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Development of a Coordination Chemistry-Based Approach for Functional Supramolecular Structures

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ABSTRACT

The weak-link approach (WLA) to supramolecular assemblies allows for the design of multimetallic two- and three-dimensional arrays, host−guest architectures, sensors, catalysts, switches, and signal amplification devices. This Account describes the course of our investigations in this area beginning with the development of a chemical tool kit of building blocks consisting of multiple metals and ligands. These building blocks can be rationally mixed and matched to provide structures with a wide range of properties that have been used to develop functional supramolecular architectures, including chemical sensors and allosteric catalysts.

Introduction

Our interest in supramolecular chemistry is, in part, inspired by the challenge to mimic the complex and cooperative functions of natural systems. Biological systems routinely store information in the shape, size, and electronic properties of molecules.[1] This information is read by the way the molecules recognize and interact with each other. For example, DNA is the central carrier of information in cells; however, interactions with a myriad of other molecules via complex and cooperative recognition chemistry are required to have that information read, copied, and repaired.[1,2] As chemists learn to manipulate molecules with increasing dexterity, synthetic and semisynthetic systems may not only mimic biological systems, but they may surpass them in both biological and abiotic applications.

Cooperative interactions are ubiquitous in biological systems. When cooperative interactions can be deliberately designed into synthetic systems, new and otherwise inaccessible chemistry can be realized. Ultimately, when one has control over the synthesis of structures containing well-defined cavities, species can be designed that arrange molecules in a specific and predictable fashion for catalysis and detection of analytes. If these systems respond to input signals, arrays can be developed that perform multiple functions autocatalytically, cross-catalytically, or with feedback. These are functions that are performed routinely by biological systems but remain rare in synthetic ones.[3] To understand and utilize cooperative intermolecular interactions, chemists have developed a number of strategies for generating supramolecular assemblies.[4−10] The utility of these supramolecular architectures is in the realization of enzyme-like catalytic systems and addressable molecular sensors.[11,12]

In this Account, we describe the development of a novel supramolecular assembly method, termed the weak-

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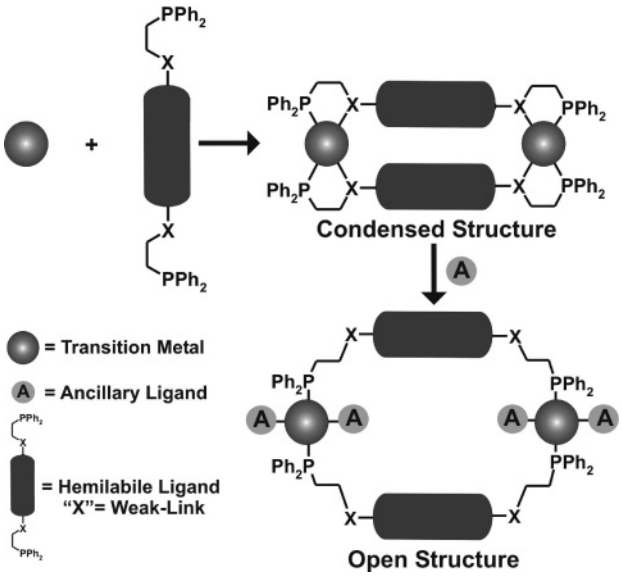


FIGURE 1. General strategy of the WLA.

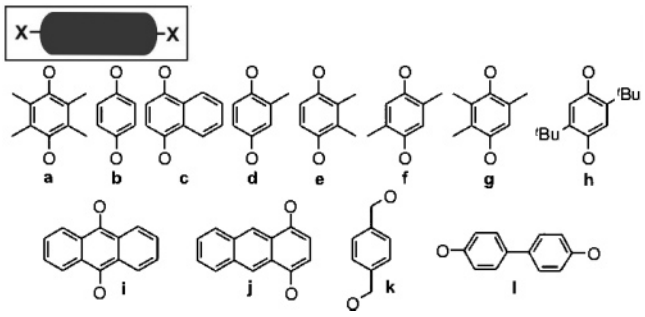
link approach (WLA). The depth and versatility of this methodology are illustrated via the generation of a variety of multimetallic supramolecular assemblies. Also, the realization of functional supramolecular structures is demonstrated in the areas of catalysis and molecular sensing.

The Weak-Link Approach

Coordinate-covalent bonds have been used extensively in the construction of supramolecular assemblies.[5,7−10] This has paralleled the use of hydrogen bonding to assemble molecules into discrete systems.[4,6,13] Importantly, transition metal centers allow for the convergent synthesis of complex structures in high yields. Several general approaches have emerged that rely on metal−ligand interactions to generate discrete supramolecular complexes, such as the directional-bonding approach,[7,10] the symmetry-interaction approach,[5,9] and the WLA.

The WLA is a coordination chemistry-driven assembly process for flexible multidomain supramolecular architectures. A critical feature of this approach is that the metals used in the assembly process are available for further reactions without destroying the supramolecular structure. The WLA employs elements of thermodynamic and kinetic control to provide access to a variety of flexible two- and three-dimensional supramolecular structures with tailorable properties. This approach targets condensed structures that contain strategically placed strong (metal−phosphine) and weak (metal−X) bonds (Figure 1).

Chart 1. P,O Hemilabile Ligands 1 Used in the WLA



The formation of these complexes is driven by the formation of favorable five-membered chelate rings about the metal centers and $\pi-\pi$ interactions between the aromatic spacers in the ligands. The weaker metal−heteroatom bonds can be selectively cleaved by introduction of small molecules or ions that have a stronger binding affinity for the metal center to generate flexible macrocyclic structures in nearly quantitative yield.[14−36]

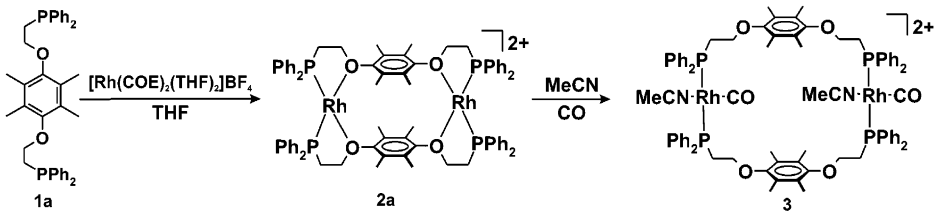
Generality of the WLA

With this strategy in mind, an understanding of the breadth and utility of this approach was developed. In our studies, we found that three variables can be used to control the properties of the assembly: (1) the hemilabile ligand, (2) the metal center, and (3) the ancillary ligands. The WLA has been used to generate over 200 examples of two- and three-dimensional supramolecular structures with control over size, shape, hydrophobicity, and chirality by the rational choice of these three elements.

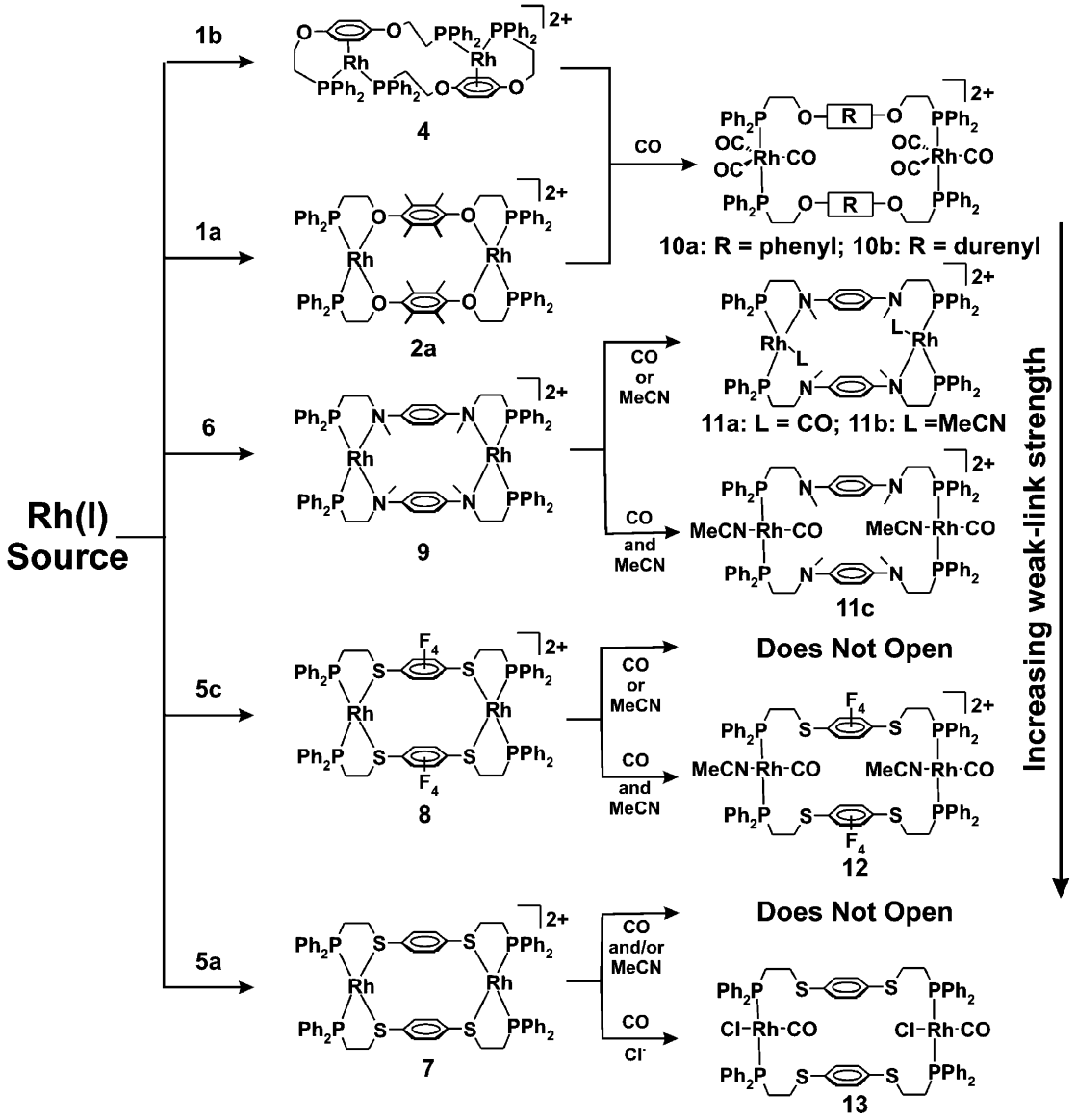
Hemilabile Ligands. A primary source of tailorability in this approach pertains to the organic ligands that are used to generate the supramolecular structures. The ligands are used to control the reactivity of the condensed structures and incorporate functionality, such as fluorescent, redox-active, or catalytic moieties, into the final supramolecular architecture. Examples are given below.

The WLA was first demonstrated by reacting ligand **1a** with a Rh(I) starting material in a 1:1 stoichiometric ratio to provide the condensed structure **2a** (Scheme 1).[14] The weak Rh−O links of **2a** are broken by coordinating ligands, such as CO, CH_3CN, or both, to form 26-membered macrocycles, such as **3**, in nearly quantitative yields. From this initial success, the scope of this approach was broadened to incorporate other phosphinoalkyl ether ligands (Chart 1). This set of ligands allows one to probe how ligand properties (such as size, electronics, and sterics) affect the formation of the resulting macro-

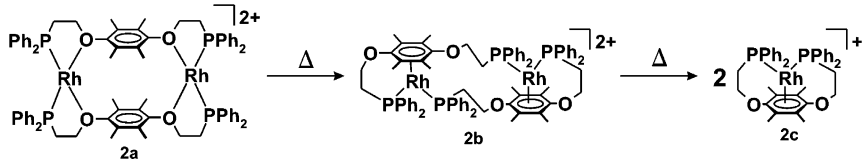
Scheme 1



Scheme 2. Examples of the Small Molecule Reactivity of Supramolecular Assemblies Generated via the WLA



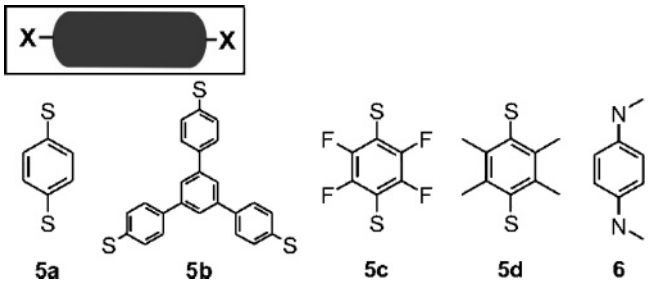
Scheme 3. Conversion of the Kinetic Product 2a to the Thermodynamic Product 2c



cycles.[15,28] These studies also demonstrate how choice of ligand can lead to macrocycles with different structural properties and reactivity. For example, reaction of ligand **1b** with a Rh(I) precursor leads to the formation of the "slipped" η^6-piano stool complex **4** under similar conditions where the "condensed" *cis*-phosphine, *cis*-ether complex **2a** was formed with the durenyl ligand **1a** (Scheme 2). These observations led us to probe the steric and electronic factors that influence the formation of the condensed Rh(P_2O_2) versus slipped Rh(P_2-arene) intermediates.[15,26] In the case of **4**, the formation of the slipped structure is due to the benzene ring of **1b** bearing less electron density than the durene ring of **1a**, which results in less basic ether moieties. Also, the methyl groups on the durenyl moieties of **1a** offer increased stabilization through van der Waals interactions.[15]

Critical for optimizing the WLA, the ether-containing macrocycles have provided insight into mechanistic aspects of the approach.[15] Specifically, combination of ligand **1a** with Rh(I) in THF at −78 °C, followed by warming the reaction mixture to RT, leads to formation of **2a** exclusively. However, upon refluxing, a slow increase in the concentration of **2b** at the expense of **2a** is observed (Scheme 3). Upon increased heating for an extended period of time, the conversion of **2b** to the monomeric structure **2c** is observed. An additional study revealed an

Chart 2. Other Hemilabile Ligands Used in the WLA



associative mechanism for this conversion, catalyzed by the addition of phosphine ligands, and highlights the importance of reaction conditions.[21]

In addition to the ether-based hemilabile ligands discussed above, other weak links, such as thioethers and amines, can be utilized in this approach (Chart 2).[17,19,23,27] For example, the bimetallic Rh(I) condensed structure **7** can be generated via the reaction of the thioether-containing ligand **5a** and a Rh(I) source (Scheme 2).[17] Similarly, a trimetallic three-dimensional macrocycle was synthesized using ligand **5b** in nearly quantitative yield.[23] As expected, these results suggest that the metal−thioether bonds in the condensed structures are significantly stronger than their metal−ether analogues. For instance, the metal−thioether bonds of **7** are inert under conditions that result in the displacement of the ether moieties in complex **2a**. Additionally, altering the electronics of the aromatic core in the thioether-containing ligands allows one to control which ancillary ligands are used to open the condensed structures. For example, using the tetrafluoroarylthioetheralkylphosphine **5c** instead of the benzene-based **5a** allows for the synthesis of condensed structures that react similarly to the ether-based macrocycles.[27] The phosphinoalkylamine ligand **6** provides architectures (e.g., **9**) with weak links of intermediate strength between ethers and thioethers.[19] For instance, only two of the four Rh(I)−N bonds are cleaved in **9** in the presence of CO or MeCN to give the half-open structures **11**. Fully opened structures, such as **11c**, have been generated by treating **9** with one σ-donating (MeCN, Cl^-) and one π-accepting ligand (CO).

Transition Metal. Expanding the types of transition metals used in this approach provides increased control over the resulting macrocyclic properties, such as air and water sensitivity, charge, cavity shape, and small molecule reactivity. In addition, the ability to generate structures with different types of metal centers provides access to supramolecular architectures with desirable and tailorable catalytic and photophysical properties.

Following the initial success with Rh(I), other d^8 square planar metals, such as Pd(II) and Ir(I), were used to generate supramolecular structures via the WLA (Scheme 4).[18,23,27] For example, Pd(II) complexes are generated via reaction of $[Pd(MeCN)_4][BF_4]_2$ with ligands **1a**, **1b**, or **5** to give complexes **14a**−**c**, which can be opened into macrocycles by introducing them to small molecules or ions (e.g., MeCN, CN^-).[18] Similarly, reaction of an Ir(I) starting material with ligands **5b,c** generates condensed structures **15** and **16**, respectively. Addition of small molecules, such as CO/Cl^- or MeCN/^{t}BuNC, to **15** and **16** cleaves the Ir−S bonds to yield open macrocycles.[23,27] While the weak-link routes for Pd(II), Ir(I), and Rh(I) assemblies are similar, they exhibit some distinct characteristics. In particular, Rh(I) complexes have been shown to form η^6-arene interactions, while the Pd(II) analogues do not,[18] and the Ir(I) complex **16** demonstrates different reactivity with CO as compared to its Rh(I) analogue **8**.[27]

Metal centers with d^{10} tetrahedral and d^6 octahedral coordination geometries were employed to understand the versatility and tolerance of the WLA to significant changes in the coordination geometry of the metal center. For example, cationic bimetallic Cu(I) macrocycles have been generated in high yield via the addition of small molecules such as acetonitrile, isonitriles, diimines, or pyridine to the condensed structures **17** (Scheme 4).[31] Also, neutral

Scheme 4. Examples of Assemblies Containing Metal Centers Other than Rh(I)

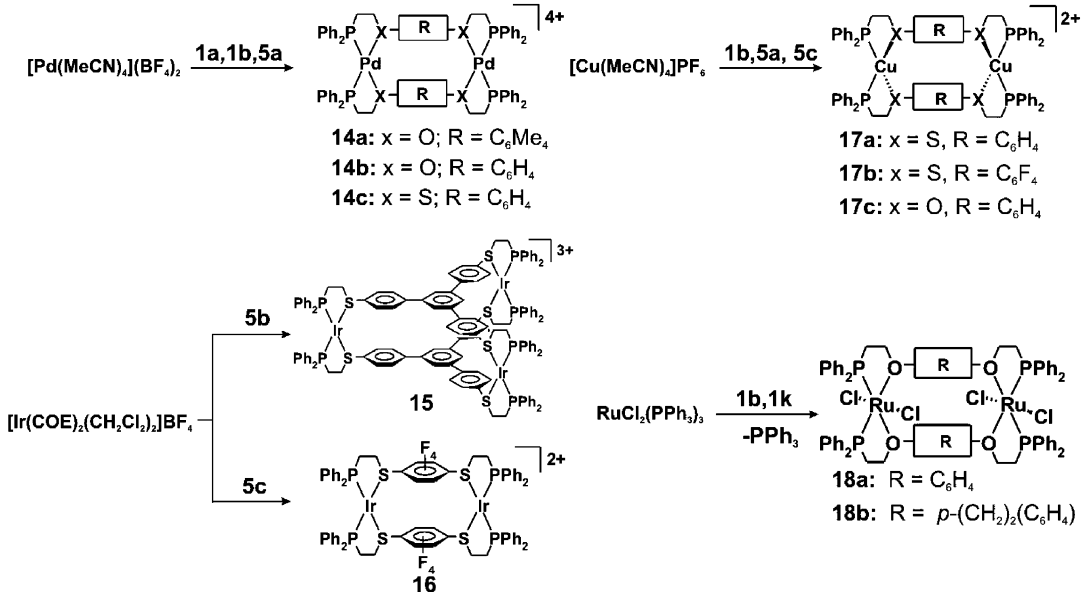
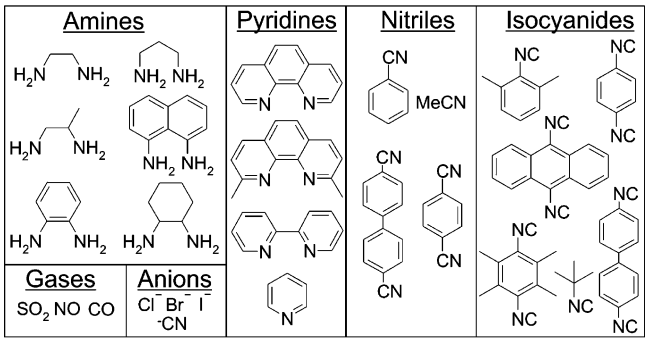


Chart 3. Examples of Ancillary Ligands Used in the WLA

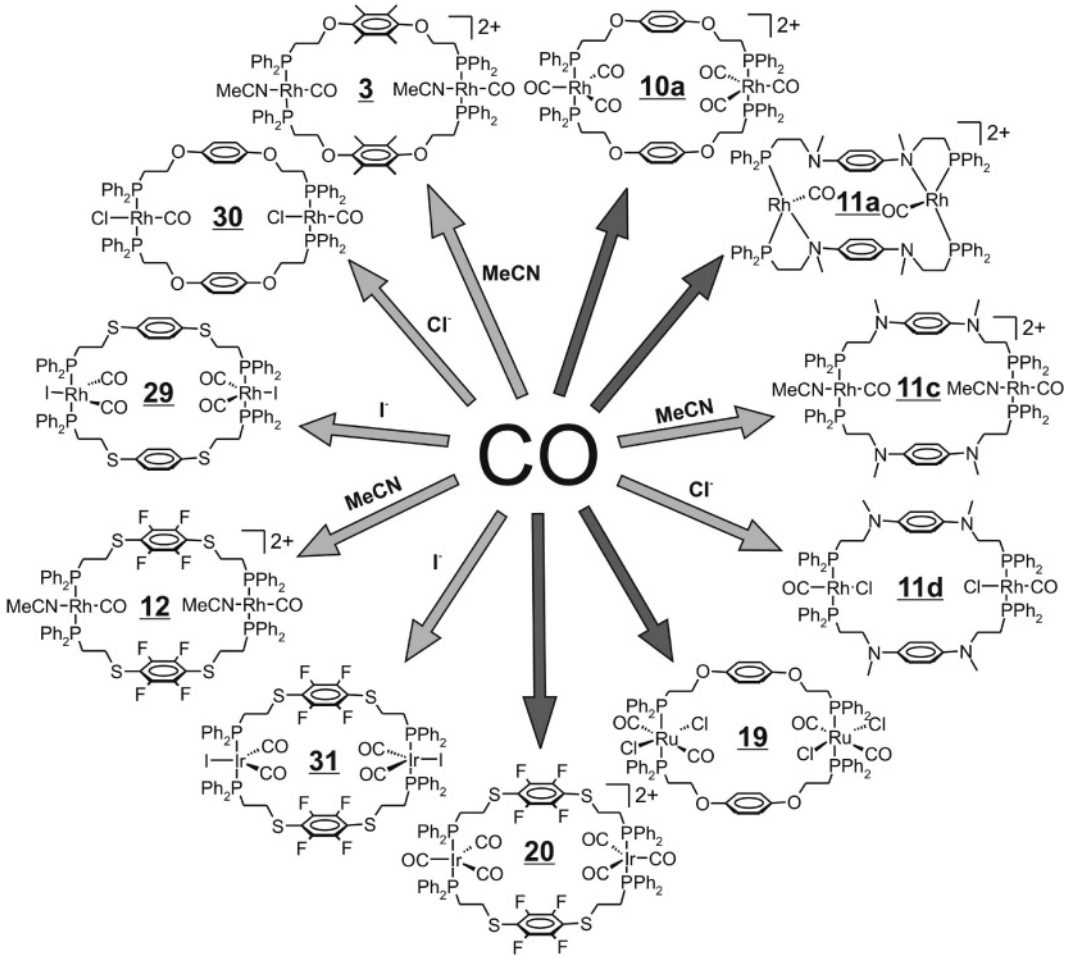


bimetallic Ru(II) macrocycles have been synthesized in high yield from the condensed structures **18** via addition of CO, pyridine, or alkyl diamines.[33]

Ancillary Ligands. The WLA generates assemblies with coordinatively labile metal centers that react with a variety of small molecules and ions without destroying the overall assembly. The binding of ancillary ligands to the metal centers in these structures provides a route to change the size and shape of the cavity within the assembly. The reactivity of a supramolecular compound with a specific molecule is dependent on the building blocks used to synthesize it. Through rational choice of metal center, weak link, and bridging arene group, the reactivity of the assembly can be attenuated and, in certain cases, made reversible. Developing an understanding of the reactivity of these assemblies with a variety of small molecules and ions (Chart 3) has been a critically important step toward designing catalytic and detection systems involving these compounds. In this section, a survey of some of the ancillary ligands is presented.

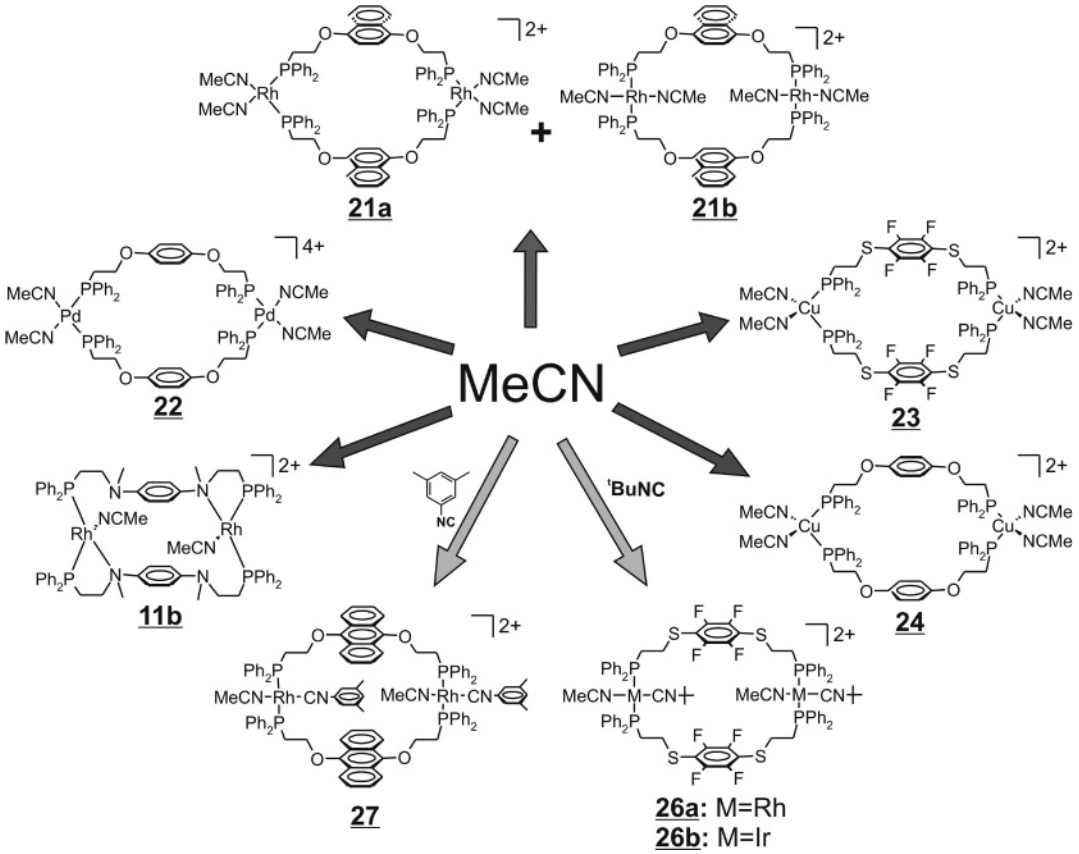
1. Carbon Monoxide and Nitriles. Carbon monoxide (CO) reacts with a number of supramolecular assemblies with different metal centers and hemilabile ligands (Scheme 5).[14,15,19,21,27,37] The most reactive class of assembly is the Rh(I) P,O structures in which the Rh(I)−O bonds are cleaved, while the Rh(I)−P ligands are left intact (e.g., **10a**).[14,15,21,37] Also, Ru(II) P,O structures react with CO to generate assemblies (e.g., **19**) that contain octahedral metal centers with trans phosphine, halide, and CO ligands.[33] In contrast, systems with stronger binding weak links, such as amines and thioethers, exhibit different reactivity toward CO.[17,19,27] For instance, the Rh(I) P,N complex **9** reacts with CO to generate the half-open complex **11a** where two of the four Rh(I)−N bonds have been cleaved.[19] In addition, CO reacts with the Rh(I) P,S structure **7** to generate five-coordinate CO adducts with all of the Rh(I)−S bonds intact.[17] The electron-withdrawing arenes in the ligand backbone of the Ir(I) P,S structure **16**

Scheme 5. Assemblies Generated via Reaction of CO with Condensed Structures[a]



[a] Dark arrows = direct reaction; light arrows = reaction in conjunction with other small molecules.

Scheme 6. Assemblies Generated via Reaction of MeCN with Condensed Structures[a]



[a] Dark arrows = direct reaction; light arrows = reaction in conjunction with other small molecules.

serve to weaken the Ir−S bonds to a degree that allows CO to cleave these bonds and generate the open structure **20**.[27] The reactivity trend established by this series of reactions corresponds with the trend in the basicity of the weak link. It also demonstrates that altering the components of an assembly results in different shape changes upon exposure to CO. In addition to CO, we have studied the reactivity of NO and SO_2 with assemblies generated via the WLA.[38]

Acetonitrile (MeCN) displays reactivity trends similar to that observed for CO in that it cleaves M−O and M−arene bonds to generate open macrocycles (Scheme 6, **21**).[18,21,31,37] There are several differences between the complexes formed using CO and MeCN as an ancillary ligand: (1) the coordination environment about the metal is four-coordinate with two MeCN molecules and two phosphines bound as opposed to the five-coordinate CO adducts; (2) structures containing metal centers that do not react with CO, such as Pd(II)[18] and Cu(I),[31] react with MeCN to generate open structures (**22**−**24**); (3) geometric isomers, such as **21a**,**b**, are observed where the phosphines of the hemilabile ligands are bound in cis and trans arrangements.[16,18,21,37] Also, the Rh(I) P,N complex **9** reacts with MeCN to generate a structure that is analogous to its CO adduct,[19] and the Cu(I) P,S complex **17b** opens completely to give **23** upon treatment of MeCN.[31]

While both CO and MeCN individually react with certain supramolecular assemblies to generate open structures, the combination of both ligands provides a method for fully opening additional assemblies due to the "push−pull" effect of the trans σ-donating and π-accepting ligands (Scheme 2).[14,15] For example, the Rh(I) P,N complex **9** when treated with CO and MeCN opens cleanly to **11c** in which all four Rh(I)−N bonds are cleaved.[19] Also, the Rh−S bonds in complex **8** can be cleaved by introduction of the combination of CO and MeCN, while they stay intact when either CO or MeCN is introduced independently.[27] In addition, the metal centers in complexes **10b** and **25** are available for ligand substitution reactions, which allows further control over the resultant macrocyclic properties (Scheme 7).[14,15,21]

2. Isocyanides. Changing the size of the ancillary ligands used to open the condensed structures easily controls the steric environment around the metal centers. In lieu of CO, isoelectronic isocyanides can be used to break the weak metal−heteroatom bonds.[14−16,27,31,37] In many of these structures, isocyanides are used in conjunction with nitriles to form "push−pull" complexes (Scheme 6). For example, complexes **26a**,**b** can be generated by treating compounds **8** and **16** with ^{t}BuNC and MeCN.[27] Similar reactivity is observed in Rh(I) P,O systems (e.g., **27**).[14−16,37] In addition, ^{t}BuNC alone can open Cu(I) assemblies (e.g., **17**) to give open macrocycles, such as **28**, in which two isonitrile and two phosphine ligands are bound to the metal tetrahedrally (Chart 4).[31] Owing to the large number of commercially available isocyanides, the steric and electronic properties of the metal center and

Scheme 7. Two Pathways to 3 via Ligand Substitution Reactions

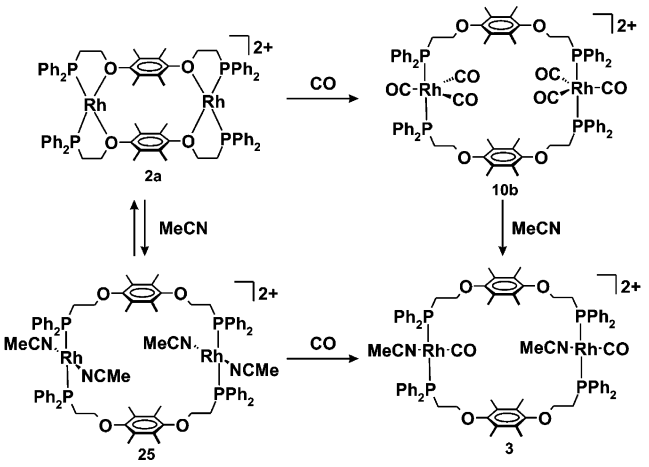
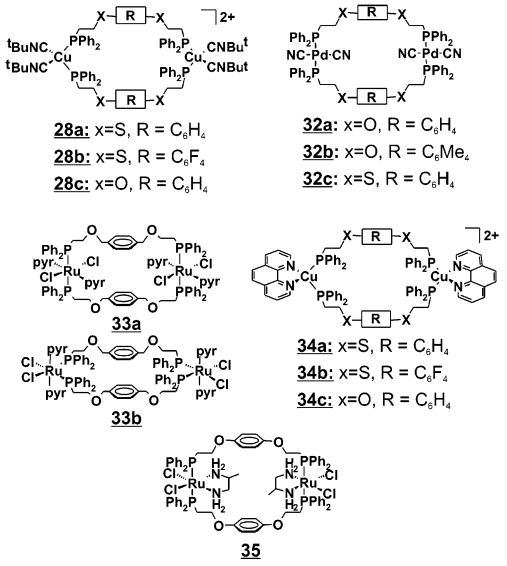


Chart 4



the cavity of the assembly can be easily tailored via choice of isocyanide.

3. Anion-Induced Opening. A majority of the ancillary ligands discussed thus far have been useful in opening assemblies that are comprised of P,O ligands. These ancillary ligands have had limited success in opening structures containing thioether (and to some extent, amine) weak links. Due to the strength of the M−S bond in structures such as **7**, ancillary ligands with a stronger affinity for the metal center are necessary to generate the fully opened structures, such as halide ions in conjunction with CO.[17] For example, treating complex **7** with Cl^- and CO gives structure **13** in which each Rh center is square planar with trans Cl^-/CO and trans phosphine ligands (Scheme 2).[17,23] Substitution of I^- for Cl^- yields structures in which the Rh(I) centers are in a trigonal bipyramidal arrangement with two CO and one I^- ligand equatorial and two axial phosphine ligands (**29**, Scheme 5).[17,27] This halide-induced ring opening also opens assemblies generated from P,O and P,N ligands to give flexible neutral macrocycles, such as **30** and **11d**, as well as Ir P,S assemblies, such as **31**.[17,19] Neutral assemblies also can be synthesized with Pd(II) macrocycles, such as **14**, by treatment with KCN to give **32** (Chart 4).[18]

4. Pyridines and Diamines. N-donor ligands, such as pyridine, diimines, and alkyldiamines, have been used to cleave metal weak links to generate open structures. For example, pyridine can be used to open Cu(I) or Ru(II) assemblies (e.g., **17** and **18**, Scheme 4) to give cationic macrocycles with 2 equiv of pyridine bound to each metal.[31,33] The structure containing octahedral Ru(II) centers opens to give two isomers, **33a**,**b** (Chart 4). Bidentate diimine ligands, such as 2,2′-bipyridine, can be used to generate the open cationic structures using Cu(I) and Ru(II) assemblies, such as **34**, as well.[31,33] Additionally, alkyl diamines, such as 1,2-diaminopropane, can be used to cleave the Ru(II)−O bonds in structures such as **18** to generate assemblies like **35**.[33]

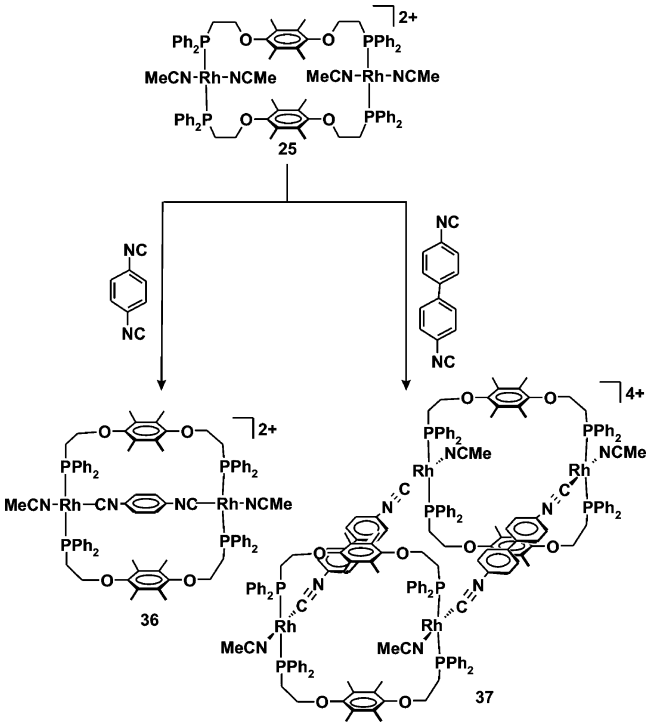
Supramolecular Assemblies of Increasing Complexity

The supramolecular assemblies discussed above provide a fundamental understanding of the nature of the WLA, as well as a reliable toolkit for the assembly of increasingly complex structures that take advantage of attributes garnered by the WLA. With a predictable synthetic methodology in hand, supramolecular assemblies of increasing intricacy can be generated. Importantly, the unique features of the WLA, such as the differences in weak-link strength and the ability to rationally tailor the assemblies by choice of metal and ligand precursors, allow one to generate supramolecular cylinders, tetranuclear squares, heterobimetallic assemblies, and ligand dissymmetric structures.

Cylinders and Trilayered Structures. The metal centers in the condensed structures generated via the WLA, as well as those in some open complexes (e.g., **25**), are available for further reaction. Hence, appropriately sized bifunctional molecules can be sequestered inside the cavity of the arrays to give structures such as **36** (Scheme 8).[14−16,27] The use of rigid bifunctional molecules that are too large to fit inside the cavity results in the nearly quantitative formation of molecular cylinders, such as **37**, which are comprised of two macrocycles and two linker molecules with an interior cavity of ∼1100 Å^3.[37]

Heterobimetallic and Heteroligated Assemblies. Heterobimetallic supramolecular assemblies **41** and **42** are generated by reaction of ligand **38**, which contains P,S and P,O moieties, with late transition metal centers, such as Rh(I) and Pd(II) (Scheme 9).[24] The differences in binding strengths of these weak links can be used to form structures in which the position of each metal center can be controlled by choice of reaction conditions (**39**−**42**). The weak bonds of these assemblies can be sequentially broken through appropriate ligand substitution reactions to generate a number of half- and fully opened complexes, **43**−**46**. Another example of a supramolecular assembly containing two different metal centers was generated from a bifunctional ligand that is capable of specifically binding Zn(II) and Rh(I) in different binding pockets.[20]

Scheme 8. Examples of Triple-Layered and Cylindrical Structures

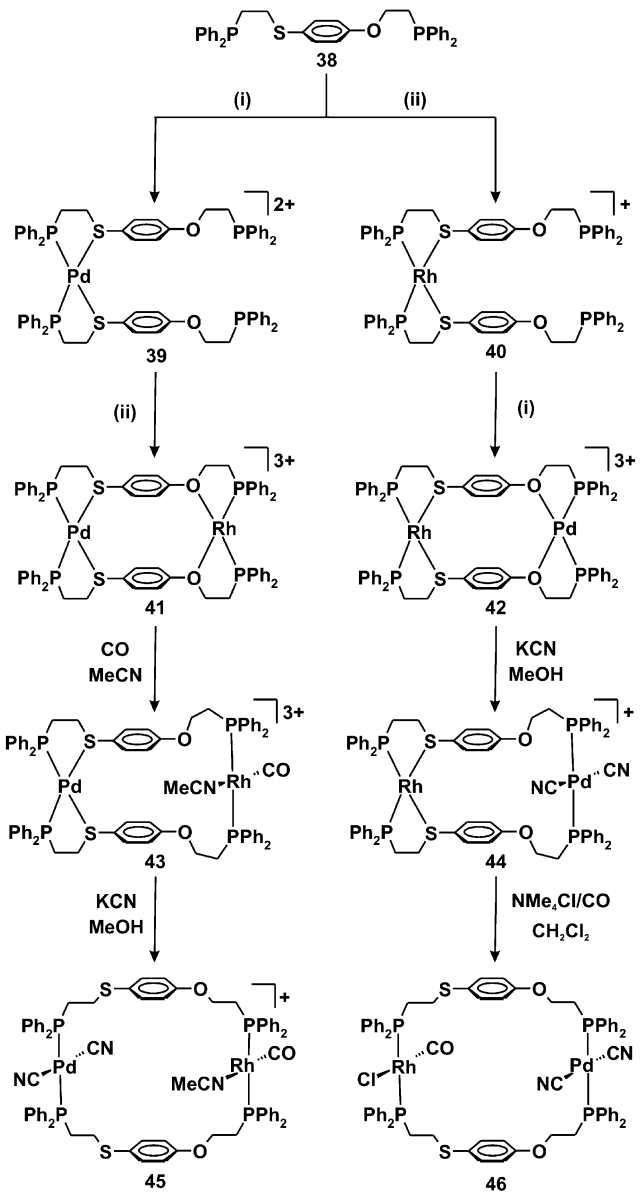


The WLA approach is useful for the construction of structures in which two distinct ligands are arranged around the metal centers (Scheme 10).[32] In this approach, the combination of a ligand (e.g., **5a**) with Rh(I) in 1:2 stoichiometry results in the formation of complex **47**. This complex can be combined with a variety of other hemilabile ligands (**1i**, **5d**, **6**) to generate ligand dissymmetric condensed assemblies, such as **48**. These condensed structures are opened using the halide-induced method to give the neutral macrocyclic arrays **49**.

Counterion-Driven Assemblies. Other pieces of the assembly besides the hemilabile ligand can play a role in the formation and function of supramolecular arrays. For example, an anion-dependent route for generating large flexible supramolecular squares has been demonstrated.[22] The 28-membered square assembly **50** is generated by adding ligand **6** to a Rh(I) source with a tosylate counterion. The use of other anions leads to the formation of complexes isostructural with **9**. Also, **50** can be converted to an analogous binuclear macrocycle upon heating (Scheme 11). This study suggests that many structures can be formed, but often not observed, en route to the condensed structures in the WLA.

An anion-dependent route for generating heteroligated supramolecular structures has been developed (Scheme 12).[30,42] In this methodology, halide ions cause a rearrangement in assemblies such as **51**, in which the ligands rotate to give structures that contain metal centers bound to one thioether, one chloride, and two phosphine ligands in a square planar arrangement (**52**). The chloride ligands can be abstracted to generate complexes (**53**) that resemble other bimetallic condensed structures with the important distinction of each Rh(I) center being bound heterotopically to one P,S and one P,O binding pocket.

Scheme 9. Cationic and Neutral Heterobimetallic Supramolecular Arrays[a]



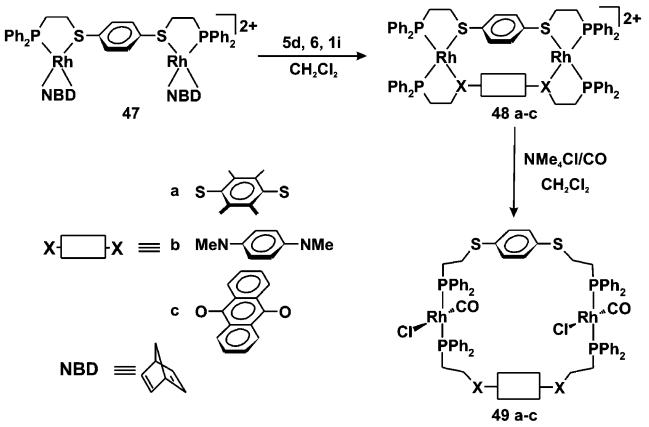
[a] (i) $Pd(MeCN)_4][BF_4]_2$, acetone; (ii) product of $[Rh(COE)_2Cl]_X + AgBF_4$, CH_2Cl_2.

Treatment of these condensed structures with small molecules, such as CO or MeCN, results in the cleavage of the Rh−O bonds to give half-open structures (**54**).

Functional Supramolecular Systems

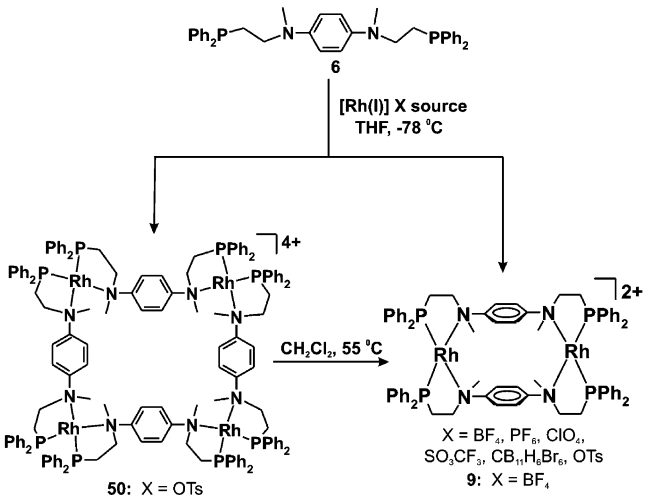
The development of the WLA has been driven by and has provided the impetus for the construction of several unique functional supramolecular systems. Reactivity diagrams, such as Scheme 5, and supramolecular assembly pathways (Scheme 8) are highly instructive tools for the design of hosts capable of incorporating guest molecules and catalysts that stabilize substrate interactions for reaction. The development of supramolecular architectures intended to function in a specific manner involves unique challenges in terms of synthesis as well

Scheme 10. Heteroligated Supramolecular Assemblies[a]



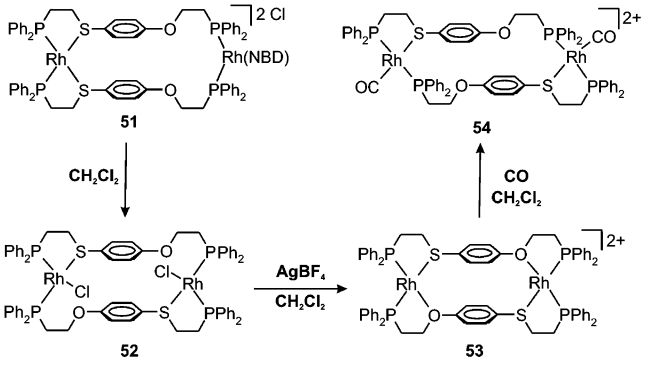
[a] **47** was treated with H_2 (1 atm) at −78 °C to hydrogenate NBD prior to addition of **6** and **1i** to generate **48b**,**c**. **5d** reacted with **47** at rt with no H_2 added to give **48a**.

Scheme 11. Anion-Dependent Synthesis of a Tetranuclear Supramolecular Square[a]



[a] [Rh(I)]X source generated from $[Rh(COE)_2Cl]_n$ + AgX.

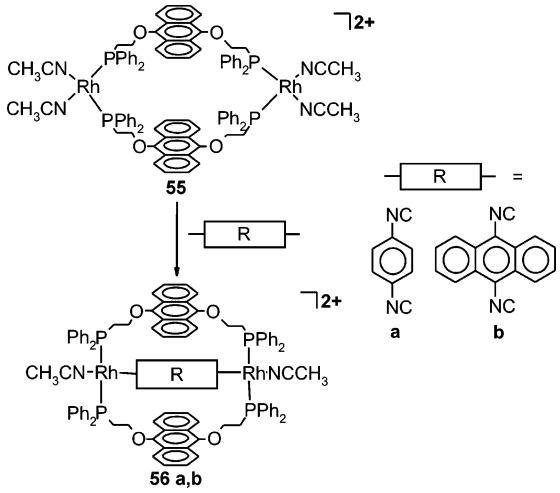
Scheme 12. Halide-Induced Ligand Rearrangement in Supramolecular Assemblies



as in the compatibility of the chemistry used to generate the assembly with that occurring at the active sites.

Host−Guest Systems as Molecular Sensors. The ability to design a cavity capable of recognizing specific guest molecules is of great interest.[12] Supramolecular chemistry has the potential to provide the requisite level of control over large assemblies possessing the well-defined cavities

Scheme 13. Fluorescent Donor−Acceptor−Donor Sensors



necessary for this type of sensor. However, actual implementation of supramolecular arrays in host−guest chemistry and molecular sensing is rare.[4] The WLA provides a unique opportunity to assemble structures that incorporate guest or analyte molecules into their cavities using the unsaturated metal centers as docking sites or through noncovalent interactions with a carefully designed cavity.

1. Metal-Directed Sequestration of Guest Molecules. A number of systems were discussed in the previous section that are capable of incorporating guest molecules within the cavity of open macrocycles (Scheme 8). The systems in this section differ from the previous examples in that the presence of the guest molecule is conveniently detected using properties of the macrocyclic cavity and spectroscopy. For example, incorporation of a redox-active group in the macrocyclic backbone allows for electrochemistry to be used as a probe of the coordination environment about the metal centers.[19] Specifically, irreversible oxidation is observed for the condensed structure **9** (E_{pa} = 320 mV) in which the Rh(I)−N bonds are intact. Upon coordination of molecules such as CO or MeCN, two of the four Rh(I)−N bonds are broken, which results in a shift in the oxidation potential (**11a**,**b**: E_{pa} = 170, 205 mV, respectively). Furthermore, when all of the Rh(I)−N contacts are broken, these macrocycles exhibit reversible redox behavior (**11d**, $E_{1/2}$ = −120 mV).

Concurrently, a system has been developed that takes advantage of the properties of the internal macrocyclic cavity and the transition metal centers to direct the sequestration of guest molecules resulting in the high yield synthesis of triple-layered fluorescent metallocyclophanes (Scheme 13).[16] In this system, the combination of coordinative unsaturation at the metal centers and the use of appropriately sized bifunctional guest molecules drives the formation of the triple-layered structures **56**. The aromatic group of the guest molecule aligns cofacially with the aromatic rings in **55** to give a donor−acceptor−donor arrangement. The photophysical properties of these structures allow for these assemblies to be used as synthetic receptors that give a measurable spectrophotometric response upon guest binding. More specifically, the pres-

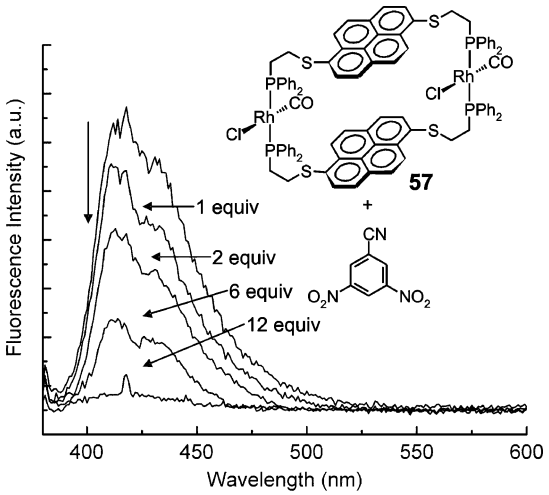


FIGURE 2. Noncovalent host–guest sensor.

ence of the analyte is detected by monitoring the quenching of the fluorescence from **55** upon addition of the guest.

2. Cavity-Driven Sequestration of Guest Molecules. The supramolecular sensor concept has been extended to the challenge of encapsulating guest molecules via weak interactions with the macrocyclic environment. This type of sensor is demonstrated by the molecular recognition properties of bimetallic macrocycles (such as **57**) that contain large aromatic groups in their backbones, which provide the potential for $\pi-\pi$ stacking interactions with analytes (Figure 2).[39] The incorporation of electron-deficient aromatic guests results in significant fluorescence quenching, which signals the presence of the guest. Critically, the use of Cu(I) in lieu of Rh(I) in the formation of the metallopyrenophanes results in assemblies with larger quantum yields in the absence of guest. This result illustrates how the WLA allows one to tailor aspects of these structures through rational choice of building blocks while maintaining a high synthetic yield.

A second approach to the noncovalent incorporation of small molecules utilizes an enantiomerically pure monometallic assembly in which guest binding is pseudoallosterically initiated by the binding of an ancillary ligand that results in an increased cavity size (Figure 3).[35] In this case, positive heterotropic pseudoallosteric interactions occur at structure control site (Cu) of **58** that influence the cavity size and shape, and hence the binding properties of the system. Upon opening of the cavity, the chiral BINOL moieties in the macrocycle direct guest molecules of specific chirality into the assembly to interact with the hydrogen bonding sites in the cavity. Changes in fluorescence intensity show that complex **59** has a higher affinity for *(S)*-mandelic acid over the (*R*) enantiomer. This type of pseudoallosteric switch for guest incorporation can lead to sensors capable of undergoing uptake and release cycles for separation of enantiomers or sensor recycling.

Catalytic Systems. The WLA provides a route to flexible supramolecular catalysts that have the additional capability of adjusting cavity size and shape. With any supramolecular synthetic strategy, a certain amount of rigidity is necessary to generate systems selectively and in high yield, although, in most cases, it is a mistaken strategy to target only the most rigid structures.[11] With control over the shape and flexibility of a supramolecular catalyst, allosteric abiotic catalysts can be developed that address the fact that allosteric regulation is a ubiquitous form of control in biological systems[1] yet remains a rarity in synthetic catalysts.[12]

Through development of the WLA, it became apparent that catalytic systems could be synthesized that provide a platform for the introduction of a range of allosteric protagonists (i.e., ancillary ligands) that would operate as on/off switches. This methodology provides an avenue to synthetic systems that utilize biological-like control over catalytic processes. A key aim is to develop systems that

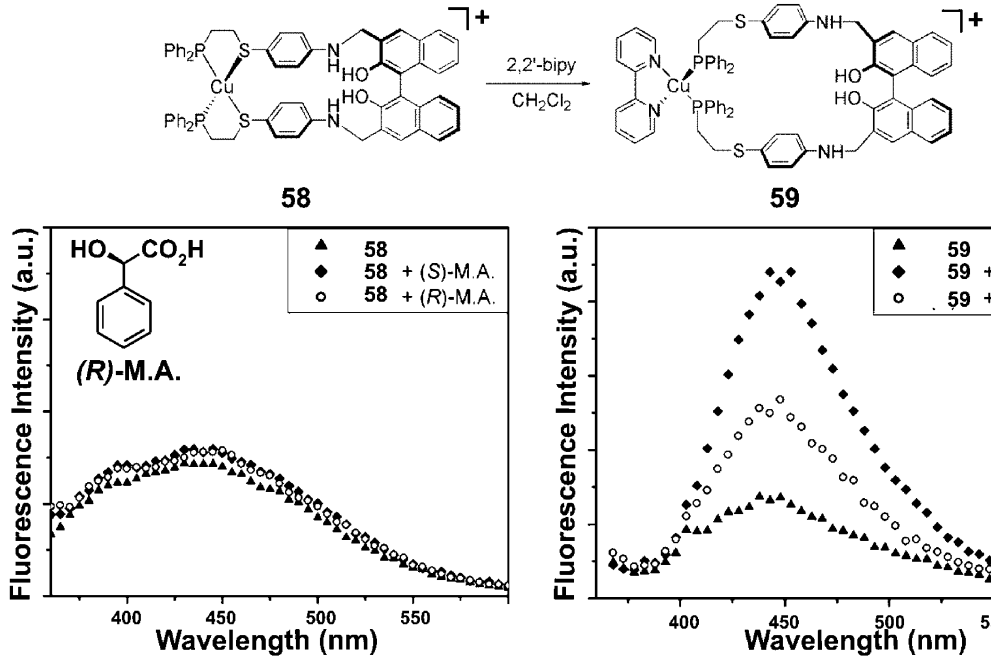
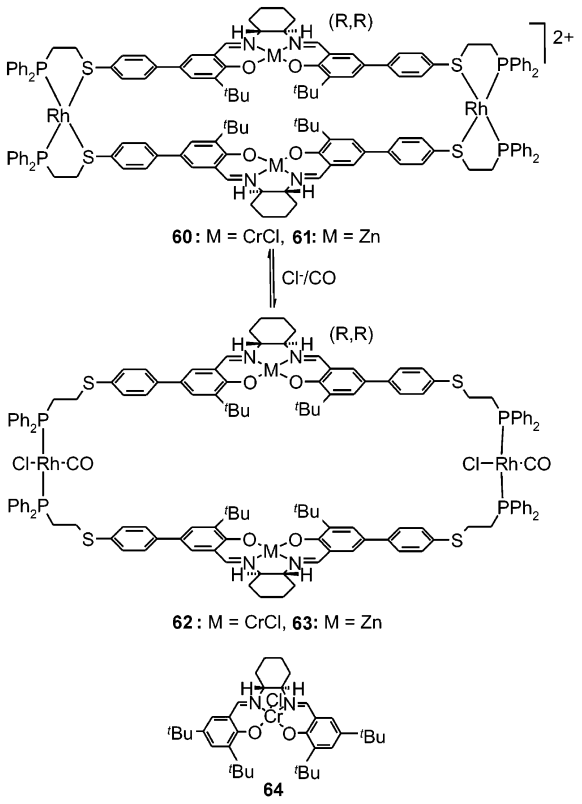


FIGURE 3. Pseudoallosteric chiral detectors.

Scheme 14. Macrocyclic Supramolecular Allosteric Catalysts and Monomeric Analogue



are fully addressable in the presence of substrate molecules providing for in situ switches for catalysis. Critical to the design of functioning supramolecular catalysts is that the chemistry used in the assembly process be orthogonal to that occurring at the catalytic centers. This provides reliable catalytic systems that can further enable independent addressability of metal centers. Initially, we established the viability of the WLA in the assembly of an addressable allosteric catalyst.[25] Given that metallosalens catalyze certain reactions in a bimetallic fashion and given the array of catalytic transformations that are possible with metallosalens,[40] the initial architectures containing Cr(III) metal centers (**60**, **62**) and Zn(II) centers (**61**, **63**) were synthesized (Scheme 14). An essential design feature of this first generation allosteric catalyst is the structural Rh(I) metal centers that flank the catalytic metal centers. When the catalytic sites are built into the macrocyclic cavity, substrate and catalyst interactions can be controlled. A significant allosteric effect is generated by adjusting the distance between the catalytic metal centers using chemistry occurring at the Rh(I) metal centers. For instance, the rate of asymmetric ring opening of epoxide doubles upon opening **60** with CO/Cl^- to give **62**. While demonstrating a significant allosteric effect in terms of rate of reaction, both catalysts give very similar ee's (~70%). This is a marked improvement compared to the 12% ee achievable using the monomeric analogue **64**[40] at the same catalyst loading with respect to the Cr(III) centers (0.12 mol %) under these conditions.

The second generation allosteric catalysts make use of a tweezer configuration of catalytic active sites (Figure 4).[29]

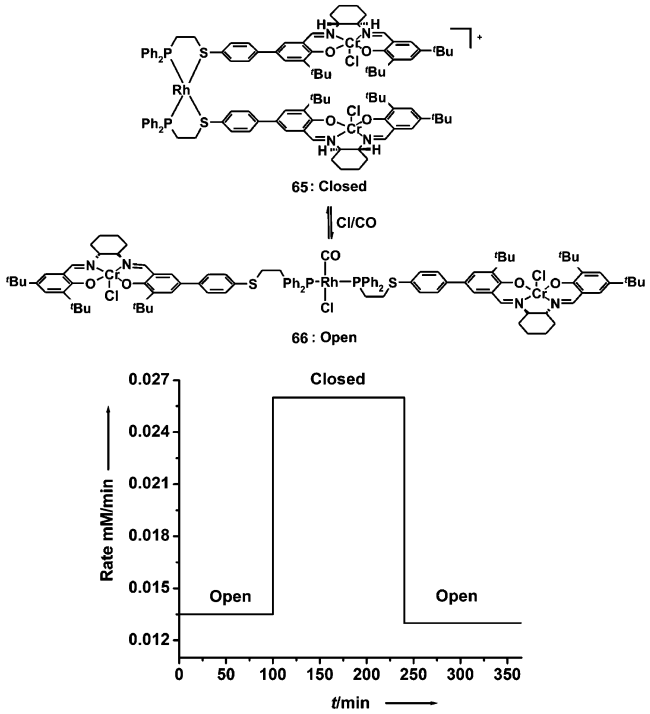


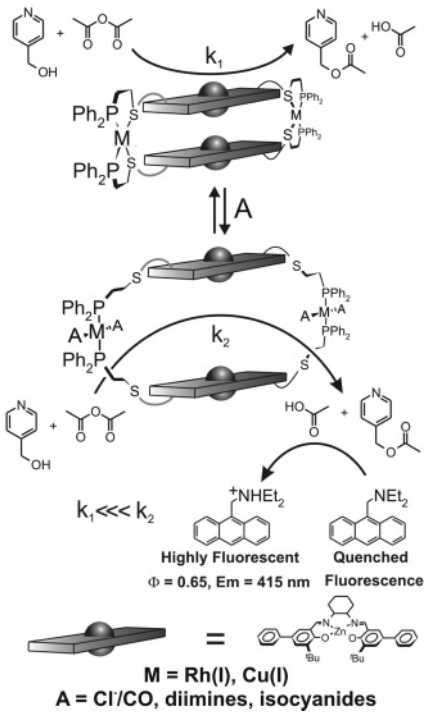
FIGURE 4. Allosteric catalytic tweezers.

The hemilabile switch described above for the macrocyclic system was adapted to form the hinge of the molecular tweezers **65** and **66**. This assembly provides a much larger shape change upon binding of the allosteric effectors than in the macrocycle, resulting in a greater ability for rate and enantioselectivity switching. Importantly, the shape change and, subsequently, the activity switching occur reversibly in situ. This ability opens up possibilities in terms of catalytic regulation, including substrate switching and block copolymerization.

This approach to supramolecular catalysts may have broader implications in the study of other bimetallic reactions and in reactions involving combinations of catalysts and cocatalysts operating in the same supramolecular assembly. Furthermore, the generality of the WLA provides the means for the development of specifically addressable structure control elements compatible with any catalytic process one wishes to control by means of a chemical on/off switch. This work represents some of the initial demonstrations of allosteric catalysts made possible through supramolecular coordination chemistry. More importantly, they represent some of the closest mimics of biological allosteric enzymes in terms of possessing addressable structural sites and well-defined distal catalytic sites.

Signal Amplification and Detection via a Supramolecular Allosteric Catalyst. One of the goals of mimicking control mechanisms used in biological systems is to access chemistry amenable to abiotic applications. One such possibility involves adapting the systems described above for use as allosteric catalytic amplification devices.[41] Indeed, an abiotic assay similar to enzyme-linked immunosorbent assay (ELISA) capable of detecting a broad range of analytes would be a major advance. If an

Scheme 15. Signal Amplification and Detection Using a Supramolecular Allosteric Catalyst



allosteric binding event is viewed as a small molecule detection event, then an allosteric catalyst can be used as a catalytic signal enhancement agent. This hypothesis led to the development and demonstration of a supramolecular allosteric detection and signal amplification system (Scheme 15).[34,36] This approach brings together three key elements to effect efficient and facile recognition, amplification, and detection of analyte. First, the analyte binds to the allosteric catalyst. Second, the binding results in a topological change that switches on the catalyst giving a significant increase in the rate of acyl transfer from acetic anhydride to pyridylcarbinol. Third, the products of the reaction can be measured by GC or coupled to a pH-sensitive fluorophore to generate a visible response. In this manner, nanomolar concentrations of Cl^- ions and diimine molecules were catalytically amplified and detected. The essential component is the allosteric effect that gives rise to the significant rate difference and allows for differentiation between the activated and inactive catalyst, both by GC and by the fluorescence method. In light of the generality of the WLA demonstrated above, several strategies for the expansion of this detection scheme are apparent. For example, Chart 3 illustrates several opportunities for expanding this detection strategy to a range of chemically and biologically relevant analytes.[36]

Conclusions and Outlook

Ultimately, the power of the WLA lies in the ability to arrange multiple components within the context of a structurally flexible macrocyclic assembly to design and build novel systems not attainable by other approaches. Expanding the scope of the WLA has provided and will continue to provide avenues for the investigation and development of functional systems including catalytic and host−guest arrays. Biology ubiquitously employs complex systems, such as signal cascades, molecular shuttles, chaperones, and highly specialized channels. Many of these systems are enabled by the careful deployment of multisubunit polypeptides held together by noncovalent interactions. These structures and the processes they facilitate establish a set of challenges and, in some cases, a blueprint for the supramolecular chemist. As we develop synthetic methodologies for assembling large supramolecular arrays, the plausibility of achieving the majesty of cellular processes in entirely nonbiological systems can become a reality.

Note Added after ASAP Publication: An error was discovered in the catalyst loading for analogue **64** in the version published ASAP September 16, 2005. The corrected version was published ASAP September 28, 2005.

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