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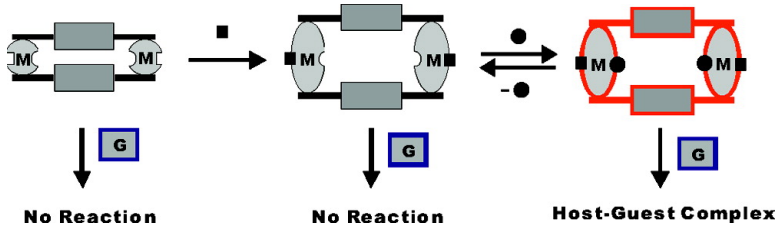

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A Coordination Chemistry Approach to a Multieffector Enzyme Mimic

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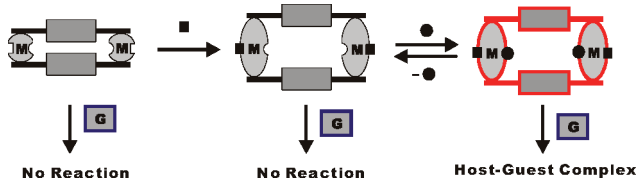
Recently, we reported examples of coordination complexes that behave as allosteric catalysts and begin to mimic the properties of allosteric enzymes.[1] Allosteric enzymes often have specificities for substrates that can be triggered through shape, hydrophobicity, and charge distribution changes, typically induced by their reaction with small molecules at peripheral regulatory sites, hence the term "allosteric regulation".[2] Some allosteric enzymes have multiple regulatory sites that require different small molecule or elemental ion effectors. For example, protein kinase C is activated through step-by-step binding of three effectors including diacylglycerol, Ca^{2+}, and a phospholipid to provide a suitable structure for catalysis.[2c] If we can begin to mimic such multieffector regulation it may be possible to realize many new classes of catalysts that can be modulated in situ[1] and a wide variety of molecular devices with complex functions.[3−5]

Our group has been developing the weak-link approach (WLA) to supramolecular coordination complexes.[6] The WLA allows one to construct multimetallic macrocycles with flexible hemilabile ligands that form both strong and weak coordination bonds with a metal center. These macrocycles can be toggled between structures with very different shapes and rigidities by selectively and reversibly breaking the weak coordination bonds with small molecules. This property, which is a hallmark feature of all structures prepared via the WLA, makes the approach ideal for preparing systems that exhibit allostric control. Thus far, we have demonstrated approaches to allosteric catalysts that can function as highly sensitive detection systems with signals that can be catalytically amplified[1b] and other systems that can regulate the recognition and differentiation of enantiomers.[5] Herein, we report a new artificial allosteric system that regulates pseudorotaxane formation by changing the shape and charge of a macrocyclic complex through the stepwise binding of multiple effector molecules, Schemes 1 and 2 . This function is reminiscent of the way protein kinase C works (mentioned above). The binding of the first small molecule regulates the shape of the complex and the binding of the second one regulates the charge of the complex, which results in the active species and guest sequestration, Scheme 1.

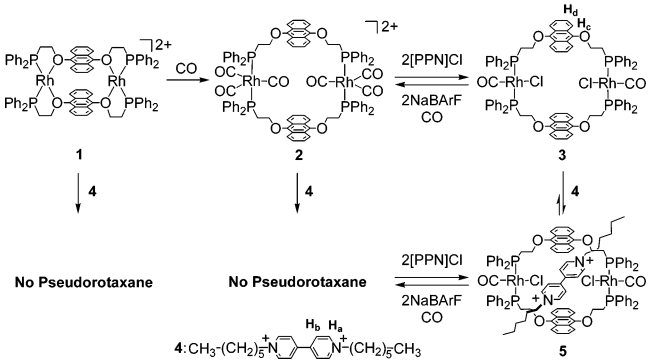
In designing a multieffector enzyme mimic, we focused on a molecule and reaction that require a large cavity and specific type of charge to recognize a guest molecule. Pseudorotaxanes, pioneered by Stoddart, are one class of molecules where host−guest chemistry relies on a large electron-rich cavity for guest molecule (typically a positively charged viologen) sequestration to take place.[4,7] We hypothesized that one could use the WLA to prepare a condensed macrocycle that could be opened with a small molecule effector into a structure with a cavity large enough to generate a pseudorotaxane but not of the appropriate charge to initiate guest binding. In this way, one could envision using a second small molecule or halide ion to bind to the metal centers that make up the macrocycle to change their charge and induce guest molecule uptake and pseudorotaxane formation.

Scheme 1. Schematic Representation of Two-Step Allosteric Regulation[a]



[a] The black filled square and circle represent allosteric-effectors: M = the transition metal center at the allosteric regulatory sites; G = a guest molecule. The first binding events involving an initial small molecule regulator (the filled squares) changes the shape of the molecule, while the second binding event involving a different regulator (filled circles) changes the charge on the molecule and its ability to recognize a guest molecule.

Scheme 2. Allosteric Regulation of Pseudorotaxane Formation[a]



[a] Counter anions are BArF for **1**, **2**, **4**, and **5** (PPN is $Ph_3P{=}N{=}PPh_3$).

The closed macrocycle, enzyme mimic **1** was synthesized from 9-10-bis(2-(diphenylphosphino)ethoxy)anthracene, $[RhCl(cod)]_2$ (cod = 1,5-cyclooctadiene) and NaBArF (BArF = $B[3,5\text{-}C_6H_3(CF_3)_2]_4$), Scheme 2. The BF_4 salt of this complex was previously synthesized and fully characterized,[6d] but the BArF salt is more soluble in CH_2Cl_2 and therefore more suitable for the studies herein. The cavity in complex **1** is too small to support sequestration of hexyl viologen, therefore pseudorotaxane formation does not occur. Similar to analogous Rh(I) complexes, compound **1** can be opened with six equivalents of CO (1 atm) to form cationic open complex **2**.[6c] Although the cavity in complex **2** is large enough to support the sequestration of hexyl viologen, the pseudorotaxane structure still does not form. However, when 2 equiv of [PPN]Cl is added to a CD_2Cl_2 solution of **2**, the neutral open complex **3** forms, which cleanly reacts with hexyl viologen to form pseudorotaxane complex **5**.

Complexes **1**−**3** have been characterized by ^1H and $^{31}P\{^1H\}$ NMR, IR and mass spectrometry in solution, and the solid-state structures of **1** and **3** have been determined by single-crystal X-ray diffraction studies (see Supporting Information). The solid state intra-anthracenyl distances are 3.2 and 7.7 Å for the condensed complex (**1**) and the open neutral complex (**3**), respectively. This

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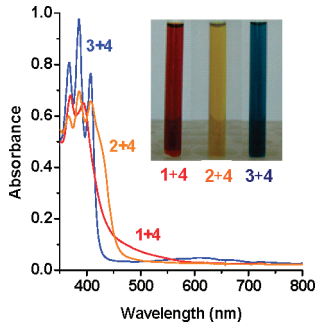

Figure 1. UV−vis spectra of **1**+**4**, **2**+**4**, and **3**+**4** (3.75×10^{-5} M, 25 °C) in CH_2Cl_2. A photograph of solution of a mixtures of the macrocycles (**1**−**3**) and the guest **4** (ca. 1×10^{-2} M, CD_2Cl_2) is shown in the inset.

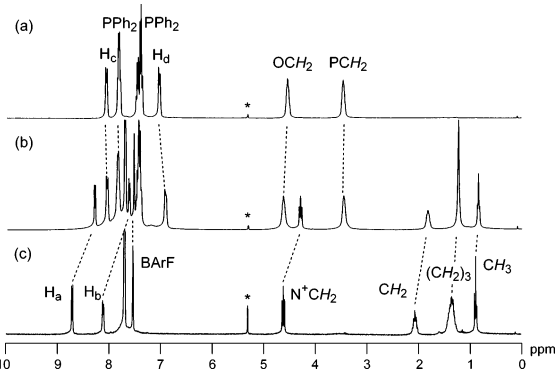

Figure 2. ^{1}H NMR (300 MHz, CD_2Cl_2, 1×10^{-2} M, 22 °C) spectra of (a) **3**, (b) **5**, and (c) **4**. The signal labeled with an asterisk represents solvent.

confirms the conclusion that the closed macrocycle does not have a large enough cavity to support pseudorotaxane formation. The cavity size of the cationic open macrocycle **2** is likely to be similar to that of neutral complex **3** in solution because the phosphine ligands with flexible arms are coordinated to the Rh(I) metal centers in a trans configuration in both complexes.[6] Since the pseudorotaxane formed from a bis-*p*-phenylene-34-crown-10 host and methyl viologen guest exhibit a distance of 7.4 Å between the two phenylene groups of the host,[7a] **2** and **3** have enough room to accommodate the hexyl viologen **4**. The extent of reactions can be monitored by ^{1}H NMR, ^{31}P{^{1}H} NMR, UV−vis spectroscopy, and colorimetrically (Figures 1 and 2). First, all three spectroscopies are consistent with the conclusion that the viologen does not react with **1** or **2**. Closed macrocycle **1** exhibits a single ^{31}P{^{1}H} NMR resonance at 62.5 ppm, which upon the addition of CO (1 atm) shifts to 16.9 ppm, a diagnostic indicator of the formation of open complex **2**.[6c] This reaction is accompanied by a color change from red to yellow (Figure 1). Addition of Cl anion as the second effector molecule to the mixture of **2** and **4** in CD_2Cl_2 results in the loss of two CO groups at each metal center and neutralizes the macrocycle, which results in formation of the pseudorotaxane **5**. This process is accompanied by a color change of the solution from yellow to blue. The blue color is due to the charge transfer interaction between the electron-rich anthracenyl groups in the neutral host molecule **3** and the electron deficient cationic viologen unit in the guest molecule **4** ($\lambda_{max} = 613$ nm) (Figure 1).[7]

The formation of pseudorotaxane **5** also was monitored by ^{1}H NMR spectroscopy (Figure 2). The resonances for the viologen (H_a, H_b, and N^+CH_2) in **5** exhibit a significant upfield shift compared to those of the uncomplexed viologen ($\Delta\delta = 0.42$, 0.49, and 0.36 ppm, respectively). The 2D NOESY spectrum of **5** at −65 °C shows that the N^+CH_2 protons of the guest viologen are in close proximity to the ortho protons of the PPh_2 groups in the host (Figure S-3, Supporting Information). A Job plot, based on the ^{1}H NMR data, confirms a 1:1 stoichiometry of **5** (Figure S-4).[8] Electrospray ionization mass spectrometry (ESI-MS) also is consistent with the formation of pseudorotaxane **5**. The value observed by ESI-MS *m*/*z* 964 matches the expected value for the pseudorotaxane product after the loss of two counteranions [**5**-2BArF]$^{2+}$. Measurement of the association constant (K_a) of **5** employing a titration methodology[8] at 25 °C gave 777 ± 64 M^{-1}, which is similar to the reported data for the pseudorotaxane formed from an organic bis-*p*-phenylene-34-crown-10 host and methyl viologen guest (730 M^{-1}).[7] Significantly, the reaction involving pseudorotaxane formation can be reversed. The addition of NaBArF, which acts as a Cl anion abstracting agent, to a solution of **5** under an atmosphere of CO instantly induces a color change from blue to yellow and results in the formation of **2** and liberates the viologen **4**. The reaction is clean and quantitative as confirmed by ^{1}H and ^{31}P{^{1}H} NMR spectroscopy.

In summary, we have developed and synthesized a complex that behaves as a multieffector enzyme mimic in the context of pseudorotaxane formation. This system is noteworthy because it has allowed us to realize the first example of a pseudorotaxane coordination complex formed via the WLA, and it nicely mimics the ability of an enzyme to selectively bind a substrate by using complementary shape and charge changes induced through ligand displacement and coordination at a distal regulatory site.

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Supporting Information Available: Experimental procedures for synthesis of the complexes, experimental data, and X-ray crystal structures of **1** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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