

# Effect of Solvent on the Dimerization of the *ansa*-Molybdocene Catalyst $[\text{C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)]^+[\text{OTs}]^-$

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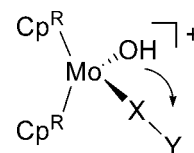
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The monomer–dimer equilibrium behavior of the  $[\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)]^+[\text{OTs}]^-$  and  $[\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\mu\text{-OH})_2]^+[\text{OTs}]_2^-$  complexes was explored in a variety of solvents. Only the monomer was detected spectroscopically in water, aqueous tetrahydrofuran, aqueous acetone, or aqueous dimethylsulfoxide, while appreciable dimerization was noted in aqueous solutions containing 50% ethanol or methanol. Several equilibrium constants ( $K_{\text{eq}}$ ) were estimated. In water,  $K_{\text{eq}} \geq 2 \text{ M}$  at 25 °C. In ethanol at 25 °C,  $K_{\text{eq}}$  is on the order of  $10^{-2} \text{ M}$ . In methanol at 25 °C,  $K_{\text{eq}} \approx 10^{-6} \text{ M}$ . The strong dependence of the monomer–dimer equilibrium on the solvent medium does not correlate with solvent polarity, hydrogen-bonding ability, or solvent basicity. These findings illustrate that catalyst dimerization can be suppressed more effectively by solvent choice than by electronic or steric modification of the Cp ligands. Because only the monomer is catalytically active, the effect of the monomer–dimer equilibrium on molybdocene-catalyzed nitrile hydration rates was investigated. Using 0.58 mM molybdocene in water, the rate of 3-hydroxypropionitrile hydration decreased in the order  $[\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)]^+[\text{OTs}]^- > [\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)]^+[\text{OTs}]^- \sim [\text{Cp}'_2\text{Mo}(\text{OH})(\text{OH}_2)]^+[\text{OTs}]^-$  ( $\text{Cp}' = \eta^5\text{-C}_5\text{H}_4\text{Me}$ ). Using 2.8 mM molybdocene in water, the rate of 3-hydroxypropionitrile hydration catalyzed by  $[\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)]^+[\text{OTs}]^-$  is equal to that catalyzed by  $[\text{Cp}'_2\text{Mo}(\text{OH})(\text{OH}_2)]^+[\text{OTs}]^-$ . These trends demonstrate that (1) an effective method for increasing the rate of catalysis using  $\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)^+$  is to suppress its dimerization and (2) the effect of catalyst dimerization becomes more significant with increasing catalyst concentrations due to a concomitant increase in the percentage of  $[\text{Cp}_2\text{Mo}(\mu\text{-OH})_2]^{2+}$  present in solution.

## Introduction

The monomeric  $\text{Cp}'_2\text{Mo}(\text{OH})(\text{OH}_2)^+$  ( $\text{Cp}' = \text{C}_5\text{H}_5$  or  $\text{C}_5\text{H}_4\text{Me}$ ) complexes are excellent Lewis acids that facilitate the hydrolysis of coordinated nitriles and esters by intramolecular nucleophilic attack of the hydroxo ligand (Figure 1).<sup>1–7</sup> The rate accelerations achieved for nitrile hydration and ester hydrolysis reactions using the  $\text{Cp}'_2\text{Mo}(\text{OH})(\text{OH}_2)^+$  complexes range from modest to stellar ( $10^1$ – $10^7$  times). In an effort to increase the practical utility of molybdocenes by modulating the electronics of the catalyst, the catalytic activity of the *ansa*-molybdocene  $\text{C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)^+$  (**1**) was explored.<sup>1</sup> The tetramethylethylene *ansa*-bridge did lead to an increase in the Lewis acidity of the Mo center;<sup>8–10</sup> however, the increased Lewis acidity did not lead to faster reactivity. Specifically, the rate



**Figure 1.** Intramolecular attack of the hydroxo ligand on a substrate coordinated to  $\text{Cp}'_2\text{Mo}(\text{OH})(\text{OH}_2)^+$ .

constants for *ansa*- $\text{C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)^+$ -promoted nitrile hydration, phosphate ester hydrolysis, and carboxylic ester hydrolysis were shown to be 2–10 times *smaller* than the rate constants obtained using the  $\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)^+$  complex. This result demonstrated that altering the electron density on the Mo center oppositely affects the reactivity of the bound substrate and the bound nucleophile. Although the catalytic activity of the *ansa*- $\text{C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)^+$  complex was disappointing, intriguing differences were noted in the synthesis and equilibrium behavior of the *ansa*- $\text{C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)^+$  and non-*ansa* complexes.

Previous reports showed that the  $\text{Cp}'_2\text{Mo}(\text{OH})(\text{OH}_2)^+$  species are in equilibrium with the hydroxo-bridged dimer  $[\text{Cp}'_2\text{Mo}(\mu\text{-OH})_2]^{2+}$ , eg 1.<sup>1,11</sup> When  $\text{R} = \text{H}$ ,  $K_{\text{eq}}$  is  $(2.7 \pm 0.1) \times 10^{-4} \text{ M}$  in MOPS-buffered  $\text{D}_2\text{O}$  (0.13 M, pD 6.8) at 25 °C. The addition of one methyl group to each Cp ring increased the equilibrium constant by 2 orders of magnitude to  $(2.5 \pm 0.1) \times 10^{-2} \text{ M}$ . The large increase in  $K_{\text{eq}}$  in the latter species was attributed primarily to the decrease in the Lewis acidity of the metal center of the  $\text{Cp}'\text{Mo}^{2+}$  unit (leading to weaker

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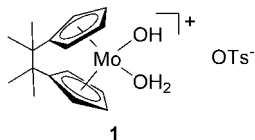
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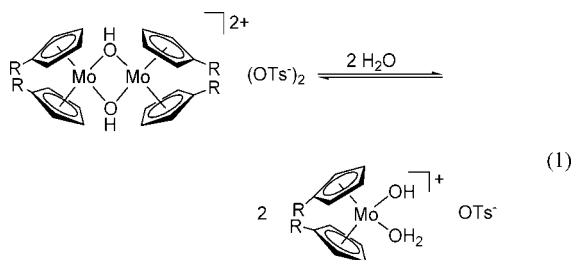
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Mo–OH bonds in the dimeric structure) and to unfavorable steric interactions between the Cp' methyl substituents upon dimerization. On the basis of the results obtained for the Cp'<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> complex, we originally postulated that the equilibrium for *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> would lie in favor of the dimeric [C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> species due to the fixed position of the rings and the increased Lewis acidity of the complex. Surprisingly, no [*ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> was detected by <sup>1</sup>H NMR spectroscopy in pure or buffered water solutions of *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup>.<sup>1</sup> This result was puzzling because [*ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)]<sup>+</sup>[OTs]<sup>−</sup> crystallizes as [*ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub>[OTs]<sub>2</sub> from a supersaturated solution in water.



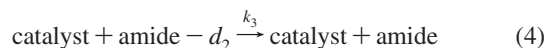
The extent of the monomer–dimer equilibrium has practical consequences. For example, the tendency of molybdocenes to dimerize may adversely affect the rates achieved by (Cp'<sup>R</sup>)<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup>-promoted reactions.<sup>12,13</sup> As mentioned above, although the Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> complex appeared to be the most reactive toward intramolecular nucleophilic attack, this complex also has the greatest tendency to dimerize, giving rise to large amounts of the catalytically inactive [Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup>. As a result, the rate of reaction per molybdenum center obtained using the Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> complex may actually be smaller than that obtained for slightly less reactive molybdocene complexes (i.e., *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> and Cp'<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup>), which have a lesser tendency to dimerize. This result suggests that suppressing catalyst dimerization may be a more effective method of achieving faster rates than tuning the electrophilicity of the metal center. Furthermore, if catalyst dimerization does have a significant effect on the rate of molybdocene-promoted reactions, it is expected to be most significant in the molybdocene-catalyzed hydration of nitriles where the difference in the rate constants for the variously substituted molybdocenes is marginal.<sup>1</sup>

In this paper, we explore the factors that control the monomer–dimer equilibrium for *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup>. In addition, the consequences of dimer formation with respect to the catalytic hydration activity of water-soluble molybdocene complexes are discussed.

## Experimental Section

**General Procedures.** All experiments were performed under a nitrogen atmosphere using standard glovebox techniques. Solvents were prepared by purging with nitrogen or using three freeze–

pump–thaw cycles. All catalyst mixtures were prepared in J-Young tubes or 9 in. NMR tubes that were subsequently flame-sealed to prevent oxidation. The compounds [*ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)]<sup>+</sup>[OTs]<sup>−</sup>,<sup>1</sup> [C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup>[OTs]<sub>2</sub><sup>−</sup>,<sup>1</sup> [Cp'<sub>2</sub>Mo(μ-OH)]<sub>2</sub>[OTs]<sub>2</sub>,<sup>14</sup> and [Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub>[OTs]<sub>2</sub><sup>15</sup> were prepared as previously described. Nitrile hydration kinetics were modeled using an iterative fitting program, GIT,<sup>16,17</sup> and the following equations.



A representative GIT fit is shown in Figure 4. The apparent second-order rate constants, *k*<sub>app</sub>, obtained for nitrile hydration were used to calculate rates and turnover frequencies. The rate constants obtained for the H/D exchange of the α-hydrogens<sup>1</sup> (*k*<sub>2</sub> and *k*<sub>3</sub>) are reported in the Supporting Information.

**Investigation of Solvent Effects on the Behavior of C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup>.** Crystalline [C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> (0.0045 g) was allowed to hydrolyze in D<sub>2</sub>O (1.50 mL) at 70 °C for 3 h. Then 250 μL of deuterated acetone, methanol, ethanol, dimethyl sulfoxide, or tetrahydrofuran was added to a 250 μL aliquot of the hydrolyzed solution in a J-Young tube and mixed. The resulting mixture was monitored by <sup>1</sup>H NMR spectroscopy until it remained unchanged for at least 10 h.

**Nitrile Hydration.** Stock solutions of C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup>, Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup>, and Cp'<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> were prepared by dissolving the respective dimers in 0.13 M MOPS-buffered D<sub>2</sub>O. The catalyst concentrations were confirmed using tetrabutylammonium tetrafluoroborate as an internal standard. In an NMR tube, 7 μL of 3-hydroxypropionitrile was added to 0.500 mL of catalyst solution. The tube was then heated to 80 °C for 14 days. Addition of 3-HPN caused the stock solution of [Cp'<sub>2</sub>Mo(OH)(OH<sub>2</sub>)]<sup>+</sup>[OTs]<sup>−</sup> to turn pink, while the other two solutions remained yellow. <sup>1</sup>H NMR spectroscopy (D<sub>2</sub>O) was used to monitor the disappearance of 3-hydroxypropionitrile at 3.78 ppm (t, *J* = 6.0 Hz, 2H, HOCH<sub>2</sub>CH<sub>2</sub>CN) and 2.67 ppm (t, *J* = 6.0 Hz, 2H, HOCH<sub>2</sub>CH<sub>2</sub>CN) and the appearance of 3-hydroxypropionamide at 3.76 ppm (t, *J* = 6.0 Hz, 2H, HOCH<sub>2</sub>CH<sub>2</sub>CONH<sub>2</sub>) and 2.45 ppm (t, *J* = 6.0 Hz, 2H, HOCH<sub>2</sub>CH<sub>2</sub>CONH<sub>2</sub>).

## Results and Discussion

**Investigation of the Equilibrium Behavior of *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup>.** The *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> monomer exhibits hydrolytic behavior both similar to and distinct from the non-*ansa* Cp'(')<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> monomers. An important similarity is that the *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> monomer crystallizes as the *ansa*-[C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> dimer. In addition, the *ansa*-[C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> dimer dissolves in water to give the *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> monomer (Figure 2). This behavior is also observed for the non-*ansa* complexes and is described by eq 1. However, the behavior of the *ansa*-molybdocene differs from that of the non-*ansa* complexes in two important ways. First,

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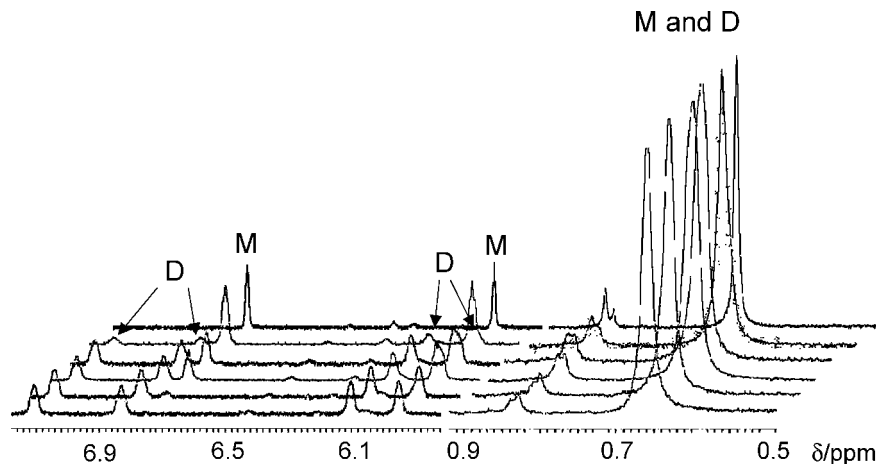
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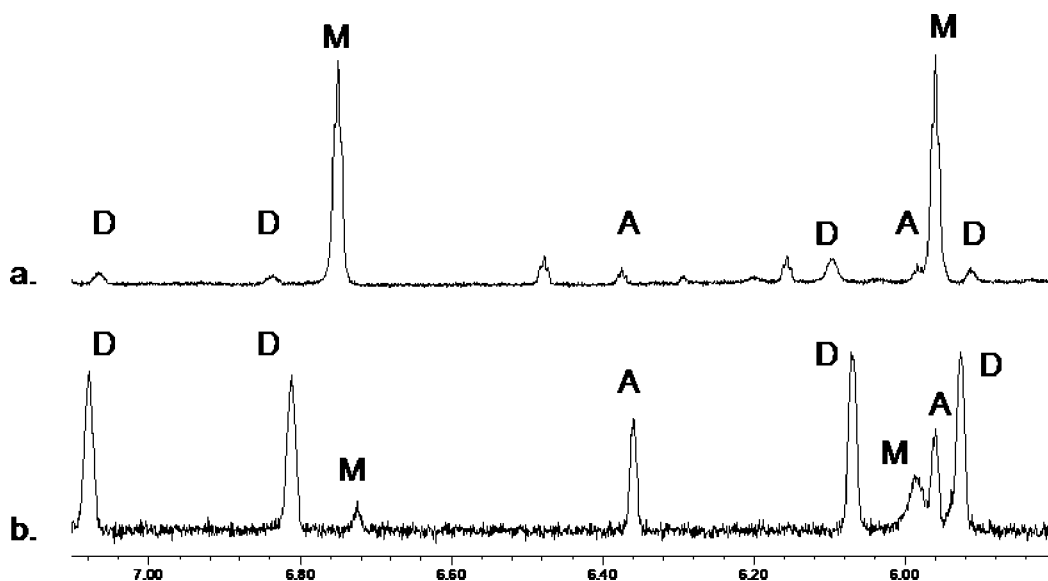
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**Figure 2.** Stacked  $^1\text{H}$  NMR spectra showing the hydrolysis of  $[\text{C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\mu\text{-OH})_2][\text{OTs}]_2$  to  $[\text{C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\mu\text{-OH})_2][\text{OTs}]_2$  in  $\text{D}_2\text{O}$ . (From bottom to top: 0 h, 23 h, 84 h, 96 h, 108 h, and 168 h.)  $\text{D} = [\text{C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\mu\text{-OH})_2]^{2+}$ ,  $\text{M} = [\text{C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)]^+$ .

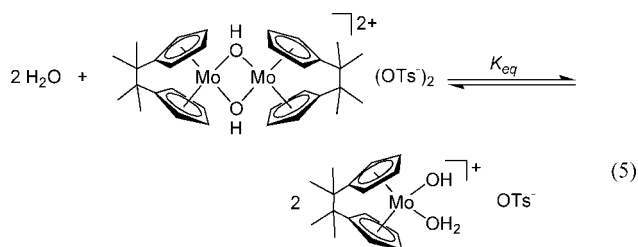


**Figure 3.** Aromatic region of  $^1\text{H}$  NMR spectra of  $\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)^+$  dissolved in 1:1 mixtures of (a)  $\text{D}_2\text{O}/\text{C}_2\text{D}_5\text{OD}$  and (b)  $\text{D}_2\text{O}/\text{CD}_3\text{OD}$ .  $\text{D} = [\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\mu\text{-OH})_2]^{2+}$ ,  $\text{M} = [\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)]^+$ ,  $\text{A} = [\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\text{OH})(\text{X})]^+$  or  $[\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\text{X})_2]$ , where  $\text{X} = \text{OC}_2\text{D}_5$  or  $\text{OCD}_3$ .

the  $[\text{Cp}'(\text{Cp})\text{Mo}(\mu\text{-OH})_2]^{2+}$  dimers dissolve readily in water, yet the  $\text{ansa-}[\text{C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\mu\text{-OH})_2]^{2+}$  dimer is only sparingly soluble in  $\text{H}_2\text{O}$  ( $<1$  mM). Furthermore, as shown in Figure 2, the small amount of  $\text{ansa-}[\text{C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\mu\text{-OH})_2]^{2+}$  dimer that does dissolve slowly hydrolyzes over hours to the  $\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)^+$  monomer. Second, hydrolysis of the  $\text{ansa-dimer}$  appears to proceed to completion. No  $[\text{C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\mu\text{-OH})_2]^{2+}$  is detectable in the aromatic region of the  $^1\text{H}$  NMR spectrum once hydrolysis is complete at  $25^\circ\text{C}$  or at elevated temperatures.<sup>18</sup>

Because  $[\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\mu\text{-OH})_2]^{2+}$  was not detectable in solutions of the  $\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)^+$  monomer in water, it was unclear whether the  $[\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\mu\text{-OH})_2]^{2+}$  and  $\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)^+$  species were in an equilibrium analogous to eq 1. Crystallization of  $[\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\mu\text{-OH})_2][\text{OTs}]_2$  from supersaturated solutions of  $[\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)][\text{OTs}]$  suggests that the two

species are in equilibrium; however, dehydration of  $[\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)][\text{OTs}]$  upon crystallization to give  $[\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\mu\text{-OH})_2][\text{OTs}]_2$  cannot be ruled out. Dimerization of  $\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)^+$  was observed in aqueous alcoholic solutions to give a mixture of the  $[\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\mu\text{-OH})_2]^{2+}$  dimer and the  $\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)^+$  monomer, which indicates that the monomer and dimer are in equilibrium (eq 5), and the equilibrium has a strong solvent dependence. This observation led us to further investigate the behavior of the  $\text{ansa-complexes}$  in organic solvent mixtures.

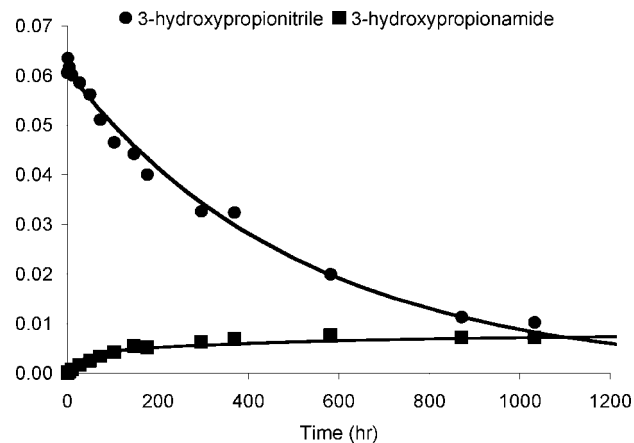


(18) Note that the other spectroscopic handles in the  $[\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\mu\text{-OH})_2]^{2+}$  species, namely, the methyl substituents on the bridging atoms, could not be used to detect the dimer because they resonate at the same frequency as in the  $\text{ansa-C}_2\text{Me}_4\text{Cp}_2\text{Mo}(\text{OH})(\text{OH}_2)^+$  monomer in  $\text{D}_2\text{O}$ .

To explore the behavior of the *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> complex in various solvent mixtures, aqueous solutions containing only *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> (as indicated by the <sup>1</sup>H NMR spectra) were diluted with water-miscible organic solvents. Addition of an equal volume of methanol or ethanol to an aqueous solution of the monomeric species resulted in a mixture of *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup>, [C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup>, and a third *ansa*-molybdocene species assigned to [C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(X)]<sup>+</sup> or [C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(X)<sub>2</sub>], where X = OCD<sub>3</sub> or OC<sub>2</sub>D<sub>5</sub>, respectively (Figure 3). (The resonances for these latter species, labeled A in Figure 3, have been observed before.<sup>1</sup> Because the A resonances are always observed upon addition of an alcohol to *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup>, assignment to the [C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(X)]<sup>+</sup> or [C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(X)<sub>2</sub>] species is logically suggested.<sup>1</sup> Furthermore, the alkoxide ligands may bridge the *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo<sup>2+</sup> fragments, leading to the formation of [C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(μ-X)]<sub>2</sub><sup>2+</sup> instead of [C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> or to an equilibrium mixture of both species. Assignment of the dimeric species formed in aqueous alcohol as [C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> instead of [C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(μ-X)]<sub>2</sub><sup>2+</sup> was based on excellent agreement with the <sup>1</sup>H NMR spectrum of [C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> in pure water.) Note that, for the experiment depicted in Figure 3, 76% of the *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> monomer is converted to the [C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> dimer in the presence of methanol, while only 7% dimerized in the solution containing aqueous ethanol. In contrast, no dimer was observed on addition of an equal volume of THF, DMSO, or acetone to an aqueous solution of *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup>. In fact, crystals of [C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> are immediately dissolved and completely hydrolyzed to the monomer in slightly wet DMSO or THF, as shown by the appearance of resonances at 7.0 and 6.2 ppm in the <sup>1</sup>H NMR spectra, which demonstrates that *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> is the preferred species in these wet solvents as well as in water; that is, the monomer is more stable than the dimer in these solvents. Such stabilization of the monomeric species is unprecedented using the non-*ansa* molybdocenes. Note that both non-*ansa* [Cp(′)<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> dimers are more stable than their respective Cp(′)<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> monomers (as indicated by the equilibrium constants, see the Introduction) under all aqueous conditions examined thus far.<sup>1,11</sup> On the basis of the available spectroscopic data, as well as the limit of detection for a 600 MHz NMR spectrometer, *K*<sub>eq</sub> ≥ 2 M for eq 5 in water (25 °C, pD 6.8), which is 4 orders of magnitude greater than the *K*<sub>eq</sub> found for [Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup>. In contrast, *K*<sub>eq</sub> is approximately 9 × 10<sup>−2</sup> and 7 × 10<sup>−6</sup> M at 25 °C in ethanol and methanol, respectively, based on the ratio of monomer to dimer present in the 50% aqueous solutions previously discussed.<sup>19</sup>

The large differences in the estimated equilibrium constants for eq 5 illustrate that the equilibrium established by the tetramethylethylene-bridged *ansa*-molybdocenes is not de-

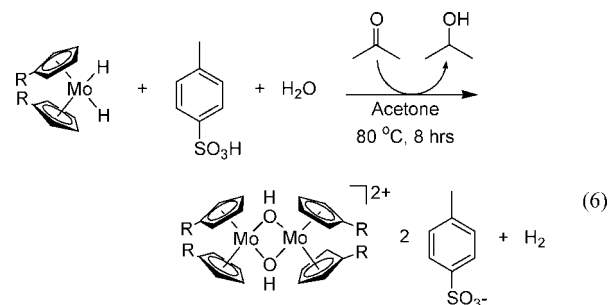
(19) The *K*<sub>eq</sub> values in the aqueous methanol and ethanol solutions were determined using an activity of 1 for H<sub>2</sub>O rather than using the molar concentration of water. This was done to facilitate comparisons with the *K*<sub>eq</sub> values for the non-*ansa* complexes obtained in dilute aqueous solution, for which a value of 1 was used for the activity of water. If the molar concentration of water is used instead of an activity of 1, then the *K*<sub>eq</sub> values for the non-*ansa* complexes are (8.8 ± 0.3) × 10<sup>−8</sup> and (8.1 ± 0.3) × 10<sup>−6</sup> M<sup>−1</sup> for Cp and Cp′, respectively. Using the molar concentration of water for the equilibrium constants measured for the *ansa*-bridged species, *K*<sub>eq</sub> is at least 7 × 10<sup>−4</sup> M<sup>−1</sup> in dilute water and approximately 1 × 10<sup>−4</sup> and 9 × 10<sup>−9</sup> M<sup>−1</sup> in aqueous ethanol and methanol, respectively.



**Figure 4.** Graph of concentration versus time and the GIT fit for the *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup>-catalyzed hydration of 3-hydroxypropionitrile.

termined by sterics or electronics. The *ansa*-linkage minimizes, if not eliminates, steric interactions between the Cp rings on different Mo centers. Moreover, the increased electrophilicity of the *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo<sup>2+</sup> cation should promote dimerization of the monomer. This statement is based on the equilibrium data previously measured for the non-*ansa* complexes, which showed more favorable dimerization of the relatively electrophilic Cp complexes compared with the Cp′ species due to a larger enthalpic gain achieved upon formation of the Mo–OH bonds in [Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> compared to [Cp′<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> ( $\Delta H^\circ = 6.2 \pm 0.5$  and  $1.5 \pm 0.1$  kcal/mol for Cp and Cp′, respectively, in eq 1). Because the absence of dimerization noted for the *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> monomer cannot be attributed to the steric or electronic effects of the ligand, it is suggested that the equilibrium established by the *ansa*-molybdocenes is largely determined by the ability of the chosen medium to solvate either the *ansa*-monomer or -dimer species. Effective solvation of the *ansa*-dimer is likely dependent on the solvent polarity, dielectric constant, hydrogen-bonding ability, and/or solvent basicity; however, no correlation could be made between the estimated *K*<sub>eq</sub> values and any one of these factors (see Supporting Information).

The strong solvent dependence of *K*<sub>eq</sub> in the *ansa*-complexes is consistent with prior observations noted in the synthesis of the *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> monomer.<sup>1</sup> The Cp(′)<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> catalysts are accessed by hydrolysis of the [Cp(′)<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> dimers, which are prepared by reaction of the respective molybdocene dihydride with *p*-toluene sulfonic acid in aqueous acetone (eq 6).<sup>14,15</sup> In contrast, reaction of the



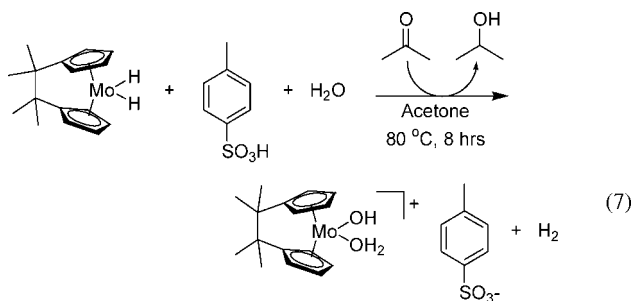
analogous tetramethylethylene-bridged *ansa*-molybdocene dihydride with tosic acid did not give the [C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> dimer. Instead, the monomeric *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo-



**Table 1.** Comparison of Kinetic Data Obtained for the Hydration of 0.060 M 3-Hydroxypropionitrile at 80 °C Using a Total Mo Concentration of 0.58 mM in 0.13 M MOPS-Buffered D<sub>2</sub>O

ligand	[monomer] (mM)	rate (M s <sup>-1</sup> × 10 <sup>8</sup> )	TOF (mol amide/mol monomer · s × 10 <sup>5</sup> )
{C <sub>2</sub> Me <sub>4</sub> (C <sub>5</sub> H <sub>4</sub> ) <sub>2</sub> }	0.58	3.2 ± 0.2	5.6 ± 0.3
(C <sub>5</sub> H <sub>5</sub> ) <sub>2</sub>	0.39	3.9 ± 0.3	10 ± 1
(C <sub>5</sub> H <sub>4</sub> Me) <sub>2</sub>	0.56	3.0 ± 0.2	5.4 ± 0.4

(OH)(OH<sub>2</sub>)<sup>+</sup> species (eq 7) precipitates from this reaction because, as this work has demonstrated, it is the thermodynamically favored product in aqueous acetone.



**Effect of Molybdocene Dimerization on the Rate of Catalytic Nitrile Hydration.** To investigate the impact of catalyst dimerization on the rate of nitrile hydration, rates for the Cp<sup>2</sup>Mo(OH)(OH<sub>2</sub>)<sup>+</sup>- and Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup>-catalyzed hydration of 3-hydroxypropionitrile (3-HPN) were compared to those obtained with the *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> catalyst. The experimental plan was for each reaction to be performed using identical concentrations of nitrile and total Mo. Therefore, if dimerization of the non-*ansa* molybdocenes has a significant effect on the reaction rates, the rates will decrease with increasing dimer formation in the order *ansa*-C<sub>2</sub>Me<sub>4</sub>-Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> > Cp<sup>2</sup>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> > Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> due to a decrease in the concentration of the active monomer. (To summarize why this ordering is predicted: no [*ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> is observed in solutions of *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> at any temperature. In the case of the Cp<sup>2</sup>-containing molecule, the [Cp<sup>2</sup>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> dimer is slightly more stable than Cp<sup>2</sup>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> (eq 2, ΔG° = 2.2 kcal/mol at pH 7.2, 25 °C), and consequently only a small amount of dimerization is observed in aqueous solution. Appreciable catalyst dimerization is observed only for the Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> catalyst.) Because of the low solubility of the *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> complex in water (<5 mM), nitrile hydration was carried out using a total Mo concentration of 0.58 mM in 0.13 M MOPS buffer. The resulting concentration of monomer and the kinetic data for the three catalysts are compared in Table 1. A sample kinetic trace and the calculated fit are shown in Figure 4. The second-order rate constants (*k*<sub>app</sub>) for nitrile hydration and the first-order rate constants for H–D exchange (*k*<sub>2</sub> and *k*<sub>3</sub>) are found in the Supporting Information.

Comparison of the turnover frequencies in Table 1 shows that Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> is almost twice as reactive as the *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> and Cp<sup>2</sup>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> complexes. However, because of the increased amount of dimer in solution for the Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> complex, the net reaction rate is only 22% and 30% faster than the rates for the *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> and Cp<sup>2</sup>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> catalysts, respectively. These data show that a small increase in reaction rate can be achieved by suppressing catalyst dimerization using the slightly less reactive *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> com-

**Table 2.** Comparison of Kinetic Data Obtained for the Hydration of 0.26 M 3-Hydroxypropionitrile at 80 °C Using a Total Mo Concentration of 2.8 mM in 0.13 M MOPS-Buffered D<sub>2</sub>O

ligand(s)	[monomer] (mM)	rate (M s <sup>-1</sup> × 10 <sup>6</sup> )	TOF (mol amide/mol monomer · s × 10 <sup>4</sup> )
(C <sub>5</sub> H <sub>5</sub> ) <sub>2</sub>	1.1	1.3 ± 0.1	12 ± 1
(C <sub>5</sub> H <sub>4</sub> Me) <sub>2</sub>	2.5	1.3 ± 0.2	5.3 ± 0.4

plex. Note that an equilibrium mixture of Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> containing a 0.58 mM concentration of the Cp<sub>2</sub>Mo<sup>2+</sup> unit contains only 17% of the dimeric [Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> species at 80 °C. To test whether dimerization affects the reaction rate at higher concentrations of molybdocene, where the percentage of dimer in solution is higher, a second comparison was made using a total molybdenum concentration of 2.8 mM of the non-*ansa* Cp<sup>2</sup>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> and Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> catalysts, which contain approximately 6% [Cp<sup>2</sup>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> and 30% [Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup>, respectively. The results are shown in Table 2. Note that the rate of Cp<sup>2</sup>Mo(OH)(OH<sub>2</sub>)<sup>+</sup>-catalyzed HPN hydration is virtually identical to the rate obtained using the Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> catalyst when the concentrations of catalyst and the associated dimer are increased. These data indicate that a significant reduction in catalyst dimerization does counterbalance the slight, yet significant, activity loss exhibited by the Cp<sup>2</sup>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> complex. It may be inferred by comparison of this trend with that obtained at lower concentrations of catalyst that the effect of dimerization will continue to increase with increasing catalyst concentration.

A comparison of the turnover frequencies in Table 2 indicates that the Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> monomer is 2 times more reactive than the Cp<sup>2</sup>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> monomer toward the hydration of 3-HPN. Data reported previously<sup>1</sup> found that the rate constants for these reactions are the same within error. The discrepancy can be attributed to a difference in the concentration of total molybdenum and substrate concentration for the two sets of experiments, because both parameters affect *k*<sub>app</sub>. Although the trends reported herein are slightly different, all of the data show that Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> is more reactive than the Cp-substituted molybdocene complexes. In summary of this section, the dimerization of molybdocene complexes does not have an appreciable effect on the rate of nitrile hydration at low catalyst concentration. However, at high concentrations, the percentage of dimer present in solution becomes significant and the net rate of hydration may be affected.

## Summary

The [Cp(′)<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> dimers are more thermodynamically stable than two Cp(′)<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> molecules (ΔG° = 2.2 and 4.9 kcal/mol for Cp and Cp′, respectively, at 25 °C) in water. A consequence of this dimer stability is that a significant fraction of the catalytically active Cp<sup>2</sup>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> monomer is inactive because it is tied up in dimeric form. In contrast, the experiments reported herein demonstrate that the monomeric *ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(OH)(OH<sub>2</sub>)<sup>+</sup> complex is significantly more stable than the [*ansa*-C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> dimer in water, as well as in aqueous mixtures of THF, DMSO, and acetone. Experiments showed that the destabilization of *ansa*-[C<sub>2</sub>Me<sub>4</sub>Cp<sub>2</sub>Mo(μ-OH)]<sub>2</sub><sup>2+</sup> relative to the monomer is due to solvation changes. Specifically, because the *ansa*-dimer crystallizes from aqueous solution at low concentration, it is suggested that in water the dimer is solvated more poorly than the monomer. However, the *ansa*-dimer is soluble in DMSO and THF, and it is unclear whether the energy of monomer or dimer

is most affected by solvation in these solvents. Overall, these results show that careful solvent selection is an effective method of suppressing catalyst dimerization, which can lead to faster rates of catalytic hydration.

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**Supporting Information Available:** All rate constants ( $k_{\text{app}}$ ,  $k_2$ , and  $k_3$ ) obtained for catalysis experiments reported in Tables 1 and 2. A table of solvent properties (i.e., dielectric constants,  $\text{p}K_{\text{a}}$  values, etc.) for solvents used in this study. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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