Organometallic Chemistry in Aqueous Solution. Hydration of Nitriles to Amides Catalyzed by a Water-Soluble Molybdocene, $(MeCp)_2Mo(OH)(H_2O)^+$

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$[Cp'_2Mo(\mu\text{-}OH)_2MoCp'_2]^{2+}$ (**1**) ($Cp' = \eta^5\text{-}CH_3C_5H_4$) is a precatalyst for the hydration of nitriles in aqueous solution under mild conditions (∼80 °C). Among the nitriles hydrated were acetonitrile, isobutyronitrile, benzonitrile, 3-hydroxypropionitrile, 3-bromopropioamide, 4-cyanopyridine, succinonitrile, methyl cyanoacetate, 2-methoxyacetonitrile, and acrylonitrile. Except in the case of 2-methoxyacetonitrile, hydrolysis of the resulting amide products did not occur. Hydration of the C═C double bond did not occur in acrylonitrile, but hydrolysis of ester and ether linkages did occur in nitriles containing those functional groups. The apparent rate constants and turnover frequencies of the catalytic reactions were determined using an iterative kinetics-fitting program. The rates and turnover frequencies are comparable to those reported for many homogeneous nitrile hydration catalysts described in the literature. In aqueous solution, **1** is in equilibrium with $[Cp'_2Mo(OH)(H_2O)]^+$ (**2**), and this monomer is proposed to be the active hydration catalyst. The hydration is proposed to occur by an intramolecular attack of a hydroxide ligand on a coordinated nitrile. The hydration reaction is irreversibly inhibited by product and reversibly inhibited by substrate (nitrile).

Introduction

The reaction of nitriles with water to form amides (eq 1) is important both in the academic laboratory and in industry.[1] Amides are used in a wide variety of industrial applications as lubricants, detergent additives, drug stabilizers, and monomers.[2] One of the most noteworthy industrially important amides is acrylamide. Acrylamide production has increased consider-

$$R{-}C{\equiv}N \xrightarrow{H_2O} R{-}\overset{O}{\overset{\|}{C}}{-}NH_2 \qquad (1)$$

ably because of the demand for polyacrylamide, which is used in mobile oil recovery, waste flocculation, paper strengthening, and electrophoresis gels.[2] According to Gaffar and Parkins, the annual industrial consumption of acrylamide in 1999 was 170 million pounds, and there is a growing demand of 4% per year for acrylamide feedstocks.[3] While nitrile hydration is the chosen method of synthesis, current technologies for acrylamide production are limited and improvements in the hydration catalysts are actively being investigated (see Supporting Information). In particular, new catalysts are sought that will selectively hydrate only the C≡N bond and that will not hydrolyze the resulting acrylamide product. (Note that hydration of the olefin in acrylonitrile produces products incapable of polymerization, namely, the industrially unimportant β-cyanoethanol and β-cyanoethyl ether.[5]) In addition to these chemoselective properties, any new catalyst must operate under reaction conditions mild enough to prevent the autocatalytic polymerization of acrylamide. We describe herein the development of a reactive, aqueous molybdocene catalyst ($[Cp'_2Mo(OH)(H_2O)]^+$, **2**) for the hydration of nitriles, including acrylonitrile, under mild conditions. A mechanism for amide formation with the catalyst is also described, as are rate and selectivity data.

Experimental Section

General Procedures. All experiments were performed under a nitrogen atmosphere in a Vacuum Atmospheres glovebox or using Schlenk line techniques. Liquid substrates were degassed using the freeze−pump−thaw method except for D_2O, which was purged with nitrogen for at least 30 min prior to use. All NMR samples were prepared in a glovebox. The samples of acetamide, 3-bromopropionitrile, and isobutyronitrile, as well as the first acetonitrile sample, were flame sealed in Wilmad 9 in. precision NMR tubes while frozen in liquid nitrogen. All other samples were sealed in Wilmad J-Young screw-cap NMR tubes. Reaction samples in NMR

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(1) Matsuda, F. *Chemtech* **1977**, *7*, 306.

(2) (a) Haberman, C. E. Acrylamide. In *Encyclopedia of Chemical Technology*; Kroschwitz, J. J., Howe-Grand, M., Eds.; John Wiley and Sons: New York, 1991; Vol. 1, p 251. (b) Opsahl, Ross; Amides. In *Encyclopedia of Chemical Technology*; Kroschwitz, J. J., Howe-Grand, M., Eds.; John Wiley and Sons: New York, 1991; Vol. 1, p 346.

(3) Gaffar, T.; Parkins, A. W. *J. Mol. Catal. A* **2000**, *160*, 249.

(4) (a) Stabler R. N.; Chesick, J. *Int. J. Kinet.* **1978**, *10*, 461. (b) McKinney, R. J.; Weigert F. J. Quantum Chemistry Program Exchange, Program # QCMPO22. (c) Weigert, F. J. *Comput. Chem.* **1987**, *11*, 273.

(5) (a) *CRC Handbook of Chemistry and Physics*, 82nd ed. Linde, D. R., Ed.; CRC Press LLC: New York, NY, 2001. (b) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman: Essex, UK, 1999. (c) *Aldrich Library of FT-IR Spectra*, 2nd ed.; Pouchart, C. J., Ed.; Sigma Aldrich Co.: Milwaukee, WI, 1997; Vol. 1, p 1292(c).

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Table 1. Comparison of the Catalytic Activity for the Hydration of Acetonitrile by Various Catalysts

catalyst	temp, °C	turnover frequency[a]	turnover number[b]	ref
$[(Cp'_2Mo(OH)(OH)_2]^+$	80	4.77[c]	114	this work
$[PtH(PMe_2OH)(PMe_2O)_2H]$	90	380	5700	3
$[PtH(PPh_2OH)(PPh_2O)_2H]$	90	23	369	3
$[PtH(H_2O)(PMe_3)_2][OH]$	78	178	not reported	6
$[PtH(H_2O)(PEt_3)_2][OH]$	78	69.9	5000−6000	6
$PdCl(OH)(bipy)(H_2O)$	76	29.4	not reported	19, 35
$C_{23}H_{29}N_4O_2SPd_2(CH_3CONH)$	80	not reported	4000	36
$Pt(PEt_3)_3$	80	2.7	54	25
$Pt(P(i\text{-}Pr)_3)_3$	80	20.3	405	25
$[Rh(COD)Cl]_2$/TPPTS/NaOH	90	50.8	295.3	34
$[Rh(OH)(CO)(PPh_3)_2]$	80	50	not reported	37
$[Ir(OH)(CO)(PPh_3)_2]$	reflux	50	150	37
$Cp^*Ir(\eta^3\text{-}CH_2CHCHCHPh)(NCCH_3)]^+$	70	8.25	not reported	36
$RuH_2(PPh_3)_4$	120	1.28	not reported	38
NaOH	78	0.4		6, 25

[a] mol/(mol of catalyst h). [b] mol/(mol of catalyst). [c] Average turnover frequency, sample 6, Table 2.

tubes were heated in a Therm-o-watch temperature-controlled oil bath unless otherwise specified. ^1H, ^2H, and ^{13}C NMR spectra were measured on a Varian Inova 300 (299.95 MHz for ^1H, 46.04 MHz for ^2H, and 75.42 MHz for ^{13}C). ^1H NMR resonances were referenced to the 7.69 ppm tosylate peak from the $[Cp'_2Mo(\mu\text{-}OH)_2MoCp'_2][OTs^-]_2$ complex (**1**) unless otherwise specified. IR spectra were measured on a Nicolet Magna IR 530 spectrometer. pH readings were measured on an Orion Model 230 pH meter with a Corning NMR Micro Combo pH electrode. All pH values reported herein are uncorrected. Mass spectra were obtained with an Agilent 1100 Series LC/MS with an electrospray head. All reaction kinetics were modeled using an iterative kinetics data-fitting program, GIT,[4] using the following equations unless otherwise noted. (As discussed below, the reactions are not saturated in substrate and therefore kinetics analysis yields a rate constant k_{app} (for $k_{apparent}$) that is an "apparent" second-order rate constant for the hydration reaction.)

$$\text{catalyst} + \text{nitrile} \xrightarrow{k_{app}} \text{catalyst} + \text{amide} \qquad (2)$$

$$\text{catalyst} + \text{amide} \xrightarrow{k_2} \text{inactive product} \qquad (3)$$

Materials. The nitrile substrates were used without further purification except for acetonitrile and isobutyronitrile, which were distilled over CaH_2. Liquid substrates were degassed as described above. The following chemicals were obtained from Aldrich: acrylamide (97%), benzonitrile (99+% anhydrous), 4-cyanopyridine (98%), 3-hydroxypropionitrile (99%), isobutyronitrile (99%), methoxyacetonitrile (99+%), methyl cyanoacetate (99%), and tetrabutylammonium tetrafluoroborate (99%). Acetamide (99%) was obtained from Mallinckrodt, acetonitrile (99.9%) from Fischer Scientific, acrylonitrile (99+%) from Acros Organics, and 3-bromopropionitrile and succinonitrile were obtained from Matheson Coleman & Bell. Pyridine, 1-bromopentane, and 1-pentanol were obtained from J. T. Baker Inc. D_2O (99.0% D) and $CDCl_3$ (99.9% D) were obtained from Cambridge Isotope Laboratory. Complex **1** was prepared as described in the literature.[7]

Catalyst Stock Solution Preparation. Stock solutions containing compounds **1** and **2** were prepared as followed. (Note that prior work showed that **1** and **2** are in equilibrium in aqueous solution.[8]) The catalyst solution denoted in the following sections as "stock solution **2A**" was prepared by adding **1** (0.1128 g, 127 μmol) to 25 mL of D_2O. This dark green-brown solution delivered 5.10 μmol of total monomeric molybdenum in a 500 μL aliquot. The catalyst solution denoted "stock solution **2B**" was prepared by adding **1** (0.0440 g, 49.7 μmol) to 10 mL of D_2O. A 500 μL aliquot of this solution delivered 4.970 μmol of total monomeric molybdenum complex. The catalyst solution denoted "stock solution **2C**" was prepared by adding **1** (0.2255 g, 255 μmol) and tetrabutylammonium tetrafluoroborate (0.5 mg, 1.52 μmol) to 50 mL of D_2O. A 500 μL aliquot of this solution delivered 5.10 μmol of total monomeric molybdenum complex.

Acetamide Control Reaction. A 25 μL aliquot (0.15 mmol) of a 6.15 M stock solution of acetamide in D_2O was added to 500 μL (2.55 μmol) of stock solution **2A**. Before heating, the ^1H NMR (D_2O) spectrum of the solution showed a resonance at δ 1.99 (s, CH_3CONH_2). The tube was then heated at 80 °C for 11 days in an oil bath. Throughout the heating period there was no change in the green-brown color of the solution, and there was no change in the ^1H NMR spectrum.

Acetonitrile. Complex **1** (0.0407 g, 45.9 μmol) was added to 5 mL of D_2O, and then a 750 μL aliquot of this solution (containing 12.78 μmol of total monomeric molybdenum complex) was added to 100 μL of acetonitrile (1.91 mmol). The resulting solution, which immediately turned pink, was flame sealed while frozen in liquid nitrogen. The sample was heated at 75 °C for 9 days in an oil bath. Before heating, the ^1H NMR (D_2O) resonance of the substrate was at δ 2.08 (s, 3H, CH_3CN); after heating for 9 days, a new resonance appeared at 1.98 (s, 3H, CH_3CONH_2). After heating for 9 days, the ^{13}C NMR (D_2O) showed four resonances at δ 177.3 (s, CH_3CONH_2), 119.2 (s, CH_3CN), 21.4 (s, CH_3CONH_2), and 1.0 (CH_3CN). After 30 days of heating, only the ^{13}C resonances at δ 177.3 and 21.4 remained. Gas chromatography of the reacted solution showed that the only product was acetamide.

Acetamide Inhibition of Acetonitrile Hydration. Acetonitrile (25 μL, 0.479 mmol) and acetamide (0.0143 g, 0.2421 mmol) were added to 500 μL (2.55 μmol) of stock solution **2C** in an NMR tube. The reaction solution was heated at 82 °C and monitored for 18 days by NMR. The acetonitrile was converted to acetamide at a reduced rate (Table 2).

Acrylamide Control Reaction. Acrylamide (1.7763 g, 25.0 mmol) was added to 5 mL of D_2O to give a 5.00 M solution. An aliquot of this solution (100 μL, 0.500 mmol) was added to 500 μL (2.55 μmol) of stock solution **2A**. The ^1H NMR resonances (D_2O) of the solution before heating were at δ 6.24 (t, J = 1.5 Hz, 1H, $H_2C{=}CHCONH_2$) and 5.82 (t, J = 3.0 Hz, $H_2C{=}CHCONH_2$). The tube was heated at 90 °C for 9 days in an oil bath. Throughout the heating period there was no change in the green-brown color of the solution, and no changes occurred in the ^1H NMR spectrum. Similarly, during the reaction there were no changes in the ^{13}C NMR resonances

(6) Jensen, C. M.; Trogler, W. C. *J. Am. Chem. Soc.* **1986**, *108*, 723.
(7) Balzarek, C.; Tyler, D. R. *Angew. Chem., Int. Ed. Engl.* **1999**, *2406*, 6.
(8) Balzarek, C.; Weakley, T. J. R.; Tyler, D. R. *J. Am. Chem. Soc.* **2000**, *122*, 9427.

Table 2. Hydration of Nitriles with the $[Cp'_2Mo(OH)(OH_2)]^+$ Catalyst

	substrate	substrate (M)	[2] (M)	salt	k_{app} (M^{-1} h^{-1})	k_2 (M^{-1} h^{-1})	temp (°C)	time (h)	maximum conversion (%)	initial turnover frequency (mol product/ mol catalyst h)	average turnover frequency (mol product/ mol catalyst h)	TON (mol product/ mol catalyst)	initial rate (mol product/ L h)
1	acetamide	12.30	0.010	n	0	0	80	264	0	0.00	0.0	0.0	0.00×10^0
2	acrylamide	0.83	0.009	n	0	0	90	214	0	0.00	0.00	0.0	0.00×10^0
3	acetonitrile	0.38	0.010	y	1.39	1.28×10^{-2}	82	280	92	0.52	0.12	34.6	5.22×10^{-3}
4	acetonitrile	0.91	0.010	y	0.99	1.10×10^{-2}	82	524	67	0.90	0.12	62.9	8.75×10^{-3}
5	acetonitrile	0.91	0.022	n	1.35	1.29×10^{-2}	80	140	90	1.23	0.27	38.1	2.66×10^{-2}
6	acetonitrile	1.74	0.009	n	2.23	1.61×10^{-3}	80	24	61[a]	3.88	4.77	114	3.59×10^{-2}
7	acetonitrile	3.18	0.009	n	0.75	3.33×10^{-3}	80	216	80	2.39	1.39	300	2.03×10^{-3}
8	acetonitrile/acetamide	0.87	0.009	y	0.37	3.16×10^{-3}	82	431	43	0.32	0.09	40.4	3.00×10^{-3}
9	acrylonitrile	0.72	0.010	y	1.86	8.35×10^{-3}	75	264	83	1.35	0.23	61.8	1.31×10^{-2}
10	benzonitrile	0.19	0.010	y	1.56	5.10×10^{-3}	82	794	63	0.30	0.02	12.1	3.00×10^{-3}
11	benzonitrile	0.89	0.009	n	4.07	7.07×10^{-4}	85	72	93[a]	3.63	1.25	89.4	3.36×10^{-2}
12	3-bromopropionitrile	1.09	0.009	n	1.50	0.00×10^0	90	215	98[a]	1.64	0.54	115	1.52×10^{-2}
13	4-cyanopyridine	0.33	0.009	n	2.22	2.68×10^{-2}	90	142	78	0.74	0.22	30.6	6.29×10^{-3}
14	3-hydroxypropionitrile	2.43	0.009	n	15.9	0.00×10^0	90	189	100	38.7	1.51	286	3.29×10^{-1}
15	isobutyronitrile	1.00	0.009	y	1.18	5.34×10^{-3}	82	464	84	1.18	0.20	90.6	1.10×10^{-2}
16	isobutyronitrile	1.02	0.009	n	1.33	3.52×10^{-4}	85	309	95[a]	1.36	0.34	104	1.26×10^{-2}
17	isobutyronitrile	1.87	0.009	y	1.43	8.55×10^{-3}	85	259	64[a]	2.68	0.54	141	2.28×10^{-2}
18	isobutyronitrile/pyridine	0.86	0.008	y	0.46	2.78×10^{-2}	85	259	25	0.40	0.11	27.5	3.12×10^{-3}
19	isobutyronitrile/pyridine	1.60	0.007	y	0.79	2.02×10^{-2}	75	130	49	1.26	0.92	119	8.95×10^{-3}
20	methoxyacetonitrile	2.23	0.009	n	13.5	1.32×10^{-2}	85	68	97	30.2	3.75	255	2.56×10^{-1}
21	succinonitrile	0.32	0.009	n	14.7	3.45×10^{-2}	80	94	100[e]	4.65	0.40	37.3	3.95×10^{-2}
22	succinonitrile	0.56	0.007	n	15.1	1.25×10^{-1}	80	168	100[e]	8.42	0.46	76.5	6.14×10^{-2}

[a] The reaction was not complete at the time indicated. [b] The rate constant for the hydroysis of 3-bromopropionamide, k_3, is 1.93×10^{-6} M^{-1} h^{-1}. [c] The rate constant for the hydration of 3-cyanopropionamide (line 21), k_7, is 6.00 M^{-1} h^{-1}. [d] The rate constant for the hydration of 3-cyanopropionamide (line 22), k_7, is 2.80 M^{-1} h^{-1}. [e] No succinonitrile is left at this time.

(D_2O) of acrylamide: δ 171.1 (s, $H_2C{=}CHCONH_2$), 129.7 (s, $H_2C{=}CHCONH_2$), and 128.7 (s, $H_2C{=}CHCONH_2$).

Acrylonitrile. Acrylonitrile (25 μL, 0.38 mmol) was added to 500 μL (2.55 μmol) of stock solution **2A**. The solution immediately turned pink. The solution was heated to 75 °C for 13 days, during which time the color of the solution slowly returned to the green-brown color of the pure catalyst solution. The ^{1}H NMR resonances (D_2O) of the solution before heating were at δ 6.29 (dd, J = 18.0 Hz, 2H, $H_2C{=}CHCN$) and 5.82 (q, J = 12.0 Hz, 1H, $H_2C{=}CHCN$). During heating, these resonances decreased and the resonances for acrylamide appeared: δ 6.24 (t, J = 1.5 Hz, 1H, $H_2C{=}CHCONH_2$) and 5.83 (t, J = 3.0 Hz, 2H, $H_2C{=}CHCONH_2$).

Benzonitrile. Benzonitrile (50 μL, 0.49 mmol) was added to 500 μL (2.55 μmol) of stock solution **2A**. The solution turned slightly pink, but the nitrile was not completely soluble in the D_2O and the excess benzonitrile formed a clear layer on top of the solution. The ^{1}H NMR spectrum (referenced to 4.80 HDO) before heating showed resonances for benzonitrile at δ 7.78 (d, J = 3.45 Hz, 2H, *o*-Ar), 7.72 (t, J = 7.5 Hz, 2H, *m*-Ar), and 7.56 (t, J = 7.8 Hz, 1H, *p*-Ar). The sample was heated at 85 °C for 3 days in an oil bath. A white precipitate formed when the tube was cooled to room temperature for NMR analysis. The precipitate was filtered and dissolved in $CDCl_3$. The white precipitate was benzamide, as characterized by its ^{1}H NMR resonances in $CDCl_3$ at (referenced to 7.27 $CHCl_3$) δ 7.81 (d, J = 7.5 Hz, 2H, *o*-Ar), 7.55 (t, J = 10.8 Hz, 1H, *p*-Ar), and 7.47 (t, J = 7.8 Hz, 2H, *m*-Ar).

3-Bromopropionitrile. 3-Bromopropionitrile (50 μL, 0.60 mmol) was added to 500 μL (2.55 μmol) of stock solution **2A**. The 3-bromopropionitrile was sparingly soluble in D_2O and formed a dark layer on the bottom of the tube. The solution produced a slightly darker pink than other nitriles, possibly due to the yellow coloration of the nitrile. The ^{1}H NMR resonances (D_2O) before heating were at δ 3.68 (br t, J = 6.0 Hz, 2H, $BrCH_2CH_2CN$) and 3.16 (br t, J = 6.0 Hz, 2H, $BrCH_2CH_2CN$). The sample was heated at 90 °C for 10 days in an oil bath. During this time, the layer of 3-bromopropionitrile on the bottom of the tube slowly disappeared and the following resonances for 3-bromopropionamide appeared in the ^{1}H NMR spectrum (D_2O): δ 3.68 (t, J = 6.1 Hz, 2H, $BrCH_2CH_2CONH_2$) and 2.72 (t, J = 6.0 Hz, 2H, $BrCH_2CH_2CONH_2$). Less intense resonances, attributed to 3-hydroxypropioamide, also appeared at 3.85 (t, J = 6.2 Hz, 2H, $HOCH_2CH_2CONH_2$) and 2.62 (t, J = 6.0 Hz, 2H, $HOCH_2CH_2CONH_2$). After heating, the solution returned to its original green-brown color. The kinetics of the reaction were modeled by GIT[4] using the following equations:

$$\text{catalyst} + \text{3-bromopropionitrile} \xrightarrow{k_{app}} \text{catalyst} + \text{3-bromopropionamide} \quad (4)$$

$$\text{3-bromopropionitrile} \xrightarrow{k_3} \text{3-hydroxypropionamide} \quad (5)$$

3-Hydroxypropionitrile. 3-Hydroxypropionitrile (100 μL, 1.46 mmol) was added to 500 μL (2.55 μmol) of stock solution **2A**. The resulting solution turned pink and was sealed in a screw-cap NMR tube. The ^{1}H NMR resonances (D_2O) before heating were at δ 3.81 (t, J = 6.0 Hz, 2H, $HOCH_2CH_2CN$) and 2.74 (t, J = 6.0 Hz, 2H, $HOCH_2CH_2CN$). The tube was heated at 90 °C for 8 days. During heating, the nitrile resonances decreased and the following resonances for 3-hydroxypropionamide appeared: δ 3.77 (t, J = 6.6 Hz, 2H, $HOCH_2CH_2CONH_2$) and 2.63 (t, J = 6.0 Hz, 2H, $HOCH_2CH_2CONH_2$).

Isobutyronitrile. Isobutyronitrile (50 μL, 0.56 mmol) was added to 500 μL (2.55 μmol) of stock solution **2A**. The resulting solution turned pink. The ^{1}H NMR resonances (D_2O) before heating were at δ 2.84 (heptet, J = 21.0 Hz, 1H, $(CH_3)_2CHCN$) and 1.29 (d, J = 9.0 Hz, 6H, $(CH_3)_2CHCN$). The sample was heated at 85 °C for 13 days. During this time, the nitrile resonances decreased and the resonances for isobutyramide

appeared at δ 2.52 (heptet, $J = 21.0$ Hz, 1H, $(CH_3)_2CHCONH_2$) and 1.12 (d, $J = 6.0$ Hz, 6H, $(CH_3)_2CHCONH_2$). ^{13}C NMR (D_2O): δ 184.4 (s, $(CH_3)_2CHCONH_2$), 34.7 (s, $(CH_3)_2CHCONH_2$), 19.6 (s, $(CH_3)_2CHCH$), 19.1 (s, $(CH_3)_2CHCN$), and 18.9 (s, $(CH_3)_2CHCONH_2$).

2-Methoxyacetonitrile. 2-Methoxyacetonitrile (100 μL, 1.34 mmol) was added to 500 μL (2.55 μmol) of stock solution **2A** and sealed in a screw-cap NMR tube. The resulting solution turned a light pink color. The sample was heated at 85 °C for 7 days in an oil bath. The ^1H NMR resonances (D_2O) before heating were at δ 4.41 (s, 2H, CH_3OCH_2CN) and 3.50 (s, 3H, CH_3OCH_2CN). During heating the following ^1H NMR resonances (D_2O) for 2-methoxyacetamide appeared: δ 4.22 (s, 2H, $CH_3OCH_2CONH_2$) and 3.43 (s, 3H, $CH_3OCH_2CONH_2$). In addition, methanol (δ 3.35 (s, 3H), glycolic acid 3.99 (s, 2H, $HOCH_2C(O)OH$), and an unidentified peak at 3.86 (s) were detected. After heating, only a slight pink coloration remained in the sample. The kinetics of the reaction were modeled by GIT[4] using the following equations:

$$\text{catalyst} + \text{3-methoxyacetonitrile} \xrightarrow{k_{app}} \text{catalyst} + \text{methanol} + \text{cyanohydrin} \quad (6)$$

$$\text{catalyst} + \text{cyanohydrin} \xrightarrow{k_4} \text{catalyst} + \text{hydroxyacetamide} \quad (7)$$

$$\text{hydroxyacetamide} \underset{k_6}{\xrightarrow{k_5}} \text{glycolic acid} \quad (8)$$

$$\text{catalyst} + \text{hydroxyacetamide} \xrightarrow{k_2} \text{inhibition product} \quad (9)$$

Methyl Cyanoacetate. Methyl cyanoacetate (100 μL, 1.13 mmol) was added to 500 μL (2.55 μmol) of stock solution **2B** and sealed in a screw-cap NMR tube. The resulting solution was a light pink color. The ^1H NMR spectrum (D_2O) before heating showed a resonance at δ 3.82 (s, 3H, $NCCH_2CO_2CH_3$). The sample was heated in an oil bath at 75 °C for 13 days. During the reaction, intense resonances for methanol and acetamide appeared: 3.35 (br, s, 3H, CH_3OH) and 2.05 (m, CHD_2CONH_2). After heating, the ^{13}C NMR spectrum (D_2O) showed the following resonances: δ 167.7 (s, $NCCH_2CO_2CH_3$), 115.7 (s, $NCCH_2CO_2CH_3$), 53.9 (s, $NCCH_2CO_2CH_3$), and 49.0 (s, CH_3OH). The ^2H NMR spectrum (D_2O) showed resonances at δ 3.59 (s, 3D, CD_3OH) and 1.88 (s, 3D, CD_3CONH_2). When opened, the tube released gas and the solution bubbled. The resulting pH of the solution was 2.08. The reaction did not allow for kinetic modeling because of its complexity (see Discussion section).

Succinonitrile. Succinonitrile (0.7773 g, 9.71 mmol) was added to 5 mL of D_2O, giving a 1.94 M solution. An aliquot of this solution (100 μL, 0.19 mmol) was added to 500 μL (2.55 μmol) of stock solution **2A**. The resulting solution turned pink and was sealed in a screw-cap NMR tube. The ^1H NMR spectrum (D_2O) before heating showed a resonance at δ 2.92 (s, 4H, $NCCH_2CH_2CN$). The sample was heated in an oil bath at 80 °C for 4 days. During heating, the following ^1H NMR resonances appeared: δ 2.70 (m, $J = 18.0$ Hz, $CNCH_2CH_2CONH_2$), 2.55 (d, $J = 3.0$ Hz, 4H, $H_2NOC(CH_2)_2CONH_2$), and 2.46 (d, $J = 3.0$ Hz, $CNCH_2CH_2CONH_2$). After 2 days of heating, a white precipitate formed, which was filtered and showed a ^1H NMR resonance ($CDCl_3$) at δ 2.56 (d, $J = 3.0$ Hz, 4H, $H_2NOC(CH_2)_2CONH_2$). The solid was recrystallized from hot water to yield a white crystalline solid. In a mp tube, the solid started to look wet at 128 °C and decomposed at 256 °C, as reported for succinamide.[5] The IR spectrum (KBr: 3345, 3176, 2935, 2814, 1679, 1630, 1426, 1410, 1223, and 1140 cm^{-1}) is identical to that reported for succinamide.[5c]

The kinetics of the reaction were modeled by GIT[4] using the following equations:

$$\text{catalyst} + \text{succinonitrile} \xrightarrow{k_1} \text{catalyst} + \text{3-cyanopropionamide} \quad (10)$$

$$\text{catalyst} + \text{3-cyanopropionamide} \xrightarrow{k_7} \text{catalyst} + \text{succinamide} \quad (11)$$

$$\text{catalyst} + \text{succinamide} \xrightarrow{k_2} \text{inhibition product} \quad (12)$$

4-Cyanopyridine. 4-Cyanopyridine (0.1043 g, 1.00 mmol) was added to 5 mL of D_2O to form a 0.20 M solution. An aliquot of this solution (100 μL, 20.0 μmol) was added to 500 μL (2.55 μmol) of stock solution **2A** and sealed in a screw-cap NMR tube. The solution originally turned pink and then became a darker red-brown color as time elapsed. The ^1H NMR resonances (D_2O; referenced to 4.80 HDO) before heating were at δ 8.69 (dd, $J = 3.0$ Hz, 2H, $-NCH-$, C_5H_4NCN) and 7.72 (dd, $J = 3.0$ Hz, 2H, $-CHCHN-$, C_5H_4NCN). The sample was heated at 90 °C for 8 days in an oil bath. New ^1H NMR resonances (D_2O) for nicotinamide appeared at δ 8.62 (dd, $J = 3.0$ Hz, 2H, $-NCH-$, $C_5H_4NCONH_2$) and 7.76 (dd, $J = 3.0$ Hz, 2H, $-CHCHN-$, $C_5H_4NCONH_2$).

Pyridine. Pyridine (100 μL, 1.24 mmol) was added to 500 μL (2.485 μmol) of stock solution **2B** and sealed in a screw-cap NMR tube. The resulting solution turned pink-brown. This solution was heated at 80 °C for 12 days without any change in the ^1H NMR spectrum. The ^1H NMR resonances (D_2O, referenced to 4.80 HDO) before and after heating were at δ 8.2 (d, $J = 5.9$ Hz, 2H, *o*-Ar, C_5H_5N), 7.52 (t, $J = 7.5$ Hz, 1H, *p*-Ar, C_5H_5N), and 7.09 (t, $J = 6.6$ Hz, 2H, *m*-Ar, C_5H_5N).

Pyridine and Isobutyronitrile. Pyridine (100 μL, 1.24 mmol) and isobutyronitrile (100 μL, 1.12 mmol) were added to 500 μL (2.485 μmol) of stock solution **2B** and sealed in a screw-top NMR tube. The solution turned dark pink/light red. The sample was heated for 5 days at 75 °C. The ^1H NMR resonances (D_2O, referenced to 4.80 HDO) before heating were at δ 8.28 (d, $J = 4.7$ Hz, 2H, $-NCH-$, C_5H_5N), 7.57 (t, $J = 8.5$ Hz, 1H, $-NCHCHCH-$, C_5H_5N), 7.15 (t, $J = 6.6$ Hz, 2H, $-NCHCH-$, C_5H_5N), 2.56 (m, $J = 7.2$ Hz, 1H, $-CH(CH_3)_2$-$(CH_3)_2CHCN$), and 1.03 (d, $J = 3.5$ Hz, 6H, $(CH_3)_2CHCN$). After heating, the following resonances appeared: δ 2.32 (m, $J = 7.1$ Hz, 1H, $(CH_3)_2CHCONH_2$) and 0.93 (d, $J = 3.5$ Hz, 6H, $(CH_3)_2CHCONH_2$). At the end of the reaction, the sample had returned to its original green-brown color.

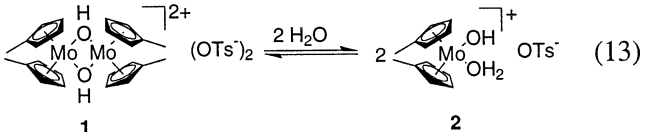
Intermediate Studies with 4-Cyanopyridine. Compound **1** (0.0462 g, 52.2 μmol) was dissolved in 1.0 mL of water in a 1 mL volumetric flask, and 4-cyanopyridine (0.0245 g, 235 μmol) was dissolved in 5.0 mL of water in a volumetric flask. The two solutions were mixed and gently heated, producing a dark red solution. The solution was evaporated until approximately 0.5 mL was left and was then washed with ether to remove excess 4-cyanopyridine. The remaining solution was then evaporated, leaving behind a dark red solid. Repeated recrystallizations to form a crystal suitable for X-ray crystallography were unsuccessful. IR (KBr): 3370, 3184, 1674, 1624, 1597, and 1411 cm^{-1} (contains the amide hydration product and the red intermediate species). MS *m*/*z* (relative intensity): 378.2 (100%), 123.2 (87%).

Intermediate Studies with Acetonitrile. A 1 mL aliquot of a stock solution containing 2.26×10^{-3} mM **2** in D_2O was prepared in an NMR tube. Upon addition of 50 μL of acetonitrile (0.958 mmol), the solution turned red. The tube was heated in an oil bath at 80 °C and monitored by NMR and MS. MS *m*/*z* (relative intensity): 273 (100%), 427 (41.2%), attributable to $[Cp'_2Mo(OH)]^+$ and $[Cp'_2Mo]^{2+}[OTs]^-$, respectively. A *m*/*z* peak at 314 ($[Cp'_2Mo(OH)NCCH_3]^+$) was observed after heating and decreased over the course of the reaction. The NMR of the heated sample displayed resonances at δ 5.7 (t), 5.52 (m), 5.47 (m), 5.38 (m), 5.28 (q), and 5.18 (m), which cannot be attributed to either **1** or **2**: δ 5.89 (m), **1**; 5.61 (m), **1**; 5.46 (m), **2**; 5.42 (m), **2**. A related sample prepared in H_2O

was monitored by MS. Concomitant with the decrease in a peak at 314 (which can be attributed to one of the species **4**−**6** in Scheme 5), a parent ion at *m*/*z* 422, with the splitting pattern of a single Mo center, dominated the spectrum. This parent ion is attributed to the inhibition product. Unfortunately, isolation and further characterization have not been possible.

Results and Discussion

Catalysis of Nitrile Hydration. Both simple and functionalized nitriles were catalytically hydrated when aqueous solutions of the nitriles were heated at 75−90 °C in the presence of **1** (0.1−2.5%). (Note that prior work showed that **1** is in equilibrium with **2** in aqueous solution, eq 7; $K_{eq} = 7.9 \times 10^{-2}$ M at 23 °C, pD 7.[8])



1 **2** (13)

The aqueous solution containing **1** and **2** was initially green-brown, but addition of the nitrile caused the solution to immediately turn red-pink. Some nitriles were quantitatively converted to their amides and others only to some (generally large) fraction conversion (Table 2). In those instances where quantitative conversion occurred, the red color faded as the reaction proceeded and the green-brown color of the catalyst solution reappeared. A summary of the nitrile hydration results appears in Table 2. The discussion below elaborates on the reactions reported in Table 2.

Hydration of Monofunctional Nitriles. Acetonitrile, isobutyronitrile, and benzonitrile[10] were hydrated to their respective amides by the aqueous catalyst system. No hydrolyses of the product amides were detected by NMR. Notice in Table 2 that the maximum percent conversion of nitrile substrate to amide product is dependent on the initial concentration of the substrate. In particular, an increase in the initial substrate concentration led to a smaller maximum percent conversion. For example, 92% of acetonitrile was converted to acetamide for an initial concentration of 0.38 M, whereas only 67% conversion occurred for an initial concentration of 0.91 M. Similar results were found with isobutyronitrile: the maximum conversion was 84% for an initial concentration of 1 M and only 64% for 1.87 M. Control experiments (entry 8 in Table 2) showed that the nitrile hydration reactions were subject to irreversible product inhibition, and this feature is proposed to be responsible for the dependence of the percent conversion on the initial concentration. The explanation is that a higher concentration of substrate leads to a higher concentration of product, which leads to greater product inhibition and a lower fraction of conversion. Note that the dependence of the percent conversion on the substrate concentration cannot be attributed to a reversible hydration/dehydration reaction: control experiments (entry 1 and 2 in Table 2) showed that acetamide and acrylamide did not revert to their respective nitriles under the reaction conditions. Computer fits of the kinetics data are also consistent with product inhibition of the reaction. These simulations are discussed in a section below.

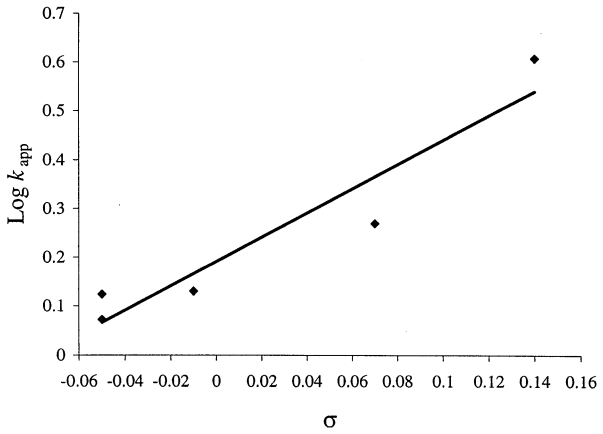


Figure 1. Hammett plot of nitrile hydration for substrates near 1 M nitrile and 1% catalyst **2**.

The rates of nitrile hydration are also dependent on the salt concentration in the aqueous solution (Table 2; entries 15 and 16). For many of the kinetics experiments, an internal NMR reference standard, tetrabutylammonium tetrafluoroborate, was added to the catalyst solution. Solutions containing this salt reacted more slowly than identical solutions without the salt. Measurements showed that the additional salt affects the monomer−dimer equilibrium, thus changing the effective catalyst concentration. ($K_{eq} = 1.9 \times 10^{-2}$ M at 23 °C, with salt; 7.9×10^{-2} M at 23 °C, without salt.)

Sterically bulkier nitriles did not react more slowly than less bulky nitriles (for equal nitrile concentrations). For example, note in Table 2 that isobutyronitrile reacted *faster* than acetonitrile (8.75 mmol of acetamide L^{-1} h^{-1} vs 11.0 mmol isobutyramide L^{-1} h^{-1}). The rate decrease in this case may be attributable to more efficient product inhibition with the less bulky nitrile ($k_{2,acetonitrile} = 1.10 \times 10^{-2}$ M^{-1} h^{-1}; $k_{2,isobutyronitrile} = 3.52 \times 10^{-4}$ M^{-1} h^{-1}). Product inhibition is discussed more completely below.

Finally, it was observed that increasing the electron-withdrawing nature of the nitrile increased the rate of the reaction. (For example, in Table 2 compare benzonitrile to isobutyronitrile: the rates under comparable conditions were 33.6 mmol of benzamide L^{-1} h^{-1} vs 12.6 mmol isobutyramide L^{-1} h^{-1}.) This trend was observed with both monofunctional and bifunctional nitriles, and a Hammett plot is shown in Figure 1. (The mechanistic implications of the Hammett plot are discussed below.)

Hydration of Bifunctional Nitriles. Acrylonitrile. Catalyst **2** is an excellent hydration catalyst for acrylonitrile, which is hydrated exclusively at the C≡N position, with an apparent rate constant of 1.86 M^{-1} h^{-1}. There is no formation of β-cyanoethanol or β-dicyanoethyl ether, which are often detected during acrylonitrile hydration with other catalysts (Table 3). In addition, the reaction proceeded at atmospheric pressure and required no cosolvent because the catalyst was water-soluble. An incomplete list of acrylonitrile

(9) Balzarek, C. Ph.D. Dissertation, University of Oregon, Eugene, OR, June 2000.

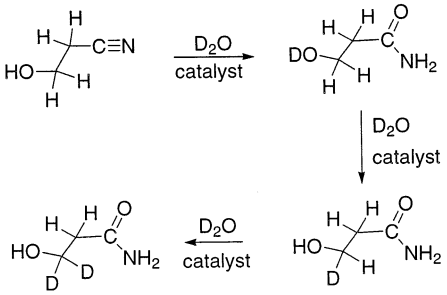
(10) The rate constants reported for benzonitrile are approximate. Benzamide is not water-soluble, and it precipitates from solution. The slight differences in temperature and concentration that affect the solubility of benzamide in the reaction solution, and therefore the concentration of amide measured by NMR, may cause an error in the calculation of the observed rate constant.

Table 3. Acrylonitrile Hydration Catalysts

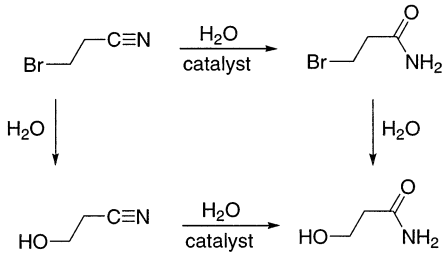
catalyst	temp (°C)	turnover frequency (mol/mol catalyst h) $CH_2{=}CHC(O)NH_2$	$HOCH_2{-}CH_2C{\equiv}N$	$(N{\equiv}CCH_2CH_2)_2O$	selectivity for nitrile (%)	ref
$[Cp'_2Mo(OH)(OH_2)]^+$	75	1.35[a]	0	0	>99	*b*
$[PtH(PMe_2OH)(PMe_2O)_2H]$	90	1485	0	0	>99	1
$[PtH(H_2O)(PMe_3)_2][OH]$	25	6.2	0.02	0.19	97	2
$[PtH(H_2O)(PMe_3)_2][OH]$	80	65.0	84.5	10.5	41	2
$Pt(PPh_3)_2(OH)(CCl{=}CCl_2)$	80	0.5	Trace	0.06	89	25
$Pt[P(i\text{-}Pr_3)]_3$	80	1.8	2.5	20.9	7	25
$Pt(C_6H_8)(DPPE)$	80	0.68	trace	0.14	83	27
$Pt(PPh_3)_2(Ph)(NHCOMe)$	80	2.6	0.4	1.0	65	27
NaOH	80	0.43	1.16	0.94	17	2

[a] Initial turnover frequency, sample 9, Table 2. [b] This work.

Scheme 1. Hydration and H/D Exchange in 3-Hydroxyacetonitrile



Scheme 2. Hydration and Substitution of 3-Bromopropionitrile



hydration catalysts is shown in Table 3 for reference, but it is difficult to compare the various relative catalytic activities for reasons discussed in the section below titled Rate Constants and Product Inhibition. Regardless, it is apparent that the catalyst is remarkably selective and reasonably active. (The initial turnover frequency is 1.35 mol amide/(mol catalyst h).)

3-Hydroxypropionitrile. In addition to nitrile hydration, H/D exchange of the α-H was observed for 3-hydroxypropionitrile (Scheme 1). The H/D exchange was expected because our previous work showed that aqueous solutions of $[Cp'_2Mo(\mu\text{-}OH)_2MoCp'_2][OTs^-]_2$ (specifically $[Cp'_2Mo(OH)(OH_2)]^+$, which is in equilibrium with $[Cp'_2Mo(\mu\text{-}OH)_2MoCp'_2][OTs^-]_2$) catalyzes H/D exchange in alcohols in D_2O.[7–9,11] No inhibition reaction was observed with 3-hydroxypropionitrile.

3-Bromopropionitrile. This nitrile was hydrated to 3-bromopropioamide as expected. In addition, the substitution product 3-hydroxypropioamide was detected. The substitution reaction could occur before or after the nitrile hydration (Scheme 2). Although 3-hydroxypropionitrile was not detected by NMR, control experiments showed that the hydration of 3-hydroxypropionitrile is about 10 times faster than the hydration of 3-bromopropionitrile (15.9 M^{-1} h^{-1} vs 1.50 M^{-1} h^{-1}); thus, 3-hydroxypropionitrile would not necessarily be observed if substitution occurred first. In addition, no inhibition reaction was observed with 3-bromopropioamide because of the facile production of 3-hydroxypropionamide. (Recall this product showed no product inhibition; see preceding paragraph.)

4-Cyanopyridine. This nitrile was hydrated to form isonicotinamide. The reaction was significantly slower (k_{app} = 2.22 M^{-1} h^{-1}; k_{app} refers to the computer-fitted second-order observed rate constant for the conversion of nitrile to amide) than the reaction with the electronically similar benzonitrile (k_{app} = 4.07 M^{-1} h^{-1}). One reasonable explanation for the decreased rate is that competitive binding of the pyridine ring to the catalyst would cause substrate inhibition. To investigate this hypothesis, pyridine (1.24 mmol) was added to an aqueous solution of the catalyst and isobutyronitrile. The initial rate of isobutyronitrile hydration was decreased by about one-half (from 22.8 mmol isobutryamide L^{-1} h^{-1} to 8.95 mmol isobutyramide L^{-1} h^{-1}), consistent with the competitive bonding hypothesis. Note that pyridine coordination has previously been observed in nonaqueous solvents: Dias and Calhorda reported forming $[Cp_2MoH(4\text{-vinylpy})][PF_6]$ as well as other pyridine-containing complexes in acetone.[12,13]

Succinonitrile. Succinonitrile was hydrated to the 3-cyanopropionamide and then slowly hydrated to succinamide ($k_{app(3\text{-cyanopropionamide})}$ = 15.1 M^{-1} h^{-1}, $k_{app(succinamide)}$ = 2.80 M^{-1} h^{-1}; see Experimental Section) (eq 14). Note the observed rate constant for the hydration of 3-cyanopropionamide to succinamide may be low because the succinamide precipitated from solution and therefore the latter product was not fully detected by NMR. The precipitate was collected and the sublimation temperature, ^1H NMR in $CDCl_3$, and the IR spectrum confirmed that pure succinamide was formed (see Experimental Section).[14]

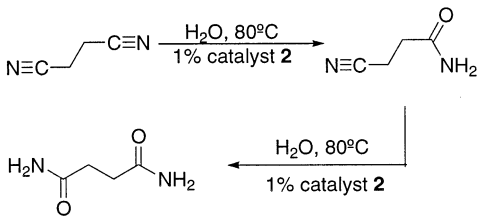
Methyl Cyanoacetate. Both ester hydrolysis and nitrile hydration were observed for methyl cyanoacetate

(11) Breno, K. L.; Tyler, D. R.*Organometallics* **2001**, *20*, 3864.

(12) Calhorda, M. J.; Dias, A. R. *J. Organomet. Chem.* **1980**, *198*, 41.

(13) Also note that visual inspection showed a color change from green-brown (the color of the catalyst solution) to pink-brown when pyridine was added to the catalyst solution, consistent with the color change observed when nitriles are added to a solution of the catalyst.

(14) The conversion of succinonitrile to either 3-cyanopropionamide or succinamide is notably high, 100%, likely because the precipitation of the succinamide drives the reaction. The precipitation of the succinamide slows the inhibition reaction as well, leading to high conversion. One might postulate therefore that slightly soluble or nonsoluble amides could be produced readily in high yield using this catalyst without concern about catalyst poisoning (by product inhibition).



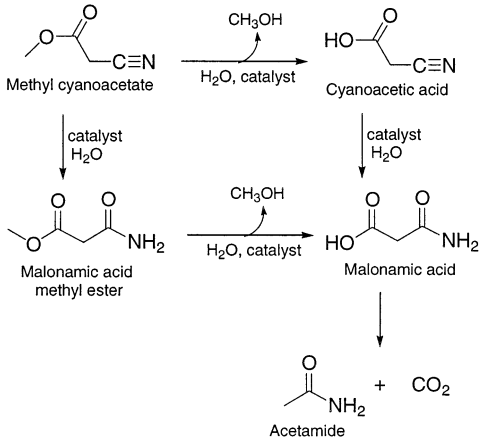
(14)

(Scheme 3). The methanol, acetamide, and methyl cyanoacetate products were observed by NMR. (Methanol and acetamide were completely deuterated and were observed in the ^2H spectrum.) As mentioned in the Experimental Section, pressure built up in the NMR reaction tube during this reaction. The likely source of the increased pressure is CO_2, which would be released when the screw-top NMR tube is opened. NMR monitoring of the reaction showed that ester hydrolysis occurred as well as nitrile hydration (Scheme 3).[15] Note that malonamic acid is unstable and quickly cleaves to form the thermodynamically favored carbon dioxide and acetamide. Because of H/D exchange in the acetamide and methanol, concentration vs time data were obtained only for methyl cyanoacetate. Therefore, the rate of the reaction could not be analyzed further.

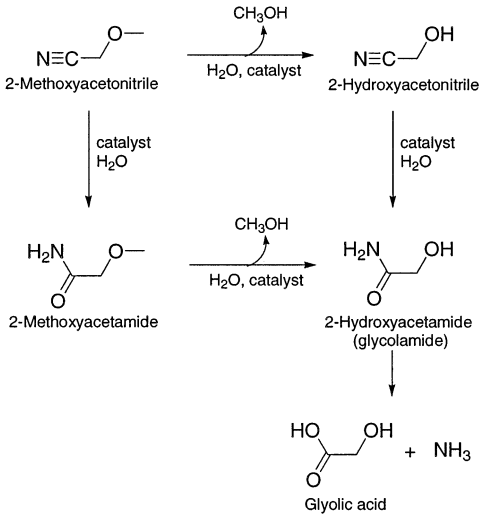
2-Methoxyacetonitrile. Nitrile hydration and ether hydrolysis were observed in the case of 2-methoxyacetonitrile. The hydration product 2-methoxyacetamide as well as the hydrolysis products methanol and glycolic acid were detected by NMR. 2-Hydroxyacetonitrile (cyanohydrin) and 2-hydroxyacetamide were not detected due to their instability in water.[16] The observation of 2-methoxyacetamide by NMR established that ether hydrolysis and nitrile hydration are competitive.[17] Therefore, two pathways to form glycolamide are proposed (Scheme 4). In the first pathway, nitrile hydration is followed by ether hydrolysis to form the glycolamide and methanol. In the second pathway, ether hydrolysis to form methanol and 2-hydroxyacetonitrile is followed by nitrile hydration to form glycolamide, which is then hydrolyzed to glycolic acid. This is the only nitrile of those studied that underwent hydrolysis to the carboxylic acid. It is suggested that hydrogen bonding occurs between the alcohol and carbonyl groups (of the glycoamide) and that this decreases the electron density at the carbonyl carbon. This may increase the likelihood of a second nucleophillic attack to yield glyolic acid, the fully hydrolyzed product.

Rate Constants and Product Inhibition. Control experiments established that the hydration reactions were inhibited by amide product, and therefore the concentration vs time data were analyzed by the iterative fitting program GIT. The fits were to the various simplified mechanisms described in the Experimental Section, and the resulting rate constants are therefore "apparent" second-order rate constants (k_{app}).[18] (The

Scheme 3. Reaction of 2-Methylcyanoacetate with $[Cp'_2Mo(OH)(OH_2)]^+$



Scheme 4. Reaction of 2-Methoxyacetonitrile with $[Cp'_2Mo(OH)(OH_2)]^+$



second-order fit is appropriate because the reactions could not be run under saturation conditions; the substrates were generally not soluble enough in water to reach saturation conditions.) The apparent rate constants (k_{app}) for the various nitrile hydration reactions are shown in Table 2. The turnover frequencies for each sample are also included in Table 2. These data show that the reactions are also inhibited by substrate (e.g., compare k_{app} for entries 3 and 4). The apparent rate constants could not be reliably corrected for substrate inhibition using GIT because the introduction of additional variables led to nonunique solutions. Nevertheless, relative reactivities can be approximated by comparing reactions run at similar substrate concentrations.

Note in the simplified schemes used to extract the apparent rate constants that each reaction is proposed to be irreversible. Several results support this supposition. First, as previously discussed, the dehydration of the amides does not occur under the reaction conditions. Second, reactions of the same nitrile at different concentrations should have the same maximum percent conversion if the product inhibition step is reversible. In fact, different concentrations had different maximum percent conversions, as would be expected for the irreversible formation of an inactive species. Finally,

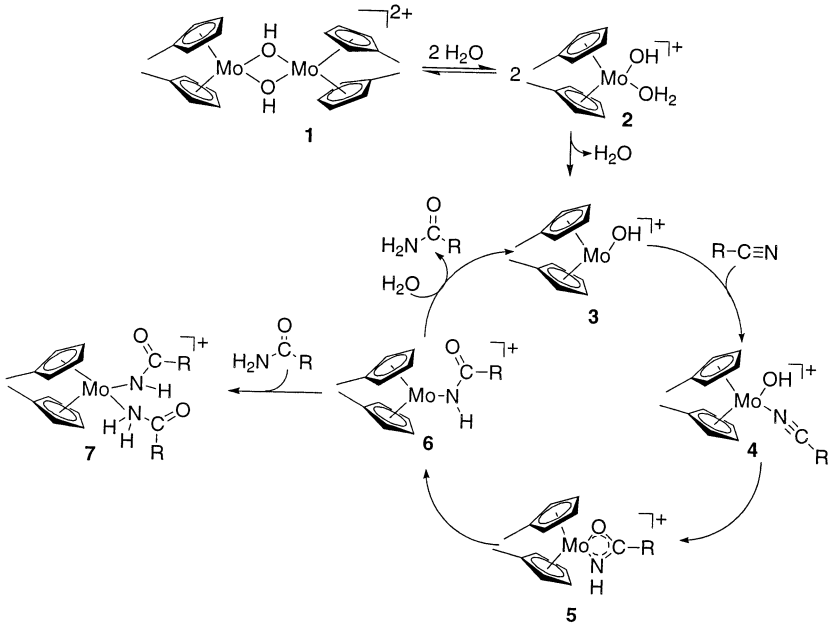
(15) This result is expected. Our prior results showed that esters hydrolyze at room temperature in aqueous solution in the presence of the catalyst.[9]

(16) Ether hydrolysis with catalyst **2** is also expected. Our prior studies showed that ethyl vinyl ether hydrolysis proceeded rapidly, producing ethanol and aldehyde within 8 h at 80 °C.[9]

(17) Cyanohydrin (2-hydroxyacetonitrile) is known to rapidly equilibrate between the hydroxyl and aldehyde forms.

(18) As described in the Experimental Section, hydrolysis and substitution reactions were also included where appropriate in the case of bifunctional nitriles.

Scheme 5. Proposed Mechanism of Nitrile Hydration via $[Cp'_2Mo(OH)(OH_2)]^+$



note that care should be taken in making comparisons of the various turnover frequencies in Tables 1 and 3 because the data are affected by the salt concentration, the pH, and the water/nitrile ratio.[20]

Mechanism of Nitrile Hydration. A proposed mechanism for the hydration of nitriles in aqueous solution using species **2** as a catalyst is shown in Scheme 5. The mechanism is similar to that proposed for the catalytic hydration of nitriles using $[Co(1,4,7,11\text{-tetraazacyclododecane})(OH_2)_2]^{3+}$.[21,22] Note that the catalytically active species is proposed to be the monomeric $[Cp'Mo(OH)(OH_2)]^+$ complex (**2**). Our prior work on H/D exchange in alcohols catalyzed by aqueous solutions of $[Cp'_2Mo(\mu\text{-}OH)_2MoCp'_2][OTs^-]_2$ showed that $[Cp'_2Mo(\mu\text{-}OH)_2MoCp'_2]^{2+}$ is in equilibrium with $[Cp'_2Mo(OH)(OH_2)]^+$ (eq 3)[7−9] and that the monomeric complex is the catalytically active species in the exchange. This result was established by studying the rates of H/D exchange as a function of metal complex concentration and then comparing those rates to the predicted rates, which were based on knowledge of the dimer−monomer equilibrium constant. Unfortunately, in the nitrile system, the inhibition reaction prevented studying the rates in this manner, and it was not possible to unambiguously establish that the monomer was the active catalyst. However, the fact that added salt (in this case tetrabutylammonium tetrafluoroborate) decreases the rate of the reaction and also decreases the amount of monomer is consistent with the suggestion that the monomer (**1**) is the active form of the catalyst.The proposed initial step in the catalytic cycle is dissociation of the water ligand, which creates a vacant coordination site for the association of the nitrile. In Scheme 5, the nitrile is shown as bonding end-on, consistent with the work of Wilkinson et al. and Dias et al.[23−27] Note that the positive slope in the Hammett plot in Figure 1 indicates that the rate-limiting step is facilitated by electron-withdrawing groups.[28] Nitrile coordination to the vacant coordination site would be facilitated by electron-donating groups, and thus this step is not the rate-determining step of the catalytic cycle.

Nucleophilic attack on the nitrile is the next step in the proposed catalytic cycle. This attack can be postulated to occur in one of three ways: (a) intramolecular attack of a coordinated OH ligand, (b) intermolecular attack, or (c) general base-catalyzed attack. In pathway (a), the bound hydroxide is the nucleophile,[29] and the resulting amidate is stabilized as an η^2-amidate (**5**). There are several literature precedents for this intermediate. For example, an η^2-amidate intermediate has been observed in the related Cp_2Ti(amidate) complexes.[30] In addition, the η^2-amidate was trapped in the $[Co(cyclen)(OH_2)_2]^{3+}$-catalyzed hydration of nitriles.[21,22] Some of the most active platinum catalysts for nitrile hydration are also thought to proceed via intramolecular hydroxide attack.[3,6,31]

The mechanism in pathway (b) involves nucleophilic attack by water on the carbon of a coordinated nitrile.

(19) Villain, G.; Gasket, A.; Kalck, P. H. *J. Mol. Catal.* **1981**, *12*, 103.

(20) Factors including pH and water/nitrile ratio can affect the rate of hydration. Previous studies showed that increasing the concentration of hydroxide ions can speed up the elimination of the amide from the catalyst center.[19] Therefore, many catalyst systems are observed to have enhanced performance with the optimization of the solution pH.[33] Because the pH of the catalyst solution after hydration is 6.61, the activity of the catalyst and the rate of the hydration might be enhanced by adjusting the pH. In addition, the water/nitrile ratio is often optimized to compensate for the inhibitory effects observed.[19]

(21) Kim, J. H.; Britten, J.; Chin, J. *J. Am. Chem. Soc.* **1993**, *115*, 3618.

(22) Chin, J.; Kim, J. H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 523.

(23) McGilligan, B. S.; Wright, T. C.; Wilkinson, G.; Motevalli, M.; Hursthouse, M. B. *J. Chem. Soc., Dalton Trans.* **1988**, 1737.

(24) Calhorda, M. J.; Carrondo, M. C.; Dias, A. R.; Domingos, A. M. T.; Duarte, M. T. L. S.; Garcia, M. H.; Romão, C. C. *J. Organomet. Chem.* **1987**, *320*, 63.

(25) Yoshida, T.; Matsuda, T.; Okano, T.; Kitani, T.; Otsuka, S. *J. Am. Chem. Soc.* **1979**, *101*, 2027.

(26) Calhorda, M. J.; Dias, A. R.; Martins, A. M.; Romão, C. C. *Polyhedron* **1989**, *8*, 1802.

(27) Lauher, J. W.; Hoffmann, R. *J. Am. Chem. Soc.* **1976**, *98*, 1729.

(28) A reviewer points out that the Hammett plot may be biphasic (indicative of a change in the rate-determining step). However, the experimental error in the plotted values prevents one from concluding this with any certainty.

H/D exchange is expected at the α-carbon with this mechanism due to the uncoordinated amide that is formed. (Exchange would be caused by enolate formation, which allows for the acidic protons to be exchanged.) In pathway (c) (general base-catalyzed attack), the first step is nucleophilic attack of water on the carbon of a coordinated nitrile. The coordinated hydroxide then acts as a general base and deprotonates the amidate ligand. The coordinated hydroxide stabilizes the newly formed coordinated amidate. Again H/D exchange is expected at the α-carbon.[32]

Scheme 5 proposes that the nitrile hydration reactions occur via an intramolecular attack of a coordinated hydroxy ligand (pathway (a)). This pathway is consistent with the key observation of no short-term H/D exchange at the α-carbon. To date, repeated attempts to isolate the coordinated amide or η^2-amidate have been unsuccessful, but work in this area continues.

The next step (**5**−**6**) in the catalytic cycle could occur by two pathways. The first is the coordination of water, followed by proton transfer, and finally dissociation of the amide, leaving the active catalyst. The second pathway involves the oxidative addition of water to the metal center. While unusual, the oxidative addition of water has been observed in molybdocene complexes and other organometallic complexes.[25,33−38] After the addition of water, a reductive elimination would occur to form free amide and the active catalyst would be regenerated.

However step **5**−**6** proceeds, there is competition for the open coordination site on the catalyst. For example, an amide can bind to the site irreversibly to inhibit the catalytic cycle, step **6**−**7** (see the earlier discussion on product inhibition). Or, a second nitrile can bond to the vacant coordination site (**6**) in a reversible manner to slow the production of amide (see the earlier discussion on substrate inhibition).

Summary

$[Cp'_2Mo(OH)(OH_2)]^+$ is a water-soluble, comparatively reactive catalyst for the hydration of nitriles. The hydration reaction is straightforward, and no subsequent hydrolysis of the amide occurs (except in the special case of 2-methoxyacetonitrile). In addition, the hydration of acrylonitrile is highly chemoselective. This is of particular importance in the production of acrylamide, where side products of olefin hydration often produce substantial impurities. Other functionalized nitriles are also hydrated, and the hydrolysis of ethers and esters was observed in these molecules. It is interesting to note that increasing the electron-withdrawing ability of the nitrile (substrate) enhances the rate of the reaction (Figure 1). Inhibition was observed by both the amide products and the nitriles (i.e., the substrate). A mechanism consistent with the observed hydration postulates an intramolecular attack of hydroxide on a coordinated nitrile leading to a η^2-amidate intermediate.

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Supporting Information Available: A brief, introductory discussion outlining the history of nitrile hydration; graphs of concentration vs time for various nitrile hydration reactions showing the fits obtained with the GIT kinetics-fitting program. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) The conversion of **4** to **5** should be facile. First, for intramolecular attack to occur, it is necessary for the sp^3 orbital of the oxygen on the coordinated hydroxide to overlap with the nitrile carbon.[15] The nitrile and hydroxide ligands in **4** are properly disposed for such nucleophilic attack. Second, the crowding caused by the steric bulkiness of the Cp′ ligands will facilitate intramolecular attack. Note that hydrolysis of the amide product does not occur with any transition metal hydroxide catalyst that proceeds by an intramolecular pathway. A possible explanation is that formation of a hydrogen-bonded six-membered ring may decrease the nucleophilicity of the hydroxide ligand in these catalysts, thus preventing intramolecular attack on the carbonyl group. For examples of intramolecular −OH attack, see: (a) Kuo, L. Y.; Barnes, L. A. *Inorg. Chem.* **1999**, *38* (4), 814. (b) Kuo, L. Y.; Kuhn, S.; Ly, D. *Inorg. Chem.* **1995**, *34* (21), 5. (c) Wall, M.; Linkletter, B.; Williams, D.; Lebuis, A.; Hynes, R. C., Chin, J. *J. Am. Chem. Soc.* **1999**, *121*, 4710.

(30) Arndt, P.; Lifeber, C.; Kempe, R.; Tillack, A.; Rosenthanl, U. *Chem. Ber.* **1996**, *129*, 1281.

(31) Gaffar, T.; Parkins, A. W. *Tetrahedron Lett.* **1995**, *36*, 8657.

(32) Buckingham, D. A.; Keene, F. R.; Sargeson, A. M. *J. Am. Chem. Soc.* **1973**, *95*, 5649.

(33) Yoon, M.; Tyler, D. R. *Chem. Commun.* **1997**, 639.

(34) Koffi-Bié Djoman, M. C.; Ajjou, A. N. *Tetrahedron Lett.* **2000**, *41*, 4845.

(35) Villain, G.; Constant, G.; Gasket, A. *J. Mol. Catal.* **1980**, *7*, 355.

(36) McKenzie, C. J.; Robson, R. *J. Chem. Soc, Chem. Commun.* **1988**, *1370*, 112.

(37) Bennet, M. A.; Yoshida, T. *J. Am. Chem. Soc.* **1973**, *95*, 5050.

(38) Murahashi, S. I.; Sasao, S.; Saito, E.; Naota, T. *J. Org. Chem.* **1992**, *57*, 2521.