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A Deprotonated Intermediate in the Amide Methanolysis Reaction of an N_4O-Ligated Mononuclear Zinc Complex

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Treatment of [(ppbpa)Zn]$(ClO_4)_2$ (**1**$(ClO_4)_2$, ppbpa = *N*-((6-(pivaloylamido)-2-pyridyl)methyl)-*N*,*N*-bis((2-pyridyl)methyl)-amine) with 1 equiv of $Me_4NOH{\cdot}5H_2O$ in methanol–acetonitrile solution results within minutes in the stoichiometric formation of a complex having a deprotonated amide, [(ppbpa$^-$)Zn]ClO_4 (**3**). Complex **3** has been characterized by ^1H and ^{13}C NMR, FTIR, and elemental analysis. Notably, upfield shifts of specific ^1H NMR resonances of the amide-appended pyridyl moiety in **3**, versus those found for **1**$(ClO_4)_2$, indicate delocalization of the anionic charge within the amide-appended pyridyl donor of this complex. Heating of analytically pure **3** in methanol–acetonitrile results in amide alcoholysis. Overall, this alcoholysis reaction is second-order, with a first-order dependence on both **3** and methanol. Analysis of the rate of decay of **3** as a function of temperature yielded activation parameters consistent with an intramolecular amide cleavage process ($\Delta H^{\ddagger} = 15.0(3)$ kcal/mol, $\Delta S^{\ddagger} = -33(1)$ eu). A possible reaction mechanism for amide alcoholysis is presented which involves reaction of the deprotonated amide intermediate **3** with methanol to produce a Lewis activated-type structure from which amide cleavage may be initiated. Additional support for this mechanistic pathway has been obtained through examination of the analogous ethanolysis reaction and via evaluation of the effect of varying steric hindrance near the amide carbonyl unit.

Introduction

Studies of metal-mediated amide cleavage reactions are of interest due to the involvement of metal cofactors in enzymes that catalyze either peptide bond scission or the cleavage of an external amide substrate.[1] However, relatively few kinetic and mechanistic studies of amide cleavage reactions mediated by mononuclear complexes of labile metals have been reported.[2−11] We have reported that structurally characterized Zn(II) and Cd(II) complexes of the amide-appended N_2S_2O-donor ligands bmppa (*N*,*N*-bis(2-methylthio)ethyl-*N*-((6-pivaloylamido-2-pyridyl)methyl)-amine) or beppa (*N*,*N*-bis(2-ethylthio)ethyl-*N*-((6-pivaloyl-amido-2-pyridyl)methyl)amine) undergo reaction with $Me_4NOH{\cdot}5H_2O$ in methanol solution to yield products of amide methanolysis (Scheme 1a), specifically methyl trimethylacetate and a primary amine-appended chelate ligand (bmapa), following removal of the zinc ion using NaCN.[12] Another research laboratory subsequently reported that treatment of a Zn(II) complex of the structurally related ppbpa ligand ([(ppbpa)Zn]$(PF_6)_2$, **1**$(PF_6)_2$, Scheme 1b, ppbpa = *N*-((6-pivaloylamido-2-pyridyl)methyl)-*N*,*N*-bis((2-pyridyl)methyl)-amine) with 1 equiv of $Me_4NOH{\cdot}5H_2O$ in acetonitrile−methanol (6:1) solution yields [(ppbpa$^-$)Zn]PF_6, a deprotonated amide complex for which no characterization data were

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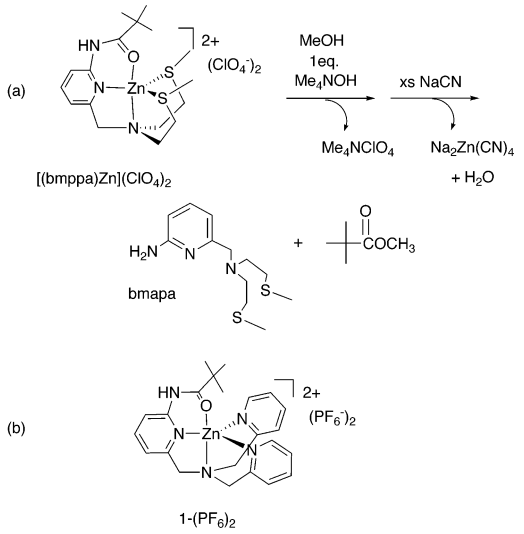
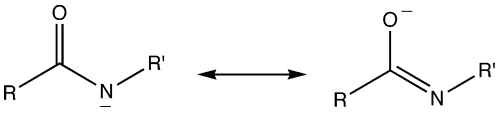
Scheme 1



Scheme 2



reported.[13,14] In an ensuing publication, the same laboratory reported that $[(ppbpa)Zn](X)_2$ ($X = PF_6^-$ (**1**$(PF_6)_2$) or ClO_4^- (**1**$(ClO_4)_2$)) underwent amide methanolysis upon reaction with $Me_4NOH{\cdot}5H_2O$ in CD_3OD with a half-life of 0.41 h at 50(1) °C.[15] No other kinetic or mechanistic data for this amide alcoholysis reaction were reported. Thus, for **1**$(X)_2$ ($X = PF_6^-$ or ClO_4^-) both amide deprotonation and methanolysis have been suggested to occur upon treatment with $Me_4NOH{\cdot}5H_2O$ in methanol-containing solutions. However, no discussion of the relationship between these two chemical processes has been reported. Generally, deprotonation of an amide N−H is regarded as making the amide less susceptible to cleavage, as the carbon−nitrogen bond order will increase with delocalization of the anion into the carbonyl moiety (Scheme 2).

Herein we present mechanistic studies of the amide alcoholysis reaction of **1**$(ClO_4)_2$. Using ^1H and ^{13}C NMR, FTIR, and elemental analysis data, we demonstrate that the initial zinc complex formed upon reaction of **1**$(ClO_4)_2$ with $Me_4NOH{\cdot}5H_2O$ in methanol−acetonitrile solution contains a deprotonated amide moiety ($[(ppbpa^-)Zn]ClO_4$, **3**). In methanol-containing solutions, analytically pure, isolated samples of **3** undergo reaction to yield products of amide methanolysis, which have been fully characterized. Kinetic analysis of this amide methanolysis reaction revealed a first-order dependence on both **3** and methanol in the rate-determining step, yielding an overall second-order reaction. Activation parameters for the reaction are similar to those previously reported for an intramolecular metal-mediated amide cleavage process.[11] A possible mechanistic pathway for the amide cleavage reaction, involving the deprotonated amide intermediate **3**, is presented.

Experimental Section

General Methods. All reagents and solvents were obtained from commercial sources and were used as received unless otherwise noted. Solvents were dried according to published procedures and were distilled under N_2 prior to use.[16] Air-sensitive procedures were performed in a MBraun Unilab glovebox under an atmosphere of purified N_2. The ligand precursor 2-(bromomethyl)-6-(pivaloylamido)pyridine was prepared according to a literature procedure.[17] The synthesis of the ligand *N*-((6-(pivaloylamido)-2-pyridyl)methyl)-*N*,*N*-bis((2-pyridyl)methyl)amine (ppbpa) has been previously reported, albeit via a different synthetic pathway from the procedure outlined herein.[18]

Physical Methods. IR spectra were recorded on a Shimadzu FTIR-8400 spectrometer as neat films between NaCl plates or as KBr pellets. ^1H and $^{13}C\{^1H\}$ NMR spectra for characterization purposes were recorded in dry CD_3CN at ambient temperature on a Bruker ARX400 spectrometer. Chemical shifts (in ppm) are referenced to the residual solvent peak(s) in CHD_2CN (^1H, 1.94 (quintet); $^{13}C\{^1H\}$, 1.39 (heptet) ppm). ^1H NMR kinetic studies were performed on a JEOL GSX-270 spectrometer having a thermally regulated probe. A temperature calibration curve was recorded for the temperature range of 297−358 K using ethylene glycol.[19] Electron impact and fast atom bombardment (FAB) mass spectra were obtained at the University of California, Riverside, CA, using a VG ZAB2SE high-resolution mass spectrometer. Elemental analyses were performed by Atlantic Microlabs of Norcross, GA.

Caution! Perchlorate salts of metal complexes with organic ligands are potentially explosive. Only small amounts of material should be prepared, and these should be handled with great care.[20]

***N*-((6-(Pivaloylamido)-2-pyridyl)methyl)-*N*,*N*-bis((2-pyridyl)methyl)amine (ppbpa).** An alternative synthetic procedure was previously reported for this ligand.[18] The overall yield is higher using the following procedure. To a 250 mL round-bottom flask was added 2-(bromomethyl)-6-(pivaloylamido)pyridine (1.25 g, 4.61 mmol), bis(2-picolyl)amine (0.92 g, 4.61 mmol), Na_2CO_3 (2.44 g), and tetrabutylammonium bromide (∼5 mg). To this mixture of solids was added CH_3CN (100 mL). The reaction mixture was heated at reflux under a nitrogen atmosphere for 21 h. At this point, the reaction mixture was cooled to ambient temperature and ∼12 mL of 1 M NaOH was added. The entire solution was extracted with methylene chloride (3 × 100 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and brought to dryness by rotary evaporation. The resulting dark brown oil was purified by column chromatography on silica gel (230−400 mesh, methanol, $R_f \sim 0.8$) to yield a yellow-brown solid (1.58 g, 88%). ^1H and $^{13}C\{^1H\}$ NMR characterization data for the ppbpa ligand in CD_3CN is included herein due to subtle differences from reported literature spectral features:[13,15] ^1H NMR (CD_3CN, 400 MHz) δ 8.46 (d, $J = 4.7$ Hz, 2H), 8.20 (br, 1H, N-*H*), 7.97 (d, $J = 8.0$ Hz, 1H), 7.70−7.65 (m, 3H), 7.57 (d, $J = 7.8$ Hz, 2H), 7.30 (d, $J = 7.5$ Hz,

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1H), 7.17 (t, $J = 6.1$ Hz, 2H), 3.81 (s, 4H), 3.72 (s, 2H), 1.26 (s, 9H); ^{1}H NMR (CD_3OD, 400 MHz) δ 8.42 (d, $J = 5.6$ Hz, 2H), 7.95 (d, $J = 8.2$ Hz, 1H), 7.77−7.73 (m, 2H), 7.70−7.62 (m, 3H), 7.27−7.21 (m, 3H), 3.85 (s, 4H), 3.74 (s, 2H), 1.29 (s, 9H); ^{13}C-{^{1}H} NMR (CD_3OD, 100 MHz) δ 179.5, 160.3, 158.7, 152.6, 149.6, 139.7, 138.7, 124.9, 123.9, 120.3, 114.0, 61.2, 61.0, 40.9, 27.8 (15 signals expected and observed); FTIR (neat, cm^{-1}) 1683 (amide I); LRFAB-MS (CH_3OH−NBA−NaCl) [*m*/*z* (relative intensity)] 390 ([M + H]$^+$, 100%), 412 ([M + Na]$^+$, 60%).

[(ppbpa)Zn](ClO$_4$)$_2$ (1(ClO$_4$)$_2$). The preparations of **1**$(PF_6)_2$ and **1**$(ClO_4)_2$ have been previously reported.[13,15] We include our own synthetic procedure here as this method (1) outlines conditions necessary for growth of X-ray-quality crystals of **1**$(ClO_4)_2$ and (2) provides **1**$(ClO_4)_2$ in slightly higher analytical purity (as judged by comparison of results of analytical combustion analyses).[15] To a methanol solution of ppbpa (56 mg, 0.14 mmol) was added a methanol solution of $Zn(ClO_4)_2$·$6H_2O$ (53 mg, 0.14 mmol). The resulting clear, colorless solution was stirred at ambient temperature for 30 min. To this mixture was added an excess of diethyl ether (∼80 mL), and the resulting cloudy solution was cooled to −28 °C overnight. A white solid that had deposited was then collected and carefully dried under vacuum. Recrystallization of this powder by diethyl ether diffusion into a 1:1 CH_3CN−CH_3OH solution yielded colorless blocks suitable for X-ray diffraction analysis (86 mg, 91%). ^{1}H NMR data for **1**$(ClO_4)_2$ in CD_3CN solution is given due to notable differences (>0.2 ppm) in the benzylic proton resonances versus those previously reported (4.57 (s, 4H), 4.33 (s, 2H)):[15] ^{1}H NMR (CD_3CN, 400 MHz) δ 9.53 (br s, 1H, N-*H*), 8.58 (d, $J = 5.2$ Hz, 2H), 8.14−8.07 (m, 3H), 7.67 (t, $J = 6.5$ Hz, 2H), 7.62 (d, $J = 8.0$ Hz, 2H), 7.53 (d, $J = 8.3$ Hz, 1H), 7.40 (d, $J = 7.6$ Hz, 1H), 4.35 (s, 4H), 4.31 (s, 2H), 1.56 (s, 9H). ^{13}C{^{1}H} NMR in CD_3CN (100 MHz) data for **1**$(ClO_4)_2$ generally match the previously reported spectral features;[15] solid state infrared spectral features have not been previously reported for **1**$(ClO_4)_2$: FTIR (KBr, cm^{-1}) 3319 (br, ν_{N-H}), 1647, 1625, 1615, 1573, 1530, 1093 (ν_{ClO_4}), 623 (ν_{ClO_4}). LRFAB-MS (CH_3OH−NBA) [*m*/*z* (relative intensity)]: 452 ([M−H]$^+$, 100%). Anal. Calcd for $C_{23}H_{27}N_5O_9$-Cl_2Zn·CH_3CN: C, 43.35; H, 4.37; N, 12.14. Found: C, 43.02; H, 4.31; N, 11.75. The presence of a noncoordinated acetonitrile solvate molecule was confirmed by X-ray crystallography.

[(ppbpa)Zn](OTf)$_2$ (1(OTf)$_2$). The preparation and characterization of **1**$(OTf)_2$ has not been previously reported. To a methanol solution of ppbpa (103 mg, 0.27 mmol) was added a methanol solution of $Zn(OTf)_2$ (97 mg, 0.27 mmol). The mixture was stirred at ambient temperature until all of the zinc starting material had dissolved (∼5 min) and then for an additional 20 min. Evaporation of the solvent under reduced pressure yielded a yellowish solid material (181 mg, 91%): ^{1}H NMR (CD_3CN, 400 MHz) δ 9.67 (br s, 1H, N-*H*), 8.56 (d, $J = 4.9$ Hz, 2H), 8.14−8.06 (m, 3H), 7.68−58 (m, 4H), 7.53 (d, $J = 8.3$ Hz, 1H), 7.38 (d, $J = 8.3$ Hz, 1H), 4.33 (s, 4H), 4.29 (s, 2H), 1.55 (s, 9H); ^{13}C{^{1}H} NMR (CD_3CN, 100 MHz) δ 187.7, 156.3, 153.9, 152.9, 149.5, 144.6, 143.1, 126.7, 126.2, 122.4, 117.6, 58.8, 58.6, 43.0, 27.5 (15 signals expected and observed); FTIR (KBr, cm^{-1}) 3312 (br, ν_{N-H}), 1646, 1624, 1576, 1533, 1278 ($\nu_{O_3SCF_3}$), 1257 ($\nu_{O_3SCF_3}$), 1162 ($\nu_{O_3SCF_3}$), 1030 (ν_{O_3}-SCF_3), 637 ($\nu_{O_3SCF_3}$); LRFAB-MS (CH_3OH/NBA) [*m*/*z* (relative intensity)] 452 ([M − H]$^+$, 100%).

Characterization of Amide Alcoholysis Reaction Products. (A) Independent Synthesis and Characterization of [(ambpa)-ZnOH(CH$_3$CN)]ClO$_4$ (2). To a CH_3CN (1 mL) solution of ambpa (isolated from large scale amide alcoholysis reaction mixture (vida infra), 24 mg, 7.8×10^{-2} mmol), was added a CH_3CN (1 mL) solution of $Zn(ClO_4)_2$·$6H_2O$ (29 mg, 7.8×10^{-2} mmol). The resulting mixture was stirred for 30 min, at which time the entire reaction mixture was transferred to a new reaction vessel containing Me_4NOH·$5H_2O$ (14.4 mg, 7.8×10^{-2} mmol). This slurry was then stirred for 12 h at room temperature. The solvent was removed under reduced pressure, and the resulting solid was dissolved in CH_2Cl_2 (5 mL). The CH_2Cl_2 solution was filtered through a Celite/glass wool plug, and the filtrate was brought to dryness under reduced pressure. The crude product was redissolved in acetonitrile (∼1 mL) and precipitated by addition of excess diethyl ether (∼15 mL). Decanting of the organic solvent yielded a white solid (31 mg, 82%) following drying under vacuum: ^{1}H NMR (CD_3CN, 400 MHz) δ 8.60 (d, $J = 5.3$ Hz, 2H), 8.06−8.01 (m, 2H), 7.60−7.57 (m, 2H), 7.54−75.0 (m, 3H), 6.96 (br, 2H, N-*H*), 6.78 (d, $J = 8.5$ Hz, 1H), 6.65 (d, $J = 7.9$ Hz, 1H), 4.17 (d, $J = 17$ Hz, 2H), 4.10 (d, $J = 17$ Hz, 2H), 3.93 (s, 2H), 2.27 (s, 3H, CH_3CN) (an O−H proton resonance could not be identified); ^{13}C{^{1}H} NMR (CD_3-CN, 100 MHz) δ 172.6, 156.6, 150.8, 149.3, 142.2, 140.2, 126.1, 125.7, 123.8, 113.6, 58.1, 57.5 (12 signals expected and observed); FTIR (KBr, cm^{-1}) ∼3570 (br), ∼3340, 1094 (ν_{ClO_4}), 623 (ν_{ClO_4}). Anal. Calcd for $C_{20}H_{23}N_6O_5ClZn$·$0.25C_4H_{10}O$: C, 46.13; H, 4.70; N, 15.37. Found: C, 46.75; H, 4.36; N, 15.57. The presence of 0.25 equiv of diethyl ether in the elemental analysis sample was confirmed by ^{1}H NMR.

(B) ^{1}H NMR Features of the Zinc-Containing Products of the Amide Methanolysis Reaction of 1(ClO$_4$)$_2$. Treatment of **1**$(ClO_4)_2$ (10.8 mg, 1.7×10^{-2} mmol) with Me_4NOH·$5H_2O$ (3.0 mg, 1.7×10^{-2} mmol) in CD_3OD−CD_3CN ultimately results in the formation of two zinc-containing products which can be differentiated on the basis of their respective ^{1}H NMR properties. On the basis of the above-described independent synthesis and characterization of **2**, one of the zinc-containing products of amide alcoholysis is this hydroxide derivative. This is evident from the presence of two doublets at 6.8 and 6.7 ppm, respectively. Two additional doublets at 6.5 and 6.4 ppm indicate the presence of a second zinc-containing species. Under these conditions, the ratio of **2** to this second product is approximately 1:1. Removal of the CD_3OD−CD_3CN solvents from this sample, followed by addition of wet CH_2Cl_2 (∼5 mL), filtration, and removal of the solvent from the filtrate under vacuum, yielded a white solid. This crude product was redissolved in CH_3CN (∼1 mL) and then precipitated by addition of excess diethyl ether. Decanting of the organic solvent yielded a white solid with a single set of ^{1}H NMR resonances in CD_3CN solution that matched identically those identified for the independently prepared sample of **2**. However, analysis of the ^{1}H NMR properties of the same white solid in CD_3OD indicated the presence of two species. The major species (∼80% of sample) has a pair of doublets at 6.9 and 6.8 ppm, respectively. The minor component, present as ∼20% of the sample at 328 K, has two doublets at 6.5 and 6.4 ppm, respectively. Raising or lowering of the temperature of the NMR cavity for the methanol sample did not produce significant change in the relative amounts of the two species. These combined studies indicate that one of the zinc-containing species produced upon treatment of **1**$(ClO_4)_2$ with Me_4-NOH·$5H_2O$ in methanol−acetonitrile solution is [(ambpa)ZnOH-(CH_3CN)] (**2**), and the second zinc-containing product is likely a methoxide derivative (e.g. [(ambpa)$ZnOCH_3$]ClO_4) produced in methanol-containing solutions.[21] Attempts to independently isolate this methoxide complex have thus far failed, due in part to the apparent instability of the complex with respect to the presence of trace water.

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(C) Isolation and Identification of *N*-((6-Amino-2-pyridyl)-methyl)-*N*,*N*-bis((2-pyridyl)methyl)amine (ambpa). This ligand has been previously generated by basic or acidic hydrolysis of ppbpa in the absence of a metal.[22,23] In this procedure, we demonstrate that the ambpa chelate ligand is produced in the amide alcoholysis reaction of **1**$(X)_2$ (X = OTf^- or ClO_4^-). To a CH_3OH solution (80 mL) of [(ppbpa)Zn]$(OTf)_2$ (**1**$(OTf)_2$) (6.72 g, 8.93 mmol) generated in-situ was added a CH_3OH solution (100 mL) of $Me_4NOH{\cdot}5H_2O$ (1.78 g, 9.83 mmol), and the resulting cloudy solution was heated for 48 h at 40(1) °C in a round-bottom flask. After cooling of the reaction mixture to ambient temperature, excess NaCN (12 equiv) was added and the resulting heterogeneous mixture was stirred until all NaCN had dissolved (~2 h). At this point, an equivalent volume of water was added (~30 mL) and the reaction mixture had a pH ≈ 12. The organic layer was then removed, and the aqueous layer was further extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and brought to dryness under reduced pressure, yielding a pale yellow oil. This oil was purified by column chromatography on silica gel (230−400 mesh, 1:1 CH_3OH−ethyl acetate, $R_f \sim 0.6$) to yield a yellow solid (2.18 g, 80%). The ^1H and ^{13}C NMR properties of this solid match those previously reported:[23] EI-MS [*m*/*z* (relative intensity)] 306 ([M + H]$^+$, 100%); HREI-MS (*m*/*z*) calcd for $C_{18}H_{19}N_5$, 305.1640, found 305.1641. Control experiments confirmed that aqueous−alcoholic sodium cyanide solutions do not cleave the amide bond of the ppbpa ligand.

(D) Identification and Quantification of Methyl Trimethylacetate Produced in the Amide Methanolysis of 1$(ClO_4)_2$. Methyl trimethylacetate formation in the amide methanolysis reaction of **1**$(ClO_4)_2$ was identified by the appearance of singlet at 1.18 ppm in the ^1H NMR spectrum.[12] Following completion of the observed amide methanolysis reaction, integration of the ester *tert*-butyl methyl proton resonance at 1.18 ppm, versus the methine resonance of a $CHPh_3$ internal standard, indicated the formation of 1 equiv of methyl trimethylacetate.

(E) Identification and Quantification of Me_4NClO_4 Formation. The production of 1 equiv of Me_4NClO_4 in the amide alcoholysis reaction of **1**$(ClO_4)_2$ was confirmed via isolation of the solid from a reaction mixture. Specifically, **1**$(ClO_4)_2$ (83 mg, 0.13 mmol) was treated with $Me_4NOH{\cdot}5H_2O$ (23 mg, 0.13 mmol) in methanol solution (~5 mL). The resulting mixture was stirred vigorously at ambient temperature for ~5 min, during which time a white precipitate appeared. The reaction mixture was allowed to settle, and the solution was carefully decanted from the solid. The solid was then dried under vacuum (17.3 mg, 77%). Analysis by FTIR (KBr pellet) indicated only the presence of Me_4NClO_4, as determined via comparison of spectral features with those produced by an authentic sample of Me_4NClO_4 purchased from a commercial source.

Isolation and Characterization of the Deprotonated Amide Complex [(ppbpa$^-$)Zn]ClO_4 (3). To a methanol (~3 mL) solution of **1**$(ClO_4)_2$ (0.083 g, 0.013 mmol) was added a methanol (12 mL) solution of $Me_4NOH{\cdot}5H_2O$ (0.023 g, 0.013 mmol). The resulting mixture was stirred for ~10 min at room temperature. The Me_4NClO_4 that formed was allowed to settle to the bottom of the reaction vial. The solution was then carefully decanted from the solid and transferred to a second clean round-bottom flask. The solvent in the flask was removed under reduced pressure yielding a white solid that was analyzed by ^1H and ^{13}C NMR and FTIR.

Table 1. Rate Constants for Amide Alcoholysis Reaction of **1**$(ClO_4)_2$ in CD_3CN-CD_3OD Solution

temp (K)	[**1**$(ClO_4)_2$] (M)	[CD_3OD] (M)	k_{obs} (s^{-1})	k_2 ($M^{-1}\,s^{-1}$)
297	0.024	15.39	$4.25(16) \times 10^{-5}$	$2.75(11) \times 10^{-6}$
308	0.023	15.39	$1.06(5) \times 10^{-4}$	$6.89(35) \times 10^{-6}$
318	0.024	15.39	$2.37(12) \times 10^{-4}$	$1.54(8) \times 10^{-5}$
328	0.024	15.39	$5.12(6) \times 10^{-4}$	$3.33(4) \times 10^{-5}$
338	0.024	15.39	$9.92(30) \times 10^{-4}$	$6.45(20) \times 10^{-5}$
338	0.021	21.5	$2.32(5) \times 10^{-3}$	$1.08(2) \times 10^{-4}$
338	0.021	9.23	$1.12(5) \times 10^{-3}$	$1.21(5) \times 10^{-4}$
338	0.021	0.92	$1.04(7) \times 10^{-4}$	$1.13(8) \times 10^{-4}$
338	0.021	0.46	$4.67(12) \times 10^{-5}$	$1.01(3) \times 10^{-4}$
338	0.021	0.21	$1.49(2) \times 10^{-5}$	$7.23(8) \times 10^{-5}$

Recrystallization of a portion of this material from CH_3CN-Et_2O (~1:10, solvents used as purchased) over the course of ~5 d at ambient temperature yielded a small amount of a polycrystalline white solid (6.3 mg, 9%) that was analyzed by ^1H NMR and combustion analysis. All data were consistent with the presence of one species, [(ppbpa$^-$)Zn]ClO_4 (**3**). The yield of [(ppbpa$^-$)Zn]ClO_4 outlined above is low due to the high solubility of the complex in the CH_3CN/Et_2O mixture. Characterization data for **3**: ^1H NMR (CD_3CN, 400 MHz) 8.59 (d, J = 5.0 Hz, 2H), 8.05 (m, 2H), 7.69 (t, J = 7.8 Hz, 1H), 7.64−7.60 (m, 2H), 7.55 (d, J = 7.9 Hz, 2H), 6.90−6.86 (m, 2H), 4.46−4.40 (m, 4H), 4.07 (s, 2H), 1.38 (s, 9H); $^{13}C\{^1H\}$ NMR (CD_3CN, 100 MHz) δ 185.8, 163.1, 156.8, 151.6, 149.2, 142.6, 142.1, 126.5, 125.9, 123.7, 113.0, 58.4, 58.2, 42.3, 29.4 (15 signals expected and observed); FTIR (KBr, cm^{-1}, 1800−1400 cm^{-1} region and ClO_4^- vibrations) 1610, 1566, 1489, 1458, 1442, 1420, 1397, 1375, 1358, 1305, 1092 (ν_{ClO_4}), 623 (ν_{ClO_4}); FTIR (CH_3CN-CH_3OH, 5:3; cm^{-1}, 1800−1550 cm^{-1} region) 1611, 1568. Anal. Calcd for $C_{23}H_{26}N_5O_5ClZn$: C, 50.08; H, 4.75; N, 12.70. Found: C, 49.66; H, 4.77; N, 12.51.

Treatment of [(ppbpa$^-$)Zn]ClO_4 (3) with CD_3CN-CD_3OD Resulting in Amide Alcoholysis. Treatment of an isolated sample of **3** with CD_3CN-CD_3OD (5:3) for ~30 min at 65(1) °C results in the formation of the products of amide alcoholysis, as previously described starting from **1**$(ClO_4)_2$.

NMR Kinetic Studies of the Amide Alcoholysis Reactions of 1$(ClO_4)_2$. Rates of the amide alcoholysis reaction starting from **1**$(ClO_4)_2$ in CD_3CN-CD_3OD were measured by ^1H NMR spectroscopy by monitoring the decrease in intensity of the *tert*-butyl methyl resonance of the deprotonated amide species [(ppbpa$^-$)Zn]ClO_4 (**3**) at 1.38 ppm as a function of time. A typical NMR sample for kinetic studies was prepared by dissolving ~10−15 mg of **1**$(ClO_4)_2$ in CD_3CN containing 1 equiv of the internal standard triphenylmethane. To this solution was added a CD_3OD solution of $Me_4NOH{\cdot}5H_2O$ (1 equiv). Following this addition, the tube was shaken vigorously for ~20−30 s. The NMR tube was then placed in a themostated probe of a JEOL GSX-270 MHz NMR spectrometer, and data were collected at regular intervals. For each spectrum acquired, the singlet proton resonance of triphenylmethane at 5.59 ppm was set to one proton. The concentration of [(ppbpa$^-$)Zn]ClO_4 (**3**) was then obtained by integration of the 1.38 ppm resonance. No variation in the total zinc complex concentration versus internal standard was observed over time, and no species other than **3** and amide alcoholysis products was detected. Pseudo-first-order rate constants (Table 1) were determined from slopes of plots of ln $[\mathbf{3}]_t$ versus time. Data included in these plots represent >3 half-lives, and typical correlation coefficients for these plots were ≥0.997. All kinetic experiments for construction of an Eyring plot were carried out in triplicate. Second-order rate constants were determined from pseudo-first-order constants using the known concentration of CD_3OD present.[24] A first-order dependence on **3** of the rate-

(22) Yamaguchi, S.; Wada, A.; Funahashi, Y.; Nagatomo, S.; Kitagawa, T.; Jitsukawa, K.; Masuda, H. *Eur. J. Inorg. Chem.* **2003**, 4378−4386.
(23) Rivas, J. C. M.; Salvagni, E.; de Rosales, R. T. M.; Parsons, S. *Dalton Trans.* **2003**, 3339−3349.

determining step for the amide alcoholysis reaction was elucidated by variation of the initial concentration of **1**$(ClO_4)_2$ from 0.0023 to 0.024 M in the presence of at least 10 equiv of CD_3OD, which produced no change in observed pseudo-first-order rate constant. A first-order dependence on methanol of the rate-determining step of the amide alcoholysis of **1**$(ClO_4)_2$ was determined by variation of the CD_3OD concentration from 0.21 to 15.39 M (Table 1).

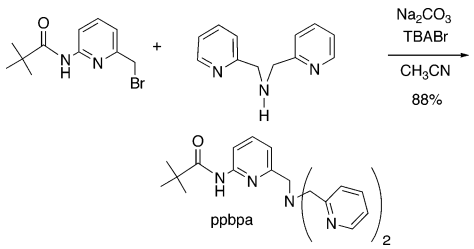
Treatment of 1$(ClO_4)_2$ with CD_3CN-CD_3OH (25:1): Isotope Experiment. Treatment of **1**$(ClO_4)_2$ (11 mg, 0.017 mmol) with $Me_4NOH{\cdot}5H_2O$ (3.0 mg, 0.017 mmol) in CD_3CN-CD_3OH (25:1; CD_3OH, 99.5% (ACROS)) followed by monitoring of the amide alcoholysis reaction by ^1H NMR yielded a pseudo-first-order rate constant of $1.01(4) \times 10^{-4}$ s^{-1}. This rate constant is identical with that obtained ($1.04(7) \times 10^{-4}$ s^{-1}) for a related reaction performed with CD_3CN-CD_3OD (25:1).

Treatment of [(ppbpa$^-$)Zn]ClO_4 (3) with $CD_3CN-CD_3CD_2OD$ (3.5:4.5) Yields Amide Ethanolysis. Preparation of **3** in CH_3CN, followed by removal of the solvent under reduced pressure for 10 h at ambient temperature and treatment with $CD_3CN-CD_3CD_2OD$ (3.5:4.5) for ~80 min at 65(1) °C, results in the formation of 1 equiv of ethyl trimethylacetate (*tert*-butyl methyl ^1H resonance at 1.18 ppm) and a mixture of zinc complexes of the ambpa ligand (not characterized). The pseudo-first-order rate constant for this reaction is $4.85(9) \times 10^{-4}$ s^{-1}.

***N*-((6-Acetamido-2-pyridyl)methyl)-*N*,*N*-bis((2-pyridyl)methyl)-amine (apbpa).** To a 100 mL round-bottom flask placed in a water/ice bath was added *N*-((6-amino-2-pyridyl)methyl)-*N*,*N*-bis((2-pyridyl)methyl)amine (ambpa) (0.311 g, 1.02 mmol), NEt_3 (0.124 g, 1.22 mmol), and CH_2Cl_2 (15 mL). After establishment of an N_2 atmosphere, acetyl chloride (0.096 g, 1.22 mmol) was added dropwise and the reaction mixture was stirred at ambient temperature for ~2 h. At this time, an equal volume of 1 M NaOH was added (~15 mL) and the entire solution was extracted with methylene chloride (3 × 20 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and brought to dryness by rotary evaporation. The resulting yellow oil was purified by column chromatography on silica gel (230−400 mesh, methanol, $R_f \sim 0.8$) to yield a yellow solid (0.313 g, 89%): ^1H NMR (CD_3CN, 400 MHz) δ 8.87 (br s, 1H, N-*H*), 8.45 (d, $J = 4.7$ Hz, 2H), 7.96−7.54 (m, 6H), 7.23 (d, $J = 7.5$ Hz, 1H), 7.20−7.14 (m, 2H), 3.80 (s, 4H), 3.68 (s, 2H), 2.11 (s, 3H); $^{13}C\{^1H\}$ NMR (CD_3CN, 100 MHz) δ 170.4, 160.5, 159.0, 152.6, 150.0, 139.2, 137.5, 124.0, 123.9, 119.5, 112.7, 60.9, 60.5, 24.7 (14 signals expected and observed); FTIR (KBr, cm^{-1}) 1684 (amide I); EI-MS [*m*/*z* (relative intensity)] 348 ($[M + H]^+$, 60%).

[(apbpa)Zn](ClO$_4$)$_2$ (4). This was prepared in an manner analogous to that for [(ppbpa)Zn]$(ClO_4)_2$ (**1**$(ClO_4)_2$). Recrystallization of a white powder from diethyl diffusion into a CH_3CN solution yielded a white polycrystalline material (60%): ^1H NMR (CD_3CN, 270 MHz) δ 10.4 (br s, 1H, N-*H*), 8.61 (d, $J = 5.3$ Hz, 2H), 8.14−8.06 (m, 3H), 7.70−7.55 (m, 4H), 7.37 (d, $J = 7.6$ Hz, 1H), 7.27 (d, $J = 8.2$ Hz, 1H), 4.34 (s, 4H), 4.29 (s, 2H), 2.59 (s, 3H); $^{13}C\{^1H\}$ NMR (CD_3CN, 100 MHz) δ 179.6, 156.3, 154.1, 152.4, 149.6, 145.0, 143.1, 126.6, 126.1, 122.3, 116.4, 58.7, 58.3, 25.6 (14 signals expected and observed); FTIR (KBr, cm^{-1}) 3228 (br, ν_{N-H}), 1663, 1655, 1625, 1615, 1577, 1535, 1092 (ν_{ClO_4}), 623 (ν_{ClO_4}); LRFAB-MS (CH_3OH/NBA) [*m*/*z* (relative intensity)] 410 ($[M - H]^+$, 70%). Anal. Calcd for $C_{20}H_{21}N_5O_9Cl_2Zn{\cdot}CH_3CN$: C, 40.61; H, 3.72; N, 12.93. Found: C, 40.64; H, 3.76; N, 12.75. The presence of a molecule of CH_3CN in the analytical sample was confirmed by ^1H NMR.

Scheme 3



NMR Kinetic Studies of the Amide Alcoholysis Reactions of 4. An approach identical with that employed for kinetic studies of **1**$(ClO_4)_2$ was used to obtain the pseudo-first-order rate constant for the alcoholysis of **4** upon treatment with $Me_4NOH{\cdot}5H_2O$ in CD_3CN-CD_3OD (3:5) at 328 K.

X-ray Crystallography. A crystal of **1**$(ClO_4)_2$ was mounted on a glass fiber with traces of viscous oil and then transferred to a Nonius KappaCCD diffractometer with Mo Kα radiation (λ = 0.710 73 Å) for data collection at 150(1) K. An initial set of cell constants was obtained from 10 frames of data that were collected with an oscillation range of 1 deg/frame and an exposure time of 20 s/frame. Indexing and unit cell refinement based on observed reflections from those 10 frames indicated a triclinic *P* lattice for **1**. Final cell constants were determined from a set of strong reflections from the actual data collection. These reflections were indexed, integrated, and corrected for Lorentz, polarization, and absorption effects using DENZO-SMN and SCALEPAC.[25] The structure was solved by a combination of direct methods and heavy atoms using SIR 97. All of the non-hydrogen atoms were refined with anisotropic displacement coefficients. Hydrogen atoms were assigned isotropic displacement coefficients $U(H) = 1.2U(C)$ or $1.5U(C_{methyl})$, and their coordinates were allowed to ride on their respective carbons using SHELXL97.[26]

Structure Solution and Refinement. The mononuclear zinc complex **1**$(ClO_4)_2$ crystallizes in the space group $P\bar{1}$. One noncoordinated acetonitrile molecule is present/formula unit. One perchlorate anion exhibits disorder in the positions of two oxygen atoms (O(4) and O(5)). These atoms were each split into two fragments, with the second being denoted by a prime, and were refined. This led to a 0.74:0.26 ratio in occupancy over two positions for each oxygen atom.

Results

Synthesis of 1$(ClO_4)_2$ and 1$(OTf)_2$. The N_4O-donor chelate ligand ppbpa (*N*-((6-(pivaloylamido)-2-pyridyl)methyl)-*N*,*N*-bis((2-pyridyl)methyl)amine was prepared in high yield (88%) as shown in Scheme 3 via a synthetic pathway that has not been previously reported. The ligand was isolated following column chromatography on silica gel as a yellow-brown solid. Treatment of ppbpa with $Zn(ClO_4)_2{\cdot}6H_2O$ in methanol solution, followed by recrystallization, yields [(ppbpa)Zn]$(ClO_4)_2$ (**1**$(ClO_4)_2$), as a crystalline solid. To perform large scale reactivity studies, a triflate analogue of **1**$(ClO_4)_2$, [(ppbpa)Zn]$(OTf)_2$ (**1**$(OTf)_2$), was generated via treatment of the ppbpa ligand with $Zn(OTf)_2$ in methanol.

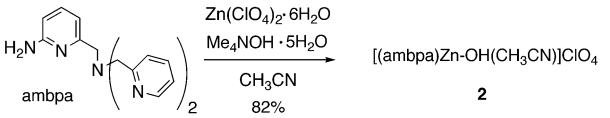
X-ray Crystallographic Studies of 1$(ClO_4)_2$. Crystals suitable for single-crystal X-ray crystallography were obtained for **1**$(ClO_4)_2$ via diethyl ether diffusion into a CH_3-

(24) Wilkins, R. G. *Kinetics and Mechanism of Reactions of Transition Metal Complexes*, 2nd ed.; VCH Publishers: New York, 1991.

(25) Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307−326.

(26) Sheldrick, G. M. *SHELXL-97, Program for the Refinement of Crystal Structures*; University of Göttingen: Göttingen, Germany, 1997.

Scheme 4



$CN-CH_3OH$ (1:1) solution of the complex. A summary of the data collection parameters and selected bond distances and angles for this complex are given in Tables S1 and S2. An ORTEP representation of the cationic portion of **1**$(ClO_4)_2$ is given in Figure S1. The zinc center exhibits a distorted trigonal bipyramidal geometry ($\tau = 0.77$).[27] The Zn−N and Zn−O bond lengths and angles in **1**$(ClO_4)_2$ are identical within experimental error with those exhibited by the hexafluorophosphate analogue ([(ppbpa)Zn]$(PF_6)_2$, **1**$(PF_6)_2$).[13]

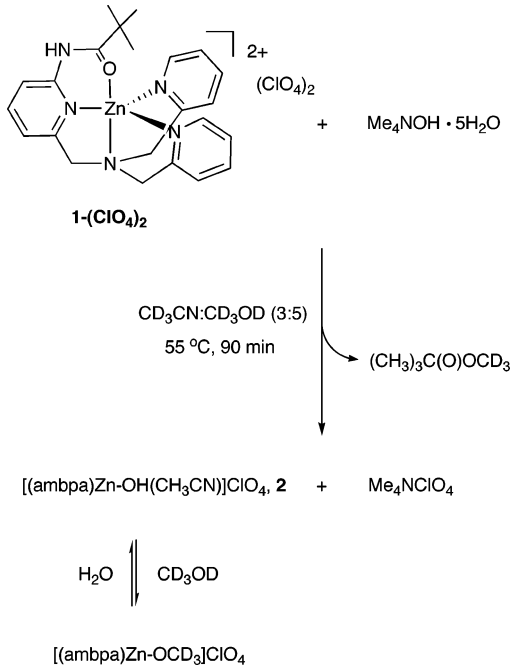
Spectroscopic Characterization of 1$(ClO_4)_2$ and 1-$(OTf)_2$. In the solid-state infrared spectrum of **1**$(ClO_4)_2$, amide vibrations are present in a broad feature in the region of 1665−1600 cm^{-1}. Overlapping the low energy portion of this region is a pyridyl ring vibration at ∼1615 cm^{-1}. Though the amide-related vibrations in this region have not been definitively assigned due to peak overlap, amide oxygen coordination is clearly evident for **1**$(ClO_4)_2$ in the solid state. Specifically, no vibration is found at ∼1680 cm^{-1}, whereas for the free ppbpa ligand the amide carbonyl stretching vibration is found at 1683 cm^{-1}.

The ^1H and ^{13}C NMR features of **1**$(ClO_4)_2$ have been discussed in detail in the literature.[13] As expected, the NMR properties of [(ppbpa)Zn]$(OTf)_2$ (**1**) are similar.

Amide Cleavage Reactivity of 1$(ClO_4)_2$ and 1$(OTf)_2$. Identification of Reaction Products. In a CD_3CN-CD_3OD solvent mixture, in the presence of 1 equiv of $Me_4NOH\cdot 5H_2O$, over the course of ∼1.5 h at 55(1) °C, complexes **1**$(X)_2$ ($X = ClO_4^-$, OTf^-) undergo alcoholysis of the *tert*-butyl amide moiety to yield quantitatively 1 equiv each of Me_4NClO_4 and methyl trimethylacetate and a mixture of two zinc complexes of the primary amine-appended chelate ligand (ambpa). The Me_4NClO_4 salt was isolated from the reaction mixture in 77% yield and was found to exhibit infrared spectroscopic properties identical with those of a commercially available sample of this perchlorate salt. The methyl trimethylacetate product was identified and quantified by ^1H NMR. It is important to note that the **1**$(X)_2$ complexes *do not* undergo amide methanolysis in the absence of added base (e.g. $Me_4NOH\cdot 5H_2O$). Furthermore, control studies have indicated that ppbpa ligand methanolysis using $Me_4NOH\cdot 5H_2O$ in methanol (without Zn(II)) is ∼130 times slower than the reaction of **1**$(ClO_4)_2$.[15]

Full identification of the zinc complexes produced in the amide alcoholysis reaction of **1**$(ClO_4)_2$ required the independent synthesis of [(ambpa)ZnOH$(CH_3CN)]ClO_4$ (**2**, Scheme 4) and examination of its reactivity with methanol. Complex **2** was produced via treatment of the isolated primary amine-appended ambpa (*N*-((6-amino-2-pyridyl)methyl)-*N*,*N*-bis-((2-pyridyl)methyl)amine) ligand (vide infra) with equimolar amounts of $Zn(ClO_4)_2\cdot 6H_2O$ and $Me_4NOH\cdot 6H_2O$ in acetonitrile solution and has been characterized by ^1H and ^{13}C NMR, FTIR, and elemental analysis. Although the nuclearity of **2** in the solid state and solution has not yet been determined, the ^1H NMR spectral properties of **2** in CD_3CN are identical with that observed for one of the two final zinc products of the amide alcoholysis reaction of **1**$(ClO_4)_2$. Specifically, the presence of two doublets at 6.8 and 6.7 ppm, respectively, exactly match the chemical shift positions of 2-aminopyridyl ring protons of **2**.

Scheme 5



The second zinc-containing product produced in the amide alcoholysis reaction of **1**$(ClO_4)_2$ similarly contains the ambpa ligand, as evidenced by ligand recovery studies (vida infra). On the basis of solution ^1H NMR studies of **2** in CD_3OD solution, coupled with the fact that the amide alcoholysis reaction of **1**$(ClO_4)_2$ is performed in methanol-containing solution, we propose that the second product is a zinc methoxide complex of the ambpa ligand. The formation of a zinc hydroxide/methoxide mixture is consistent with a previous study of the methanol reactivity of a zinc hydroxide complex of a chelate ligand having internal hydrogen bond donors.[21]

Formation of the primary amine ligand product (ambpa) in the amide alcoholysis reaction of **1**$(ClO_4)_2$ was further confirmed by performing a large scale ligand recovery experiment using **1**$(OTf)_2$. Specifically, to a CH_3OH solution of **1**$(OTf)_2$ was added a CH_3OH solution of $Me_4NOH\cdot 5H_2O$ and the resulting reaction mixture was heated for 48 h at 40(1) °C. After cooling of the reaction mixture to ambient temperature, the zinc ion was removed using sodium cyanide and the primary amine-appended ambpa ligand was isolated (80% yield) and characterized (^1H, ^{13}C, FTIR, HREIMS).

On the basis of these product identification studies, the overall reaction for the amide alcoholysis of **1**$(ClO_4)_2$ can be written as shown in Scheme 5. The formation of the zinc hydroxide/methoxide mixture in this amide alcoholysis

(27) Addison, A. W.; Rao, T. N.; Reedijk, J.; van Rijn, J.; Verschoor, G. C. *J. Chem. Soc., Dalton Trans.* **1984**, 1349−1356.

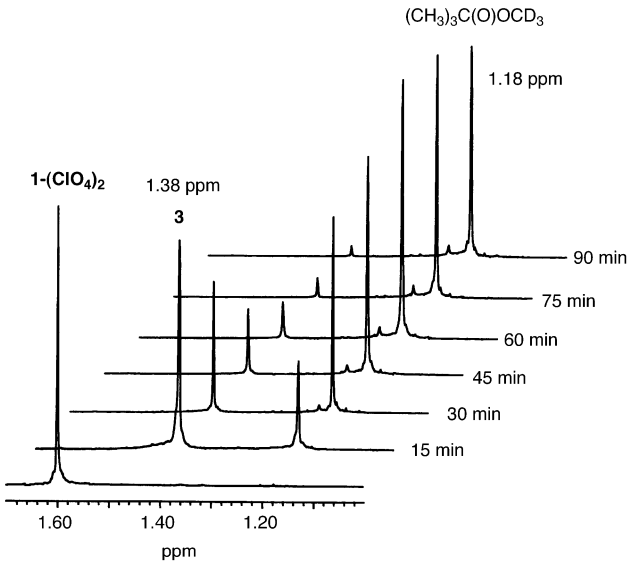


Figure 1. ^{1}H NMR spectroscopic changes observed over the time increments indicated following treatment of **1**$(ClO_4)_2$ with an equimolar amount of $Me_4NOH{\cdot}5H_2O$ in CD_3CN-CD_3OD (3:5) at 328 K.

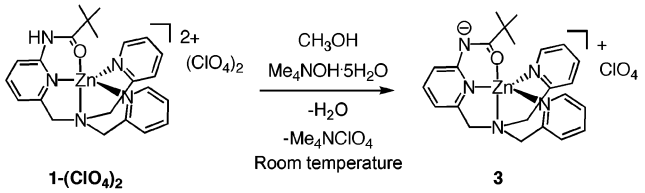
reaction results from the presence of both methanol and water (from $Me_4NOH{\cdot}5H_2O$) in the solution.[21,28]

Isolation and Characterization of the Deprotonated Amide Species [(ppbpa$^-$)Zn]ClO_4 (3). Treatment of **1**$(ClO_4)_2$ with $Me_4NOH{\cdot}5H_2O$ in CD_3CN-CD_3OD (3:5) solution initially produces a single zinc complex with a *tert*-butyl methyl resonance at 1.38 ppm. This chemical shift is upfield of that of **1**$(ClO_4)_2$ (1.54 ppm) under identical conditions. After few minutes, a second *tert*-butyl methyl resonance (1.18 ppm) for the methyl trimethylacetate product appears. The former resonance then reduces in integrated intensity while the latter resonance increases in intensity as the reaction proceeds (Figure 1). At the end of the reaction, the only *tert*-butyl methyl resonance present is for methyl trimethylacetate at 1.18 ppm.

To better understand the chemical properties of the species having a *tert*-butyl methyl proton resonance at 1.38 ppm, we isolated this complex from the reaction mixture. Treatment of 1 equiv of **1**$(ClO_4)_2$ with an equimolar amount of $Me_4NOH{\cdot}5H_2O$ in methanol results in the precipitation of 1 equiv of Me_4NClO_4, which occurs within approximately 2 min after the addition of $Me_4NOH{\cdot}5H_2O$. Filtration of the reaction mixture through a glass wool/Celite plug and evaporation of the solvent from the filtrate yielded the single clean complex, **3**, which has been characterized by elemental analysis, ^{1}H and ^{13}C NMR, and FTIR. Despite repeated attempts, a crystalline sample of **3** suitable for single-crystal X-ray crystallography has not yet been obtained.

The combustion analysis of **3** is consistent with the empirical formula required for formation of a deprotonated amide derivative ([(ppbpa$^-$)Zn]ClO_4 (**3**, Scheme 6)). The proposal of **3** as having a deprotonated amide moiety is supported by spectroscopic studies. Specifically, whereas a N−H resonance is present in the ^{1}H NMR spectrum of

Scheme 6



1$(ClO_4)_2$ at 9.53 ppm, no N−H resonance is observed for **3** under identical conditions in dry CD_3CN. In addition, the chemical shift positions of several proton resonances of the ppbpa ligand of **3** are upfield relative to the same resonances in **1**$(ClO_4)_2$. For example, large upfield shifts (∼0.4−0.6 ppm) are observed for the β-protons of the amide-appended pyridine ring in **3**. This indicates an increase in the electron density within this pyridyl ring, consistent with delocalization of the deprotonated amide anionic charge into the heterocyclic ring. Resonance structures for **3** are shown in Scheme 7. The delocalization of anionic charge density into the pyridyl ring in structures C and D explains the upfield shift of the protons attached to the β-carbons. Upfield shifts for the other protons of the ppbpa ligand in **3** are considerably smaller (∼0.06−0.20 ppm).

In the ^{13}C NMR spectrum of the free ppbpa ligand, the amide carbonyl carbon resonance is found at 179.5 ppm. For **1**$(ClO_4)_2$ the signal is observed at 187.5 ppm, and in **3**, the amide carbonyl carbon resonance is found at 185.8 ppm, indicating a subtle change in the electron density at this carbon center relative to that in **1**$(ClO_4)_2$.

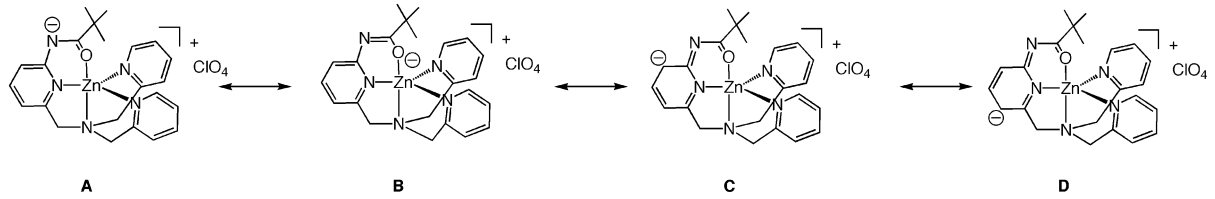
Features of the solid-state infrared spectrum of **3** also support the presence of a deprotonated amide moiety in this complex. Specifically, while a ν_{N-H} vibration is readily apparent for **1**$(ClO_4)_2$ at ∼3320 cm^{-1}, a similar vibration is not found in the solid-state infrared spectrum of **3**. In addition, as shown in Figure 2, the ν_{CO} vibration of **1**$(ClO_4)_2$ (∼1647 cm^{-1}) is missing in the spectrum of **3**. These results, combined with the ^{1}H and ^{13}C NMR differences between **1**$(ClO_4)_2$ and **3**, suggest that the electonic structure of the deprotonated amide species involves contributions from resonance structures C and D, along with structure B (Scheme 6), wherein the anionic charge is located on the zinc-coordinated oxygen atom.

Identification of 3 as an Intermediate in the Amide Methanolysis Reaction of 1$(ClO_4)_2$. Heating of an analytically pure sample of **3** in a mixed CD_3CN-CD_3OD solution at 55(1) °C for ∼90 min results in the formation of 1 equiv of methyl trimethylacetate and the mixture of zinc complexes described in Scheme 5. Thus, **3** is produced stoichiometrically as an intermediate in the reaction pathway leading to amide cleavage for **1**$(ClO_4)_2$.

Kinetic Studies of the Amide Methanolysis Reaction of 1$(ClO_4)_2$. Rate data for the amide methanolysis reaction observed upon treatment of **1**$(ClO_4)_2$ with $Me_4NOH{\cdot}5H_2O$ in a CD_3CN-CD_3OD solution was collected by ^{1}H NMR spectroscopy by monitoring the decrease in the intensity of the *tert*-butyl methyl resonance of the deprotonated amide intermediate [(ppbpa$^-$)Zn]ClO_4 (**3**) at 1.38 ppm as a function of time at a specific temperature. Pseudo-first-order rate

(28) Bergquist, C.; Storrie, H.; Koutcher, L.; Bridgewater, B. M.; Friesner, R. A.; Parkin, G. *J. Am. Chem. Soc.* **2000**, *122*, 12651−12658.

Scheme 7



constants (Table 1) were determined from slopes of plots of ln $[\mathbf{3}]_t$ versus time. A typical correlation coefficient for the first-order plot was ≥0.997. Second-order rate constants were determined from pseudo-first-order constants using the known concentration of CD_3OD present.[24] Importantly, the observed pseudo-first-order rate constant for amide alcoholysis starting from isolated, analytically pure **3** (k_{obs} = 1.17 × 10^{-4} s^{-1} (450 equiv of CD_3OD)) is within experimental error of the average rate constant obtained starting from **1**$(ClO_4)_2$ (k_{obs} = 1.04(7) × 10^{-4} s^{-1} (450 equiv of CD_3OD)) providing further evidence that **3** is an intermediate produced prior to the rate-determining step of the amide methanolysis reaction.

A first-order dependence on intermediate **3** (and therefore **1**$(ClO_4)_2$) of the rate-determining step for the amide alcoholysis reaction was determined by variation of the initial concentration of **1**$(ClO_4)_2$ from 0.0023 to 0.024 M in the presence of at least 10 equiv of CD_3OD. A first-order dependence on methanol of the rate-determining step of the amide alcoholysis of **1**$(ClO_4)_2$ was determined by variation of the CD_3OD concentration from 0.21 to 15.39 M. A plot of the CD_3OD concentration versus k_{obs} for the amide methanolysis reaction of **1**$(ClO_4)_2$ is shown in Figure 3. The linear nature and zero intercept of this plot indicates that the amide methanolysis reaction is second-order overall.[24]

Using rate data obtained for the temperature range of 24−65 °C, an Eyring plot was constructed (Figure 4), which yielded $\Delta H^{\ddagger}$ = 15.0(3) kcal/mol and $\Delta S^{\ddagger}$ = −33(1) eu.

Kinetic Studies of the Methanolysis of 1$(ClO_4)_2$ with CD_3OH. The pseudo-first-order rate constant for the amide methanolysis of **3** in CD_3CN-CD_3OH (25:1, 99.5% CD_3OH) was found to be 1.01(4) × 10^{-4} s^{-1}, identical within experimental error with the rate constant observed in CD_3CN-CD_3OD (25:1) solution (k_{obs} = 1.04(7) × 10^{-4} s^{-1}). This result indicates that proton transfer involving methanol is not involved in the rate-determining step of the amide methanolysis reaction.

Ethanolysis of 3. Treatment of **3** with $CD_3CN-CD_3CD_2OD$ (3.5:4.5 (450 eqiuv of CD_3CD_2OD)) for ∼80 min at 65(1) °C results in the formation of 1 equiv of ethyl trimethylacetate (*tert*-butyl methyl ^1H resonance at 1.18 ppm) and a mixture of zinc complexes of the ambpa ligand similar to those found for the amide methanolysis reaction (Scheme 5). The pseudo-first-order rate constant for this reaction is 4.85(9) × 10^{-4} s^{-1}. The ethanolysis reaction of **1**$(ClO_4)_2$ was also investigated using 45 equiv of CD_3CD_2OD in CD_3CN. The k_{obs} value for this reaction was 4.05(1) × 10^{-5} s^{-1}. Both measurements indicate that the rate of amide ethanolysis is just under 2-fold slower than the analogous methanolysis reaction. These results provide a preliminary indication that the alcoholysis reactivity of **3** depends on the steric properties of the alcohol.

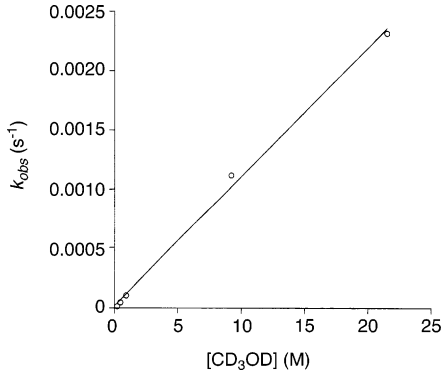


Figure 3. Pseudo-first-order rate constant k_{obs} as a function of CD_3OD concentration for the reaction of **1**$(ClO_4)_2$ with five different concentrations of CD_3OD.

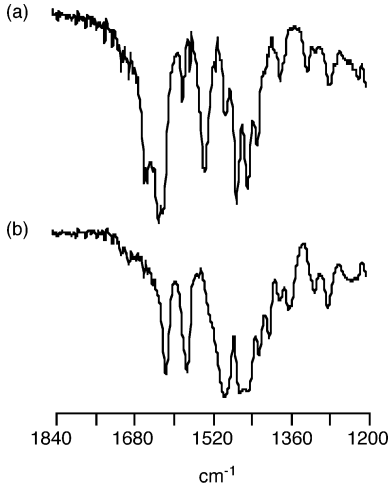


Figure 2. Features in the ∼2000−1200 cm^{-1} range of the solid state (KBr) infrared spectra of (a) **1**$(ClO_4)_2$ and (b) [(ppbpa$^-$)Zn]ClO_4 (**3**).

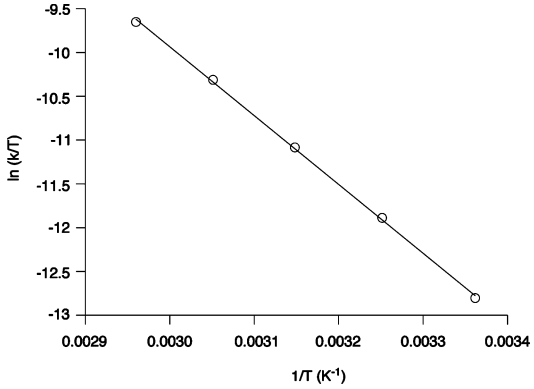
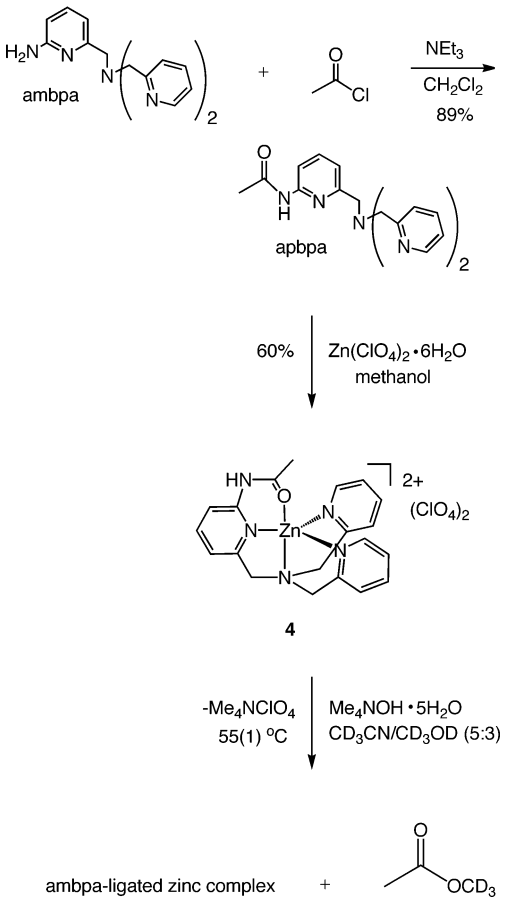


Figure 4. Eyring plot for the amide alcoholysis of reaction of **1**$(ClO_4)_2$.

Scheme 8



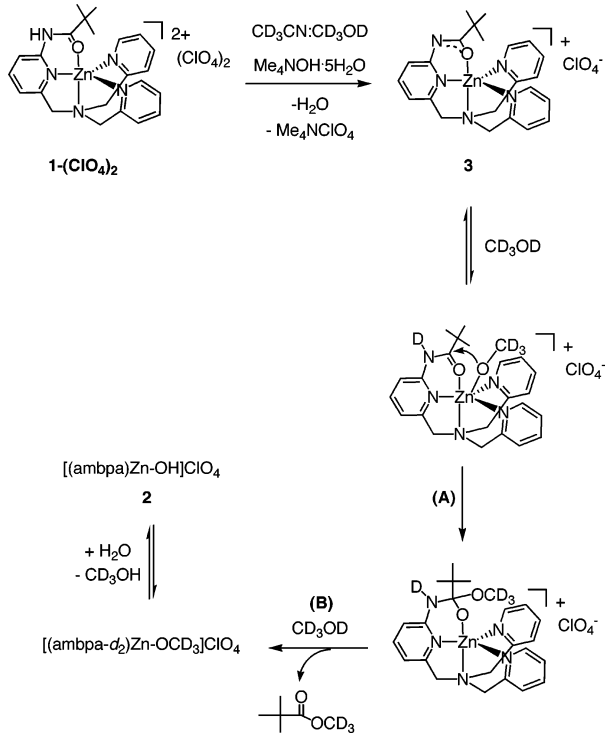
Structural Modification of the Amide Substrate. To evaluate the influence of amide steric hindrance on the rate of amide alcoholysis, a new methyl amide-appended chelate ligand, apbpa (*N*-((6-acetamido-2-pyridyl)methyl)-*N*,*N*-bis-((2-pyridyl)methyl)amine), was constructed as shown in Scheme 8. Treatment of the apbpa ligand with $Zn(ClO_4)_2 \cdot 6H_2O$ in methanol, followed by recrystallization from CH_3CN-Et_2O, yielded the polycrystalline $[(apbpa)Zn](ClO_4)_2 \cdot CH_3CN$ (**4**, Scheme 8) in 60% yield.

Treatment of **4** with an equimolar amount of $Me_4NOH \cdot 5H_2O$ in CD_3CN-CD_3OD (3:5) at 55(1) °C in an NMR tube immediately produces a set of ^1H NMR resonances consistent with the formation of a deprotonated intermediate, the signals of which quickly decay to give a new set of resonances that correspond to the previously proposed zinc methoxide product, $[(ambpa)Zn(OCD_3)]ClO_4$. A new methyl resonance for the methyl acetate being produced in this reaction was observed at 1.97 ppm, which matches that found for an authentic sample of the ester.

The intermediate produced upon treatment of **4** with $Me_4NOH \cdot 5H_2O$ has upfield-shifted aromatic and methyl resonances relative to the starting material. The magnitude of these shifts is similar to those found for the conversion of $\mathbf{1}(ClO_4)_2$ to **3**. For example, whereas the methyl resonance of **4** is found at 2.75 ppm in CD_3CN-CD_3OD (3:5), for the intermediate this signal is located at 2.35 ppm.

The pseudo-first-order rate constant for amide methanolysis of **4** is $5.0(2) \times 10^{-3}$ s^{-1}, which is 1 order of magnitude faster than the analogous reaction involving $\mathbf{1}(ClO_4)_2$.

Scheme 9



Proposed Mechanism of Amide Alcoholysis. These combined kinetic and mechanistic studies provide insight into the pathway of the amide methanolysis for $\mathbf{1}(ClO_4)_2$. Treatment of this zinc complex with $Me_4NOH \cdot 5H_2O$ in CD_3CN-CD_3OD solution initially results in the formation of the deprotonated amide intermediate **3**, which has been isolated from the reaction mixture and fully characterized. Kinetic analysis of amide methanolysis reactions of analytically pure $\mathbf{1}(ClO_4)_2$ or **3** in CD_3CN-CD_3OD solutions yields identical rate constants within experimental error, indicating that **3** is an intermediate produced prior to the rate-determining step of the reaction. The amide alcoholysis reaction is first-order in **3** (and therefore $\mathbf{1}(ClO_4)_2$) and first-order in methanol, thus yielding an overall second-order reaction. The activation parameters for this reaction ($\Delta H^{\ddagger} = 15.0(3)$ kcal/mol, $\Delta S^{\ddagger} = -33(1)$ eu) are similar to parameters reported by Groves and co-workers for a Zn(II)-mediated intramolecular amide hydrolysis reaction ($\Delta H^{\ddagger} = 22$ kcal/mol, $\Delta S^{\ddagger} = -18$ eu) involving a zinc-coordinated hydroxide as the nucleophile.[11] On this basis, we propose a mechanistic pathway for amide alcoholysis in $\mathbf{1}(ClO_4)_2$ as shown in Scheme 9. In this pathway, following formation of the deprotonated amide intermediate **3**, a rapid, reversible protonation step involving solvent is proposed to yield a structure having both amide and methoxide-d_3 nucleophile coordination to the zinc center. Attack of the nucleophile at the amide carbonyl carbon (step (A)) or breakdown of the resulting tetrahedral intermediate (step B) may be the rate-determining step in this system.[29] The observed lack of a solvent isotope effect in the alcoholysis of **3** in the presence of CD_3OH (vs CD_3OD) indicates that proton transfer from methanol does not occur during the rate-determining step.

(29) Sayre, L. M. *J. Am. Chem. Soc.* **1986**, *108*, 1632−1635.

Combined with additional preliminary kinetic studies with an alcohol of increased steric hindrance (ethanol-d_6) or an amide substrate of reduced steric hindrance ($-NC(O)CH_3$ in **4**), which indicate that steric properties of both the nucleophilic and electrophilic components of the reaction influence the rate of amide methanolysis, we currently favor rate-determining nucleophilic attack (step A) in this system.

Regarding the proposed mechanism in Scheme 9, if a rapid equilibrium protonation step involving CD_3OD does occur prior to the rate-determining step, saturation-type behavior could be expected in terms of the CD_3OD concentration.[24] However, as shown in Figure 3, the pseudo-first-order rate constant for the alcoholysis of **1**$(ClO_4)_2$ corresponds linearly to the concentration of CD_3OD up to a concentration of ~22 M CD_3OD in CD_3CN. While we cannot currently provide a rationale for the lack of observed saturation behavior in this system, we have identified saturation-type behavior for an amide methanolysis reaction in structurally similar chelate ligand system.[30] In this amide cleavage reaction, a deprotonated amide intermediate is produced similar to the reaction outlined herein.

Finally, it is important to note that **3** is the only spectroscopically identifiable species produced prior to amide cleavage in the methanolysis reaction of **1**$(ClO_4)_2$ (Figure 2). Thus, the proposed protonation equilibrium involving CD_3OD must lie far toward **3**. This may be possible in that **3** contains a resonance stabilized anion (Scheme 7), which could significantly lower the pK_a for the anilido-type amide NH moiety relative to the pK_a of CH_3OH (15.1).[31]

Discussion

Following our discovery of amide cleavage reactivity in the N_2S_2O-ligated zinc complex shown in Scheme 1a, we became interested in the mechanistic pathway of this reaction.[12] Our interest was advanced by reports from another laboratory wherein a structurally related compound was reported to undergo *both* amide deprotonation and alcoholysis, albeit conclusive characterization of both reactions was lacking.[13,15] As no explanation of the relationship of these two reactions was provided,[13,15] we decided to try to isolate the proposed deprotonated amide species and determine whether this complex was involved in the reaction pathway leading to amide cleavage. Our studies outlined herein demonstrate that [(ppbpa$^-$)Zn]ClO_4 (**3**) is an intermediate that is formed stoichiometrically from the reaction of **1**$(ClO_4)_2$ with $Me_4NOH{\cdot}5H_2O$ prior to the rate-determining step of the amide methanolysis reaction.

The reactivity of deprotonated amide species **3** is interesting in that metal complexes of a deprotonated amide ligand typically involve M$-$*N*(amide) coordination and are unreactive in regard to amide cleavage.[32] For example, Martin and co-workers have reported studies of the amide cleavage reactivity of a Cu(II)-coordinated glycinamide (Scheme 10). At low pH, where the amide is neutral, protonated, and

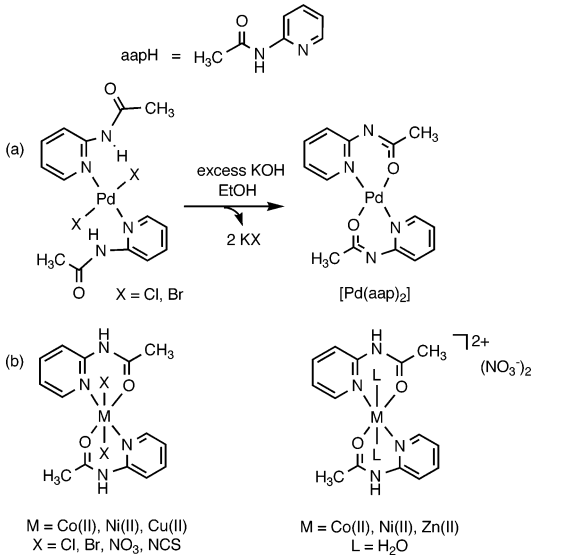
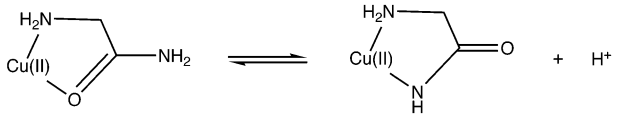


Figure 5. Metal complexes of the aap$^-$ and aapH ligands.

Scheme 10



O-coordinated, the presence of the Cu(II) ion promotes the amide hydrolysis reaction. However, at high pH, amide cleavage reactivity is inhibited due to amide deprotonation and copper coordination of the anionic amide nitrogen.

Significant literature precedent exists to support the notion that deprotonation of the amide N$-$H moiety of **1**$(ClO_4)_2$ can occur to yield **3** having O-coordination. For example, the amide oxygen binding properties of the deprotonated form of *N*-(2-pyridyl)acetamide (appH, Figure 5) ligand have been previously described.[33$-$35] In Pd(aap$^-$)$_2$ (Figure 5a), which has been characterized by X-ray crystallography, two deprotonated amide ligands form six-membered chelate rings with amide oxygen coordination to the Pd(II) center.[33] The stabilization of the oxygen-bound deprotonated amides in [Pd(aap$^-$)$_2$] is attributed to an enforced chelate effect and weak basicity of the anilido-type nitrogen. Divalent Zn(II), Co(II), Ni(II), and Cu(II) complexes having neutral appH ligation involving metal coordination of the amide oxygen have also been reported.[34,35] To our knowledge, amide cleavage reactivity has not been reported for any of these aap$^-$/aapH-ligated complexes.

The formation of the deprotonated amide moiety in **3** is also supported by the isolation of a copper complex, [(tppa$^-$)Cu]BPh_4, having a deprotonated amide within the tris(6-(pivaloylamido)-2-pyridyl)methyl)amine ligand (tppa) ligand framework.[36] Comparison of the metrical parameters

(30) Watkins, R. W.; Szajna, E.; Arif, A. M.; Berreau, L. M. Manuscript in preparation.
(31) Murto, J. *Acta Chem. Scand.* **1964**, *18*, 1043$-$1053.
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(33) Scheller-Krattiger, V.; Scheller, K. H.; Sinn, E.; Martin, R. B. *Inorg. Chim. Acta* **1982**, *60*, 45$-$52.
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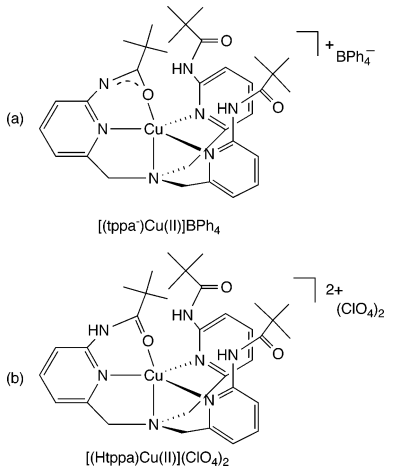

Figure 6. Structural comparison of [(tppa$^-$)Cu]BPh_4 and [(Htppa)Cu(II)]-$(ClO_4)_2$.

of the deprotonated amide unit in [(tppa$^-$)Cu(II)]BPh_4 (Figure 6a) versus the analogous bond distances in a related complex having a neutral, oxygen-coordinated protonated amide moiety, [(Htppa)Cu(II)]$(ClO_4)_2$ (two independent crystal structures reported, Figure 6b),[17,36] reveals differences. As expected, the Cu−O distance is shorter in the deprotonated amide complex by 0.037 Å and the amide C−O bond length is elongated by 0.11 Å. The amide C−N and C_{Ar}−N bond distances are shorter in the deprotonated form by approximately 0.07 and 0.02 Å, respectively. All of these structural perturbations are consistent with the increased anionic character within the deprotonated amide arm of [(tppa$^-$)Cu^{II}]BPh_4 and delocalization of the charge as depicted in the resonance structures of **3** shown in Scheme 7. To date, amide cleavage reactivity for the complexes shown in Figure 6 has not been reported.

Recently, amide alcoholysis reactivity has been reported for an amide-appended (terpyridine)copper complex (Figure 7).[38] Though not comprehensively characterized, a deprotonated amide complex is proposed as the active species for amide methanolysis in this system.

Our efforts are now focused on examining how ligand structural perturbations influence amide cleavage reactivity for mononuclear zinc derivatives. Interestingly, in the N_2S_2O ligated systems (Scheme 1a), an additional species has been identified by ^{1}H NMR to be present in solution with a deprotonated amide complex.[12] Attempts to fully characterize this additional component are currently in progress.

Finally, we have also recently reported that amide cleavage occurs upon treatment of [(bmppa)Hg(ClO_4)]ClO_4 with Me_4-$NOH{\cdot}5H_2O$, indicating that the metal ion may be changed with retention of amide cleavage reactivity.[38] An interesting

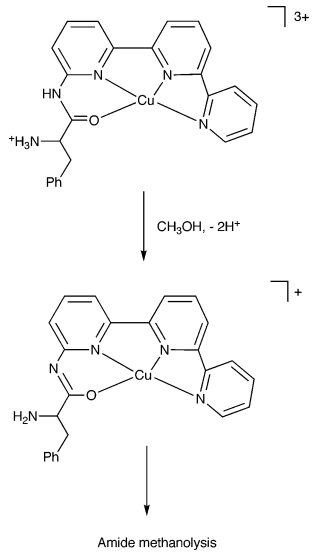

Figure 7. Amide-appended terpyridine complex reported to undergo deprotonation and subsequent amide methanolysis.

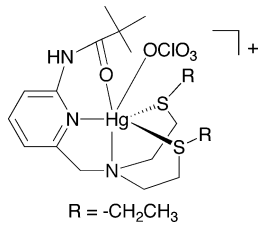

Figure 8. Drawing of the cationic portion of [(beppa)Hg(ClO_4)]ClO_4.

feature of the solid-state structure of [(beppa)Hg(ClO_4)]ClO_4 is a weak perchlorate interaction with the Hg(II) ion (Figure 8). A similar feature has been identified in the X-ray structure of the Cd(II) analogue [(bmppa)Cd(ClO_4)]ClO_4, which is also reactive toward amide cleavage.[12] The weak perchlorate interaction in these heavy group 12 derivatives produces an overall distorted trigonal-prismatic type geometry for each metal center. We hypothesize that this arrangement between coordinated amide and anion may be relevant to the active form of the metal complexes for amide methanolysis, with the anion being methoxide as proposed in Scheme 9. Current efforts are focused on testing this hypothesis via various methods, including probing the impact of chelate ligand structural modifications.

Acknowledgment. This work was supported the National Science Foundation (CAREER Award CHE-0094066). We thank Professor Alvan C. Hengge for helpful discussions.

Supporting Information Available: X-ray crystallographic details (ORTEP drawing and data tables) and a CIF file for **1**$(ClO_4)_2$. This material is available free of charge via the Internet at http://pubs.acs.org.

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