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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Perspective

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Allosteric Supramolecular Coordination Constructs

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ABSTRACT: Coordination chemistry is regularly used to generate supramolecular constructs with unique environments around embedded components to affect their intrinsic properties. In certain cases, it can also be used to effect changes in supramolecular structure reminiscent of those that occur within stimuli-responsive biological structures, such as allosteric enzymes. Indeed, among a handful of general strategies for synthesizing such supramolecular systems, the weak-link approach (WLA) uniquely allows one to toggle the frameworks' structural state post-assembly via simple reactions involving hemilabile ligands and transition metal centers. This synthetic strategy, when combined with dynamic ligand sorting processes, represents one of the few sets of general reactions in inorganic chemistry that allow one to synthesize spatially defined, stimuli-responsive, and multicomponent frameworks in high to quantitative yields and with remarkable functional group tolerance. The WLA has thus yielded a variety of functional systems that operate similarly to allosteric enzymes, toggling activity via changes in the frameworks' steric confinement or electronic state upon the recognition of small molecule inputs. In this Perspective we present the first full description of the fundamental inorganic reactions that provide the foundation for synthesizing WLA complexes. In addition, we discuss the application of regulatory strategies in biology to the design of allosteric supramolecular constructs for the regulation of various catalytic properties, electron-transfer processes, and molecular receptors, as well as for the development of sensing and signal amplification systems.

1. INTRODUCTION

The development of macromolecular structures that mimic the three-dimensional environments in enzyme active sites represents a major goal of supramolecular chemistry. The impetus behind these efforts is the remarkable performance that enzymes can achieve in terms of their catalytic and stimuli-responsive properties via the control of their supramolecular environment.[1] Thus, supramolecular chemists have used common structural themes in enzymes to design inorganic catalytic and sensing systems capable of enhanced substrate recognition, rate, selectivity, and chemically induced regulation.[2] Among the large variety of strategies available for the construction of bioinspired supramolecular systems,[3] coordination-driven assembly represents an attractive approach since it allows one to quickly synthesize sophisticated and three-dimensionally defined structures in a modular fashion.[4]

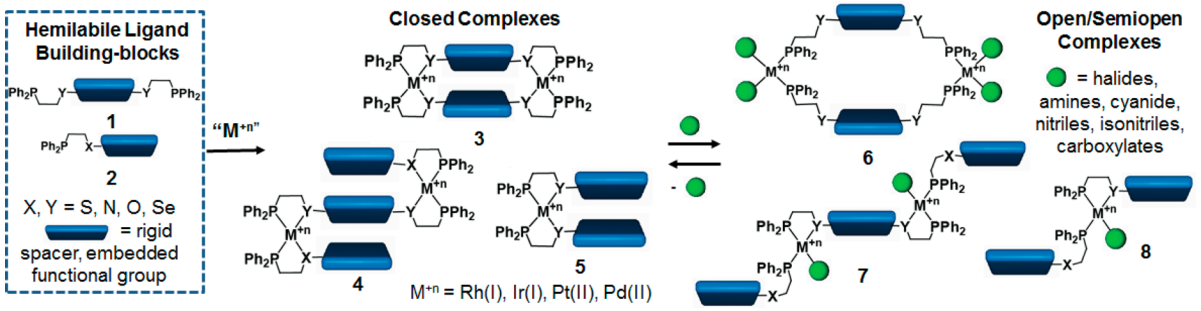
While coordination complexes have been extensively used toward the construction of functional, supramolecular systems, there are only a handful of general synthetic strategies that allow one to access coordination-driven assemblies in a reliable and predictable fashion. Namely, the symmetry interaction approach (SIA),[5−8] the directional bonding approach (DBA),[9−12] and the weak-link approach (WLA)[13,14] can be used to design structural frameworks capable of incorporating a large number of functional moieties. At the core of these three conceptually distinct synthetic approaches are a number of fundamental coordination reactions that guide the assembly of ligands and metal centers into specific structures under a wide variety of conditions. For example, both the SIA and DBA are based on imposing geometric constraints at structural coordination nodes to guide the assembly of coordinating ligands into rigid frameworks with predictable three-dimensional shapes.[4] The WLA, on the other hand, is a synthetic strategy that allows for the assembly of structurally switchable coordination scaffolds in which metal centers act as structural hinges that can be chemically and reversibly actuated (Scheme 1). Drawing from the seminal work of the Rauchfuss,[15] Sanger,[16] and Anderson groups,[17] among others, the WLA exploits well-known partial ligand displacement reactions that allow one to access a coordination site at a metal center as a means to generate supramolecular assemblies with structural switchability. As such, the WLA has been at the forefront of efforts to build stimuli-responsive and bioinspired systems that can be switched between active states by manipulating supramolecular structure.

The synthesis of WLA supramolecular frameworks does not depend on pre-templating structural nodes or trapping specific coordination states, but it is rather based on tuning the coordination behavior of metal cations, hemilabile ligands, and ancillary coordinating species, and possible interligand interactions such as $\pi-\pi$ stacking. Doing so allows one to employ hemilabile ligands of the kind of **1** and **2** to drive the exclusive formation of macrocycle (**3**) and tweezer complexes (**5**)[18] (Scheme 1). Furthermore, dynamic ligand exchange processes, collectively termed the halide-induced ligand rearrangement (HILR) reaction,[19] can be triggered by design in the context of the WLA to selectively assemble complexes in which each metal center is bound to two different ligands. These ligand sorting processes, which uniquely give rise to triple-layer (**4**)[20] and heteroligated tweezer complexes,[21] operate regardless of a broad range of ligand modifications. As a result, the combination of the WLA and the HILR represents one of the few reactions in inorganic chemistry that can be used to reliably assemble multicomponent and geometrically defined supramolecular structures

Received: January 30, 2015
Published: June 2, 2015

DOI: 10.1021/jacs.5b01054
J. Am. Chem. Soc. 2015, 137, 7252−7261

Scheme 1. Weak-Link Approach Supramolecular Coordination Complexes



in high to quantitative yields and with remarkable functional group tolerance.

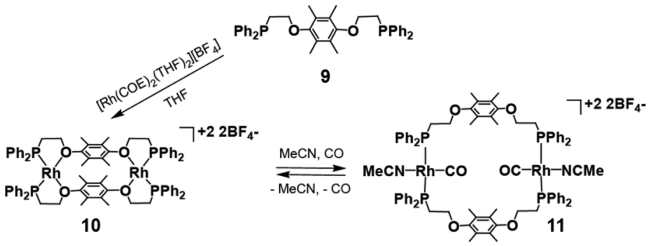
The toggling of condensed, rigid complexes (**3**−**5**) into open, flexible states (**6**−**8**) is effected by disrupting the coordination between the metal center and the weakly coordinating heteroatom in the hemilabile ligand using small molecules and/or anions (Scheme 1).[14] Importantly, the hemilabile ligands can be functionalized with a large variety of chemical species without compromising the structural switchability of the WLA complexes. Thus, by incorporating functional groups whose activity depends on their specific orientation and distance relative to the rest of the framework, the WLA can be exploited to regulate a host of physical and chemical properties via simple and reversible coordination reactions. This kind of regulation of an active site through the orthogonal coordination chemistry of a distal metal center is highly reminiscent of allosteric control of enzymatic activity.[22] That is, in both allosteric enzymes and WLA complexes, chemo-recognition events at distant allosteric receptors trigger conformational changes that affect the shape and activity of embedded active sites.[23] Thus, researchers have used the WLA to mimic various regulatory properties of natural systems, as well as applying this bioinspired strategy to the control of chemical reactions that transcend beyond the scope of biological systems.[18]

Throughout the past decade a deep understanding of the fundamental coordination reactions involving the chemistry of hemilabile ligands on d^8 metal centers has been developed. This has provided the foundation for the wide variety of structures synthesized using the WLA. Indeed, this understanding is the backdrop that has allowed us to move beyond simple, symmetrical structures to highly unsymmetrical and multifunctional, switchable frameworks. Herein, we provide the first full mechanistic description of the coordination reactions responsible for the formation of WLA frameworks with different metal centers. We also discuss recent functional structures that this mechanistic understanding has enabled for sensing, signal amplification, and catalytic applications.

2. THE WEAK-LINK APPROACH

The first WLA structures consisted of symmetric metallocyclophanes, which are reversibly toggled between rigid, closed and flexible, open states (Scheme 2).[24] For example, macrocycles **10** and **11** are composed of two Rh(I) metal centers and two homoditopic hemilabile ligands (**9**), in which the two chelating groups of each ligand are bridged by rigid spacers. This particular ligand design enables the quantitative formation of $Rh(I)_2L_2$ supramolecular structures, and thus circumvents the formation of any oligomeric or polymeric product. Key to the formation of the targeted structure is the electronic preference for the *cis*

Scheme 2. Synthesis of Macrocyclic Structures via the WLA[a]



[a]Adapted with permission from ref 24. Copyright 1998 John Wiley and Sons.

coordination mode of the phosphine−heteroatom hemilabile ligands, in addition to the energetic contribution arising from $\pi-\pi$ stacking interactions between the rigid aromatic spacers.[25] $Rh(I)_2L_2$ macrocyclic structures do not directly arise from the use of homoditopic ligands only when kinked rigid spacers are introduced between the hemilabile coordinating groups,[26] or when the coordination strength of the heteroatom is particularly weak.[27] Instead, the use of kinked ligands results in $Rh(I)_4L_4$ supramolecular squares that only transform into the expected $Rh(I)_2L_2$ macrocyclic structure upon heating. In the case of very weakly binding hemilabile heteroatoms, such as alkyl phenyl ether, prolonged heating results in displacement of the Rh(I)−O bond and metal coordination to the aryl spacer.[27] These observations suggest that the WLA macrocycle formation with Rh(I) nodes represents a local energy minimum that can be usually accessed directly or via other, more energetic oligomeric structures. In other words, WLA systems with Rh(I) are under kinetic control as opposed to the thermodynamic control typically associated with the DBA and SIA.

The introduction of ancillary ligands leads to the displacement of the weaker heteroatom coordinating units from the WLA metal center and the expansion of the overall structure into semiopen or fully open complexes. The selectivity of the WLA construct for different allosteric effectors can be tuned by replacing the Rh(I) center with other transition metal cations such as Pt(II),[28] Pd(II),[29] Ru(I),[30] Ir(I),[31] Cu(I),[32] and Ni(II).[33] The partial displacement of the hemilabile ligands can be reversed in situ in the case of halides, for example via abstraction with non-coordinating sodium, silver, and thallium salts, or via evacuation of the solvent and re-dissolution, in the case of CO and MeCN (Scheme 2). In either case, the integrity of the overall framework is not disrupted throughout multiple cycles of hemilabile ligand displacement and re-coordination.

In the case of macrocyclic structures, the moieties embedded in the hemilabile ligands are aligned in a parallel, co-planar fashion in the closed state, and the introduction of allosteric

DOI: 10.1021/jacs.5b01054
J. Am. Chem. Soc. 2015, 137, 7252−7261

effectors results in increased interligand separations (Figure 1).[23] Tweezer structures, on the other hand, generally yield closed

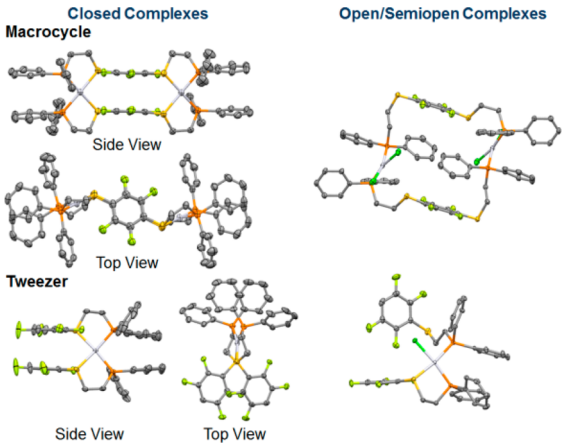


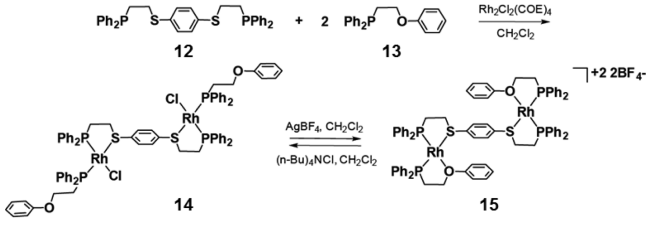
Figure 1. Single-crystal X-ray diffraction structures drawn with 50% thermal ellipsoid probability of WLA macrocycles[34] and tweezers.[35] Platinum atoms are light gray; sulfur, yellow; phosphorus, orange; fluorine, bright yellow; and carbon, dark gray. Hydrogens and counterions are omitted. Adapted with permission from refs 34 and 35. Copyright 2013 American Chemical Society and 2011 Nature Publishing Group.

complexes in which the embedded moieties are arranged in a stepped fashion.[20,34] Thus, the WLA provides a unique means toward varying the distance and orientation between functional groups embedded in the hemilabile ligands' rigid spacers using simple coordination chemistry reactions.

3. HALIDE-INDUCED LIGAND REARRANGEMENT

Synthetic routes for the construction of heteroligated complexes have been developed for SIA, DBA, and WLA systems that allow one to incorporate several functional components within the context of a single supramolecular framework. For instance, the use of pairs of pyridine ligands that differ in terms of their steric bulk can be used to drive the exclusive formation of heteroligated DBA complexes.[36] On the other hand, the electronic preference of Cu(II) metal nodes for pentacoordinate complexes can be used to sort bipyridine and terpyridine ligands into heteroligated SIA structures selectively.[37] In WLA systems, it was observed that using a halide salt in combination with two hemilabile ligands of significantly different chelating strength resulted in the clean formation of halide-bound, semiopen heteroligated structures (Scheme 3).[19,38] Systems that do not fulfill both of these requirements tend to form mixtures of two distinct homoligated

Scheme 3. Heteroligated Complexes Synthesized via the Halide-Induced Ligand Rearrangement[a]

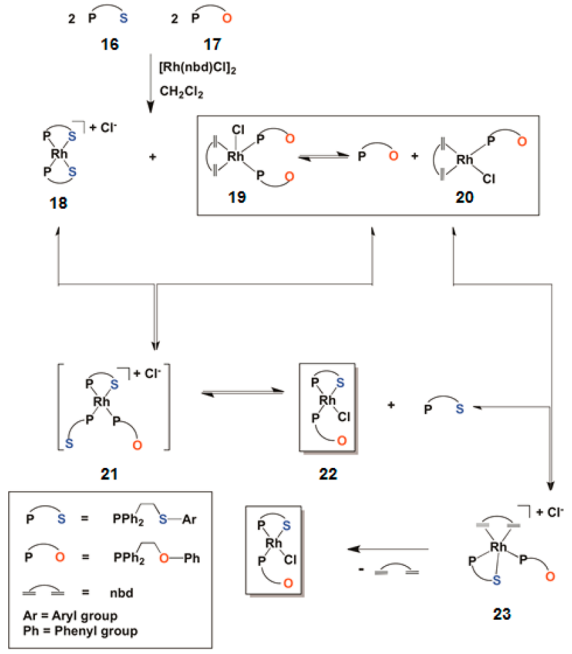


[a]Adapted with permission from ref 20. Copyright 2006 American Chemical Society.

complexes or an irresolvable complex mixture. Since the formation of heteroligated WLA complexes exclusively occurs in the presence of halide salts,[21] the ligand sorting process is termed HILR reaction. The required difference in chelating strength may be attained by varying the type of labile heteroatom (i.e., P,S **12** and P,O **13**)[19] or the electron density of the aryl spacer attached to it (i.e., P,S-benzyl and P,S-tetrafluorobenzene).[39] Sequential chloride abstraction and re-introduction steps allow for the inter-conversion between the closed (**15**) and semiopen coordination states (**14**) without shuffling the ligands into mixtures of homoligated and heteroligated products. Significantly, the ability to selectively place two different ligands around a single WLA metal center has opened the way to the high-yielding synthesis of triple layer structures (Scheme 3). As a result, the combination of the WLA and the HILR reaction enables a general coordination methodology for positioning multiple functional groups in a parallel or stepped fashion (A-B or A-B-A) and subsequently toggling the degree of spatial separation between them.

By slowing the sorting process with the use of Rh(I) ancillary ligands that are sluggishly displaced by the hemilabile moieties, it was possible to gain an insight into the mechanism of the HILR reaction (Scheme 4).[19] In particular, it was observed that the

Scheme 4. HILR Reaction Mechanism in Rh(I) Complexes[a]



[a]Adapted with permission from ref 19. Copyright 2012 American Chemical Society.

hemilabile ligand mixture initially formed two sets of homoligated Rh(I) complexes, one in which the stronger hemilabile ligands are fully chelated and the chloride remains as an outer-sphere counterion (**18**), and another one containing two of the weaker hemilabile ligands only bound through the P, an inner sphere chloride, and a chelated ancillary ligand (**19**). Importantly, **19** exists in a dynamic equilibrium with a tetracoordinate species (**20**) that results from the release of an equivalent of the weaker hemilabile ligand. The free ligand can in turn coordinate to **18**, producing the semiopen heteroligated complex **22** via **21** and transiently displacing an equivalent of the stronger ligand. The stronger ligand then binds to **20**, which

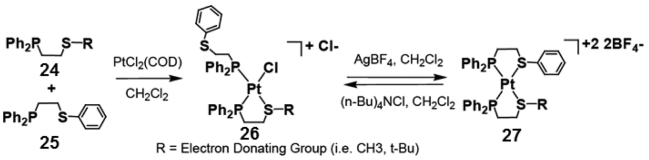
DOI: 10.1021/jacs.5b01054
J. Am. Chem. Soc. 2015, 137, 7252−7261

similarly rearranges via **23** to the target heteroligated complex. Thus, a series of hemilabile ligand displacement reactions triggered by the presence of a halide counterion results in two coordination reaction pathways that converge into the formation of a semiopen, heteroligated complex.

4. HILR IN PLATINUM(II) AND PALLADIUM(II) COMPLEXES

Following the development of a synthetic protocol for accessing heteroligated Rh(I) WLA complexes via the HILR reaction, efforts were made to apply the same methodology to Pt(II)[28] and Pd(II)[40] complexes in order to achieve air-stable systems. When the dichloride salts of these metal centers are exposed to a mixture of two different P,X hemilabile ligands in aprotic solvents, however, the mixture does not generally rearrange into a single, heteroligated product. Instead these reaction conditions lead to mixtures of heteroligated and homoligated complexes. At the core of this issue is the presence of a second chloride counterion, which introduces fluxional exchanges between coordination modes (i.e., between open, semiopen, and closed states), thereby interfering with the HILR process. It was nevertheless observed that when a very strongly chelating hemilabile ligand is employed (**24**), such as P,S-CH_3, the expected semiopen heteroligated complex **26** is obtained (Scheme 5).[41] This observation was initially attributed to the

Scheme 5. Formation of Heteroligated Pt(II) WLA Complexes[a]

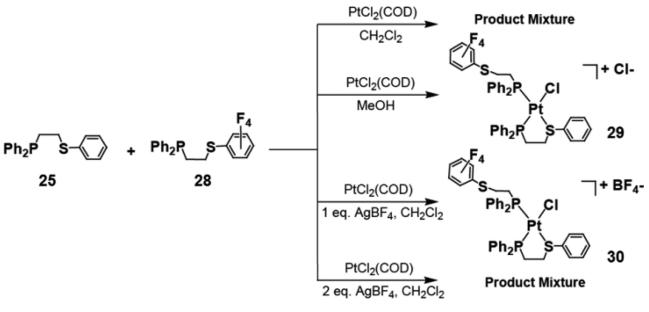


[a]Adapted with permission from ref 41. Copyright 2010 American Chemical Society.

fact that the chelation of the more strongly coordinating hemilabile ligand was an important step in stabilizing the initial formation of monoligated complexes, which subsequently leads to the ligand sorting typical of monocationic Rh(I) centers.[42]

Later observations showing that heteroligated Pt(II) complexes formed in polar protic solvents such as methanol, even when neither of the two hemilabile ligands were strong chelators (e.g., **25**, **28**), provided a different, broader perspective (Scheme 6).[34,43] That is, dilution in methanol stabilizes the second chloride as an outer-sphere counterion, thereby enhancing the relative chelating strength of the hemilabile ligands and enabling the HILR reaction. Consistent with this view, abstraction of a

Scheme 6. HILR Reaction in Pt(II) Systems



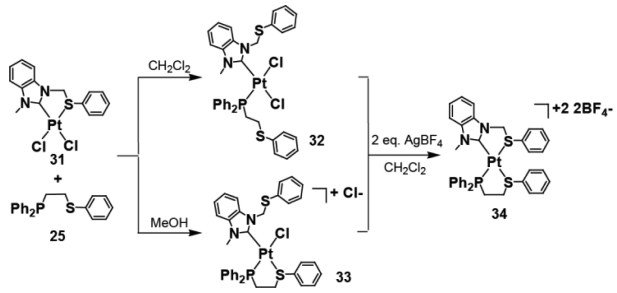
single chloride counterion in aprotic solvents resolves the complex mixture into the heteroligated semiopen **30**.

The WLA, in combination with the HILR, represents a unique set of inorganic reactions for the assembly of multicomponent systems since it is not based on imposing steric constraints or on restricting the coordination ability of the transition metal center to sort the ligands into heteroligated complexes, as is typical of other coordination assembly approaches. Instead, the assembly of heteroligated WLA complexes is based on tuning the electronic properties of hemilabile ligands by leveraging the coordination strength of the weakly coordinating heteroatom moiety and by stabilizing crucial intermediates in the ligand rearrangement process.

5. CARBENE-BASED HEMILABILE LIGANDS

Since the HILR reaction initially involves the formation of homoligated complexes, the successful synthesis of heteroligated WLA systems is highly dependent on the stabilization of all the reaction intermediates in solution. This key point becomes particularly problematic for systems employing functional hemilabile ligands that form homoligated complexes that exhibit low solubility[44] and whose precipitation can easily offset the ligand sorting process and prevent the formation of the target structures. In order to circumvent this issue, an alternative, stepwise route to Pt(II) heteroligated complexes was developed which makes use of a combination of N-heterocyclic carbene (NHC)- and diphenylphosphine-based hemilabile ligands (Scheme 7).[45] For instance, a NHC-thioether ligand can be

Scheme 7. Heteroligated Complexes with NHC Ligands[a]



[a]Adapted from ref 45 by permission of The Royal Society of Chemistry.

chelated to Pt(II) via a silver transmetalation route to give **31**. Isolation of this complex and sequential addition of a P,S hemilabile ligand in CH_2Cl_2 results in a heteroligated, open complex (**32**). In comparison, the same fully open coordination configuration is unattainable in heteroligated Pt(II) complexes composed solely of P,X ligands. It is interesting to note that, even though the NHC group is more strongly coordinating than the diphenylphosphine, dissolution of complex **32** in MeOH results in semiopen complex **33** in which the P,S ligand, rather than the carbene ligand, is chelated. This behavior is likely associated with the increased ring strain that follows chelation of the NHC ligand. Nevertheless, both chlorides in **32** and **33** can be abstracted quantitatively with a silver non-coordinating salt to access the heteroligated closed complex **34**. Unlike P,S-based WLA complexes, exposing NHC-based complexes to excess Pt(II) precursor does not result in ligand exchange between metal centers. This observation suggests that NHC-based WLA systems could be used to design systems that involve multiple active complexes, such as catalytic reaction cascades, thus

DOI: 10.1021/jacs.5b01054
J. Am. Chem. Soc. 2015, 137, 7252−7261

representing an important step toward increasing the complexity of stimuli-responsive abiotic systems.

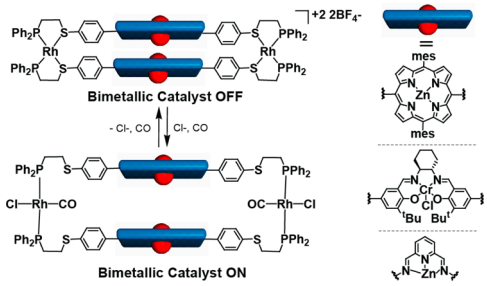
6. FUNCTIONAL WLA SYSTEMS

The ability of the WLA to regulate supramolecular structure in situ and reversibly makes it unique among other general strategies for building supramolecular constructs via coordination chemistry. In early examples of functional WLA systems, macrocycles and homoligated tweezers were synthesized as reactive cavities that are opened by small molecule effectors that bind to the structural regulator.[23] Such systems were the result of the limitations involving the sorting of hemilabile ligands around WLA metal centers, which only allowed for the design of symmetrical structures. Nevertheless, the allosteric control of sterics and cavity size in symmetric constructs enabled the regulation of molecular recognition by macrocycle receptors[46] and the control of reaction rate in bimetallic catalysts.[18] The advent of the HILR later gave way to the construction of asymmetric coordination nodes in triple-layer structures and heteroligated tweezers, thereby allowing one to manipulate single-site catalysts by controlling steric confinement around the active site with peripheral blocking groups.[47] In the past few years, we have begun to exploit coordination to the WLA metal not only as a way to manipulate steric hindrance and intercomponent distances, but also as a means to regulate the electronic environment around embedded moieties. Doing so has given rise to catalytic switches regulated by managing hydrogen-bonding interactions with embedded regulatory units.[48] Furthermore, the regulatory role of the WLA metal cation has been greatly expanded by exploiting its properties as a Lewis acid,[43] a redox site,[39] and a heavy-atom center,[49] enabling the regulation of electro- and photoactive moieties embedded in the WLA framework. This provides new venues to signal supramolecular transformations in sensors and receptors, and offers a coordination-chemistry handle on complex electron-transfer processes. Finally, electrostatic interactions involving the metal center itself have been exploited to regulate the selectivity of molecular receptor switches based on guest charge.[50]

Bimetallic Allosteric Catalysts. Allosteric regulation of enzymatic catalysis is a critical element in cellular homeostasis and biological signal transduction.[51] This regulatory capability may be mimicked by constructing structurally switchable frameworks with embedded components that can only interact with the substrate efficiently when prepositioned in specific conformations, distances and/or orientations.[52] Indeed, the majority of allosteric catalytic frameworks in the literature are based on controlling the distance between active moieties in multicomponent catalytic systems so that catalytic activity only arises when the recognition of an allosteric input brings those components in close proximity.[53] Conversely, several WLA macrocyclic systems were developed in which the distance between two embedded metallocatalysts is allosterically regulated so that bimetallic interactions with the substrate only take place in the flexible, open state (Scheme 8).[23,54−57] This may occur since the closed macrocycle prevents physical access of the substrate into the reactive cavity, or because the expanded state is able to pre-organize pairs of substrates, leading to catalytic rate enhancement.

Single-Site Allosteric Catalysts. Given the relatively small number of bi- or multi-metallic catalytic processes, methodologies for allosterically regulating the activity of single-site catalysts with WLA constructs is critical. One such strategy is based on using the WLA framework to build a sterically

Scheme 8. Regulation of Bimetallic Catalytic Processes via Control of Reactive Cavity Size[a]



[a]Adapted with permission from ref 4. Copyright 2011 John Wiley and Sons.

encumbered reactive cavity and subsequently using coordination chemistry to expose an embedded catalyst, thus destroying the cavity. Toward this end a monometallic catalyst was buried within a triple-layer structure so that, in the closed coordination state (**35**), bulky blocking ligands restrict substrate access to the active site (Figure 2).[47] Upon introduction of an allosteric input

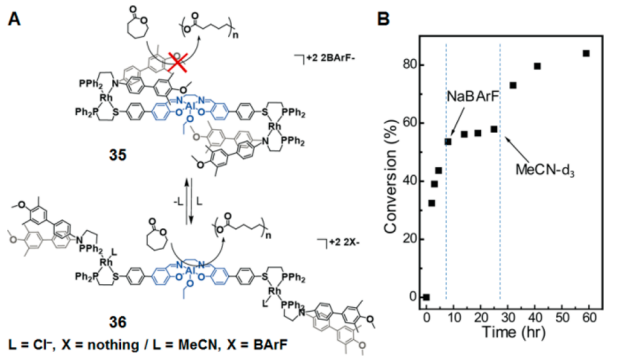


Figure 2. Incorporation of a single-site catalyst (highlighted in blue) within a triple-layer reactive cavity (A) allows for allosteric regulation of a living polymerization reaction (B). Adapted from ref 47 with permission from AAAS.

and displacement of the weakest coordination bonds in the Rh(I) regulators to give complex **36**, the blocking ligands are dislodged from the periphery of the monometallic catalyst, and catalytic activity ensues. This strategy is directly inspired by the regulation of reactive cavity size typical of allosteric enzymes and ion channels,[58] yet it can become a powerful tool when applied to the regulation of inorganic chemical process which are otherwise difficult to control. For instance, complexes **35** and **36** can be used to regulate the living polymerization of caprolactone. In this case, chemical regulation is simply achieved by using Cl^-, Na^+, and acetonitrile as allosteric inputs. The utility of this regulatory approach is highlighted by the capacity to control the average molecular weight of the polymeric product by condensing the structure into a closed complex after a given reaction time. Furthermore, reactivation of the catalyst allows for chain growth to continue and for polymer molecular weight to increase, suggesting that reactivation does not undergo via growth of new polymer chains.

Coordination chemistry can also be used to regulate electronic interactions at peripheral regulatory units that compete with the substrate for hydrogen-bonding to a central organocatalyst. For instance, semiopen complex **37** undergoes self-association via the hydrogen-bonding of a central squaramide unit and blocking

DOI: 10.1021/jacs.5b01054
J. Am. Chem. Soc. 2015, 137, 7252−7261

ester groups, thus preventing catalytic activity.[48] The increase in steric confinement around the active site and in overall complex charge afforded by the closed coordination state **38** drastically decreases the ability of the coordination framework to self-associate, yet this does not prevent interaction with small substrates in solution. As a result, allosteric regulation of complex self-association can be used to control the ability of the squaramide to catalyze a Friedel–Crafts reaction between indole and nitrostyrene in situ and reversibly (Figure 3B). In broad

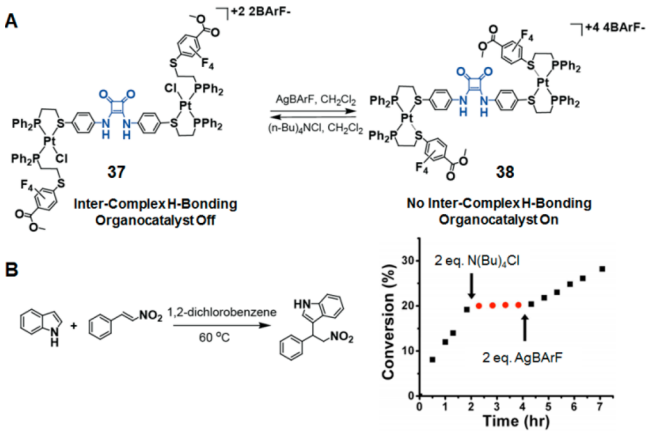


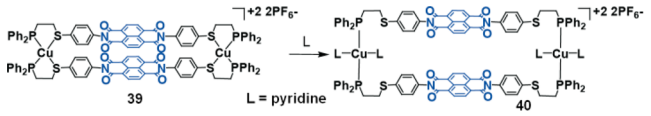
Figure 3. Activity of an embedded squaramide organocatalyst can be regulated by controlling intercomplex hydrogen bonding (A). This enables regulation of reaction rate in a Friedel–Crafts reaction between indole and nitrostyrene (B). Adapted with permission from ref 48. Copyright 2014 American Chemical Society.

terms, complexes **37** and **38** are the first examples in which allosterically triggered framework self-association is used to control the activity of a central catalytic moiety. This regulatory strategy is commonly exploited in endogenous enzymes that experience conformational changes in their active site upon self-association, and which are thus able to control catalytic activity via aggregation.[59] Similarly, enzyme oligomerization via hydrogen bonding directly involving the active site is also a common regulatory strategy exploited by allosteric enzymes,[60] and hereby mimicked by complexes **37** and **38**. Overall, the rich variety of WLA catalytic switches highlights the remarkable potential in deriving regulatory processes in biology and applying them to the control of chemical process in inorganic systems.

Regulation of Electron-Transfer Processes. Electron-transfer processes play an important role in both enzyme activity and its allosteric regulation, spanning several aspects of biosynthesis, the cellular energy cycle, and a variety of molecular recognition and signal transduction processes.[61−64] Allosteric regulation may occur, for example, by inducing structural rearrangements that change the redox potential of active species or by controlling the distance between redox and photoredox pairs that undergo through-space interactions. Furthermore, structural changes may be triggered via the binding of redox-inactive allosteric inputs or via the interaction of redox-active cofactors that engage in electron-transfer processes with the peptide framework, such as disulfide linkages,[65] or with the active site itself, such as transition metal complexes.[66] The rich variety of strategies to control redox processes in biology can be applied to man-made systems to target specific technological needs in sensing, molecular electronics, solar energy conversion, and photonic devices.[67] WLA complexes offer a unique framework to study fundamental variables that control electron-transfer rates and efficiencies, such as changes in distance and orientation between components, as well as changes in framework properties, such as charge and polarity. Thus, new allosteric regulation strategies have been developed to control redox and photoinduced electron-transfer processes between electroactive components and between electroactive components and the WLA metal center.

In an early example, Cu(I) homoligated macrocycles **39** and **40** were used to probe the effects of distance and framework charge on the oxidation potential of cofacial naphthalene diimide units (Scheme 9).[68] Both complexes have the same overall +2

Scheme 9. Effects of Distance on the Interactions between Embedded Electroactive Units Can Be Probed with the WLA[a]



[a]Adapted with permission from ref 68. Copyright 2006 John Wiley and Sons.

charge but they display different through-bond inductive contributions from the charged metal centers on the electroactive ligand substituents. It was found that similar potential differences between the oxidation of the first and second naphthalene diimide units arise in both complexes, suggesting that the electrostatic coupling between the oxidized species does not change significantly over the distance regime studied. On the other hand, chelation of the hemilabile ligands to the charged metal centers in **39** pulls electron density away from the diimide substituents and, thus, shifts the oxidation of both the first and the second ligand to higher potentials by ∼60 mV. Undergoing similar investigations with homoligated and heteroligated complexes incorporating porphyrins, in which interligand distance, complex charge, and porphyrin core modification are varied, may also yield important design parameters relevant to the construction of electronic and photoactive materials.[44]

Rh(I) complexes typically used in WLA systems do not only serve as structural regulators but they can also be exploited as redox centers whose electrochemical properties are highly dependent on their coordination environment. For instance, the oxidation potential of these metal centers has been shown to vary by up to 800 mV depending on the overall charge of the Rh(I) coordination sphere.[39] As a result, the introduction of charged allosteric effectors can induce large changes in the electrochemical landscape of the overall WLA framework. Specifically, coordination of chloride in model complex **41** lowers the charge of the Rh(I) coordination sphere from +1 to 0 and shifts the Rh(I) anodic oxidation potential from about 350 mV to −450 mV, as compared to **42** (Figure 4).

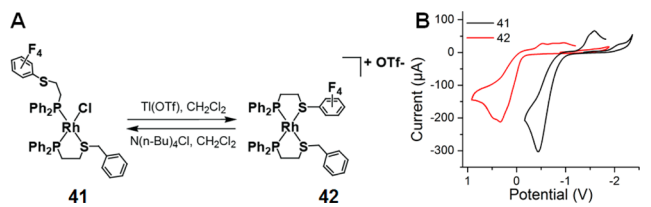


Figure 4. Rh(I) complexes (A) can be used as redox sites whose electrochemistry is dependent on their coordination state (B). Adapted from ref 39 by permission of The Royal Society of Chemistry.

DOI: 10.1021/jacs.5b01054
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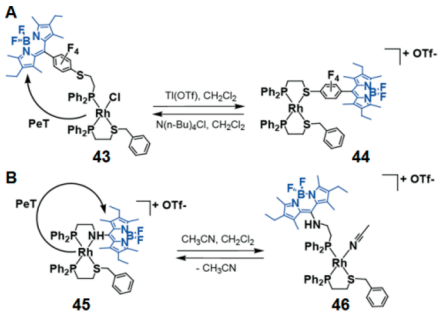
In the early stages of the development of the WLA, it was recognized that related Rh two-legged piano-stool complexes are capable of stabilizing both the Rh(I) and the more elusive Rh(II) oxidation states.[69] This suggested that WLA complexes could be employed as redox switches in which single-electron transfer from the Rh(I) center to components embedded into the complex could be controlled via coordination chemistry. For instance, chloride coordination can be employed to control the oxidation potential of Rh(I) relative to that of an embedded Bodipy fluorophore, thereby regulating photoinduced electron transfer (PeT) from the metal center (Scheme 10). In the case of complexes **43** and **44**, the Rh(I) oxidation potential is shifted between potentials below and above that of Bodipy, whose electrochemical properties remain roughly constant throughout coordination changes. Thus, PeT from the Rh(I) d_{z^2} orbital to the excited Bodipy only occurs in semiopen, neutral complex **43**. On the other hand, complexes **45** and **46** can be used to shift the oxidation potential of Bodipy via coordination to the charged Rh(I) center, whose oxidation potential remains roughly unchanged given that both complexes have a +1 charge. This results in a reverse photoredox switch in which PeT is triggered in the closed coordination state.

Scheme 10. Regulation of Photoinduced Electron Transfer from the WLA Metal Center[a]



[a]Adapted from ref 39 by permission of The Royal Society of Chemistry.

The coordination switches above can be used to regulate the Bodipy excited state by triggering kinetically fast quenching mechanisms with mild and redox-inactive coordination inputs. This enabled us to apply the switches **45** and **46** in the design of a light-harvesting antenna/reaction center mimic, complexes **47**–**49**,[70] in which photoredox catalytic activity can be regulated in situ and reversibly for the first time (Figure 5).[71,72] Inorganic analogues of the antenna and reaction center components of Photosystem II have been the focus of major research efforts in the context of sensors, energy production and materials development.[73,74] The biological system is allosterically regulated by detecting the chemical signatures of the over-harvesting of light, such as low pH values.[75,76] Protonation of regulatory proteins induces conformational changes in the antenna complex that trigger antennae quenching via inter-complex charge transfer,[77] which is kinetically faster than energy transfer to the reaction center. Similar to this biological regulatory strategy, PeT from Rh(I) to the antenna in closed complex **47** takes place with a rate value that is more than an order of magnitude higher than energy transfer to the central porphyrin-C_{60} reaction center mimic. By partially displacing the P,N ligand from Rh(I) in **47** with a neutral allosteric effector to give **48**, the antenna oxidation potential becomes lower than that of Rh(I), and an 11-fold increase in energy transfer efficiency to the reaction center ensues. If, instead, negatively charged chloride is used as an allosteric effector to obtain **49**, the Rh(I) oxidation potential is decreased more than that of Bodipy, and thus light-harvesting is not activated. The in situ chemical reversibility of these coordination reactions allows one to allosterically regulate the catalytic reduction of methyl viologen using *N*-benzyl-1,4-dihydronicotinamide as a sacrificial electron donor. Since the coordination switch is solely based on the interactions between the antenna and the WLA metal center, the reaction center unit can be in principle replaced with other redox catalysts that are sensitized by Bodipy. The ability to regulate an energetically uphill redox reaction allosterically and with coordination input selectivity highlights the potential in using electroactive WLA frameworks to regulate energy-relevant catalysts and, more broadly, to apply bioinspired regulatory mechanisms to the control of inorganic chemo-responsive materials.

Sensors and Receptors. Protein receptors in biology can recognize specific changes in their chemical environment and transduce the recognition signals to induce an appropriate biochemical response. Signal transduction often takes place by activating catalytic pathways via ligand-induced conformational changes, for example in the case of ligand-gated ion channels.[78] In a fundamentally similar fashion, the WLA has been applied to sensing and signal amplification systems in which the binding of

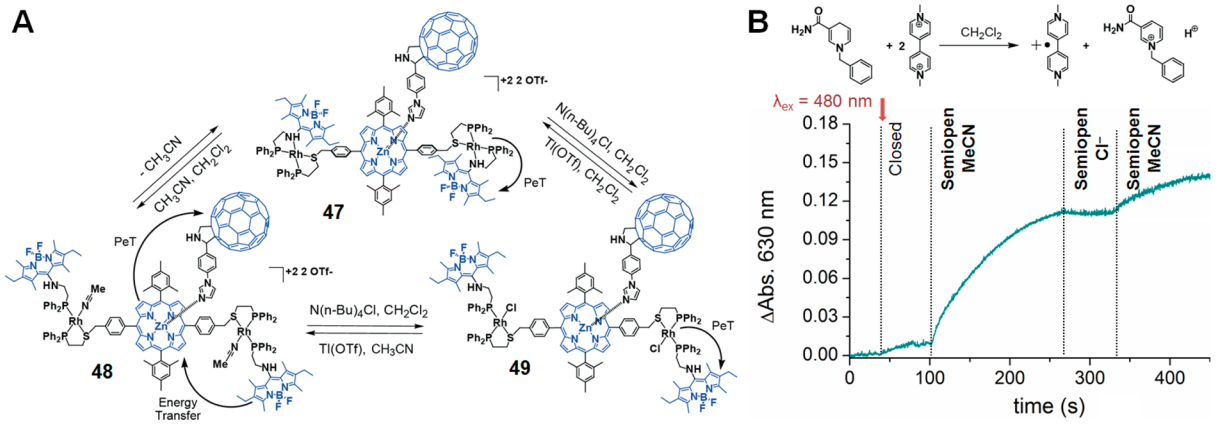
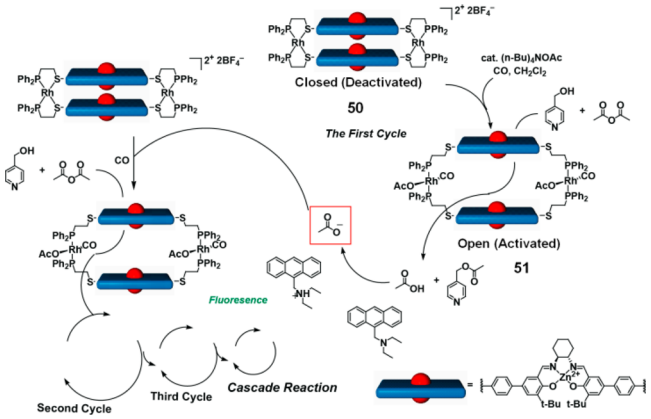


Figure 5. A light-harvesting antenna/reaction center mimic (highlighted in blue) is allosterically regulated (A), enabling control of an electron-transfer reaction (B). Reaction progress tracked via the absorbance of reduced methyl viologen at 630 nm. Adapted from ref 70.

DOI: 10.1021/jacs.5b01054
J. Am. Chem. Soc. 2015, 137, 7252–7261

an allosteric effector to a metal cation structural regulator induces conformational changes that activate embedded catalytic moieties (Scheme 11). This allows one to design signal

Scheme 11. PCR-like Signal Amplification of Small Molecules with a WLA Allosteric Catalyst[a]

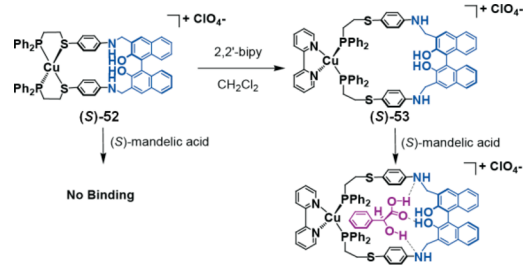


[a]Adapted with permission from ref 56. Copyright 2008 American Chemical Society.

amplification systems in which a discrete binding event elicits a large chemical response, such as acetate coordination to macrocycle **50** to give catalytically active **51**.[54] Most significantly, the catalytic response can be tailored to produce metal coordinating units, further activating more of the catalyst in solution. Thus, WLA systems are able to amplify the initial binding event in an ELISA-type fashion[55] or, in cases in which the sensing input and the product of the catalytic process are the same, in a PCR-like fashion.[56]

WLA complexes have been applied to control host–guest assemblies by tailoring the supramolecular environment around molecular and anion receptors via coordination chemistry. For instance, the WLA metal centers can act as structural regulatory sites that control the size of a binding pocket, thereby providing a coordination chemistry-based handle on substrate recognition and binding.[46] In an early example of such systems, the opening of chiral macrocycle (*S*)-**52** via the use of 2,2′-bipyridine as an allosteric effector gives rise to an enantioselective binding pocket (*S*)-**53** for an (*S*)-mandelic acid guest (Scheme 12). Aromatic groups appended to the binding site serve both a structural and a signaling role, helping define the geometry of the chiral pocket and giving rise to photophysical changes upon electronic perturbations introduced by the guest.

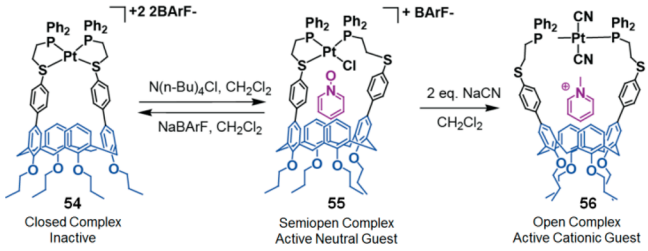
Scheme 12. Allosteric Regulation of Binding Pocket Size Allows for Enantioselective Guest Encapsulation



[a]Adapted with permission from ref 46. Copyright 2006 John Wiley and Sons.

More recently, coordination changes have been exploited to induce electrostatic interactions between the metal center regulator and the encapsulated guest, thereby giving rise to different active states of the host that depend on the charge of the WLA metal coordination sphere. Specifically, the size and selectivity of a calixarene molecular receptor can be allosterically controlled in complexes **54**–**56** (Scheme 13).[50] In the closed

Scheme 13. Substrate Encapsulation by a Molecular Flask Is Allosterically Modulated by Varying the Receptor's Size and the Charge of Its Supramolecular Environment[a]

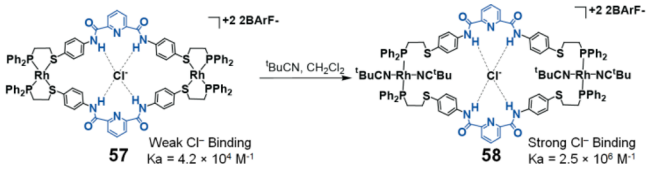


[a]Adapted with permission from ref 50. Copyright 2014 American Chemical Society.

state, the capsule is constrained into a condensed flask, leaving no room for guest encapsulation. The coordination of allosteric effectors leads to distinct active states in which different guest molecules can be encapsulated on the basis of their electron density and the charge that the effector imparts onto the metal center. Interestingly, the electrostatic interactions between the WLA metal receptor and the guest serve to distinctly orient the latter inside the cavity. A related system for the encapsulation of an electron-poor hexyl viologen guest was developed using an anthracene-functionalized Rh(I) homoligated macrocycle.[79] In this case, formation of the host–guest supramolecular assembly only occurs in open macrocycles with neutral Rh(I) centers, demonstrating that encapsulation can be selectively triggered by tuning the cavity's size and electron density.

The WLA framework can be used to pre-organize components that engage in target binding so that interactions with the guest are optimized in a given coordination state. Toward this end, a Rh(I) macrocycle containing two pyridinediamide units (**57**, **58**) was synthesized to regulate their ability to bind a chloride anion guest (Scheme 14).[80] In the closed coordination state, **57**, the

Scheme 14. Affinity of a Receptor Cavity Is Allosterically Controlled by Modulating the Cavity Size and Flexibility



[a]Adapted from ref 80 by permission of The Royal Society of Chemistry.

two pyridinediamide units can bind to a single chloride anion with an association constant of $K_a = 4.2 \times 10^4$ M^{-1}. This association constant is significantly increased to $K_a = 2.5 \times 10^6$ M^{-1} upon partial displacement of the hemilabile ligands with isocyanide allosteric effectors to give **58**. The larger cavity size and greater degree of flexibility associated with the expanded macrocycle are responsible for the modulation of the binding

DOI: 10.1021/jacs.5b01054
J. Am. Chem. Soc. 2015, 137, 7252–7261

constant. In a related example, CO coordination to a Rh(I) tweezer decorated with two P,S urea hemilabile ligands was used to shuttle a chloride guest from the urea moieties to the metal receptor.[81] Removal of CO under reduced pressure reverses the chloride shuttling process.

The strategies employed to regulate guest encapsulation in WLA systems are highly reminiscent of methodologies regularly exploited in Nature to control substrate binding to the reactive or recognition cavities of enzymes and protein receptors. In the long term, we expect that studying ways in which molecular targets can be encapsulated and released using chemical inputs will form the basis for novel inorganic materials for highly specific separations and selective cargo delivery. Furthermore, by understanding the structural parameters that guide host−guest interactions, the WLA could be used to develop coordination switches in which the electronic and chemical properties of the guest are modulated via encapsulation to give rise to new reactivities.

7. CONCLUSIONS AND OUTLOOK

The WLA, in combination with the HILR reaction, represent a unique set of fundamental reactions that allow one to incorporate a broad range of functional moieties in a spatially defined fashion using coordination chemistry. From a purely synthetic perspective, the WLA has the potential to become a ubiquitous synthetic strategy for preparing complexes that are used to investigate supramolecular interactions in multicomponent systems. Indeed, the generality of the WLA allows one to readily replace embedded components and to build large families of supramolecular structures starting from a discrete number of building blocks. As a result of these capabilities, design themes from Nature have been successfully exploited to improve existing catalysts and to discover new material properties. In the future, the WLA could be utilized to synthesize "push−pull" structures that explore emergent properties that arise from bringing two functional groups in close proximity to one another, such as catalyst−cocatalyst, catalyst−directing group, acid−base, and electron donor−electron acceptor pairs. Furthermore, WLA constructs will be applied to retroactively understand the underlying fundamental interactions that have given rise to supramolecular structures in biology. Specifically, the modularity of the WLA would allow one to rapidly assemble related structures that mimic enzyme active sites to understand the effects of supramolecular environment on activity.

In addition to serving as an assembly methodology, the WLA imparts unique stimuli-responsive properties to supramolecular frameworks in which steric, electronic, and redox environments are chemically toggled. Given the high selectivity of the coordination inputs used for soft d^8 metal centers, we expect that the WLA will be able to impart structural switchability to extended frameworks that are held together by covalent, noncovalent, or hard−hard coordination interactions. This may allow one to regulate higher-order assembly using reversible modifications in the materials' molecular structure. We anticipate that doing so will lead to extended solids with dynamically controllable catalytic properties in addition to materials with deliberately adjustable capture-and-release properties, which could become important in small molecule storage strategies.

To make the studies suggested above possible, new developments in fundamental hemilabile coordination chemistry will be necessary to address current shortfalls in the assembly and addressability of allosteric constructs in complex environments, such as biological media. Specifically, there is a strong need to develop WLA systems that remain stable in the presence of large excess of nucleophilic species and in polar environments, and which can be actuated with high input selectivity. While electronic regulation of the kind exploited by complexes **47**−**49** might hold the key to such advances, the reliance on high-lying metal-centered orbitals will surely bring about significant challenges in terms of air-stability. Thus, new strategies to control the electronic state of embedded species using air-stable metal centers will be of utmost importance.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This material is based upon work supported by the National Science Foundation (CHE-1149314) and U.S. Army (W911NF-11-1-0229).

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DOI: 10.1021/jacs.5b01054
J. Am. Chem. Soc. 2015, 137, 7252−7261