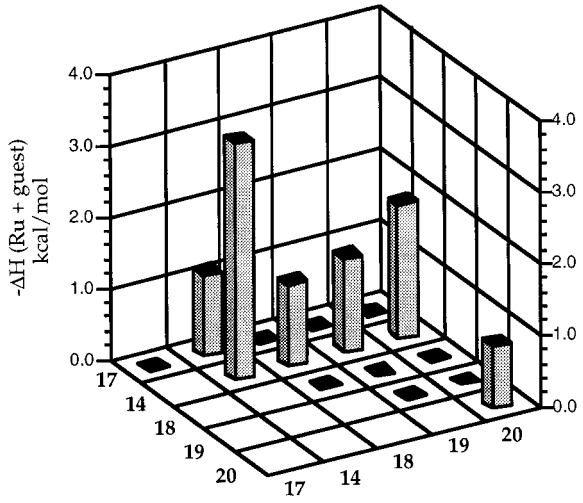
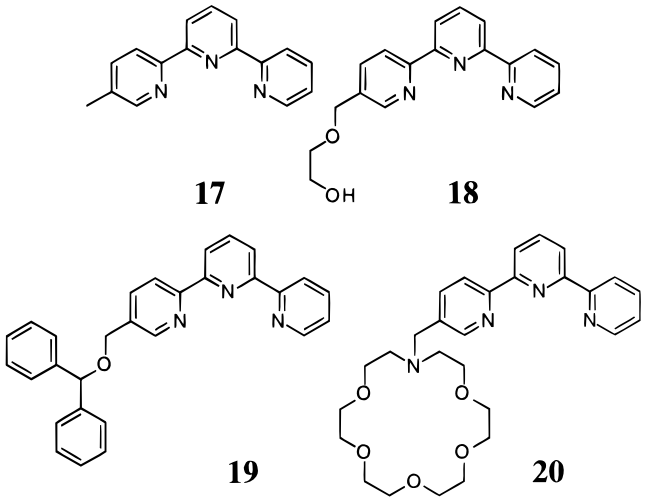


Figure 10. Association enthalpy of receptor library to pimelate.



and unsymmetrical bis-terpyridine complexes were isolated as their PF_6^- salts. As a result, 15 different and purified receptor samples can readily be prepared as shown in grid form in Figure 9.[18] This small library of receptors can then be screened for its interaction with different types of substrates. Titration microcalorimetry was used to measure the enthalpic response of the library on addition of bis-(tetrabutyl ammonium) pimelate salts in DMSO. The results are shown in Figure 10 in bar graph form.

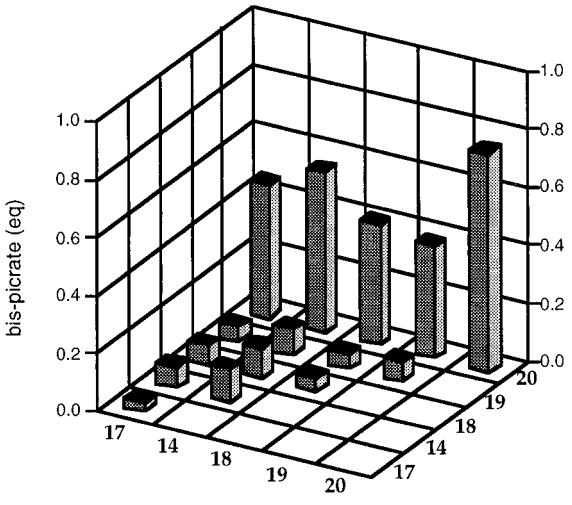
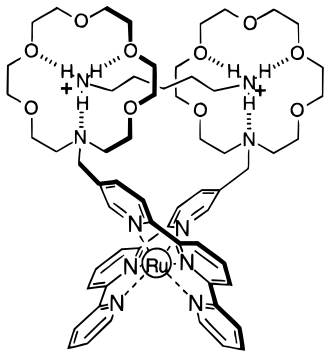


Figure 11. Complexation of pentanediylbis(ammonium picrate) salts by receptor library.

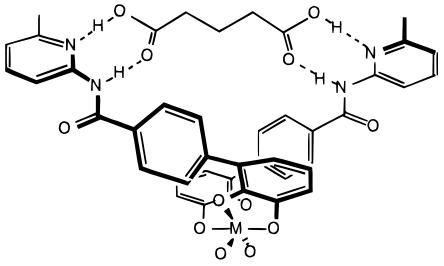
As expected receptor **14·14** (corresponding to **15**) gave the largest response due to the complementarity of bis-urea and bis-carboxylate recognition sites.

The response of the library is completely different when other substrates are investigated. For example, solid−liquid extraction techniques were used to screen the ability of the library to bind to pentane-1,5-diylbis(ammonium picrate) salt. Figure 11 shows the response of the library and confirms that strongest binding is seen to the receptor containing two crown ether recognition sites (**20·20**). The binding presumably involves a double hydrogen-bonded complex between the alkyl ammonium and crown ether groups as shown in **21** and corresponds to a binding constant of 3.2×10^4 M^{-1} in CD_3CN.



20•20 **21**

In a related approach, Weiss has linked catechol monoamides to aminopyridines as the monomeric self-assembling subunit. In the presence of molybdenum ions these ligands associate to form a receptor for dicarboxylic acids related to **10**, as in **22.**[19]



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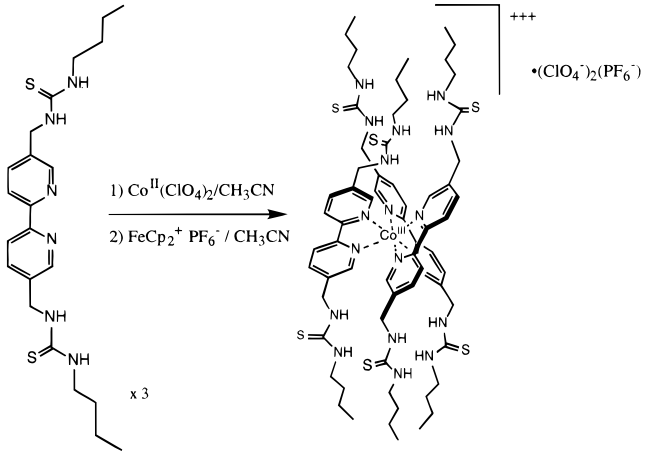
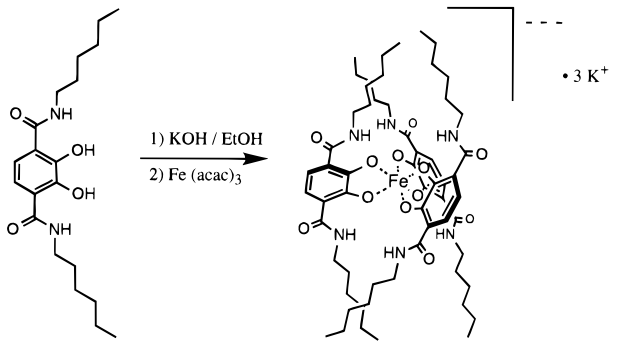
Preliminary NMR binding results with this system show some enantioselectivity when chiral guests such as *N*-CBZ-glutamic acid are used.

All of the above receptors have involved the recruitment of two ligands around the metal center. A similar strategy can be used based on a three-chelate effect as an approach to organizing three potential substrate binding sites around the metal. For example, bipyridine bis-thiourea subunit **23** will form, in the presence of cobalt(II) ions and following oxidation, the tris(bipyridine)cobalt (III) complex (**24**).[20] This has the consequence of forming two tris-



23 **24**

thiourea binding regions on opposite sides of the cobalt tris-bipyridine complex. Preliminary results show that all three thioureas participate in binding to multifunctionalized substrates, such as glutamate and aspartate. A similar approach can be taken with catechol bis-amide **25** which, in the presence of iron(III) or gallium(III) ions, will self-assemble to form an anionic receptor **26** with potentially hydrogen bonding amide sites above and below the metal complex.



25 **26**

Schepartz has elegantly exploited a similar strategy in the design of peptides linked to terpyridine derivatives.[21] Addition of metal ions causes dimerization of the functionalized peptides and introduces a leucine zipperlike ability to bind and recognize DNA. In a related development Sasaki has linked a single carbohydrate to a bipyridine subunit and used transition metal templates to assemble three closely positioned sugar groups on the periphery of a metal

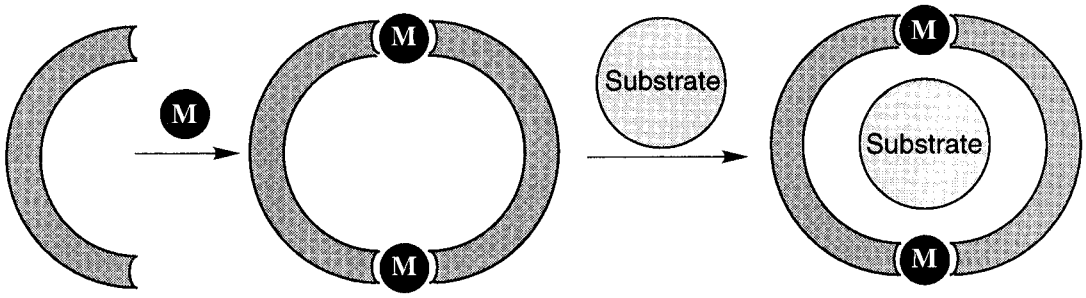


Figure 12. Schematic of binding site organization by two metal templates.

Table 2. Association constants for Substrate Binding into $Cu_2$27$_2$

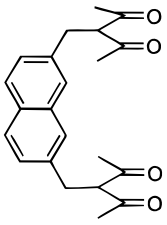
guest	binding constant (K_a), M^{-1}
pyridine	0.5
pyrazine	5
quinuclidine	7
Dabco	220

tris-bipyridine complex.[22] As a self-assembled trimeric carbohydrate, this molecule shows stronger binding to lectins than the monomeric unit.

IV. Self-Assembled Receptors Based on Two Metal Ions

The use of two metal centers in the self-assembly of receptors offers the possibility for closing a macrocyclic structure. As shown in Figure 12 this strategy has the potential to organize two (or more) components to form a large macrocyclic cavity.

The first example of this approach was reported by Maverick who prepared a series of bis-acetylacetone derivatives separated by a rigid aromatic spacer as in **27**.[23] Addition of Cu(II) ions causes the formation of a 2+2 complex in which the two metal centers are held rigidly separated from each other by the aromatic spacer, as in **28**. The two square-



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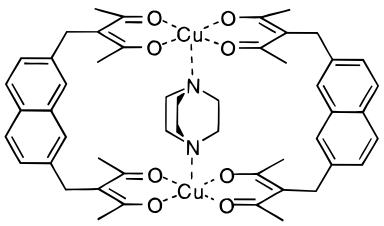
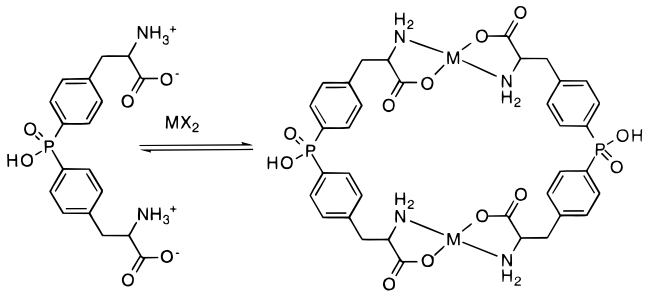


28

planar Cu(II) complexes form the walls of a cavity that can bind to substrates via metal ligand coordination. Strong selectivity is seen for those substrates that contain the correct spacing of two metal binding groups (Table 2). For example, quinuclidine binds very weakly while diazabicyclooctane (Dabco) forms strong complexes, with the two amine nitrogens coordinating to each Cu ion, as in **28**.

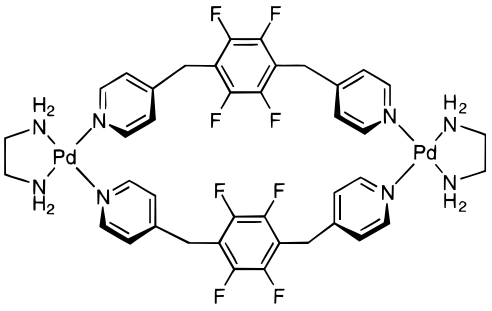
A related strategy has been used by Schwabacher in the formation of large hydrophobic cavities. A series of bis-(amino acid) derivatives such as **29** were prepared, which on addition of transition metals (e.g., Ni(II) or Co(II)) dimerize to form cyclophane-like macrocycles (**30**).[24] As with covalently constructed cyclophanes[25] these molecules can bind hydrophobic



29 **30**

guests within the macrocyclic cavity. Receptor **30** was also shown to be effective in promoting the transport of pyrene through an organic liquid membrane.[26] One advantage of these designs is that in addition to the hydrophobic interactions, the receptor can also provide electrostatic binding to polar substituents on the substrate through interaction with the metal centers. In these cases, the self-assembly is mediated through metal−amino acid interactions. Other macrocyclic designs have been based on trans-linked phosphene−Pd complexes.[27]

A particularly successful approach has exploited the strict square-planar coordination requirements of Pd(II) and Pt(II) complexes. Fujita has shown that flexibly linked bis(4-pyridine) derivatives will form binuclear macrocyclic complexes in the presence of Pd(II) salts, as in **31**.[28] This molecule showed excel-

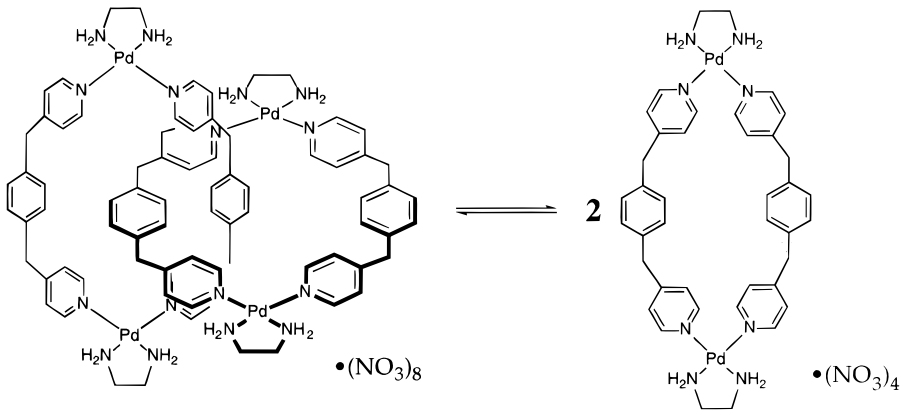


31

lent substrate binding properties for electron-rich aromatic substrates, such as 1,3,5-trimethoxybenzene (K_a = 2500 M^{-1}). The strength of binding increased as the electron density on the aromatic ring of the substrate increased, suggesting that a donor−acceptor interaction was important for host−guest recognition.

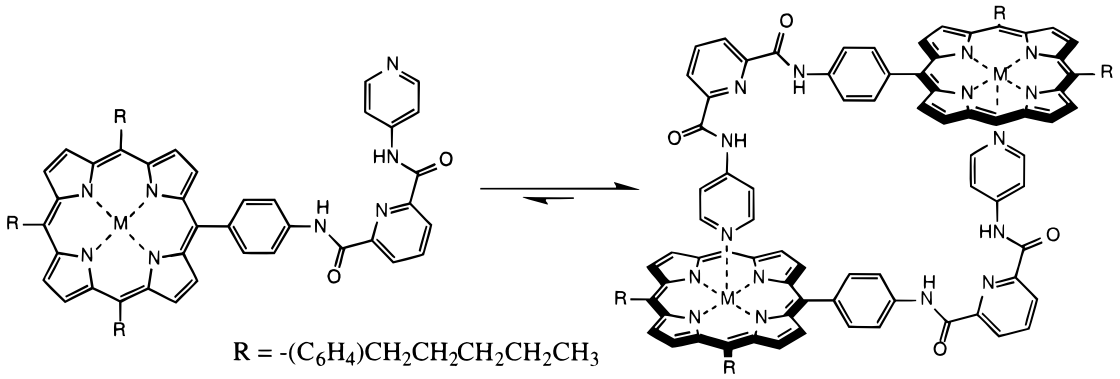
This property of facile hydrophobic receptor self-assembly was elegantly exploited by Fujita in the formation of a metal-templated [2]catenane. At low

Scheme 3



33 **32**

Scheme 4



34 **35**

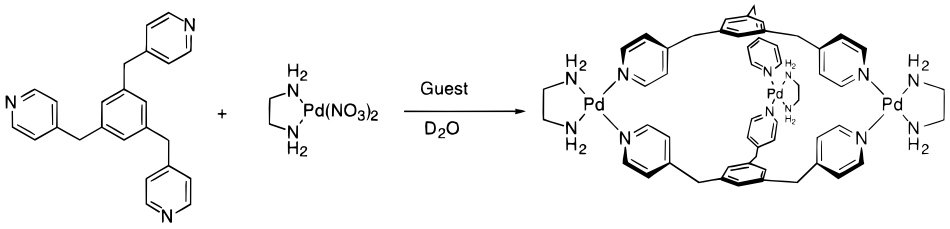
concentrations (<50 mM in D_2O) a single ring **32** was self-assembled via coordination of two bis(4-pyridyl) derivatives with two Pd(II) ions (Scheme 3). When the concentration was increased above 50 mM, more than 90% of the species in solution converted to the [2]catenane **33** in which one ring is interlocked through the center of a second. The structure of this species was confirmed by ^{1}H NMR, FAB-MS, and electrospray mass spectrometry. The equilibrium also could be controlled by varying the solvent, with more polar solvents promoting the formation of the [2]catenane. This behavior is remarkably like that of the conjurers "magic rings", however the linking and unlinking of the rings is caused by the breaking and re-forming of the palladium−nitrogen coordination. By changing the solvent, the ratio of **33** to **32** could be varied between 99:1 and 1:99. In contrast, platinum coordinates with pyridine irreversibly and this behavior is not observed when platinum is substituted for palladium.[29]

In a very different approach to two metal templation of recognition sites, Hunter has exploited the rigidity of porphyrin rings and the tendency for zinc porphyrins to favor 5-coordination. He prepared rigidly linked porphyrin−pyridine derivatives **34** and showed that this readily self-assembled in solution to macrocyclic dimer **35**[30] (Scheme 4). This molecule contains two hydrogen-bonding regions (around the pyridinecarboxamide groups) separated by the rigid pyridine-porphyrin linker. In nonpolar organic solvents diamide derivatives such as *N*,*N*′-dihexylterephthalamide bound into the central cavity presumably by hydrogen bonding to the pyridine and amide groups (K_a > 1400 M^{-1} in $CDCl_3$). The size of the self-assembled macrocycle can be controlled in the system by varying the relative angle of the pyridine and porphyrin groups in the monomeric subunit. In this way trimeric and tetrameric derivatives were also prepared.[31]

V. Self-Assembled Receptors Based on Three Metal Ions

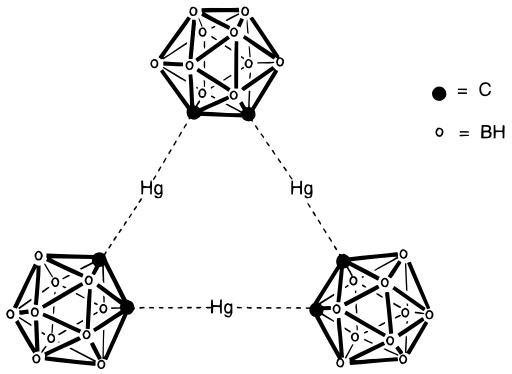
The ready formation and characterization of larger structures based on complexes of pyridine derivatives with Pd(II) or Pt(II) complexes allows the investigation of a range of differently shaped self-assembled receptors. Fujita has shown that tridentate subunits such as 1,3,5-tris(4-pyridylmethyl)benzene (**36**) will react with Pd(II) ions to form the 3+2 self-assembled complex **37**[32] (Scheme 5). A critical role in the self-assembly process is played by aromatic guests (such as (4-methoxyphenyl)acetic acid) which template the formation of the complex. In the absence of a templating guest only ill-defined oligomeric metal complexes are formed. Hawthorne has created novel receptors by assembling carborands and mercury(II) ions to form both 3+3 and 4+4 complexes.[33] The formation of the smaller 3+3 assembly **38** is favored, but templation by halide ions leads to formation of a 4+4 complex. Receptor **38** has been shown via

Scheme 5



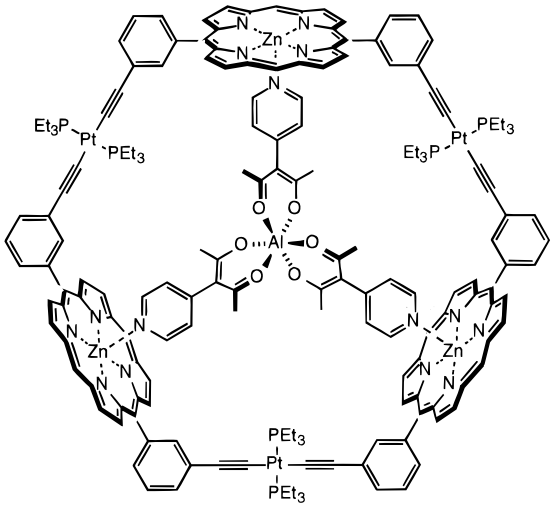
35 **37**

^{199}Hg-NMR to be capable of binding two equivalents of halide ion.



38

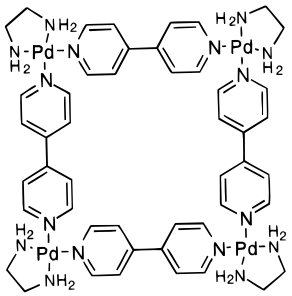
In a 2-fold exploitation of metal templation, Sanders has created a self-assembled receptor which associates with a self-assembled guest.[34] Three monomers containing zinc porphyrins are combined with three platinum atoms to form a trimeric macrocycle **39**. This receptor contains three porphyrins in an orientation to complex metal-binding guests in a very large cavity. Although this shows strong association to several tris-pyridine derivatives, the strongest association ($K_a = 1.0 \times 10^{10}$ M^{-1}) is observed with a guest which is self-assembled around an aluminum atom. This guest has the correct spacing to bind to all three zinc ions.



39

VI. Self-Assembled Receptors Based on Four or More Metal Ions

Metal ions that form 4-coordinate square-planar complexes are particularly well suited to act as the 90° corners of square supramolecular structures. In a further development of their self-assembling strategy Fujita's group has shown that Pd(II) nitrate complexes react with rigid 4,4-bipyridines to form 4+4 complexes with a square box-shaped character, as in **40**.[35] Proton NMR analysis shows that this



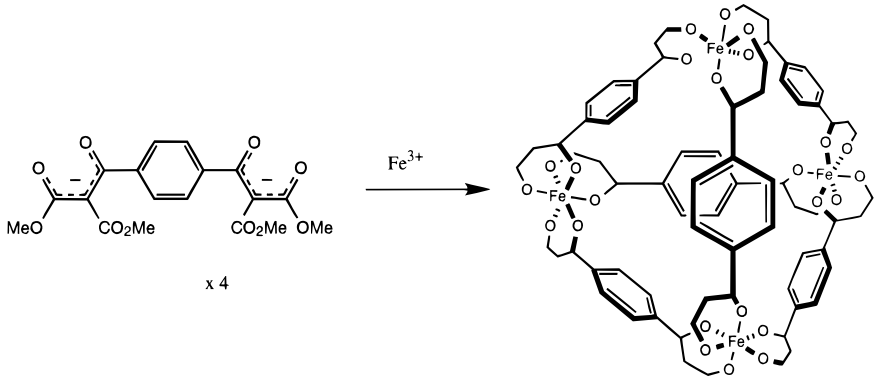
40

structure is the thermodynamically stable product of the reaction with slow exchange between **40** and other oligomeric fragments. The central cavity in **40** is reminiscent of that in cyclophanes[25] and can encapsulate small aromatic guests. Addition of 1,3,5-trimethoxybenzene to an aqueous solution of **40** results in upfield shifts of the guest resonance (due to aromatic ring current affects from the host) and a K_a value of 750 M^{-1} was measured. The size and shape of this tetranuclear cavity can be readily varied by changing the linking group between the pyridine donor sites. Stang has replaced 4,4′-bipyridine with diazapyrene and diazaperylene to form tetranuclear Pd(II)-based box structures with much larger cavity dimensions.[36]

Particularly impressive self-assembled cavities have been generated from tetraphenylporphyrin derivatives in which two adjacent or opposite phenyl groups are replaced by para-substituted pyridines. In this way exceptionally large cavities can be generated with rigid and photoactive wall components, **41** and **42**.[37] However, the substrate binding properties of these molecules have not been investigated in detail.

An elegant and different approach to tetranuclear receptor self-assembly has been reported by Saalfrank.[38] In this approach a series of spatially separated bis-(methyl acetoacetate) derivatives (e.g., **43**) were deprotonated and reacted with Fe(III) ions. The angular disposition of the two metal chelating groups

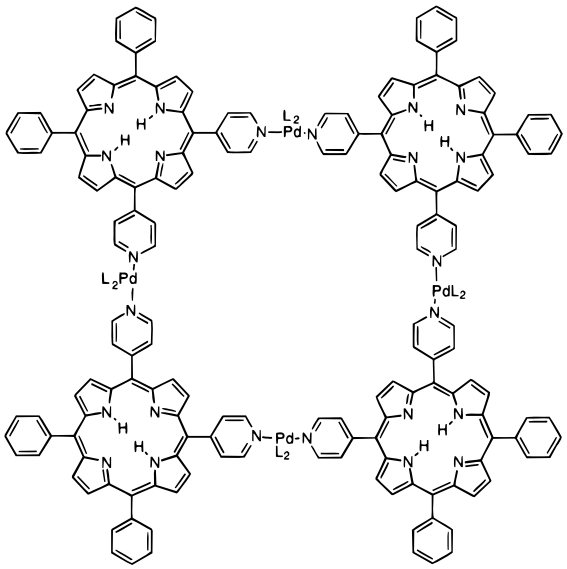
Scheme 6



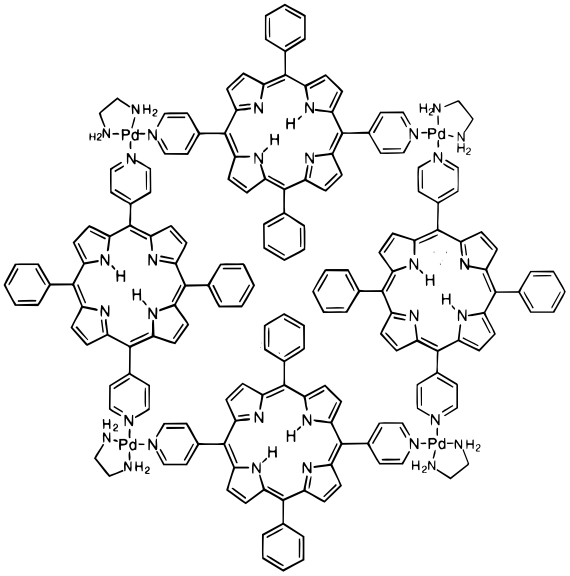
43 **44**

leads to the formation of an adamantane-like tetranuclear Fe(III) complex containing a spherical hydrophobic cavity formed by the six phenyl groups, as in **44**[39] (Scheme 6). In some cases, the binding of small ions was observed inside the central cagelike cavity.[40]

As part of a large effort to study the assembly of organic ligands and metals, Lehn has synthesized a receptor containing five metal centers.[41] Complex **45**



41



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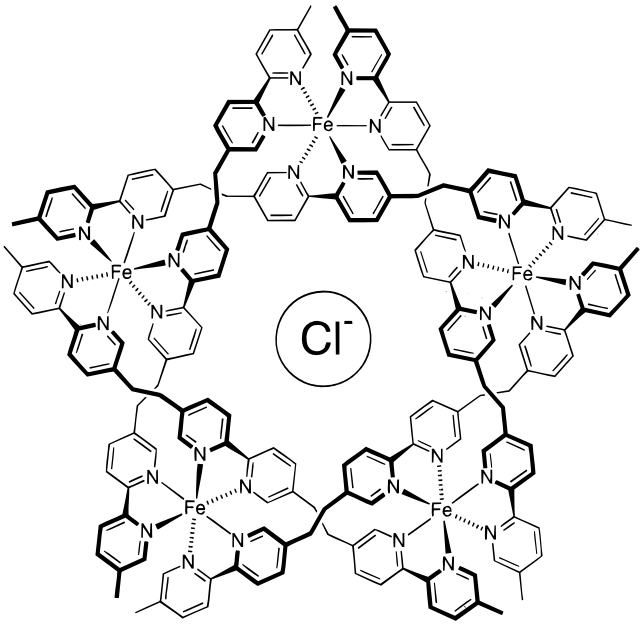

45

is formed from five tris-bipyridine ligands which form a circular double helix with five iron atoms. The assembly is templated by the presence of a chloride ion, which is held in the center of the complex. The electrospray mass spectrum of this complex contains multiple signals without external counterions, but all signals contain the chloride ion. This demonstrates that the chloride is tightly bound to this pentametal complex.

VII. Conclusions

The many examples described in this review demonstrate that metal templation offers a variable and effective approach to the self-assembly of recognition sites. In addition to the simple contribution of a chelate effect in bringing together several binding

groups, the use of metals as structural components in receptor synthesis offers the following advantages: (1) the different ligand exchange kinetics for first, second, and third row transition metals and their varied oxidation states can permit fine tuning of the dynamics of receptor assembly and disassembly, (2) similarly, changes in the coordination number and geometry of different metals can allow a modification of the shape of templated receptor sites, (3) positively or negatively charged metals complexes can contribute significantly to the binding energy by direct interaction with polar substrates, (4) certain metals can act both to organize receptor site formation, and as catalytic centers for subsequent reaction on a bound substrate.

VIII. Acknowledgments

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