Kinetics and Mechanism of a Co(III) Complex Catalyzed Hydration of Nitriles

Jung Hee Kim, James Britten, and Jik Chin*

Contribution from the Department of Chemistry, McGill University, Montreal, Canada H3A 2K6

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Abstract: [Co(cyclen)(OH$_2$)$_2$]$^{3+}$ (**1**) efficiently catalyzes hydration of acetonitrile to acetamide in a three-step cycle at pH 7, 40 °C (cyclen = 1,4,7,11-tetraazacyclododecane). The mechanism involves (a) equilibrium coordination of acetonitrile to **1** (K_1 = 2.5 M^{-1}) followed by (b) intramolecular metal hydroxide attack on the coordinated nitrile resulting in formation of the chelated acetamide (k_2 = 4.7 × 10^{-3} s^{-1}) and (c) dissociation of the chelated amide (k_3 = 3.3 × 10^{-4} s^{-1}). Both intermediates in the catalytic cycle (coordinated acetonitrile and chelated acetamide) have been detected by visible absorbance spectroscopy and ^{13}C NMR. The crystal structure of the chelated benzamide has been determined. Joint Lewis acid activation and metal hydroxide activation provides over a 10^{10}-fold rate acceleration for the hydration reaction.

Since the late sixties various metal ions have been used to catalyze the hydration of nitriles to amides. They include Cu-(II),[1,2] Ni(II),[1] Zn(II),[1] Pt(II),[3,4] Rh(II),[4] and Pd(II)[5] as well as substitutionally inert Co(III),[6] Rh(III),[7] Ru(III),[8] and Ir(III)[7] complexes. Some of the most efficient catalysts for nitrile hydration are Cu(II)[1] and Pt(II)[3] complexes. Co(III) complexes tend to be poor catalysts giving little or no catalytic turnover because of slow ligand exchange rates. However, they often provide valuable mechanistic information by forming stable intermediates. We recently showed that [Co(cyclen)(OH$_2$)$_2$]$^{3+}$ (**1**) is an excellent catalyst for hydrating nitriles to amides (cyclen
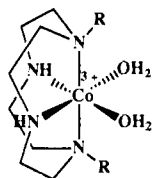
1: R = H
2: R = CH$_3$
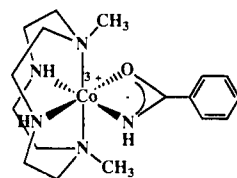
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= 1,4,7,11-tetraazacyclododecane).[9] Surprisingly, **2** does not complete the catalytic cycle. Instead, it forms a chelated benzamide (**3**) upon reacting with benzonitrile. Here we report on the mechanistic implication of a chelated amide and a detailed kinetic analysis on **1** catalyzed hydration of acetonitrile including all of the rate and equilibrium constants involved in the catalytic cycle.

Experimental Section

Instruments. ^{1}H NMR (299.3 MHz) and ^{13}C NMR (75.4 MHz) spectra were obtained with a Varian XL-300 FT spectrometer. All spectra were recorded in D$_2$O with chemical shifts reported in ppm (*tert*-butyl alcohol (30.47 and 70.59 ppm) and 3-(trimethylsilyl)-1-propanesulfonic acid (0 ppm) as internal references for ^{13}C and ^{1}H NMR, respectively).

Kinetic studies were carried out by a UV–vis method with a Hewlett-Packard 8451 diode array spectrophotometer equipped with a Lauda RM6 thermostat.

Materials. Benzonitrile was purchased from Aldrich. CH$_3$^{13}CN was purchased from Merck Sharp and Dohme. 1,4,7,10-Tetraazacyclododecane (cyclen)[10] and 1,4-dimethyl-1,4,7,10-tetraazacyclododecane (dm-cyclen)[11] were prepared according to published procedures.

[(cyclen)Co(CO$_3$)]ClO$_4$ and [(dmcyclen)Co(CO$_3$)]ClO$_4$. Crystal structures of both complexes have been published.[12] The cobalt carbonato complexes were prepared by a procedure using lead oxide.[13] The tetraamine ligand (50 mmol) dissolved in water (100 mL) was added to a stirring solution of Co(ClO$_4$)$_2$ (50 mmol) in water (250 mL). To the reaction mixture was added an aqueous solution (150 mL) of sodium bicarbonate (100 mmol) followed by PbO$_2$ (105 mmol). The resulting suspension was stirred vigorously for 2 days after which time 70% perchloric acid (50 mmol) was added slowly. After filtration, the volume of the filtrate was reduced in vacuo. The product separated as fine crystals. [(cyclen)Co(CO$_3$)]ClO$_4$: ^{13}C NMR δ 167.43 (CO$_3$), 56.47, 54.02, 50.02, 47.91. Anal. Calcd for C$_9$H$_{20}$ClCoN$_4$O$_7$: C, 27.67; H, 5.16; N, 14.34; Cl, 9.08; Co, 15.09. Found: C, 27.43; H, 4.76; N, 14.26; Cl, 8.93; Co, 15.19. [(dmcyclen)Co(CO$_3$)]ClO$_4$: ^{13}C NMR δ 168.25 (CO$_3$), 66.85, 64.06, 49.14, 48.09, 46.32 (CH$_3$). Anal. Calcd for C$_{11}$H$_{24}$ClCoN$_4$O$_7$: C, 31.55; H, 5.77; N, 13.55; Cl, 8.47; Co, 14.07. Found: C, 31.05; H, 5.40; N, 13.64; Cl, 8.61; Co, 14.23.

[(cyclen)Co(OH$_2$)$_2$](ClO$_4$)$_3$ (1) and [(dmcyclen)Co(OH$_2$)$_2$](ClO$_4$)$_3$ (2). The cobalt carbonato complexes were converted to the corresponding diaqua complexes by adding 70% perchloric acid (2.5 equiv) to the finely ground carbonato complexes. The resulting mixture was stirred under a water aspirator for 2 h. The solution was then diluted with water and freeze dried. The resulting pink solid was washed with ether and dried in vacuo over P$_2$O$_5$. [(cyclen)Co(OH$_2$)$_2$](ClO$_4$)$_3$: ^{13}C NMR δ 57.97, 54.6, 50.6, 48.6. [(dmcyclen)Co(OH$_2$)$_2$](ClO$_4$)$_3$: ^{13}C NMR δ 67.95, 64.62, 50.93, 50.51, 49.57 (CH$_3$).

[(dmcyclen)Co(η^2-*N,O*-benzamide)](ClO$_4$)$_2$ (3). To a solution of **2** (2.2 mmol) in 5.5 mL of water was added 2 N NaOH (1 equiv) and benzonitrile (1 equiv). The mixture was stirred at room temperature overnight. After filtration, 700 mg of a fine powder was obtained. The crude product was recrystallized from 25 mL of hot water (70–80 °C) and washed with 50% aqueous ethanol, ethanol, and ether yielding 370 mg of purple multifaceted crystals: ^{13}C NMR (CD$_2$Cl$_2$ 54.25 ppm) δ 185.1 (CO), 134.2, 130.9, 129.3, 126.6, 67.3, 64.9, 48.7, 47.9, 47.8.

X-ray Diffraction Studies of 3. Crystal data for C$_{17}$H$_{34}$CoN$_5$O$_{11}$Cl$_2$ (Figure 1): M = 614.32; orthorhombic, $P2_12_12_1$ (#19); a = 13.130(4) Å, b = 18.357(4) Å, c = 10.805(1) Å, β = 55°, V = 2604(1) Å^3; D_x = 1.771 g/cm^3; Z = 4. Data were collected on a Rigaku AFC6S

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Co(III) Complex Catalyzed Hydration of Nitriles

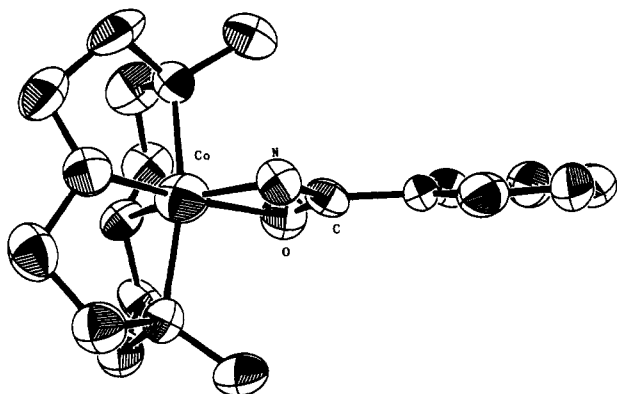*J. Am. Chem. Soc., Vol. 115, No. 9, 1993* 3619

Figure 1. ORTEP plot of **3** showing chelated benzamide. Ellipsoids are shown at 50% probability. Hydrogens have been omitted for clarity. Selected angles and lengths around the four-membered ring are as follows: O–C–N, 111.5(9)°; O–Co–N, 68.2(3)°; Co–O–C, 89.9(6)°; Co–N–C, 90.3(6)°; O–C, 1.28(1)°; N–C, 1.32(1)°; Co–O, 1.930(7)°; Co–N, 1.895(8)°.

diffractometer using graphite-monochromated Mo Kα radiation. A total of 6424 reflections were collected of which 5996 were unique after absorption correction (max and min transmission factors: 0.89–1.00) giving 3014 with $I > 3.00\sigma(I)$. All non-hydrogen atom positions were solved by direct methods (Gilmore, C. J. *J. Appl. Crystallogr.* **1984**, *17*, 42) using the TEXAN crystallographic software package of Molecular Structure Corp. All positional and thermal parameters (non-hydrogen atoms, anisotropic; hydrogen, isotropic) and an extinction parameter were refined by full-matrix least squares. Final R and R_w were 0.068 and 0.065 for 3014 observed reflections and 281 variable parameters.

Coordination and Hydration. Rates of coordination and hydration were measured by following the changes in the visible spectrum and confirmed by changes in ^{1}H and ^{13}C NMR as described below. The rate of attainment of equilibrium for coordination of acetonitrile to **1** (Figure 2) was monitored by following the increase in the visible absorbance at 460 nm (pH 2, 25 °C). In a typical experiment, 20–100 equiv of acetonitrile was injected into an aqueous solution of the cobalt complex (10 mM). Coordination of CH$_3$^{13}CN (0.05 M) to **1** (0.05 M) was also monitored by ^{13}C NMR at pD 2, 25 °C (Figure 3).

The rate of attainment of equilibrium for chelation of acetamide to **1** (Figure 5) was monitored by following the decrease in the visible absorbance at 560 nm (pH 6.4, 25 °C). In a typical experiment, 20–100 equiv of an acetamide stock solution (1 M in H$_2$O) was injected into an aqueous solution of the cobalt complex (10 mM). Chelation of CH$_3$^{13}-CONH$_2$ (0.05 M) to **1** (0.025 M) was also monitored by ^{13}C NMR at pD 6.4, 25 °C.

Formation of chelated acetamides from **1** or **2** with acetonitrile (Figure 4) was monitored by following the increase in the visible absorbance at 500 nm (for **1**) or 600 nm (for **2**). The observed first-order rate constants were obtained by fitting the data according to a first-order kinetic equation (correlation coefficient >0.995). Each kinetics run was reproducible to within 3% error. In a typical kinetic run, 1–10 equiv of acetonitrile was injected to a catalyst solution (10 mM) at 40 °C and pH 7.0.

^{1}H NMR was used to monitor **1** (10 mM) catalyzed formation of free acetamide (δ 1.88) from free acetonitrile (10 to 350 mM) at 40 °C, pD 4.4–7.2 (Figures 6 and 7).

Results and Discussion

Chelated Amide. We recently reported that **1** efficiently hydrates nitriles to amides with catalytic turnover under mild conditions.[9] By strategically placing two methyl groups on the catalyst (**2**) we have trapped a key intermediate in the catalytic cycle. Addition of benzonitrile to **2** results in the formation of a chelated benzamide (**3**) without any catalytic turnover. The chelated amide has been isolated and its crystal structure determined (Figure 1). Although X-ray structures of four-membered-ring chelates of carbonate[12] and acetate[14] have been reported, this represents the first crystal structure of a chelated amide. ^{13}C NMR of the crystal (**3**) dissolved in dichloromethane shows only one carbonyl carbon signal. However, two signals are

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Scheme I
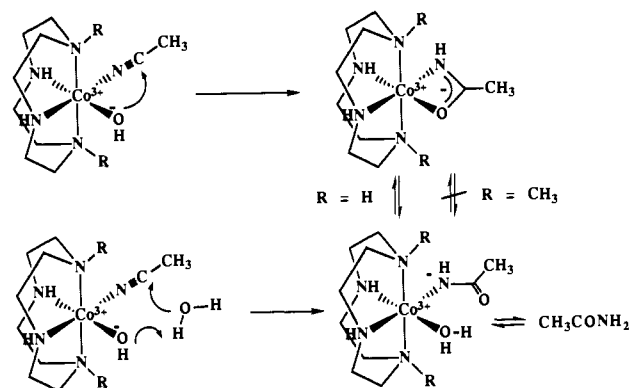
observed for the carbonyl carbon in D$_2$O (12 ppm downfield relative to free benzamide carbonyl carbon). On the basis of the crystal structure of [(cyclen)Co(CO$_3$)]ClO$_4$,[12] two isomers of **3** are expected.
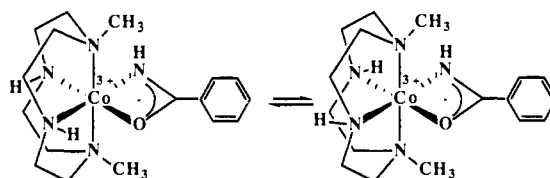

The *cis*-diaqua cobalt complex (**1**) catalyzed hydration of CH$_3$^{13}CN in neutral D$_2$O was monitored by ^{13}C NMR. With the progress of the reaction the NMR signal due to free acetonitrile (δ 121.0 ppm) decreases with an increase in the NMR signal due to free acetamide (δ 178.5). Additionally, two signals each at δ 188.5 and 190.0 ppm appear. The two signals centered at δ 188.5 ppm are assigned to N-coordinated acetamide[15] and the two signals centered at δ 190.0 ppm are assigned to N,O-chelated acetamide.[16] The NMR signals due to the N-coordinated acetamide and the N,O-chelated acetamide could also be generated by adding CH$_3$^{13}C(O)NH$_2$ to **1** in neutral D$_2$O. For comparison, reaction of **2** with CH$_3$^{13}CN was monitored by ^{13}C NMR. Interestingly, no signal due to free acetamide or N-coordinated acetamide appeared. However, two signals centered at δ 190.5 ppm, corresponding to the N,O-chelated acetamide, increased with time. Reacting **2** with CH$_3$^{13}C(O)NH$_2$ resulted in formation of the N-coordinated acetamide (δ 187.0 ppm) without formation of the N,O-chelated acetamide.
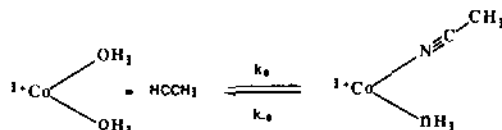
Metal Hydroxide as Nucleophile or General Base. The ^{13}C NMR data and the crystal structure provide some interesting insight into the mechanistic role of the cobalt complex (**1**) in catalyzing the hydration of nitriles. Since N,O-chelated amides can be produced from reacting **1** with either amides or nitriles, an important question is whether the chelated amide is an intermediate in the catalytic cycle or it is simply a byproduct. The chelated amide would be an intermediate if the metal hydroxide is a nucleophilic catalyst (Scheme I). On the other hand if the metal hydroxide is a general base catalyst (G.B.C., Scheme I), the chelated amide would simply be a byproduct. Interestingly, **2** reacts with nitriles to form the N,O-chelated amide but the amide does not dissociate from the metal. Amides reversibly form the N-coordinated amide with **2** without forming any of the N,O-chelated amide. It appears that the two methyl groups in **2** prevent equilibration between the bidentate and monodentated amide (Scheme I) by providing a steric barrier. The equilibration step is crucial for both chelate formation and

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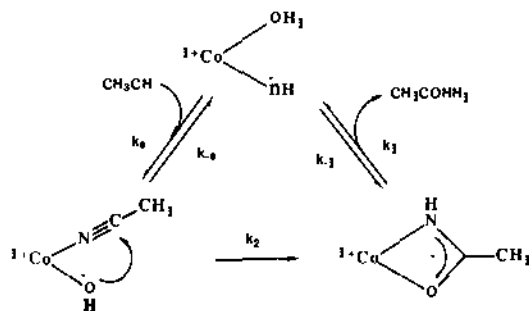
Scheme II

Scheme III

dissociation. These results strongly suggest that hydration of nitriles by 1 or 2 takes place by intramolecular nucleophilic attack of the metal hydroxide on the coordinated nitrile. If the metal hydroxide was an intramolecular general base, 2 would have reacted with nitriles to form the corresponding N-coordinated amide resulting in dissociation of the amide and detection of catalytic turnover (Scheme I). When the nitrile is coordinated to 1 or 2, the sp^3 orbitals on the oxygen of the metal hydroxide should be able to overlap with the p orbitals on the nitrile carbon.
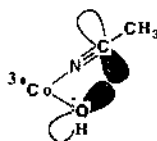
Catalytic Cycle. Consistent with Scheme I, we propose that the mechanism for 1 catalyzed hydration of nitriles to amides involves (1) coordination of the nitrile to the cobalt complex followed by (2) intramolecular metal–hydroxide attack on the coordinated nitrile and (3) dissociation of the chelated amide (Scheme II). Interestingly, all three steps can be monitored independently. As shown below, this allows for determination of all of the rate and equilibrium constants in the catalytic cycle.

Complexation of Acetonitrile (k_1, k_{-1}). Complexation of acetonitrile to 1 at pH 2 was monitored by following the change in the visible absorbance (Scheme III). The observed rate constant (k_a) for attainment of equilibrium for the complexation reaction is given by eq 1. A plot of k_a vs [CH$_3$CN] gives a straight line

$$k_a = k_1[CH_3CN] + k_{-1} \qquad (1)$$

with a slope (1.33×10^{-1} M^{-1} s^{-1}) that corresponds to k_1 and an intercept (2.28×10^{-1} s^{-1}) that corresponds to k_{-1} (Figure 2). The equilibrium constant for complexation of acetonitrile to 1 is 0.6 M^{-1}. This shows that mole per mole, acetonitrile has a higher affinity than water for the cobalt complex even though acetonitrile is *over ten orders of magnitude* less basic than water.

Complexation of acetonitrile to 1 could also be detected by ^{11}C NMR (Figure 3). Addition of acetonitrile (0.05 M) to a solution of 1 (0.05 M) at pD 2 gives rise to three nitrile carbon signals. The first signal (δ 121.0) is due to the free acetonitrile and the second and third signals (δ 135.1, 135.2) are due to the cobalt bound acetonitrile. Under the experimental conditions either of the two but not both coordinated water molecules in 1 can be replaced by acetonitrile.

The rate of exchange of the cobalt bound water molecules in 1 increases with an increase in pH. Hence the rate of complexation and dissociation of acetonitrile also increases with an increase in pH.
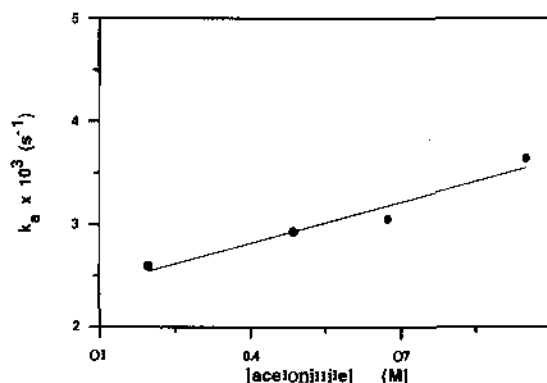

Figure 2. Plot of the observed rate constant for attainment of equilibrium (k_a) for coordination of acetonitrile to 1 (0.01 M) as a function of [CH$_3$CN] at pH 7, 25 °C.
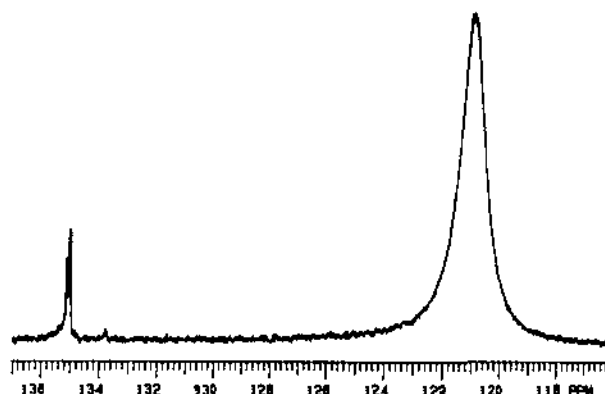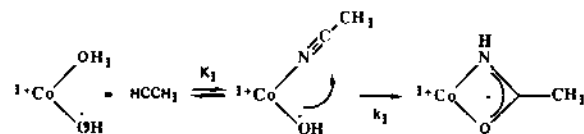

Figure 3. ^{11}C NMR of CH$_3$^{11}CN (0.05 M) in a solution of 1 (0.05 M) at pD 2, 25 °C.

Scheme IV

Conversion of Nitrile to Amide (k_2). At neutral pH, rapid equilibrium complexation of acetonitrile to 1 is followed by slow formation of chelated acetamide (Scheme IV). Both ^{1}H NMR and ^{11}C NMR show that the concentration of the chelated amide accumulates before any free amide can be detected indicating that the rate-determining step in the catalytic cycle (Scheme II) is release of the chelated amide. Conversion of free acetonitrile to the chelated amide was monitored by visible absorbance spectroscopy. The observed rate constant (k_b) for this process is given by eq 2. From a plot of $1/k_b$ vs $1/[CH_3CN]$, $K_1 = 2.5$ M^{-1} and $k_2 = 4.7 \times 10^{-1}$ s^{-1} (Figure 4).

$$k_b = (K_1 k_2[CH_3CN])/(1 + K_1[CH_3CN]) \qquad (2)$$

Formation of chelated acetamide from 2 and acetonitrile was also monitored by visible absorbance spectroscopy and analyzed by using eq 2. Both K_1 (2.3 M^{-1}) and k_2 (2.8 $\times$ 10^{-1} s^{-1}) values for 2 are comparable to those for 1.

Dissociation of the Chelated Amide (k_3, k_{-3}). The values for k_3 and k_{-3} may be obtained by monitoring the equilibrium chelation of acetamide to 1 at neutral pH (Scheme V). The equilibration reaction was followed by visible absorbance spec-

$$k_c = k_{-3}[acetamide] + k_3 \qquad (3)$$

troscopy. The observed rate constant (k_c) for equilibrium chelation of acetamide to 1 at neutral pH is given by eq 3. A plot
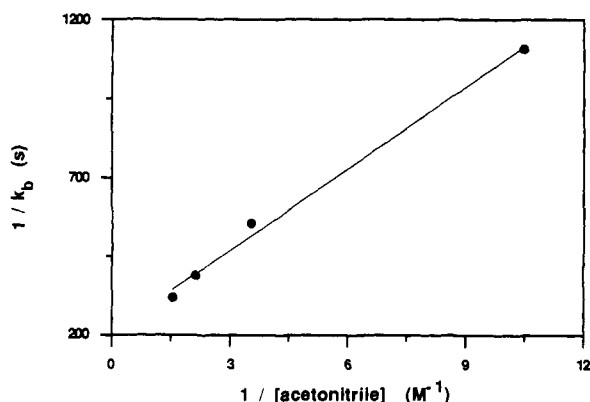
Figure 4. Plot of the inverse of the observed rate constant for chelated acetamide formation $(1/k_b)$ from 1 (0.01 M) and acetonitrile as a function of $1/[CH_3CN]$ at pH 7, 40 °C.

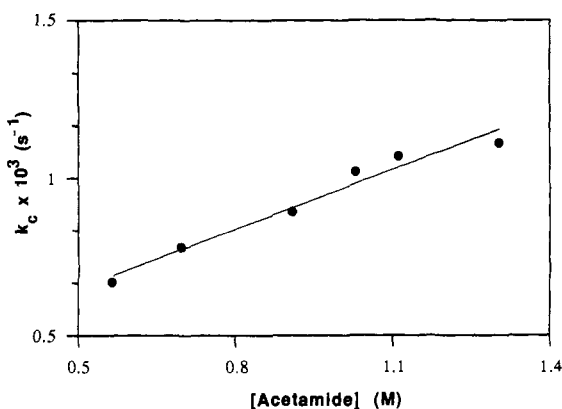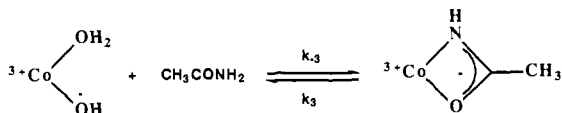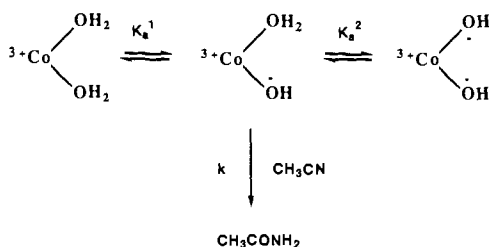**Figure 5.** Plot of the observed rate constant for attainment of equilibrium (k_c) for chelation of acetamide to 1 (0.01 M) as a function of $[CH_3C(O)NH_2]$ at pH 7, 40 °C.

Scheme V

Scheme VI

of k_c vs [acetamide] (Figure 5) gives the values for k_3 (3.3 × 10^{-4} s^{-1}) and k_{-3} (6.3 × 10^{-4} M^{-1} s^{-1}). The equilibrium constant for chelation of acetamide to 1 at neutral pH is 1.9 M^{-1}.

pH–Rate Profile. The first and second pK_a values of the two cobalt bound water molecules in 1 are 5.6 and 8.0. Hydration of nitriles takes place at the pH range in between the two pK_a values, indicating that the active form of the catalyst for hydrating nitriles is the aqua-hydroxy form (Scheme VI). The aqua-hydroxy form has also been shown to be the active form for hydrolyzing phosphate diesters.[17] The rate constant for 1 catalyzed hydration of acetonitrile in terms of the constants in Scheme VI is given by eq 4. The pD–rate profile for 1 catalyzed hydration of acetonitrile at 40 °C is shown in Figure 6. The experimental
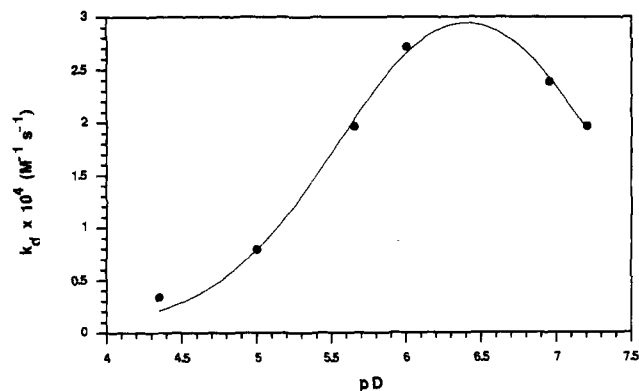
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Figure 6. Plot of the PD–rate profile for 1 (0.01 M) catalyzed formation of acetamide from acetonitrile (0.1 M) at 40 °C.

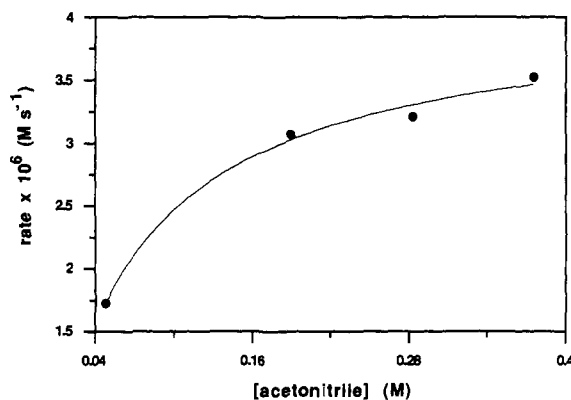**Figure 7.** Plot of the rate of 1 (0.01 M) catalyzed acetamide formation as a function of $[CH_3CN]$ at pD 7, 40 °C.

points were fit according to eq 4 with a nonlinear least-squares curve-fitting program ($pK_a^1 = 5.5$, $pK_a^2 = 7.2$, $k = 3.8 × 10^{-4}$ M^{-1} s^{-1}).

$$k_d = k[CH_3CN]K_a^{-1}[H^+]/(K_a^{-1}K_a^2 + K_a^{-1}[H^+] + [H^+]^2)$$ (4)

Concentration Dependence. The dependence of the rate of acetamide formation on the concentrations of acetonitrile and 1 was monitored by ^1H NMR (at 40 °C, pD 7). The rate of acetamide formation at a fixed concentration of 1 (0.01 M) initially increases with an increase in the concentration of acetonitrile (0.05–0.35 M) and then levels off at high concentrations of acetonitrile. Fitting this plot according to the Eadie–Hofstee[18] plot gives a k_{cat} value of 4 × 10^{-4} s^{-1} and a K_m value of 0.05 M (Figure 7). The values of k_{cat} and K_m should correspond respectively to those of k_3 and k_3/K_1k_2 (Scheme II). Indeed, there is excellent agreement between the values of k_{cat} and K_m and the values of k_3 and k_3/K_1k_2 obtained independently above.

The rate of acetamide formation at a fixed concentration of acetonitrile (0.2 M) increases linearly with an increase in the concentration of 1 (0.005–0.01 M) with a slope of 3.5 × 10^{-4} s^{-1}. Since at 0.2 M acetonitrile the cobalt complex is close to being saturated, the value of the slope approximates the value of k_3.

Rate Acceleration. The second-order rate constant for hydroxide catalyzed hydration of acetonitrile to acetamide is 1.6 × 10^{-6} M^{-1} s^{-1} (at 25 °C).[19] The second-order rate constant for hydroxide catalyzed hydration of acetonitrile coordinated to $[Co(NH_3)_5]^{3+}$ is 3.4 M^{-1} s^{-1} (at 25 °C).[19] Therefore the pseudo-first-order rate constants for hydroxide catalyzed hydration of acetonitrile and acetonitrile coordinated to $[Co(NH_3)_5]^{3+}$ at pH

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7 are 1.6×10^{-13} and 3.4×10^{-7} s^{-1}, respectively. The first-order rate constant for intramolecular metal–hydroxide attack on acetonitrile coordinated to 1 is 4.7×10^{-3} s^{-1} (at pH 7, 40 °C, k_2, Scheme IV). Hence, for hydration of acetonitrile at neutral pH, Lewis acid activation alone with $[Co(NH_3)_5]^{3+}$ gives about a 10^6-fold rate acceleration whereas joint Lewis acid activation and metal–hydroxide activation with 1 gives about a 10^{10}-fold rate acceleration for the hydration reaction. There is no catalytic turnover in hydration of $[Co(NH_3)_5NCCH_3]^{3+}$. Interestingly, the double activation with 1 allows for catalytic turnover to take place. The 10^{10}-fold rate acceleration is comparable to $CuCl_2$-promoted hydration of 2-cyanophenanthroline.[1]

rel rate: 1 10^6 10^{10}
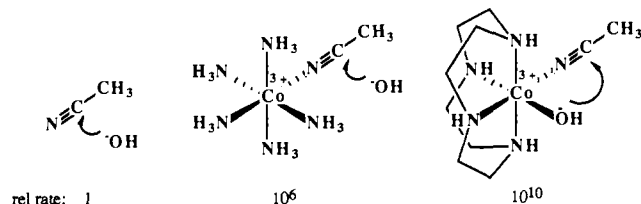
In conclusion, 1 is highly efficient at hydrating nitriles to amides with catalytic turnover under mild conditions. The catalytic mechanism involves coordination of the nitrile to the cobalt complex followed by intramolecular metal hydroxide attack on the nitrile and dissociation of the chelated amide. The two key intermediates in the catalytic cycle, coordinated nitrile and chelated amide, have been detected by visible absorption spectroscopy and ^{13}C NMR. Furthermore, crystal structure of a chelated amide has been determined. All of the rates and equilibrium constants involved in the catalytic cycle have been determined. Interestingly, acetonitrile coordinates to 1 more tightly than water even though acetonitrile is about nine orders of magnitude less basic than water. The joint Lewis acid activation and metal hydroxide activation provides over a 10^{10}-fold rate acceleration for the hydration reaction.

Supplementary Material Available: Crystallographic details for the chelated benzamide including tables of atomic coordinates, thermal parameters, bond angles, and bond lengths (17 pages). Ordering information is given on any current masthead page.