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Synthesis, Characterization, and Reactivity of Urea Derivatives Coordinated to Cobalt(III). Possible Relevance to Urease

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The syntheses of a cobalt(III) complex, **2**, containing *N*-(2-pyridylmethyl)urea and of six complexes, **3**, containing phenyl-substituted *N*-2-pyridylmethyl-*N*′-(X)phenylureas (where X = 4-H, 4-CH_3, 4-Br, 3-Cl, 4-CF_3, and 4-NO_2), have been accomplished by reaction of $[(en)_2Co(OSO_2CF_3)_2](CF_3SO_3)$ with the urea ligands in tetramethylene sulfone. The complexes have been characterized by UV−vis, FTIR, ^1H NMR, and ^{13}C NMR spectra along with elemental analysis. Also, X-ray crystallographic analysis of **2** confirms that the urea ligand chelates as a bidentate through the pyridyl nitrogen atom and the endo deprotonated, urea nitrogen atom to form a stable five-membered ring. Crystals of the perchlorate salt of **2** were monoclinic, space group $P2_1/c$ with $a = 9.743(1)$ Å, $b = 13.924(3)$ Å, $c = 15.006(4)$ Å, $\beta = 97.07(1)°$, and $Z = 4$. Reflection data (3454) with $I = 3\sigma(I)$ were refined to conventional *R* factors of 0.037 and 0.051. In acidic solution (0.05−1.00 M HCl at 55 °C), the phenyl-substituted complexes undergo hydrolysis to form the bis(ethylenediamine)(2-picolylamine-*N*,*N*′)cobalt(III) ion, **4**, aniline, and CO_2. The hydrolysis kinetics of the phenyl-substituted complexes were studied by UV−vis spectroscopy ($I = 1.00$ M HCl/LiCl). At 55 °C the observed rate constants fit the rate law $k_{obsd} = kK[H^+]/(1 + K[H^+])$. It is proposed that the protonated urea eliminates aniline to give a coordinated isocyanate intermediate that hydrolyzes rapidly to the pyridyl methylamine complex and CO_2 via the carbamate complex. Since all of the studies of this kind to date appear to involve the NCO intermediate, it raises the prospect that urease also functions by a similar path and that urease should be tested with NCO^- as a substrate.

Introduction

Previous studies have implied or shown that *N*-(2-pyridylmethyl)urea, **1**, functions as a bidentate ligand when complexed to transition metal ions. Blakeley et al. suggested in 1982 that hydrolysis of **1** by Ni(II) in aqueous ethanol proceeded through a Ni(II) complex ligated through the pyridyl nitrogen and carbonyl oxygen atoms.[1] More recently, Maslak and co-workers[2] reported structural studies involving **1** complexed to Cu(II) and Zn(II). These structural determinations illustrated two coordination modes for the ligand. When bound to Cu(II), a five-membered ring was formed via the pyridyl N-atom and the *endo*-urea-N atom. Unlike many Co(III) urea and amide complexes,[3] this binding at N occurred without loss of a proton and with loss of considerable delocalization for the amide group. The Zn(II) complex differed in that the ligand was bound through the pyridyl N atom and through the carbonyl oxygen atom to form a seven-membered ring. Infrared studies[2] of these complexes and those of related Ni(II) complexes in the solid state also implied that Ni(II) was bound through the urea N atom without loss of a proton. The N−O binding mode proposed by Blakeley et al.[1] may therefore not reflect the active binding mode, and all three types of chelates should be assessed for their reactivity.

We report here the synthesis and characterization of stable Co(III) complexes **2** and **3** containing chelated 2-pyridylmethylurea type ligands. We also report on the kinetics and mechanism of the hydrolysis reactions of the urea ligands in these complexes.

Experimental Section

General Data. All chemicals were reagent grade and used as supplied with the exception of tetramethylene sulfone, which was vacuum distilled before use. UV−vis spectra were obtained with a Perkin-Elmer Lambda 3B spectrophotometer. Mattson Research Series I FTIR and Perkin-Elmer 683 or 783 instruments were used to collect infrared spectra. ^1H NMR and ^{13}C NMR spectra were recorded with JEOL JNM-FX-200 or Varian VXR-300 instruments at ca. 20 °C. ^{13}C spectra were recorded using 1,4-dioxane ($\delta = 66.5$ ppm vs TMS) or DMSO-$^2H_6$ ($\delta = 39.5$ ppm vs TMS) as an internal reference; reported chemical shifts are referred to TMS = 0.00 ppm as an external standard. Elemental analyses were performed by the Australian National University Microanalytical Unit and Galbraith Laboratories, Inc., Knoxville, TN.

Preparation of 2 and 3. A typical synthesis is detailed here for the preparation of **3b**. $[(en)_2Co(OSO_2CF_3)_2](CF_3SO_3)$[4] (4.0 g, 6.4 mmol)

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and *N*-2-pyridylmethyl-*N′*-phenylurea[5] (1.8 g, 7.8 mmol) were stirred in dry tetramethylene sulfone (20 mL) for 3 days at ca. 20 °C. Ether (300 mL) was added to the solution with vigorous stirring to produce a red oil. The oil was diluted with distilled water (300 mL) and sorbed onto a column of Sephadex SP C-25. After washing well with water, elution was begun with 0.1 M $NaClO_4$, and two minor bands were removed. A broad red-pink band, the desired product, was then collected using 0.2 M $NaClO_4$.

The product solution was diluted 10-fold, resorbed onto a column of Sephadex SP C-25, and washed well with water. The band was then removed from the column with 0.5 M $Ba(ClO_4)_2$. Upon cooling to 4 °C, red crystals formed after agitation leaving behind a clear solution. The crystals were filtered, washed with cold ether (20 mL), and air-dried (1.2 g, 31% yield). For **2**, crystals did not form after agitation. An equivalent volume of 0.5 M K_2SO_4 was added to the solution and $KClO_4$ and $BaSO_4$ were removed by filtration. The solution was then concentrated at 35 °C under reduced pressure to 4 mL and then filtered to remove additional $KClO_4$ and $BaSO_4$. Refrigeration at 4 °C resulted in the formation of an impure precipitate. Recrystallization from a minimum amount of water resulted in pure product (0.36 g, 15% yield). **Caution**: Although we have not experienced any explosions, perchlorate salts are potentially explosive and should be handled in very small quantities.

Analysis of **2**. Anal. Calcd for $C_{11}H_{24}N_7O_9Cl_2Co$: C, 25.02; H, 4.54; N, 18.57; Cl, 13.43. Found: C, 25.2; H, 4.6; N,18.4; Cl, 13.4. UV−vis [λ_{max} in nm (ϵ_{max} in L mol^{-1} cm^{-1}); H_2O]: 489 (178); 395 (119), sh; 288 (2700), sh; 253 (7100), sh. IR [cm^{-1}, fluorolube, NaCl plates] $\upsilon_{C=O}$: 1538.

Analysis of **3**. UV spectra of **3** were similar to that of **2** with peaks ranging from 492 to 496 nm and shoulders at 395 nm. **3f** had no shoulder at 395 nm and was noticeably more orange in color than the other phenyl derivatives. Analysis of **3b**. Anal. Calcd. for $C_{17}H_{28}N_7O_9Cl_2Co$: C, 33.79; H, 4.67; N, 16.23. Found: C, 33.2; H, 4.6; N, 16.1. Analysis of **3f**. Anal. Calcd for $C_{17}H_{27}N_8O_{11}Cl_2Co{\cdot}2H_2O$: C, 29.79; H, 4.56; N, 16.35. Found: C, 29.6; H, 4.2; N, 16.5.

^{1}H and ^{13}C NMR results are reported for the complexes and noncoordinated urea ligands in Tables S-1 and S-2 (Supporting Information).

Kinetic Studies. Kinetic runs were initiated by dissolving a small portion of the solid salt in thermostated solutions of HCl (55 °C, 0.05−1.00 M) maintained at constant ionic strength of 1.00 M with LiCl. Spectral traces were recorded at 340 nm. Plots of ln $|A_t - A_8|$ vs time were linear for over 4 half-lives of the reaction. Values of k_{obsd} are summarized in Table S-3 (Supporting Information).

Product Analysis. Bis(ethylenediamine)(2-picolylamine-*N,N′*)cobalt(III), **4**, was the only Co(III) product formed during the reactions of **2** and **3** in acidic solution. It exhibits d−d absorption bands at 339 and 466 nm (in 0.2 M LiCl) as expected for a cobalt(III) complex ligated by amine ligands. The UV region below 300 nm remains highly absorbent, indicating the pyridyl group remains intact. The IR spectrum of its perchlorate salt showed no absorbance in the region from 1500 to 1800 cm^{-1} consistent with the loss of the carbonyl moiety.

In one experiment, **3b** (0.36 g) was added to 1 M HCl (5 mL) at 55 °C. Odorless bubbles quickly evolved, and the solution turned from red to a yellow/orange color. After 1 h at 55 °C, the solution was cooled to 4 °C resulting in the precipitation of **4**. ^{1}H NMR and^{13}C NMR spectra of **4** confirm its identity. In another experiment, **3b** (0.06 g) was dissolved at 55 °C in 1 M HCl that had been prepared in D_2O and treated as above. After the majority of the yellow cobalt product was removed, a ^{13}C NMR spectrum of the remaining pale yellow solution was recorded. Only **4** and aniline were detected.

Crystallography. X-ray photographs of a crystal of $[Co(C_2H_8N_2)_2(C_7H_8N_2O)](ClO_4)_2$ revealed 2/*m* Laue symmetry and systematic extinctions uniquely determining the space group $P2_1/c$. The crystal was transferred to a Philips PW 1100/20 diffractometer, and unit cell dimensions were determined by least-squares analysis of the setting angles of 25 reflections (40° < 2θ < 47°), which were accurately centered on the counter. The intensities of three standard reflections measured at intervals of 2 h decreased by ca. 3% during data collection, and all data were scaled accordingly.[6] An analytical absorption correction was applied to the data (range in *T* 0.668−0.767).[7]

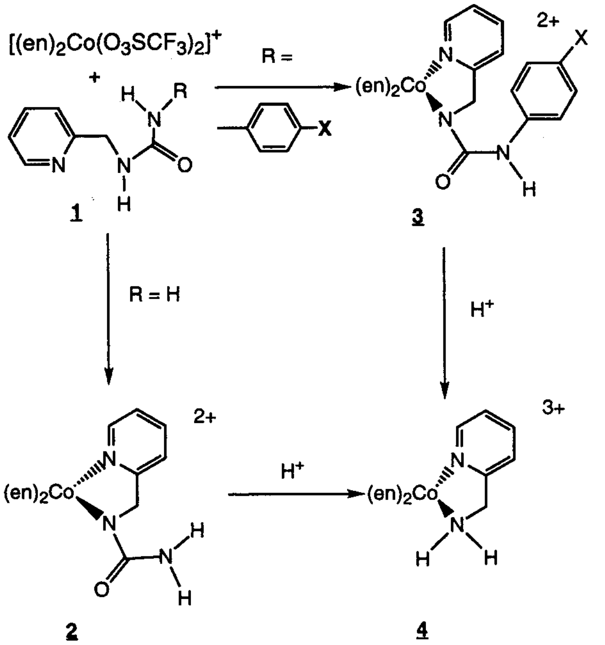

Figure 1. Structures and reactions of the ligands and complexes in this study. The substituents, X, in **3** are as follows: **3a**, $-CH_3$; **3b**, −H; **3c**, −Br; **3d**, −Cl (in meta position); **3e**, $-CF_3$; and **3f** $-NO_2$.

Structure Solution and Refinement. The structure was solved by conventional heavy atom techniques resulting in the location of all non-hydrogen atoms. Least-squares refinement was performed using, initially, isotropic and then anisotropic temperature factors for these atoms. Examination of the U_{ij} values for O(1) and the electron density difference map implied that O(1) should be regarded as being disordered over two (isotropic) sites [O(1A) and O(1B)]. Coordinates for all H atoms except those on N(7) were calculated geometrically (r_{C-H} = 0.95 Å, r_{N-H} = 0.85 Å). H(N7A) and H(N7B) were located in a difference map. B_H's were set at 1.2B_{eq} of the respective atoms to which they were bonded. H atoms were included in the structure factor calculations but their parameters were not refined. A secondary extinction parameter, β, was also included.[8] Refinement was continued, using full-matrix least-squares, until all shift/error ratios were <0.1. The final value for β was 1.3(1) × 10^{-5}.

Least-squares refinement was performed minimizing the function $\sum w(|F_o| - |F_c|)^2$ where $w = 1$ in the early stages and $w = 1/[(\sigma(F_o))^2 + 0.25(pF_o)^2]$ in the final cycles. The parameter *p* was varied to give a minimum variation in average $\sum w(|F_o| - |F_c|)^2$ as a function of F_o and (sin θ)/λ (final $p = 0.06$). The largest features in a final difference map were peaks of <0.7 e Å^{-3} in the vicinity of the perchlorate O atoms. Neutral-atom scattering factors with anomalous dispersion corrections were used throughout.[9] The conventional *R* factors converged to $R_F = 0.037$ and $R_{wF} = 0.051$. Computer programs[10] were run on a UNIVAC-1100/82 computer.

An ORTEP diagram[11] of the cation showing the atom labeling scheme is given in Figure 2. Selected bond parameters are in Tables 1 and 2.

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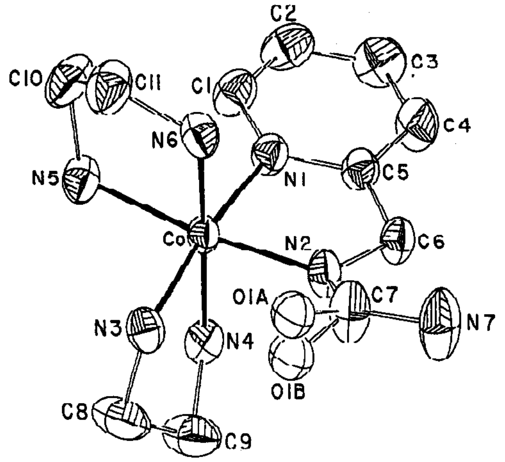

Figure 2. View of the $[Co(C_2H_8N_2)_2(C_7H_8N_2O)]^{2+}$ cation showing the atomic-labeling scheme of the non-hydrogen atoms. Note the disorder of the carbonyl oxygen atom. Thermal ellipsoids enclose 50% probability levels. The hydrogen atoms have been omitted for clarity.

Table 1. Selected Interatomic Distances (Å) in $[Co(C_2H_8N_2)_2(C_7H_8N_2O)](ClO_4)_2$

atoms	distance	atoms	distance
Co−N(1)	1.971(2)	Co−N(4)	1.966(3)
Co−N(2)	1.941(2)	Co−N(5)	1.993(3)
Co−N(3)	1.949(2)	Co−N(6)	1.954(3)
N(1)−C(1)	1.359(4)	C(5)−C(6)	1.492(4)
N(1)−C(5)	1.345(3)	C(6)−N(2)	1.445(3)
C(1)−C(2)	1.367(5)	N(2)−C(7)	1.338(4)
C(2)−C(3)	1.368(5)	C(7)−O(1A)	1.306(6)
C(3)−C(4)	1.380(5)	C(7)−O(1B)	1.299(6)
C(4)−C(5)	1.381(4)	C(7)−N(7)	1.348(4)
N(3)−C(8)	1.484(4)	N(5)−C(10)	1.490(4)
C(8)−C(9)	1.478(5)	C(10)−C(11)	1.495(5)
C(9)−N(4)	1.483(4)	C(11)−N(6)	1.477(4)

Table 2. Selected Bond Angles (Deg) in $[Co(C_2H_8N_2)_2(C_7H_8N_2O)](ClO_4)_2$

atoms	angle	atoms	angle
Coordination Sphere			
N(1)−Co−N(2)	83.42(9)	N(2)−Co−N(6)	88.73(10)
N(1)−Co−N(3)	171.99(10)	N(3)−Co−N(4)	84.88(10)
N(1)−Co−N(4)	87.95(10)	N(3)−Co−N(5)	89.36(11)
N(1)−Co−N(5)	94.93(10)	N(3)−Co−N(6)	91.18(11)
N(1)−Co−N(6)	95.95(10)	N(4)−Co−N(5)	96.04(10)
N(2)−Co−N(3)	93.13(10)	N(4)−Co−N(6)	176.01(10)
N(2)−Co−N(4)	90.90(10)	N(5)−Co−N(6)	84.47(10)
N(2)−Co−N(5)	172.81(10)		
N-(2-Pyridylmethyl)urea Ligand			
Co−N(1)−C(1)	127.9(2)	Co−N(2)−C(7)	128.0(2)
Co−N(1)−C(5)	114.3(2)	C(6)−N(2)−C(7)	116.7(2)
C(1)−N(1)−C(5)	117.5(2)	C(5)−C(6)−N(2)	110.7(2)
N(1)−C(1)−C(2)	122.6(3)	N(2)−C(7)−O(1A)	121.5(3)
C(1)−C(2)−C(3)	119.7(3)	N(2)−C(7)−O(1B)	120.8(3)
C(2)−C(3)−C(4)	118.7(3)	N(2)−C(7)−N(7)	120.0(3)
C(3)−C(4)−C(5)	119.5(3)	O(1A)−C(7)−N(7)	116.1(3)
N(1)−C(5)−C(4)	122.1(3)	O(1B)−C(7)−N(7)	117.6(3)
N(1)−C(5)−C(6)	116.3(2)	Co−N(2)−C(6)	114.3(2)
C(4)−C(5)−C(6)	121.5(3)	C(8)−C(9)−N(4)	106.6(3)
Co−N(3)−C(8)	110.4(2)	Co−N(5)−C(10)	108.9(2)
Co−N(4)−C(9)	109.0(2)	Co−N(6)−C(11)	111.8(2)
N(3)−C(8)−C(9)	108.2(3)	N(5)−C(10)−C(11)	107.6(3)
C(10)−C(11)−N(6)	107.4(3)		

Results and Discussion

Syntheses of the complexes were accomplished by the reaction of urea ligands with $[(en)_2Co(OSO_2CF_3)_2]^+$ as illustrated in Figure 1. The triflato ion is readily substituted under mild conditions, and the synthesis is another example of the synthetic versatility of labile trifluoromethanesulfonato complexes.[4,12] The low product yields of 15−35%, however, were disappointing given the nearly quantitative yields often reported for similar reactions. The majority of the cobalt was contained in a purple band that sorbed irreversibly to Sephadex SP C-25 cation-exchange resin. Aside from the desired product band, ^{13}C NMR spectra of the other bands that were removed demonstrated that none contained a pyridine ligand. Several attempts were made to increase the yield of **2**. Alternative preparations included (a) using a greater excess of ligand, (b) heating the tetramethylenesulfone solution to 80 °C, and (c) performing the reaction in a melt of the pure ligand. The first attempt resulted in no increase in yield, while the later two attempts resulted in decreased yields.

Solid State Characterization. Structural Analysis of 2. The structural refinement establishes the identity of the complex and confirms that a deprotonated urea N-atom is coordinated to Co(III). The charge on the cation is consistent with this mode of binding. As expected, the cobalt(III) center is six-coordinate with an approximately octahedral coordination environment. Bond angles about the metal range from 83.42(9)° for the N(1)−Co−N(2) angle to 96.04(10)° for the N(4)−Co−N(5) angle.

Deprotonation of the nitrogen center results in extensive delocalization throughout the urea moiety. The short N(2)−C(7) distance of 1.338(4) Å and the long C(7)−O distance of 1.302(8) Å (average of disordered sites) are to be compared to the analogous distances of 1.45(2) and 1.22(1) Å, respectively, in the protonated ligand of the Cu(II) complex.[2] The geometry about the deprotonated urea nitrogen atom is approximately trigonal planar with bond angles ranging from 114.3° to 128.0°. The Co−N(2)−C(7) angle of 128° could reflect the effect of the carbonyl oxygen hydrogen bonding with N(3) since N(3) is close (2.56 Å) to both the disordered oxygen sites O(1A) and O(1B). This intramolecular hydrogen bonding appears to be maintained in solution in DMSO as evidenced by ^1H NMR spectroscopy (vide infra). Intramolecular hydrogen bonding has also been observed in $[(NH_3)_5CoNHC(O)NHC_6H_5]^{2+}$ where a close contact of 2.80 Å is evident between the carbonyl oxygen and a cis ammonia.[3a] The weaker hydrogen bond in this complex is reflected in less delocalization in the carbonyl group with the distances analogous to those of N(2)−C(7) and C(7)−O in **2** being 1.310(14) and 1.240(13) Å, respectively.

The coordinated nitrogen moiety is planar with the root mean square deviation from the plane, defined by Co−N(2)−C(7)−C(6), being only 0.036 Å. This is in contrast to the Cu(II) structure, which shows the coordinated nitrogen center to be largely deconjugated from the carbonyl group and to sustain an approximate tetrahedral geometry.[2] Coordination through oxygen as in the Zn(II) complex leaves bond angles and distances in **1** almost unchanged relative to noncoordinated urea with C−N(2) and C−O bond lengths of 1.359(6) and 1.263(7) Å, respectively.[2] In urea, the C−N bond length is 1.333(1) Å and the C−O bond length is 1.246(2) Å.[13]

The Co−N(en) bond trans to the deprotonated urea nitrogen, 1.993(3) Å, is significantly longer than those of the two Co−N(en) bonds, which are trans to each other, 1.966(3) and 1.954-

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(3) Å. Thus, there is an observable structural trans effect induced by the deprotonated urea atom of 0.033(4) Å. The magnitude of the trans effect is smaller than that observed in the deprotonated cobalt(III) pentaammine *N*-phenylurea complex where a structural trans effect of 0.1 Å has been reported.[3a] The presence of the structural trans effect and consequent lability could explain our inability to isolate the analogous tetraammine complex by similar procedures.

Infrared Analysis of 2. Infrared data of **2** are consistent with the structural data in regard to delocalization. The carbonyl stretching frequency at 1538 cm^{-1} is lower than that observed in the Cu(II) and Zn(II) complexes where $\nu_{C=O}$ is 1714 and 1613 cm^{-1}, respectively. A linear relationship is observed between the carbonyl stretching frequencies and C−O distances of the Co(III), Cu(II), and Zn(II) complexes of **1**: $\nu_{C=O} = -2.1(\pm 0.1) \times 10^3(d_{C=O}, Å) + 4.3(\pm 0.2) \times 10^3$, $r^2 = 0.997$. For every 0.01 Å increase in C−O bond length, the carbonyl stretching frequency decreases by 21(1) cm^{-1}. Protonation of the cobalt(III) complex results in the disappearance of the band at 1538 cm^{-1} and the appearance of a band at 1735 cm^{-1}.[14] In $[(NH_3)_5RhNH_2C(O)NH_2]^{3+}$ $\nu_{C=O}$ is at 1740 cm^{-1}, implying that protonation occurs at the coordinated nitrogen[15] and delocalization at the bound N is lost. The extension of this argument to protonation of **2** implies the same conclusion.

Solution Characterization of 2 and 3. In contrast to the Ni(II), Zn(II), and Cu(II) complexes of the urea derivatives, the solubility of the Co(III) complexes allows a variety of techniques to aid in their characterization and in the study of their reactivity. Small changes are observed immediately in the visible spectrum of **2** upon the addition of acid. The peak at 489 nm shifts to 485 nm, the overall bandwidth narrows, and the shoulder at 395 nm disappears. The original spectrum is regenerated by the addition of hydroxide ion. The UV region shows a strong absorption as expected for a complex containing a coordinated pyridyl ligand with intense shoulders at 288 and 253 nm. In neutral solution, the UV−vis spectra of **3a**−**f** are very similar to that of **2** except that **3f** does not have a shoulder at 395 nm. The phenyl derivatives, however, react more readily in acidic solution. The peak at 489 nm shifts to 470 nm while the UV region displays a large decrease in absorbance at all wavelengths.

Additional structural information can be deduced from the ^1H NMR and ^{13}C NMR spectra. Figure 3 shows the ^1H NMR spectra for **1** and its cobalt(III) complex from 5.0 to 9.0 ppm in DMSO-$^2H_6$. Coordination of **1** to Co(III) results in no change in the position of the $-C(O)NH_2$ resonance at 5.7 ppm. However, the $-C(O)NH_2$ resonance of **2** is 0.9 ppm upfield from the analogous resonance observed in $[(NH_3)_5Co-OC(NH_2)_2]^{3+}$ as might be expected given the more electron-rich nature of the deprotonated ligand in **2**. The most striking feature in the ^1H NMR spectroscopy is the absence of the triplet at 6.6 ppm in the spectrum of **2** that is present in the spectrum of the free ligand which is consistent with the deprotonated N center. The NMR parameters are very similar to those reported by Toscano and co-workers for Co(III) complexes of a similar ligand, *N*-((2-pyridyl)methyl)-2-((2-aminoethyl)thio)acetamide.[16]

The triplets of the phenylurea ligands, due to the $-CH_2NHC(O)$ protons, also disappear upon coordination of the ligands to Co(III) as shown in Figure 4. The resonance found at 6.8 ppm in the free ligand is absent in this spectrum. Note that the triplet at 6.9 ppm in Figure 4 is due to the para hydrogen of the phenyl group. The singlet at 8.14 ppm is due the $-NHC_6H_5X$ proton and is sensitive to the nature of X. This resonance shifts from 8.04 to 8.95 ppm as X is changed from $-CH_3$ to $-NO_2$ ($\rho = 0.046(6)$, $r^2 = 0.943$). In the noncoordinated ligand the same resonance shifts from from 8.69 to 9.62 ppm as X is changed from $-CH_3$ to $-NO_2$ ($\rho = 0.044(7)$, $r^2 = 0.903$).

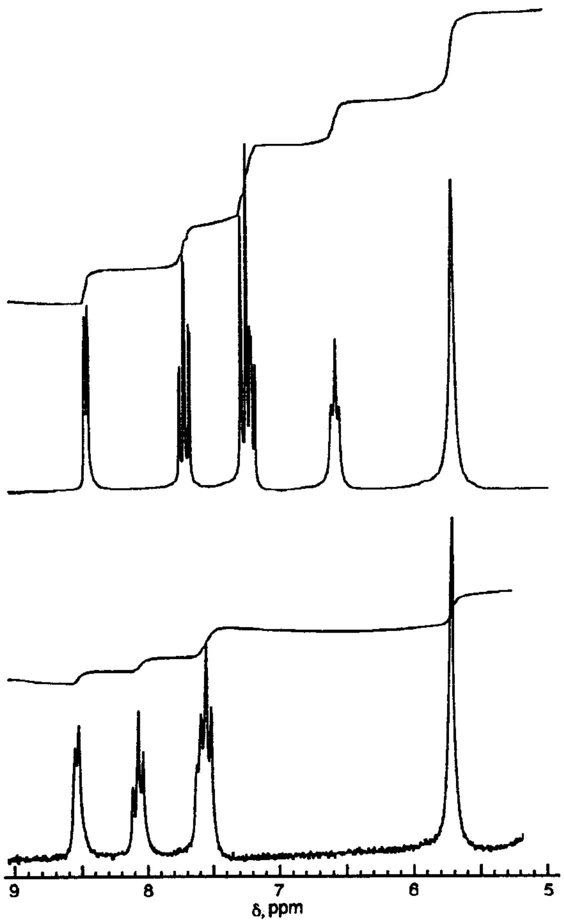

Figure 3. Proton NMR of *N*-(2-pyridylmethyl)urea (upper) and of its cobalt(III) complex (lower) from 5.0 to 9. 0 ppm in DMSO-$^2H_6$.

^1H NMR spectra also show that the intramolecular hydrogen bond formed between the carbonyl oxygen and an ethylenediamine hydrogen found in the solid state persists in DMSO. In all complexes a broad downfield resonance that integrates for one proton is evident around 9 ppm as illustrated in Figure 5. This resonance is attributed to an ethylenediamine hydrogen that is intramolecularly hydrogen bonded to the urea oxygen. The resonance shifts from 9.19 for X = $-CH_3$ to 8.58 ppm for X = $-NO_2$ ($\rho = -0.030(3)$, $r^2 = 0.972$). Increasing the electron-withdrawing abilities of the substituent makes the hydrogen bond stronger by placing more electron density on the carbonyl oxygen as a result of increased delocalization throughout the amide moiety as shown in Scheme 1. Additional evidence for the hydrogen bond is found in the NH_2 region of the spectrum. For all of the complexes, this region contains 1 proton less than would be expected in the absence of a hydrogen bond. We would also expect that the other hydrogen on the ethylenediamine involved in hydrogen bonding to the carbonyl oxygen to be shifted upfield due to an overall increase in electron density. Since resonances from ethylenediamine hydrogens are generally found only above 4.4 ppm in bis(ethylenediamine)

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(14) Roecker, L. Work in progress. **2** can be isolated in a protonated form and we have recovered crystals consistent with the formula $\mathbf{2}H(ClO_4)_3 \cdot 2H_2O$.

(15) Curtis, N. J.; Dixon, N. E.; Sargeson, A. M. *J. Am. Chem. Soc.* **1983**, *105*, 5347.

(16) Toscano, P. J.; Belsky, K. A.; Hsieh, T. C.; Nicholoson, T.; Zubieta, J. *Polyhedron* **1991**, *10*, 977.

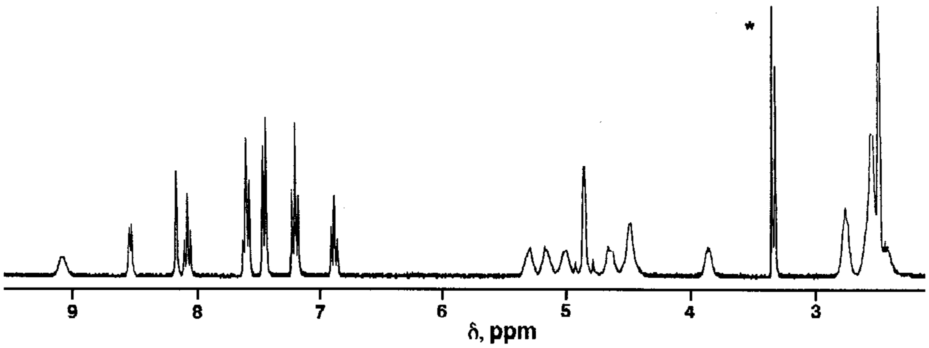


Figure 4. Proton NMR of **3b** in DMSO-$^2H_6$. The peak marked with the asterisk is due to HDO.

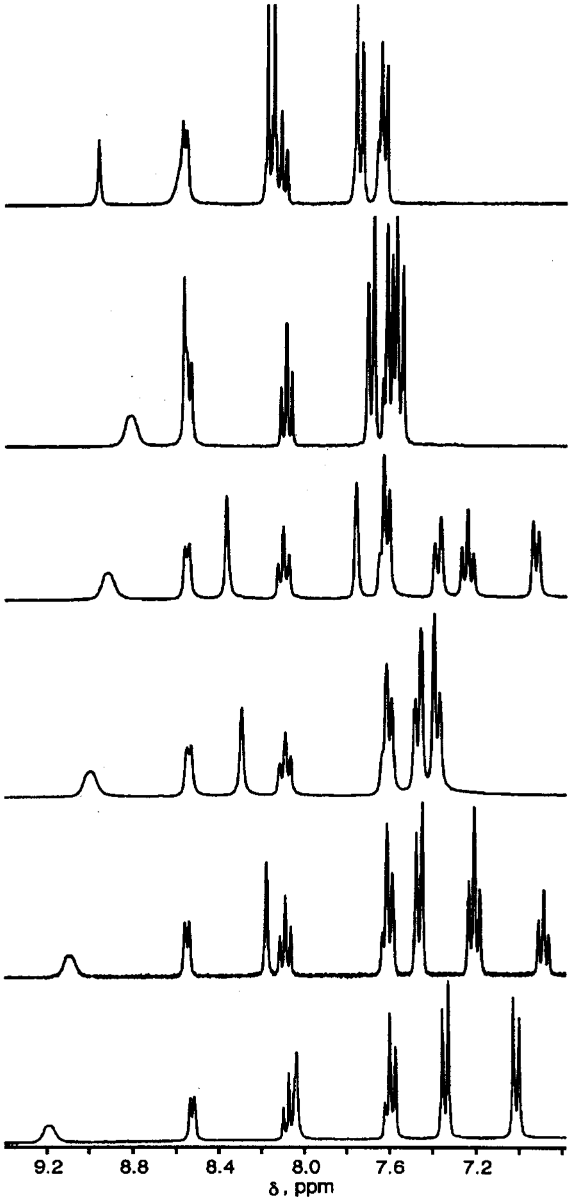
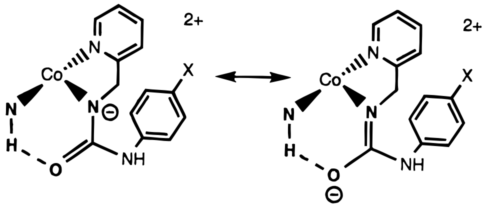


Figure 5. Proton NMR of **3** (**a**,**b**,**c**,**d**,**e**,**f**) from 6.6 to 9.4 ppm in DMSO-$^2H_6$. **3a** is at the bottom; **3f** is at the top.

Scheme 1



complexes of Co(III)[17] the peak around 3.9 ppm is probably due to the hydrogen in question. In addition, this upfield resonance shifts downfield as the phenyl substituent becomes more electron-withdrawing ($\rho = 0.017(1)$, $r^2 = 0.987$). This is also consistent with the delocalization depicted in Scheme 1. As the hydrogen-bonded hydrogen is pulled farther away from the ethylenediamine nitrogen (a result of X becoming more electron withdrawing) electron density is removed from the region around the remaining hydrogen and it resonates at a lower field. The 3.9 ppm resonance integrates as 1 H while the entire region from 3.5 to 5.5 ppm integrates as 9 H. Note that the hydrogens from the $-CH_2-$ group adjacent to the pyridine ring account for the AB quartet at 4.9 ppm and two hydrogens, thus leaving only seven hydrogen atom signals to be attributed to the ethylenediamine protons.

While the literature abounds with examples of hydrogen bonding effects in solid state NMR, we have not found any examples that relate directly to what we have observed in solution. Although the crystal structure of $[(NH_3)_5CoNHC(O)NHC_6H_5]^{2+}$ implies hydrogen bonding between a cis NH_3 and carbonyl oxygen in the solid state, ^1H NMR shows that the hydrogen bond is not detectable in solution.[3a] Two features of the complexes we have prepared might explain why the hydrogen bond appears to be maintained in **3**. CPK molecular models and the structural study imply that the carbonyl group is in close contact with the ethylenediamine ligand. The oxygen sits in a pocket formed on an octahedral face of the complex, and it cannot easily leave due to interference by the ethylenediamine backbone. On top of this barrier, free rotation about the C−N bond is restricted by delocalization over both urea nitrogen atoms. Second, the delocalization present in the urea moiety places a greater negative charge on the carbonyl oxygen than it usually would possess allowing for stronger hydrogen bond formation. The sum of these two effects allows the hydrogen bond to be observed even in a solvent as polar as DMSO. Thus, it appears that there is a significant amount of imidol character in this functional group as a result of the intramolecular hydrogen bond.

Reactivity. Kinetics of 2. Consistent with previous work relating to the reactivity of N-coordinated urea ligands, the coordinated deprotonated urea ligand is quite unreactive in base. For example, stirring the complex overnight in 0.01 M NaOH resulted in only slight decomposition of the complex to produce some dark brown material that was sorbed irreversibly on Sephadex SP C-25 cation-exchange resin. After the mixture was

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(17) Roecker, L.; Dickman, M. H.; Nosco, D. L.; Doedens, R. J.; Deutsch, E. *Inorg. Chem.* **1982**, *22,* 2022.

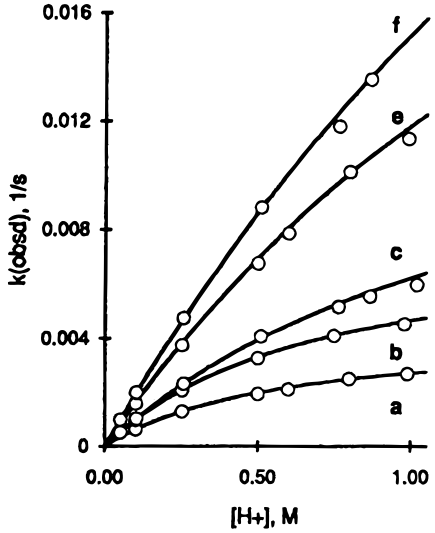


Figure 6. Plots of k_{obsd} vs [H$^+$] for the reaction of **3** (**a**,**b**,**c**,**d**,**f**) at 55.0 °C, $I = 1.00$ M (LiCl).

stirred for 24 h at 80 °C in 95% ethanol−water, no reaction or decomposition was observed. In comparison, both the Ni(II) and the Cu(II) complexes undergo slow decomposition (ca. 10^{-5} s^{-1}) in aqueous ethanol.[1,2] The lack of reactivity of the cobalt(III) complex toward nucleophiles is presumably due to the electron rich nature of the carbonyl carbon arising from the deprotonated urea moiety. The protonated form of the complex **2**, however, reacted slowly in acidic aqueous ethanol or in aqueous acid to produce the chelated picolylamine, **4** (for 2.0 M HCl at 50 °C, $k_{obsd} = 7.7(1) \times 10^{-6}$ s^{-1}). Due to the slowness of this reaction, we have not investigated the reactivity of **2** in depth.

Kinetics of 3. Addition of a phenyl group greatly increased the susceptibility of the coordinated urea ligand toward acid and base hydrolysis. In acidic solution, kinetic data were obtained over a range of [H$^+$] concentrations. Figure 6 shows that plots of k_{obsd} vs [H$^+$] are not linear. Plots of $1/k_{obsd}$ vs $1/[H^+]$, however, are linear consistent with the rate law $k_{obsd} = a[H^+]/(1 + b[H^+])$. The mechanism proposed in Scheme 2 leads to a rate law with $a = kK$ and $b = K$. Table 3 summarizes the k and K values for five phenylurea complexes derived from the data in Figure 6. The product analyses are also consistent with Scheme 2. An important feature of the mechanism is the proposed formation of a chelated isocyanate ligand that rapidly decomposes to yield the final products. This mechanism is similar to that proposed for the reaction of $[(NH_3)_5RhNH_2C(O)NH_2]^{3+}$ and $[(NH_3)_5CoNHC(O)NHC_6H_5]^{2+}$ in acid where an intermediate coordinated isocyanate was observed.[3a,15] In the present example the intermediate was not observed, but it is implied by the previous studies and by the absence of phenylisocyanate as a product. The chelated isocyanate intermediate is presumably too reactive to be observed directly here, and it should be more reactive than the $[(NH_3)_5CoNCO]^{2+}$ ion, as a neutral ligand.

The proton clearly triggers the urea elimination reaction, but the site of protonation in the process can only be inferred. Four possibilities in Scheme 3 seem obvious and would account for the observed products. Of these **C** is the most attractive in that protonation of the leaving group provides the trigger for the cascade leading to spontaneous bond rupture. However, it is not likely that the pK_a observed correlates with this activated protonated intermediate. The most basic sites in the parent molecule are likely to be the endo urea N atom or possibly the oxygen in the imidol form.[3b,15,18] However, even if these sites are the most basic, **C** may still be the most reactive species.

Intermediates **A** and **B** are feasible reactants, but they require more concerted rearrangements than **C** and seem, on balance, to be less likely. Initial protonation at the carbonyl oxygen is usually proposed for the acid hydrolysis of amides.[18] However,

Scheme 2

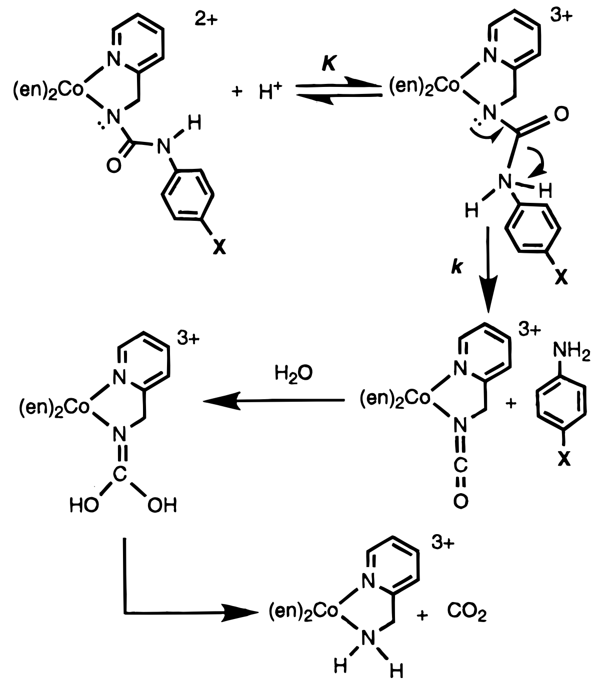
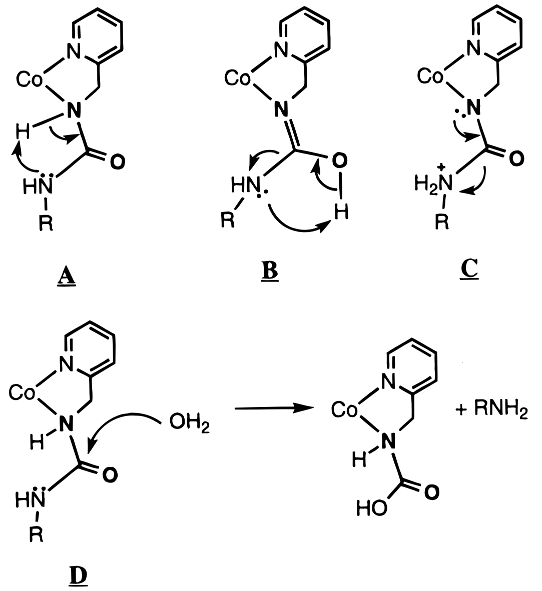


Table 3. Values of k and K for the Acid Hydrolysis of **3a**−**c**,**e**,**f** at 55 °C, $I = 1.0$ M

X	k, s^{-1}	K, M^{-1}
$-CH_3$	$4.3(3) \times 10^{-3}$	1.7(1)
−H	$8(1) \times 10^{-3}$	1.4(2)
−Br	$1.5(2) \times 10^{-2}$	0.71(7)
$-CF_3$	$4.0(7) \times 10^{-2}$	0.42(7)
$-NO_2$	$6.6(5) \times 10^{-2}$	0.30(2)

Scheme 3



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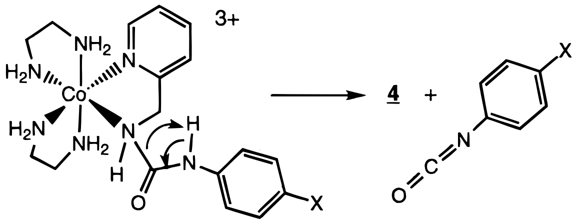
(18) Sigel, H.; Martin, R. B. *Chem. Rev.* **1982**, *82*, 385.

Scheme 4



previous work has indicated that the bound, deprotonated nitrogen of urea ligands coordinated to the metal ion is the most likely site of protonation in $[(NH_3)_5RhNHC(O)NH_2]^{2+}$ and $[(NH_3)_5CoNHC(O)N(CH_3)_2]^{2+}$.[3b,15] Also, the crystal structure of the Cu(II) complex of **1** has clearly demonstrated that N protonation of a coordinated urea ligand is possible.[2] Similarly, when **2** was isolated from acidic solution, the absorbance at 1538 cm^{-1} shifted to 1735 cm^{-1}, which can be attributed to the increasing double-bond character in the carbonyl moiety as expected for N protonation and reduced delocalization. **D** would account for the endo protonation but is inconsistent with the general results of metal ion activation of urea toward elimination and is therefore discounted.

Once the alkyl isocyanate intermediate is formed still chelated to the Co(III) it should be very susceptible to attack by a water molecule to give the carbamate and thence decomposition to the picolylamine chelate and CO_2, Scheme 2. In this respect, the reactant differs considerably from the Rh and Co urea complexes studied earlier and phenyl isocyanate itself where a proton takes the role of the metal ion to initiate isocyanate hydrolysis. It is not surprising, therefore, that the isocyanate intermediate is difficult to detect in this instance. Only a single pathway is observed compared with the complexity of the $[(NH_3)_5CoNHC(O)NH(C_6H_5)]^{2+}$ decomposition in acid.[3a] This presumably arises from the high stability of the bidentate chelate picolyl intermediates compared with the monodenate equivalent in the pentaammine complex.

Another mechanism we considered initially was one in which **4** and an organic isocyanate are formed directly as shown in Scheme 4. This pathway is not consistent with the product analysis, however, and therefore it cannot be obtained. Under the conditions of our kinetics experiments, phenyl isocyanate itself forms a white precipitate of diphenylurea in nearly quantitative yield. The slow formation of the precipitate is accompanied by the slow evolution of CO_2. In our product analysis studies, rapid evolution of CO_2 and no trace of diphenylurea were observed.

As the phenyl substituent, X, became more electron-withdrawing k_{obsd} increased. In terms of Scheme 2, k increased from $4.3(3) \times 10^{-3}$ s^{-1} to $6.6(5) \times 10^{-2}$ s^{-1} from X = $-CH_3$ to $-NO_2$. A Hammett plot of all the data is linear with $\rho = +1.25(5)$ for the k term ($r^2 = 0.995$). Electron-withdrawing substituents enhance the prospect of N−C bond breaking. On the other hand, K decreases as X becomes more electron withdrawing. From X = $-CH_3$ to $-NO_2$, K falls from 1.7(1) M^{-1} to 0.30(2) M^{-1}. A Hammett plot for these data is also linear with $\rho = -0.83(6)$ ($r^2 = 0.984$). The trends in the Hammett plots are conflicting for the mechanism proposed in Scheme 2 in that the protonated intermediates with the most electron-donating substituents are the easiest to protonate and have the larger values of K. However, the fact that the rate increases most for the least basic protonated substrate implies that weakening the C−N bond of the leaving group is the more significant factor and protonation at that site would be the most effective process to assist the bond rupture.

The pK_a's of the coordinated urea ligands [0.23(3) for X = $-CH_3$ to $-0.52(3)$ for X = $-NO_2$] are illustrative of the strongly acidic nature of the coordinated ligands at 55.0 °C. These urea complexes are much more acidic than related complexes such as $[(NH_3)_5RhNH_2C(O)NH_2]^{3+}$ and $[(NH_3)_5CoNH_2C(O)N(CH_3)_2]^{3+}$, which have p$K_a$'s of 3.93 and 2.92, respectively at 25.0 °C.[3b,15] Despite the temperature difference, the variation is largely due to the inherent differences between ammonia and aniline basicities (ca. 10^4). This factor is also evident in the rate of elimination of the base. The fastest reaction is observed with the strongest electron-withdrawing substituent and therefore the weakest base and best leaving group.

CPK models imply that the hydrogen bonding is more efficient with the nitrogen atom in a trigonal planar geometry. The ^1H NMR spectra and the kinetic studies provide some evidence for this as the hydrogen bond strength increases as the corresponding protonated complex becomes more acidic. For example, as X becomes more electron withdrawing the ethylenediamine hydrogen involved in hydrogen bonding to the carbonyl oxygen shifts from 9.19 ppm (X = $-CH_3$) to 8.58 ppm (X = $-NO_2$). The increase of electron density in the region of the ethylenediamine hydrogen, as reflected in the upfield chemical shift, implies that the intramolecular hydrogen bond is strongest in the complex with X = $-NO_2$. The complex with X = $-NO_2$ is also the most acidic.

Given the series of structural and reactivity studies now on metal-coordinated urea complexes, it seems desirable that the urease mechanism be reexamined. Ni(II) coordinated NCO^- could be an intermediate if it reacted rapidly to carbamate ion and then to NH_3 and CO_2. It is suspicious that there is no sign yet of direct attack of a nucleophile at coordinated urea in any of the model systems despite several attempts to see this path. In this context, it also seems likely that the Ni pyridylmethyl urea reactivity in ethanol[1] arises from addition of the solvent to a coordinated isocyanate ligand intermediate rather than attack at the urea derivative.

In 0.01 M NaOH at 25 °C, **3a** reacted overnight and the solution turned from red to orange while an increase in absorbance was observed in the UV. Chromatography of the product solution on Sephadex SP C-25 cation-exchange resin showed a trace of a yellow product that eluted with 0.2 M $LiClO_4$ and a higher charged orange band. These products are not yet characterized, and the investigation of their reactivity in basic solution is continuing.

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Supporting Information Available: Tables S-1 and S-2 summarize the ^1H and ^{13}C NMR data, respectively, for the free ligands and their Co(III) complexes. Table S-3 provides the pseudo-first-order rate constants for the hydrolysis reactions. Tables S-4−S-8 relate to the crystallographic determination of **2** and include crystal data, details of data collection and refinement, non-hydrogen atom thermal parameters, hydrogen atom parameters, and the final fractional coordinates for the non-hydrogen atoms. Figure S-1 provides the numbering scheme used to assign the ^1H and ^{13}C NMR resonances in Tables S-1 and S-2. This material is available free of charge via the Internet at http://pubs.acs.org.

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