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Cu(II)-Promoted Methanolysis of *N,N*-Dipicolylacetamide. Multistep Activation by Decoupling of >N̈–C═O Resonance via Cu(II)–N Binding, Delivery of the Cu(II):($^-OCH_3$) Nucleophile, and Metal Ion Assistance of the Departure of the Leaving Group

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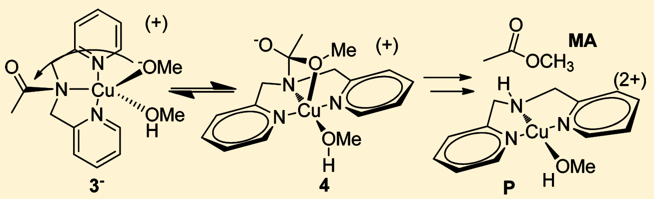
Supporting Information

ABSTRACT: The methanolysis of the Cu(II) complex of *N*-acetyl-*N,N*-bis(2-picolyl)amine (**2**) was investigated by a kinetic study as a function of pH in methanol at 25 °C and computationally by DFT calculations. The active species is the basic form of the complex (3^-), or (**1**:Cu(II))($^-OCH_3$)($HOCH_3$)), and the rate constant for its solvolysis is $k^{max} = 1.5 \times 10^{-4}\ s^{-1}$. The mechanism involves Cu(II) binding to the amide N lone pair, decoupling it from >N–C═O resonance, concomitant with Cu(II):($^-OCH_3$) delivery to the adjacent >N–C═O unit, followed by Cu(II)-assisted departure of the *N,N*-bis(2-picolyl)amide from a tetrahedral intermediate.



Recent studies from these laboratories have delineated the ability of metal ions to promote phosphoryl and acyl transfer from phosphate mono-, di-, and triesters and carboxylic esters and amides to light alcohols such as methanol and ethanol.[1] The ways that metal ions might facilitate such processes have been discussed[2] in terms of: (1) Lewis acid activation of the substrate; (2) intramolecular delivery of a metal-coordinated alkoxide nucleophile; (3) electrostatic stabilization of the transforming substrate–nucleophile species; and (4) assistance of leaving group departure (LGA).[3] The latter mode is particularly important with amides and phosphates where the conjugate acid of the departing group has a high pK_a. Alcoholysis reactions of amides exhibiting strong LGA promoted by metal ions are rare, notable examples being Zn^{2+}- and La^{3+}-ion-catalyzed methanolysis of acetylimidazole,[4] a palladacycle-catalyzed cleavage of thioamides,[5] and a process first described by Houghton and Puttner[6] involving Cu(II)-promoted methanolysis of *N*-acyl derivatives of *N,N*-bis(2-picolyl)amine of the general structure **1**.

Structural and physical aspects of Cu(II) complexes of **1** were reported[7,8] as was the synthetic utility of the M(II)-promoted removal of a bis(2-picolyl)amine protecting group from various derivatives of **1**.[9,10] The catalytic mechanism was reasonably proposed to involve Cu(II) coordination to the pyridine residues that positions the Cu(II) close to the amide nitrogen, which promotes Cu(II) interaction with the N lone pair along with significant pyramidalization.[7] Leckta[11] has reported that the presence of Cu(II) decreases the rotational barrier for dipicolylamides in solution, consistent with a strong interaction between Cu(II) and the N–C═O as in **2** or **3**.

While the available data support the contention that Cu(II) coordination to the amidic nitrogen (at least partly) is responsible for the lability of the >N–C═O bond of Cu(II):**1** in methanol,[7] reliable kinetic data in CH_3OH or CH_3OH/CH_2Cl_2 were not obtained using UV/vis spectroscopy since the absorbance versus time data did not fit any acceptable rate law. In view of: (1) our interest in metal-ion-promoted alcoholysis reactions of amides, esters, and phosphates; (2) the unusual nature of metal-ion-promoted methanolysis of substrates **1** in methanol; and (3) the emerging synthetic utility of the use of a metal-coordinating amide as a protecting group removable under mild conditions,[9,10] we commenced a detailed kinetic study under ^s_spH-controlled[12] conditions supported by DFT computations.

Kinetics Results. Reliable kinetic data are obtained after consideration that **1** binds Cu(II) less strongly than does the bis(2-picolyl)amine product of cleavage. Cu(II):**1** is slightly dissociated in methanol at the small concentrations required for kinetic studies. Thus, first-order kinetic behavior is not obeyed because the dipicolylamine product binds free Cu(II), causing further dissociation of Cu(II):**1** and an overall reduction in its rate of solvolysis. When cleavage of the Cu(II) complex of *N,N*-bis(2-picolyl)acetamide (**2**) was performed in the presence of excess Cu(II) (1–3 mM) in buffered methanol, the absorbance versus time traces follow first-order behavior to at least five halftimes. In methanol, the triflate anions of **2** are dissociated, producing a solvated form such as **3** having one or probably two coordinated methanols at low ^s_spH and a methoxide and (perhaps) one methanol at higher ^s_spH, **3′** as shown later. To account for possible ionic strength and specific salt effects, as well as buffer catalysis, kinetic experiments were performed at two [Cu(II)(triflate)$_2$] and three [buffer]. First-order rate

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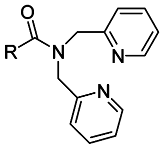
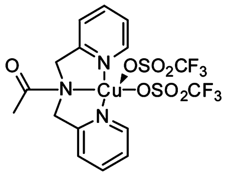


1



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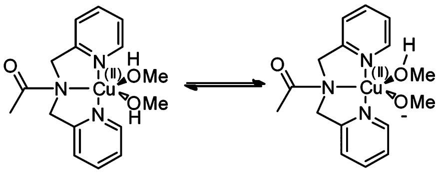


3 $\quad$ **3⁻**

constants (k_{obs}), obtained from NLLSQ fits of the absorbance versus time plots to a standard exponential equation, were extrapolated to zero [buffer] for each [Cu(II)(triflate)$_2$]. These extrapolated k_{obs} values were then used to extrapolate to zero [Cu(II)] to give corrected rate constants (k^{corr}) for the cleavage of **3**/**3**$^-$ at a given ${}_{s}^{s}\text{pH}$. The final log(k^{corr}) versus ${}_{s}^{s}\text{pH}$ profile (Figure 1) comprises a plateau in the ${}_{s}^{s}\text{pH}$ 7−10 region attributable to reaction of **3**$^-$, with a descending wing below ${}_{s}^{s}\text{pH}$ 6.5 due to the formation of the less active or inactive acidic form of the complex, **3**, as in Scheme 1. Product analysis for a completed reaction mixture in CD$_3$OD using ^{1}H NMR demonstrated the formation of methyl acetate (**MA**) as the only observable reaction product,[13] with the signals from the Cu(II):bis(2-picolyl)amine product complex (**P**) not being observed due to paramagnetic broadening.

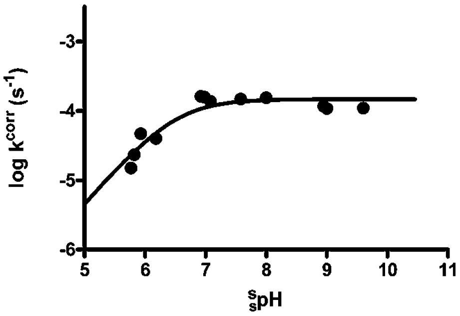


Figure 1. Plot of log(k^{corr}) versus ${}_{s}^{s}\text{pH}$ for the methanolysis of **2** (2×10^{-4} M) in MeOH at 25 °C; fitting the data to eq 1 gives $k^{max} = (1.5 \pm 0.2) \times 10^{-4}$ s^{-1}, and a kinetic ${}_{s}^{s}\text{p}K_a$of 6.5 ± 0.1.

When fitted to eq 1, derived for the simplified process in Scheme 1, the data give $k^{max} = (1.5 \pm 0.2) \times 10^{-4}$ s^{-1} and a kinetic ${}_{s}^{s}\text{p}K_a$ of 6.5 ± 0.1. Half-neutralization experiments give a thermodynamic ${}_{s}^{s}\text{p}K_a$

$$\log(k^{corr}) = \log(k^{max} \times (K_a/([H^+] + K_a))) \qquad (1)$$

for deprotonation of **3** of 6.32 ± 0.07, experimentally identical to the kinetic ${}_{s}^{s}\text{p}K_a$. This ${}_{s}^{s}\text{p}K_a$ is similar to that reported for Cu(OTf)$_2$ in methanol (6.5),[14] which is consistent with this being attributable to deprotonation of a Cu(II)-bound methanol.

Additional information regarding the nature of the transition state is obtained from the solvent deuterium kinetic isotope effect (sdkie) in CD$_3$OD of $k_H/k_D = 0.90$ in at ${}_{s}^{s}\text{pH} = 7.7$. The activation free energy, $\Delta G^{\ddagger}$, at 25.0 °C for cleavage of **3**$^-$, computed from k^{max}, is 22.6 kcal mol^{-1}.

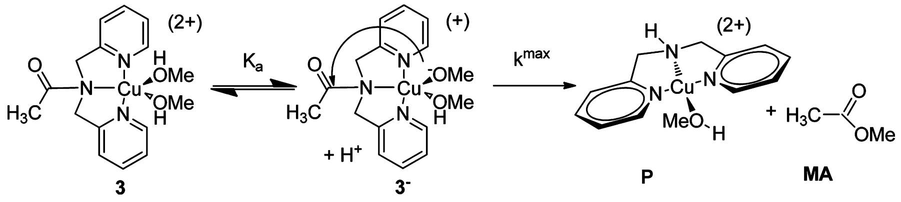
The involvement of a Cu(II)-coordinated methoxide has not previously been proposed for the solvolyses of complexes such as **3**. Its role could be as a general base to deliver CH$_3$OH to the C═O of **3**$^-$ or as a direct intramolecular nucleophile. The observed inverse sdkie of 0.9 does not support the general base mechanism which should exhibit a normal primary dkie of $k_H/k_D > 1$ (often between 2 and 4) arising from a proton in flight between the attacking CH$_3$OH and Cu(II):($^-$OCH$_3$) base. The same is expected for a solvent-assisted delivery of methanol. Large normal sdkie values of $k_H/k_D > 2$ are commonly found for general base-catalyzed processes, whereas direct nucleophilic addition usually involves little or no isotopic distinction[15] unless large secondary effects associated with solvation changes are at play, which is not the case here. We previously demonstrated that processes involving direct nucleophilic attack of metal-ion-bound methoxide on phosphoryl or acyl groups exhibit a near unit, or slightly inverse, sdkie.[16] For the attack of the Zn(II):($^-$OCH$_3$) complex of 1,5,9-triazacyclododecane on *p*-nitrophenyl acetate, the sdkie is 0.9 ± 0.2.

On the basis of the experimental evidence, the process given in Scheme 2 is suggested for the Cu(II)-promoted cleavage of **3**$^-$. This involves formation of a tetrahedral intermediate (**4**), coordinated to Cu(II) by way of intramolecular delivery of a Cu(II)-coordinated $^-$OCH$_3$ to the CH$_3$C(═O) unit which lies roughly perpendicular to the Pyr−Cu(II)−Pyr plane. The experimental data do not indicate whether the formation of **4** is reversible, as drawn in the scheme, nor whether there are additional intermediates leading from **4** to the products, **P** + **MA**. More light is shed on this process by the DFT calculations reported below.

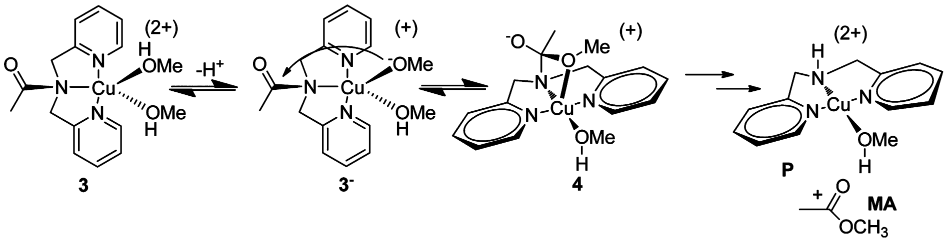
DFT Computations. The lowest energy pathway for cleavage of **3**$^-$ modeled using DFT was found to involve several transition states and intermediates (Figure 2). Several geometries of **3**$^-$ were modeled (Supporting Information). The square pyramidal structure **GS** involving axial methoxide and apical methanol was found to have the lowest free energy and thus was treated as the ground state for this process (all free energies are reported relative to this structure). The geometry of the amide nitrogen in this structure suggests a degree of metal−nitrogen interaction (Table 1).

The nucleophilic attack step involves prior formation of the distorted square pyramidal complex **INT$_1$** with an apical pyridyl moiety, the free energy of which is 1.4 kcal mol^{-1} higher than that of the ground state. Interestingly, relative to the **GS** structure, **INT$_1$** exhibits a lesser degree of metal−amide nitrogen interaction, characterized by an increased Cu(II)−N distance and decreased nitrogen pyramidalization (Table 1). The rearrangement of **GS** → **INT$_1$** was not modeled as it is not expected to be kinetically relevant. Attempts to optimize the equivalent square pyramidal structure with methoxide in the apical position resulted in the apical pyridine structure **INT$_1$**. While four other potential ground state geometries were modeled (Supporting Information), they are readily interconverted and all have free energies within ±1.6 kcal/mol, so **INT$_1$** was chosen as a starting point as it contains metal-bound methoxide in a position that allows direct nucleophilic attack on the CH$_3$C═O unit. The transition state for nucleophilic attack, **TS$_{Nu}$**, has a calculated free energy of 20.1 kcal mol^{-1} and involves both the shortening of the O═C−methoxide distance by 1.57 Å as well as a shortening of the Cu(II) trigonal nitrogen distance (by 0.64 Å) and an increased pyramidalization of that nitrogen (Table 1). The nucleophilic attack transition state leads to a tetrahedral intermediate, **INT$_2$**, that is roughly trigonal bipyramidal about Cu(II) and lies in a shallow minimum on the

Scheme 1. Simplified Process for the Kinetic Cleavage of 3/3$^-$ Consistent with Kinetic Data in Figure 1



Scheme 2. ^s_spH-Dependent Process for the Cleavage of 3



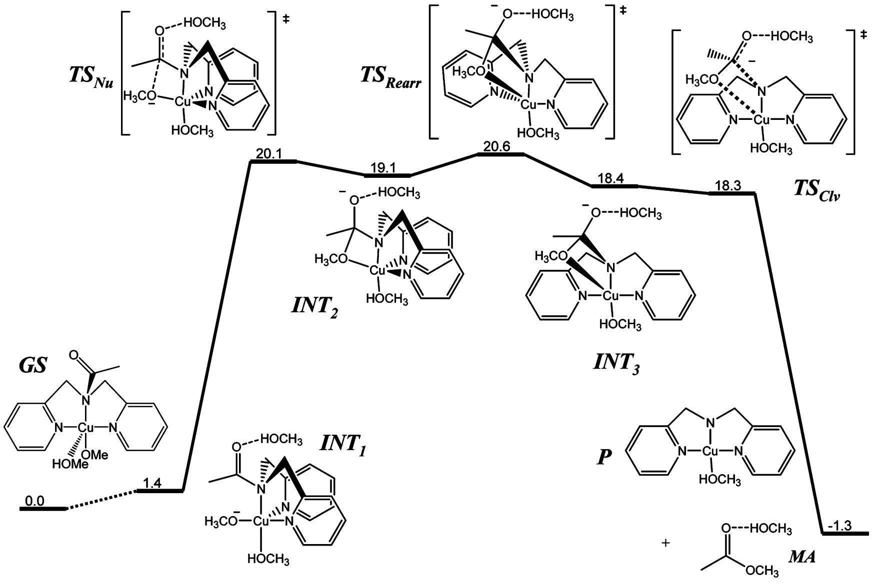


Figure 2. DFT-computed reaction pathway for the cleavage of 3$^-$ in methanol. All free energy values are reported in kcal mol^{-1} at 298 K. Free energy values are relative to the **GS** structure (computed for 3$^-$), and diagram is to scale. Charges are omitted for simplicity.

Table 1. Structural Data for DFT-Calculated Structures

structure	(Py)N−Cu−N(Py)	χ_N[a]	Cu(II)−N_{trig} (Å)	Cu(II)−OMe (Å)	MeO−C(=O) (Å)	N−C(=O) (Å)
GS	159.9°	139.2°	2.34	1.91	4.71	1.42
INT$_1$	105.5°	152.6°	2.67	1.84	3.26	1.38
TS$_{Nu}$	110.2°	136.5°	2.03	1.99	1.69	1.57
INT$_2$	114.8°	117.5°	2.01	2.12	1.57	1.62
TS$_{Rearr}$	140.1°	134.0°	2.03	2.33	1.49	1.62
INT$_3$	159.5°	133.7°	2.04	2.27	1.50	1.67
TS$_{Clv}$	158.7°	131.8°	2.01	2.38	1.47	1.82
P	161.6°		1.97			

[a] Corresponds to the C−C−N−C(O) dihedral and is a measure of the trigonal nitrogen's pyramidalization that varies from 180° (sp^2 hybridization) to 120° (sp^3 hybridization).[17]

free energy surface. Prior to carbon−nitrogen bond scission, the complex undergoes a rearrangement step (**TS$_{Rearr}$**), where the geometry around Cu(II) becomes square pyramidal through an increase of the angle formed by the pyridyl nitrogens and copper (Table 1). The resulting intermediate, **INT$_3$**, is tetrahedral about the acetyl carbon and subsequently decomposes to product in a virtually barrierless process involving carbon−nitrogen cleavage and methyl acetate dissociation, **TS$_{Clv}$**, leading to the square planar [*N*,*N*-bis(2-picolyl)amide:Cu(II):(MeOH)]$^+$ complex **P**. No intermediate comprising a resulting metal-coordinated methyl acetate bound through the methoxide could be optimized. Overall, the transition state associated with the highest free energy is $\mathbf{TS}_{\mathbf{Rearr}}$, although the nucleophilic attack transition state $\mathbf{TS}_{\mathbf{Nu}}$ is similar in terms of energy. Nevertheless, it is notable that all intermediates and their associated transition states for interconversion lie within a 2.7 kcal/mol window.

An alternative mechanism involving the departure of the acetyl group without Cu(II):($^{-}$OCH$_3$) involvement was also modeled computationally (see Supporting Information for computational details). This involved nucleophilic attack of solvent methanol on the **GS** structure, assisted by a second solvent molecule acting as a general base, and a lengthening of the carbon−nitrogen bond with no reduction of the acetyl carbon−methoxide distance. This transition state is associated with a free energy of activation (38.5 kcal mol^{-1}) which is significantly higher than is observed experimentally (22.6 kcal mol^{-1}). Thus, direct acetyl group departure assisted by the solvent nucleophilic attack is unlikely to be the mechanism of methanolysis of **3**$^{-}$, and the nucleophilic Cu(II)-coordinated methoxide mechanism is more probable and is consistent with the lack of a substantial sdkie value.

Overall Mechanism. The pattern that emerges has the Cu(II) closely positioned to coordinate to the N of an amide N−C═O unit in a Werner-type complex.[7−11] Several critical roles are identified for the metal ion during the cleavage process: (1) to associate with the amide N to decrease amidic resonance; (2) to deliver a Cu(II)-coordinated nucleophile to the C═O unit; (3) effect an increasing interaction with the trigonal N, thereby lowering the energy of the tetrahedral intermediate; and (4) to facilitate, through coordination of the departing N, the breakdown of a rearranged tetrahedral intermediate via a concerted syn-elimination of the methyl acetate product. It is important to note that, in this specific reaction, one of the often-cited roles for the metal ion, namely, Lewis acid activation by N−C═O···Cu(II) coordination to make the carbon susceptible to nucleophilic attack, is replaced by a new role of increasing Cu(II)−N−C═O interaction in the TS, which also effectively diminishes the amide resonance in the starting complex, increasingly so as the transition state for Cu(II):($^{-}$OCH$_3$) attack is surmounted. This sort of interaction provides an alternative method of binding of a catalyst to a transition state comprising nucleophilic attack on a N−C═X or N−P═X unit[5,18] (X = O, S) and one that may, with future development of related systems, prove more generally useful in synthetic applications and possibly metalloenzymatic systems where the tertiary structure of the enzyme holds the essential metal ion close to the N.

■ EXPERIMENTAL SECTION

Kinetics of the Cleavage of 2 in Methanol Using UV−Visible Spectroscopy: The [CH$_3$OH$_2$$^{+}$] was determined potentiometrically using a combination glass electrode (Radiometer model XC100-111-120-161) calibrated with certified standard aqueous buffers (pH = 4.00 and 10.00) using methods and procedures described previously.[12]

Reactions were initiated by the addition of stock solutions of **2** in methanol to 2.5 mL of buffered methanol in quartz cuvettes. Buffer solutions were prepared at 10−20 mM from the following amines and triflic acid (HOTf) in methanol to adjust the ${}^{s}_{s}$pH[12] (2,6-lutidine, 2,4,6-collidine and *N*-ethylmorpholine) and 2−20 mM of La(OTf)$_3$, Yb(OTf)$_3$ and Eu(OTf)$_3$ partially neutralized by sodium methoxide. Generally, no significant buffer inhibition was observed; however, k_{obs} values were plotted versus [buffer], and extrapolation of the plots to zero concentration gave a buffer independent rate constant that was used to correct the original experimental data.

The rates of the cleavage of **2** (immediately forming **3** or **3**$^{-}$ when introduced into the buffered medium) (0.2 to 1.0 mM in methanol) were monitored by UV−vis spectrophotometry at 25.0 ± 0.1 °C by observing the decrease in absorbance at 360 nm (${}^{s}_{s}$pH > 6.2) or 235 nm (${}^{s}_{s}$pH < 6.2). Kinetic studies above ${}^{s}_{s}$pH 6.2 were performed in the presence of excess Cu(II) triflate (1−3 mM), and good first-order behavior was observed for at least 5$t_{1/2}$. (At lower ${}^{s}_{s}$pH, good first-order kinetics are observed without added excess of Cu(II).) First-order rate constants (k_{obs}) were obtained from fitting the absorbance versus time traces to a standard exponential model. When excess metal ion was used, initial rates obtained were within experimental error of those obtained in the absence of excess of Cu(II) triflate, signifying that the excess Cu(II) triflate does not significantly affect rate of the reaction but does provide more consistency during the course of the reaction. In order to eliminate any ionic strength and specific salt effects, kinetic experiments were performed using at least two [Cu(II) triflate] and three buffer concentrations. First-order rate constants were extrapolated to zero buffer concentration for each concentration of Cu(II) triflate, and the obtained data extrapolated to zero [Cu(II) triflate] to give a corrected rate constant, k^{corr}, for the cleavage of **3** at a given ${}^{s}_{s}$pH. Original data are given in the Supporting Information.

Due to instability of **3** in solution, a full potentiometric titration study could not be performed and the ${}^{s}_{s}$pK_a of the Cu(II)-coordinated CH$_3$OH in **3** was determined in quadruplicate by measuring the solution ${}^{s}_{s}$pH at half-neutralization at 1 mM.

***N,N*-Bis((pyridin-2-yl)methyl)acetamide or *N*-Acetyl-*N,N*-bis-(2-picolyl)amine (1, R = Me).**[11] A mixture of dipicolylamine (Sigma-Aldrich) (1.27 g; 6.18 mmol), acetyl chloride (0.528 mL; 7.42 mmol), and triethylamine (1.03 mL; 7.42 mmol) in CH$_2$Cl$_2$ was heated at reflux for 2 h. The resulting mixture was washed with water (2×), sodium carbonate solution (2×), and finally with water. The CH$_2$Cl$_2$ was removed, and the resulting oil was dried at room temperature under vacuum (∼3 mm Hg) for 1 h: HRMS (ES^{+}) calcd for C$_{14}$H$_{15}$N$_3$O 241.1215, found 241.1219; ^{1}H NMR (400 MHz, CD$_2$Cl$_2$) δ 8.56 (d, J = 4.8 Hz, 1H), 8.49 (d, J = 4.8 Hz, 1H), 7.68−7.51 (m, 2H), 7.33 (d, J = 7.9 Hz, 1H), 7.20−7.14 (m, 3H), 4.78 (s, 2H), 4.71 (s, 2H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 171.6, 157.3, 156.7, 149.9, 149.1, 136.7, 122.5, 122.4, 122.3, 120.7, 53.9, 51.2, 21.7.

***N,N*-Bis((pyridin-2-yl)methyl)acetamide:Cu(II)-bis(trifluoromethane sulfonate) Complex (2).** This was prepared by the general procedure reported.[7] *N,N*-Bis((pyridin-2-yl)methyl)acetamide (0.477 g, 1.98 mmol) was dissolved in 10 mL of acetonitrile, and 0.729 g (1.98 mmol) of solid Cu(II)(CF$_3$SO$_3$$^{-}$)$_2$ was added to produce a deep greenish-blue solution. The solvent was removed under vacuum, and the crude product was dissolved in 20 mL of CH$_2$Cl$_2$, and within a few minutes, a blue precipitate was formed. After filtration and drying under vacuum, **2** was obtained as a deep green solid: HRMS (ES^{+}) calcd for CuC$_{14}$H$_{15}$N$_3$OCF$_3$SO$_3$$^{+}$ 453.0031, found 453.0022; ^{1}H NMR (400 MHz, D$_2$O/HClO$_4$, reported resonances for protonated, non-Cu(II)-bound amide) δ 8.70−8.40 (m, 4H), 7.95−7.80 (m, 4H), 5.20 (s, 2H), 4.90 (s, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, D$_2$O/HClO$_4$, reported resonances for protonated, non-Cu(II)-bound amide) δ 175.9, 150.8, 150.5, 147.8, 147.5, 142.3, 141.3, 126.5, 126.3, 125.7, 125.1 (124.3, 121.2, 118.0, 114.9 CF$_3$$^{-}$), 50.8, 48.1, 20.6.

Computational Details. Geometry optimizations and energy determinations of intermediates and transition states were performed using unrestricted B3LYP[19] functional as implemented in the Gaussian 09[20] package with the IEFPCM[21] (methanol) solvation model. The 6-31G(d,p) basis set was used for C and H, while 6-31++G(d,p) was used for N and O. The LANL2DZ[22] pseudopotential was used for Cu. Frequency calculations were conducted at this level of theory to characterize transition states and intermediates and as a basis for free energy corrections at 298 K. In addition to the continuum solvation, a single explicit solvent−substrate interaction was included in the form of a hydrogen bond between a methanol molecule and the carbonyl oxygen to stabilize the developing negative charge on that atom over the course of the reaction.

ASSOCIATED CONTENT

Supporting Information

Additional computational details including calculated structures of intermediates and transition states for Figure 2 and tables of atomic positions for the first-order rate constants for reactions of **2**, and ^{1}H NMR and ^{13}C NMR spectra of **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) The designation of pH in non-aqueous solvents is given by the IUPAC, *Compendium of Analytical Nomenclature Definitive Rules 1997*, 3rd ed.; Blackwell: Oxford, UK, 1998. The pH of an aqueous solution determined with an electrode calibrated with aqueous buffers is designated as ${}^{w}_{w}$pH; if the electrode is calibrated in water and the "pH" of a methanol solution is measured, one obtains ${}^{s}_{w}$pH; and if the electrode is calibrated in the same solvent where the "pH" reading is made, then the term ${}^{s}_{s}$pH is used. In methanol, ${}^{s}_{w}$pH $-(-2.24) =$ ${}^{s}_{s}$pH, and since K_{auto} of methanol is $10^{-16.77}$ M^{2}, neutral ${}^{s}_{s}$pH is 8.4.

(13) Due to the paramagnetic properties of copper(II), ^{1}H NMR peaks corresponding to copper complexes of dipicolylacetamine and dipicolylamine were not observed.

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