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High-Turnover Supramolecular Catalysis by a Protected Ruthenium(II) Complex in Aqueous Solution

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Supporting Information

ABSTRACT: The design of a supramolecular catalyst capable of high-turnover catalysis is reported. A ruthenium(II) catalyst is incorporated into a water-soluble supramolecular assembly, imparting the ability to catalyze allyl alcohol isomerization. The catalyst is protected from decomposition by sequestration inside the host but retains its catalytic activity with scope governed by confinement within the host. This host–guest complex is a uniquely active supramolecular catalyst, capable of >1000 turnovers.

Supramolecular catalysts offer chemists precise spatial control over chemical transformations.[1] Binding within the supramolecular cavity can bring substrates into close proximity, accelerating bimolecular reactions and influencing regiochemistry. Supramolecular assemblies have also been shown to select the reactive conformations of substrates and even exhibit true transition-state stabilization as the mechanism of catalysis.[2] Unfortunately, supramolecular catalysts also frequently suffer from product inhibition and require relatively large catalyst loadings. An alternative strategy for engineering catalytic hosts is the functionalization of the host cavity with an active catalyst. Segregation inside the assembly could promote substrate binding, stabilize rate-limiting transition states, or affect the chemoselectivity of the catalysis. However, examples of transition metal complexes that carry out active catalysis while encapsulated inside supramolecular assemblies remain extremely rare.[3] We report here the encapsulation of a cationic ruthenium half-sandwich complex in an aqueous supramolecular host. The host–guest complex retains the activity of the organometallic guest and protects it from decomposition in aqueous solution, creating a high-turnover supramolecular catalyst.

Raymond and co-workers have developed supramolecular $[M_4L_6]^{12-}$ assembly **1** (Figure 1), a homochiral and water-soluble molecular tetrahedron.[4] This structure self-assembles in the presence of an appropriate trivalent metal ($M = Al^{3+}$, Fe^{3+}, Ga^{3+}) and the ligand (L = 1,5-bis(2,3-dihydroxybenzoylamino)-naphthalene). Mechanical coupling between the vertices results in the exclusive formation of the enantiomeric homochiral structures (ΔΔΔΔ and ΛΛΛΛ). Monocationic guests are bound tightly within the assembly interior, which has a variable volume of 350–500 Å^3. This flexibility allows the incorporation of guests which range in size from NMe_4^+ to large, organometallic complexes including $Cp^*_2Co^+$. Preference for cationic guests allows for the perturbation of chemical equilibria inside the assembly, which has been exploited to increase the basicity of amines and carry out acid-catalyzed reactions in basic solution.[1a]

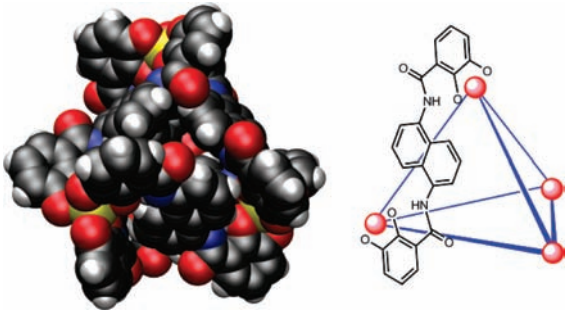

Figure 1. Space-filling (left) and schematic (right) diagrams of supramolecular assembly **1**.

Additionally, assembly **1** can bind the reactive conformations of substrates to promote their reactivity.[5] Since iridium(III) half-sandwich complexes are strongly bound and are active as stoichiometric C–H activation reagents,[6] we sought structurally similar organometallic complexes as potential encapsulated catalysts.

$[RuCp(PMe_3)(MeCN)_2][PF_6]$ is an active and efficient catalyst for allyl alcohol isomerization.[7] We hypothesized that the labile acetonitrile ligands would exchange readily in an aqueous medium and that the resulting $[RuCp(PMe_3)(D_2O)_2]^+$ cation would still be sufficiently hydrophobic to bind tightly to the interior of **1**. The ruthenium complex is encapsulated, but remarkably the acetonitrile ligands remain bound to the metal center (Figure 2). Their methyl signals can be resolved in the NMR spectrum of $[RuCp(PMe_3)(MeCN)_2]^+\subset\mathbf{1}]^{11-}$; the two acetonitrile ligands are no longer equivalent, since the assembly itself is chiral. The complexity in the host region is due to the presence of both the host–guest complex and excess **1**.

The $[RuCp(PMe_3)(MeCN)_2]^+$ cation is bound quantitatively, and no signals corresponding to the external species are observed by ^{1}H NMR (Figure 2), unless an excess of the free cation is present. The complex is stable for days in aqueous solution. In contrast, the unbound $[RuCp(PMe_3)(MeCN)_2][PF_6]$ complex is unstable in aqueous solution; loss of the acetonitrile ligands is rapid ($t_{1/2} \approx 60$ min, see Supporting Information), and the resulting complex further decomposes to a catalytically inactive unidentified species. Furthermore, encapsulation of the ruthenium complex improved its solubility in aqueous solution by at least an order of magnitude — while a solution of the $[RuCp(PMe_3)(MeCN)_2][PF_6]$ complex saturates below 1 mM, 10 mM homogeneous solutions of the encapsulated ruthenium catalyst were readily prepared.

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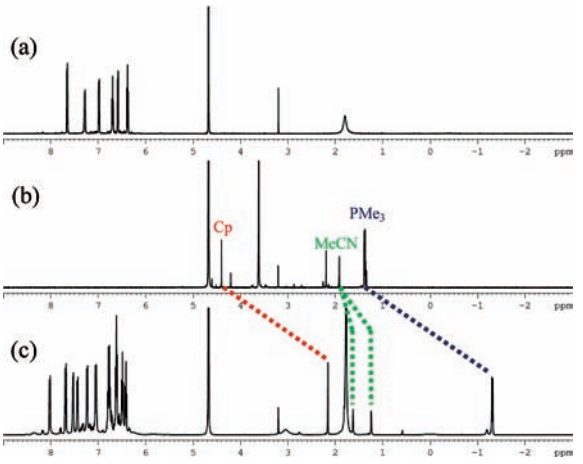

Figure 2. ^{1}H NMR spectra of (a) **1** alone, (b) organometallic complex $[RuCp(PMe_3)(MeCN)_2][PF_6]$ in aqueous solution (with *p*-dioxane as an internal standard), and (c) $[RuCp(PMe_3)(MeCN)_2]^+\subset\mathbf{1}]^{11-}$ in D_2O.

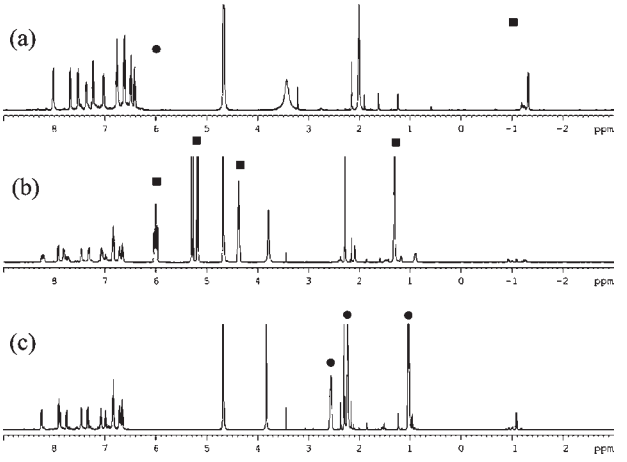

Figure 3. ^{1}H NMR spectra of (a) **2** alone and (b,c) **2** catalyzing the isomerization of 50 equiv of 3-buten-2-ol (■) to methyl ethyl ketone (●) after 10 min at 50 °C (b) and at time t = 35 min (c).

The catalytic activity of the $[RuCp(PMe_3)(MeCN)_2^+\subset\mathbf{1}]$ complex (**2**) was evaluated using 3-buten-2-ol (**3b**). Immediately upon exposure of **2** to this substrate, new upfield resonances were observed in the ^{1}H NMR spectrum. These signals are presumed to correspond to the catalyst resting state, though the complex system of resonances precludes definitive assignment. Catalysis proceeds very slowly at room temperature but is efficient above 35 °C (Figure 3).

Supramolecular catalyst **2** efficiently catalyzed the isomerization of allyl alcohol (**3a**) or 3-buten-2-ol (**3b**) (Figure 4). Secondary alkene **3c** did not isomerize even at 75 °C in the presence of **2**. However, new upfield resonances suggested that **3c** was able to coordinate to the encapsulated ruthenium complex, but no reactivity was observed. The unencapsulated $[RuCp(PMe_3)(MeCN)_2][PF_6]$ complex also did not catalyze the isomerization of **3c**; thus, this was a consequence of the reactivity of the metal center and not a limitation imposed by encapsulation in **1**. Larger substrate **3d** is known to react with $[RuCp(PMe_3)(MeCN)_2][PF_6]$ in $CDCl_3$,[7] and indeed this complex was a competent catalyst for the isomerization of **3d** in D_2O. However, **3d** was unreactive in the presence of **2**, and no evidence for coordination to the

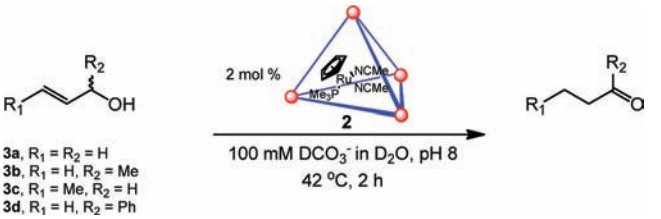

Figure 4. Allyl alcohol isomerization catalyzed by supramolecular catalyst **2**.

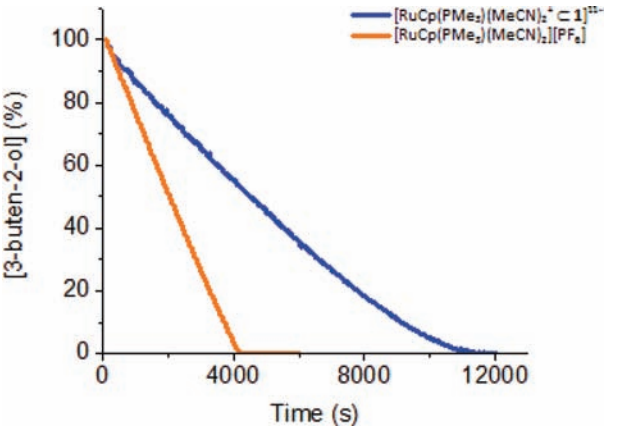

Figure 5. Conversion of 3-buten-2-ol at 42 °C with encapsulated and unencapsulated $[RuCp(PMe_3)(MeCN)_2]^+$. The concentration of the ruthenium species is 0.7 mM in both experiments, and excess host (1 mM) is used to analyze the kinetics of the encapsulated complex.

encapsulated ruthenium complex was seen by ^{1}H NMR. This substrate is too sterically demanding to access the encapsulated catalyst. Importantly, this is further evidence that the $[RuCp(PMe_3)(MeCN)_2]$ guest is not able to exchange into the bulk solvent under the catalytic conditions.

To compare the rates of the encapsulated and unencapsulated catalysts, the reaction kinetics were analyzed. Simple pseudo-first-order kinetics were not observed (Figure 5). While supramolecular catalysts often suffer from product inhibition, this is not the case for this catalysis; the pseudo-first-order rate constant instead seems to *increase* as the reaction nears completion, resulting in a concentration vs time plot that appears zero-order. Two possibilities were envisioned for this acceleration as the reaction progressed: quasi-irreversible dissociation of the acetonitrile ligand(s) could generate a more reactive catalyst inside the assembly, or the substrate itself might inhibit catalysis.

To examine these possibilities, we first studied the effect of acetonitrile on the reaction kinetics. The initial rate of isomerization was found to vary inversely with acetonitrile concentration, but pseudo-first-order kinetics were still not obtained with up to 10 equiv of acetonitrile per mole of catalyst present in solution. To elucidate the means of substrate inhibition, we then sought to examine the effect of adding alcohols and olefins which do not isomerize under the catalytic conditions. The addition of isopropanol had no effect on the reaction kinetics, while the addition of allyl methyl ether strongly inhibited catalysis (see Supporting Information). From these experiments, we suggest that a ternary complex **6** is formed with the coordination of an olefin to the catalyst−substrate complex **5** (see Figure 6). As substrate concentration lowers, formation of this complex is disfavored, and the rate does not decrease until the reaction nears complete conversion.

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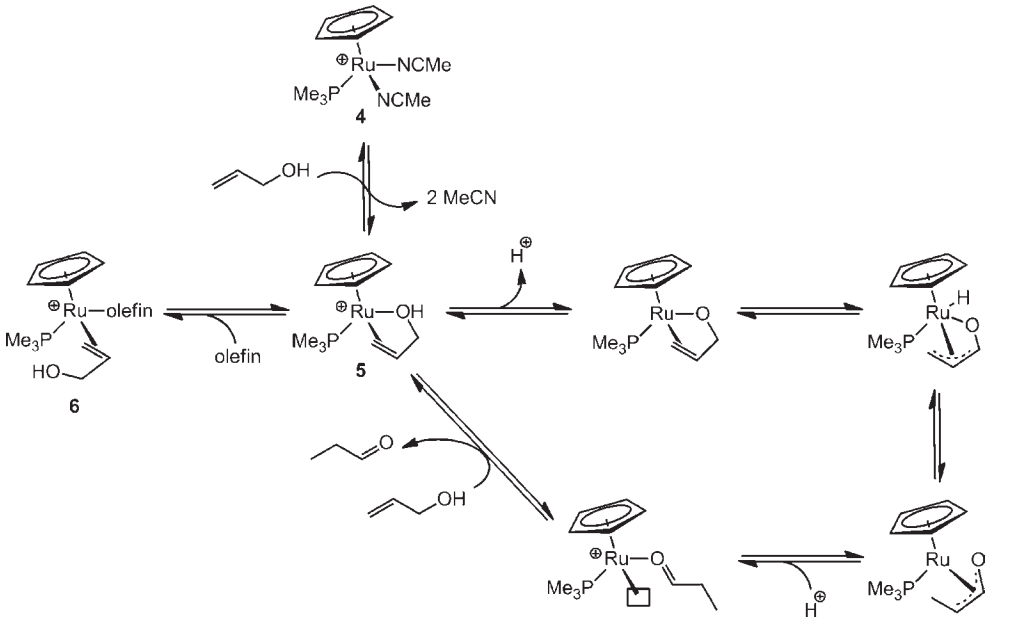

Figure 6. Putative mechanism for the ruthenium-catalyzed allyl alcohol isomerization within the cavity of **1**.

While substrate inhibition made it difficult to extract true first-order rate constants for this catalysis, qualitative comparison of the reaction rates was possible. Comparison of the encapsulated and unencapsulated complexes reveals that encapsulation of $[RuCp(PMe_3)(MeCN)_2]^+$ within **1** causes mild attenuation of the rate, decreasing the turnover frequency at 42 °C from 44 to 16 $M^{-1}\,h^{-1}$ (Figure 5). Both catalysts are able to isomerize allyl alcohol completely at 42 °C in good yield. Significantly, the encapsulated catalyst has an extremely long lifetime in water and is able to turn over 1070 times, a higher turnover than that demonstrated by the free catalyst in halogenated organic solvents.[7]

In summary, an organometallic catalyst was incorporated into water-soluble supramolecular assembly **1**. The encapsulated complex was protected from decomposition by the supramolecular assembly. Despite a slight reduction in the rate of catalysis, the incorporated catalyst remains highly active and has, to the best of our knowledge, the highest turnover reported for a supramolecular catalyst. This study demonstrates the potential of supramolecular encapsulation of organometallic complexes in developing efficient, "green" catalysts for organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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