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A Supramolecular Approach to an Allosteric Catalyst

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Allosteric regulation is a well-known form of control for biological molecules but is a rarity for synthetic catalysts.[1] However, with the advent of supramolecular approaches to building multimetallic architectures,[2] researchers now have a great deal of control over the spatial arrangement of ligand and metal building blocks so that the concept of designer catalysts, which offer more complex function by virtue of such synthetic control, may become a reality. Indeed, important recent advances have been made in the use of supramolecular compounds as catalysts.[3]

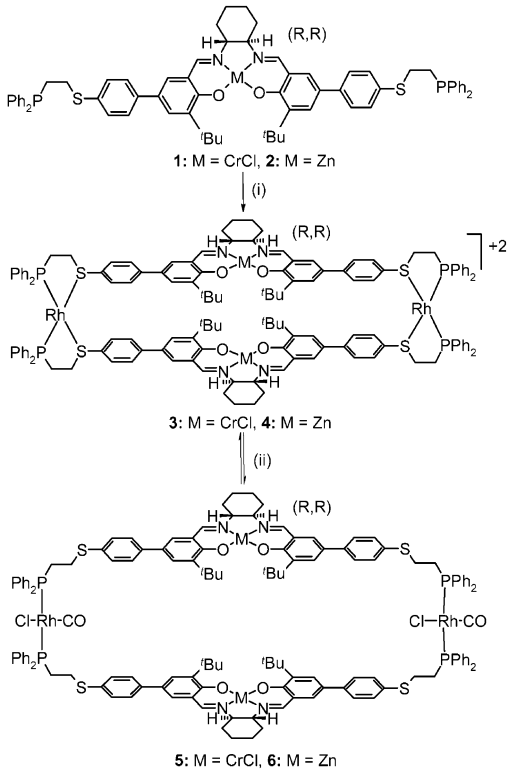
We hypothesized that it might be possible to build an allosteric supramolecular catalyst with an active site that could be opened and closed by effecting chemistry at one or more distal sites within the structure. This, in turn, could modulate the catalytic activity of the complex. Herein, we report the design and synthesis of one such compound (**3** in Scheme 1), a tetrametallic complex prepared via the weak-link approach to supramolecular chemistry,[2d,4] that behaves as an allosteric catalyst for the ring opening of cyclohexene oxide.

The weak-link approach is particularly well suited for building structures with allosteric control because it yields supramolecular entities whose cavities can be "opened" and "closed" in a reversible manner. The allosteric effect is achieved through a modification of catalytic activity via the binding of a CO molecule and a Cl^- ion to each Rh(I) metal at the structure control sites, distal from the Cr(III) metal centers at functional sites within the same macrocyclic assembly. In addition, the enhanced selectivity and activity of the supramolecular catalyst in the asymmetric ring opening of cyclohexene oxide, as compared to a Cr(III)-salen monomeric analogue, is presented.

The ring opening of epoxides using Cr(III)- and Co(III)-based salen catalysts is a well-established method for the preparation of a range of ring-opened products from a variety of epoxides and for the kinetic resolution of epoxides.[5] Jacobsen et al. have established through kinetic studies that the rate-determining step of the reaction between HN_3 and cyclohexene oxide, catalyzed by a monomeric Cr(III)-salen catalyst, involves a bimetallic intermediate.[6] In addition, macrocyclic and linear oligomeric versions of the catalyst have been synthesized and show activities significantly greater than those of their monomeric analogues.[7] In the work described here, our goal is to demonstrate the utility of directed supramolecular assembly in the creation of related catalysts that employ biologically inspired allosteric control over activity and selectivity.

In designing compound **3**, we determined that the reversible binding of Cl^- and CO at the structural Rh(I) metal centers would result in changes in the activity of the functional Cr(III) metal centers. We reasoned that such an effect would be related to the dramatic difference in shape between the closed (**3**) and open (**5**) complexes. Hence, the Rh(I) centers could act as switches for catalysis, the switches being addressable via simple ligand substitution chemistry with CO and Cl^-. Given that salen-type catalysts have been shown to catalyze several reactions in a bimetallic fashion and the vast array of catalytic transformations that are possible with metal salen complexes,[5] it was determined that a Cr(III)-salen-based active site would be an attractive candidate for incorporation in the allosteric macrocycle.

Scheme 1. The Supramolecular Allosteric Catalyst[a]



[a] Counterions are BF_4^-. Reagents and solvents: (i) Rh(norbornadiene)$_2BF_4$, CH_2Cl_2; (ii) PPNCl/CO, benzonitrile; **3** and **4** may be synthesized from **5** and **6**, respectively, by the removal of CO in vacuo or by N_2 purge.

The novel, enantiomerically pure hemilabile ligands **1** and **2** were synthesized in six steps (see Supporting Information) and incorporate binding sites for Rh(I) metal centers (Scheme 1). Compounds **3** and **4** were synthesized in almost quantitative yield by reacting **1** and **2**, respectively, with Rh-(norbornadiene)$_2BF_4$ in CH_2Cl_2. Compound **3** has been characterized by elemental analysis, ^{31}P NMR spectroscopy, and electrospray mass spectrometry, and all data are consistent with its proposed structure. In addition, **4** has been fully characterized in solution and in the solid state[8] (Figure 1). Compounds **3** and **4** can be converted to **5** and **6**, respectively,

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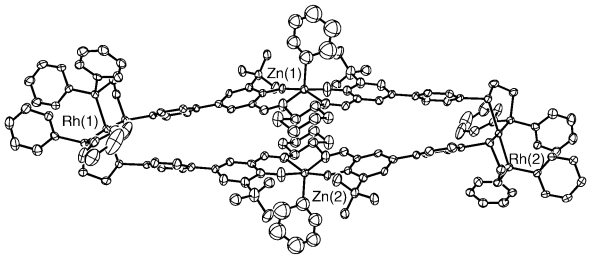

Figure 1. Thermal ellipsoid drawing of **4**-(pyridine)$_2$·CH_2Cl_2 showing the labeling scheme for selected atoms and elipsoids at 30% probability. Hydrogen atoms are omitted for clarity. Zn−Zn distance: 5.24 Å. Rh−Rh distance: 24.66 Å.

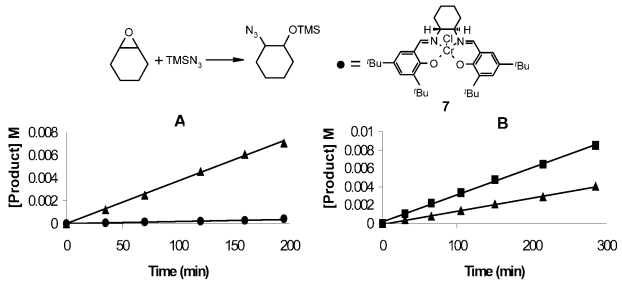

Figure 2. Graph A: Initial rate kinetics for the ring opening of cyclohexene oxide by $TMSN_3$ catalyzed by **3** (▲) (2.6 mM) and a monomeric Cr(III)-salen complex **7** (●) (5.2 mM) in benzonitrile at room temperature. The catalyst concentrations are the same with respect to Cr(III). Graph B: Initial rate kinetics for the ring opening of cyclohexene oxide by $TMSN_3$, as catalyzed by **3** (▲) and **5** (■) each at 2.6 mM, in benzonitrile/pyridine at room temperature.

by reaction with 2 equiv of PPNCl and CO (1 atm) in benzonitrile at room temperature. Compounds **5** and **6**, which exhibit diagnostic ν_{CO} bands at 1978 and 1976 cm^{-1}, respectively,[4] are only stable in solution. Vacuum removal of solvent results in their quantitative conversion to **3** and **4** as determined by ^{31}P NMR spectroscopy. The $^{31}P\{^1H\}$ NMR spectroscopy of **5** and **6** also confirms the proposed structures with each exhibiting a single resonance at δ 25. The chemical shifts and coupling constants are diagnostic of square planar *trans*-phosphine *trans*-Cl/CO complexes of Rh(I).[4e]

The catalytic properties of **3** were compared to those of a Cr(III)-salen monomeric analogue **7** in the context of the ring opening of cyclohexene oxide by $TMSN_3$ to yield 1-azido-2-(trimethylsiloxy)cyclohexane (Figure 2).

These reactions result in product formation with 68% ee for **3**, while the Cr(III)-salen monomeric analogue **7** gives 12% ee. This increased ee for our macrocyclic system is coupled with a significant 20-fold increase in rate as compared to that observed for the monomeric system under these conditions (Figure 2: Graph A). These data are consistent with supramolecular cooperativity also observed by Jacobsen and co-workers for a topologically similar oligomeric Co(III)-based catalyst.[7c]

As an initial demonstration of the ability of **3** to act as an allosteric catalyst, the ring opening of cyclohexene oxide by $TMSN_3$ was studied. The rate of formation of 1-azido-2-(trimethylsiloxy)-cyclohexane, in the presence and absence of the allosteric activators Cl^- and CO, was determined by GC analysis (Figure 2: Graph B). Consistent with our hypothesis regarding the allosteric properties of this system, a doubling of reaction rate is observed upon addition of PPNCl and CO to complex **3** to generate **5** in situ. Because of the lack of solubility of this initial system, we are unable to study **3** and **5** in solvents that have been shown to support higher ee's for **7**.[5] Subsequent versions of **3** will focus on the addition of solubilizing phosphine groups to create systems that provide a controlled basis for comparison to monomeric analogues such as **7** under optimized conditions.

This work represents the first demonstration of an allosteric catalyst made possible through supramolecular coordination chemistry. In addition, **3** exhibits a significant increase in the rate and selectivity of the ring opening of cyclohexene oxide as compared to the monomeric analogue under these reaction conditions. Taken together, these results show how one can use the weak-link approach to design and build supramolecular systems with unique function. Efforts are underway to determine the mechanistic details and differences between **3** and **5**.

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Supporting Information Available: Experimental procedures, spectral data for all new compounds (PDF), and X-ray crystallographic data for **4**-(pyridine)$_2$·CH_2Cl_2 in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Crystal data for **4**-(pyridine)$_2$·CH_2Cl_2: The asymmetric unit contains two molecules of CH_2Cl_2 that were highly disordered and treated as diffuse contributions using the program SQUEEZE (A. Spek; Platon Library). Additionally, the counterions were refined with a common B−F distance. The relatively large thermal parameters of the atoms in the pyridine molecule coordinated to the Zn atom appear to be related to a disorder in the alignment of the molecular plane. The atoms of the pyridine molecule were refined with isotropic thermal parameters and restrictions on the C−N and C−C distances. For additional crystallographic data, see the Supporting Information.

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