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Cu(II)-Promoted Methanolysis of *N,N*-Bis(2-picolyl)carbamates: Rate-Limiting Metal Ion Delivery of Coordinated Alcoholate Nucleophile Followed by Fast Partitioning of a Tetrahedral Intermediate

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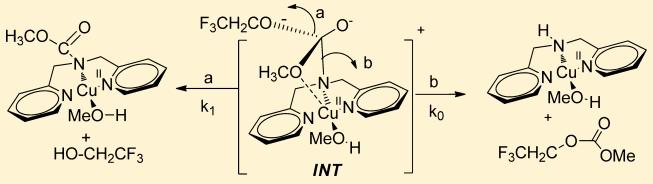
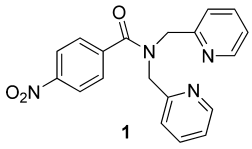
Supporting Information

ABSTRACT: Five *O*-aryl/alkyl *N,N*-bis(2-picolyl)carbamates were prepared with the *O*-aryl/alkyl portions being *p*-nitrophenoxy, *m*-nitrophenoxy, trifluoroethoxy, methoxy, and isopropoxy (**4a,b,c,d,e**, respectively) and the kinetics and reaction products of their methanolysis reactions in the presence of $Cu(O_3SCF_3)_2$ determined. The catalyzed reactions have maximal rates for each substrate at a 1:1 ratio of [**4**]:[Cu^{2+}] at $_s^s$pH 7.9, where the active forms are Cu(II):**4**:($^-OCH_3$). The reactions are fast, that for the complex of **4a** having a $t_{1/2}$ of 30 s. The products of the reaction with **4a** and **4b** arise exclusively from C−OAr cleavage: those with **4d** and **4e** arise exclusively from C−N cleavage. With **4c,** products from both C−O and C−N cleavage are observed in a 2.17:1 ratio. The common mechanism involves rate-limiting delivery of a Cu(II)-coordinated methoxide to the C═O unit to form a tetrahedral intermediate followed by fast partitioning to products by two pathways with relative barriers dependent on the $_s^sp K_a^{HOAr/HOR}$. The data allow one to predict an effective $_s^sp K_a$ of ∼15.6 for the $_s^sp K_a^{NH}$ of Cu(II):bis(2-picolyl)amine.



INTRODUCTION

Recent studies indicated that the bis(2-picolyl)amido radical activates acyl[1] and carbamoyl[2] groups toward transition-metal-catalyzed alcoholysis and hydrolysis processes. The alcoholysis reactions of the Cu(II) complexes of such species as **1** and **2** at 25 °C are fast, having respective $t_{1/2}$ values of 2 min in methanol[1b] and 16 min in ethanol.[2] Relative to the k_2^{-OR} values for methoxide attack on **1** or ethoxide attack on **2**, the presence of the Cu(II) bound to the bis(2-picolyl)amido unit accelerates the cleavage reactions by at least 10^{16} times (comparing second order rate constants for attack of alkoxide on **1** and **1**:Cu(II)),[1c] the only observed products being the Cu(II) complex of bis(2-picolyl)amine (Cu(II)BPA) and the methyl ester of **1** or *O*-ethyl *N*-(*p*-nitrophenyl)carbamate in the case of **2**. Extensive work[1a−c,2] led to a proposed trifunctional role for the Cu(II), as in Scheme 1, involving Lewis acid coordination to the amidic N (**3**), intramolecular delivery of a metal-coordinated alkoxide to the C═O (**3**$^-$) to form a transient tetrahedral intermediate and subsequent metal ion assisted leaving group departure. DFT computations[1b] indicated that the facility of this leaving group assistance (LGA) stems from the metal ion exerting a progressively larger affinity for the bis(2-picolyl)amido unit during its departure as a metal-coordinated anion, which subsequently becomes protonated by the medium or buffer components therein.



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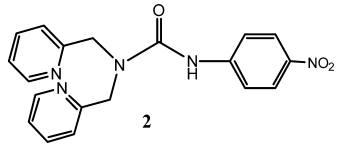

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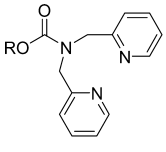
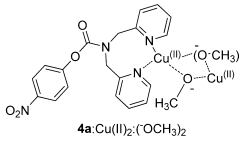
The above raises the question of the relative leaving group abilities of the Cu(II)-coordinated bis(2-picolyl)amide and alkoxyl/aryloxy groups from a series of carbamates where the goodness (as measured by $_s^sp K_a$ of the parent HOR′ alcohols[3]) of the C(═O)OR′ leaving group is varied. The partitioning of the tetrahedral intermediates formed from the methoxide addition to *O*-ethyl *N*-aryl *N*-methylcarbamates was used as a guide for the relative leaving group abilities of ethoxide and various *N*-methylanilides,[4] and there is extensive work on the relative leaving group abilities of certain amines, ammonium groups, and aryl oxides from tetrahedral intermediates formed from amine attack on bis(aryl)carbonates and similar reactions.[5] However, as far as we are aware there are no studies of the relative leaving group abilities of a metal ion coordinated amide and alkoxide/aryloxides from tetrahedral intermediates such as would be formed in the Scheme 1 process. To assess this we have investigated the kinetics and product formation for the Cu(II)-promoted methanolysis of five *O*-alkyl and *O*-aryl *N,N*-bis(2-picolyl)carbamates (**4a−e**) under $_s^s$pH-controlled conditions.



4 a R = $C_6H_4NO_2$(para)
b R = $C_6H_4NO_2$(meta)
c R = CF_3CH_2
d R = CH_3
e R = $(CH_3)_2CH$



4a:Cu(II)$_2$:($^-OCH_3$)$_2$

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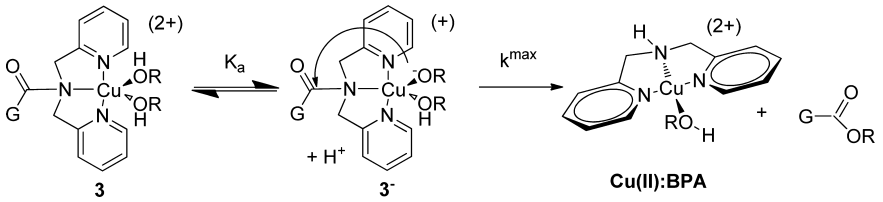
Scheme 1. Simplified Process for the Cleavage of Cu(II) Complexes of 1,2 in Alcohol (G = Aryloxy, Alkoxy, or Anilino)



RESULTS

(a) Cu(II)-Catalyzed Methanolysis of *O*-Aryl *N*,*N*-Bis(2-picolyl)carbamate (4a,b). The kinetics of methanolysis of 0.05 mM solutions of **4a** were monitored at 320 nm in the presence of various [Cu(OTf)$_2$] over a ^s_spH range of 5.2−7.8 under buffered conditions at 25 °C to determine optimal conditions for studying other members of the series. The Abs vs time plots at a given ^s_spH adhered to good first-order kinetics, and NLLSQ (nonlinear least squares) fits of these data to a standard exponential model gave first order rate constants (k_{obs}). Given in Figures 1 and 2 are examples of the ^s_spH-dependent k_{obs} vs [Cu^{2+}] profiles. At low ^s_spH (e.g., Figure 1), the plots appear to those of a normal saturation with weak binding of the metal ion to **4a**. The line through the data in Figure 1 is obtained by NLLSQ fitting the data to a standard 1:1 binding isotherm, and the maximum rate constant and binding constants are given in Table 1.

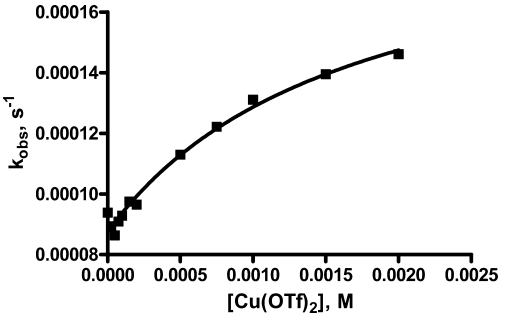


Figure 1. A plot of k_{obs} as a function of [Cu(OTf)$_2$] for the methanolysis of 0.05 mM *N*,*N*-bis(2-picolyl)-4-nitrophenylcarbamate (**4a**) at ^s_spH 5.2, T = 25 °C. The line through the data is obtained from NLLSQ fitting to a standard saturation binding model, the best fit parameters being given in Table 1

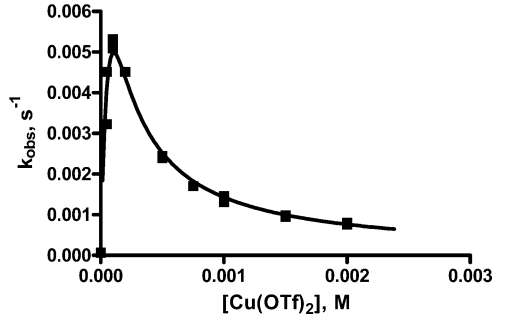


Figure 2. A plot of k_{obs} for the methanolysis of 0.05 mM **4a** as a function of [Cu(OTf)$_2$] obtained at ^s_spH 7.4, T = 25 °C; the computed line through the data is derived from the NLLSQ fit of the data to eq 1

At ^s_spH values above 6.5 the plots exhibit a rise/fall behavior as shown in Figure 2 which maximizes at a 1:1 ratio of [**4a**]:[Cu^{2+}]. Further increases in [Cu^{2+}] lead to decreases in k_{obs} indicative of an inhibitory effect in which excess Cu^{2+} (probably as Cu(II):($^-$OCH$_3$)[6a] may associate with Cu(II):**4** to form an inactive or weakly active di-Cu(II) species of proposed stoichiometry **4a**:Cu(II)$_2$:($^-$OCH$_3$)$_{1,2}$ (see structure above).[6b] NLLSQ fitting of the k_{obs} vs [Cu^{2+}] data to eq 1,[7] derived for the kinetic model shown in Scheme 2, provided k_{cat}, K (the observable association constant for Cu(II):**4a** at a given ^s_spH which is defined as the product of microscopic constants K_b (formation constant for Cu(II):**4a**) and K_a (acid−base dissociation constant for the methanol coordinated to Cu(II):**4a**) (Scheme 2)), and K_m (the dissociation constant **4a**:Cu(II)$_2$:($^-$OCH$_3$)$_{1,2}$) values shown in Table 1.

The k_{cat} rate constants in Table 1 increase with increasing ^s_spH, indicating that the active form of the system has one associated methoxide. A fit of k_{cat} vs ^s_spH to a standard equation for a single H^+ dissociation yielded a kinetic ^s_spK_a of approximately 7.6 and maximum rate constant (k_{max}) for the reaction of Cu(II):**4a**:($^-$OMe) of 2.4 × 10^{-2} s^{-1}, $t_{1/2}$ ∼ 30 s. It is also interesting that, for the limited number of examples we have available, the K_m value decreases at higher pH, meaning that the inhibition process probably involves a form of Cu(II) that is bound to methoxide[6] to form a species such as is depicted in **4a**:Cu(II)$_2$:($^-$OCH$_3$)$_2$ (shown above) where the methoxides bridging the two Cu(II) ions are weakly or non-nucleophilic.

The Cu(II)-promoted reaction of **4a** leads to replacement of the *p*-nitrophenoxy group by methoxide and by analogy with the reactions of other Cu(II):bis(2-picolyl)amido-containing substrates we have investigated,[1a−c] the proposed pathway involves formation of a tetrahedral intermediate (***INT***) as in Scheme 3. Breakdown of the intermediate formed from **4a** occurs only by path a to eliminate the *p*-nitrophenoxy group, but when the reaction is monitored longer, we observe a second, far slower, process which is completed only after ∼16 h and results in the formation of the Cu(II) complex of bis(2-picolyl)amine and dimethyl carbonate (see Figure 12S, Supporting Information). This process is similar to what is presented in Scheme 3, with ArO being replaced by CH_3O, and the ultimate product being formed by cleavage pathway b.

Similar kinetic and product formation results were obtained with the *meta* derivative of *O*-(nitrophenyl) *N*,*N*-bis(2-picolyl)-carbamate (**4b**), the Cu(II)-promoted methanolysis of which

$$k_{obs} = \frac{k_{cat}K_m(1+K[4]+K[\mathrm{Cu(OTf)_2}]-\sqrt{1+2K[4]+2K[\mathrm{Cu(OTf)_2}]+K^2[4]^2-2K^2[\mathrm{Cu(OTf)_2}][4]+[\mathrm{Cu(OTf)_2}]^2K^2}\,)}{2K[4](K_m+[\mathrm{Cu(OTf)_2}]-(1+K[4]+K[\mathrm{Cu(OTf)_2}]-\sqrt{1+2K[4]+2K[\mathrm{Cu(OTf)_2}]+K^2[4]^2-2K^2[\mathrm{Cu(OTf)_2}][4]+[\mathrm{Cu(OTf)_2}]^2K^2}\,)/(2K))} \quad (1)$$

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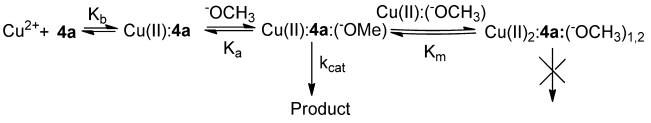
Table 1. Kinetic and Equilibrium Dissociation Constants Calculated from the Fitting of Experimental Data to eq 1 for the Cu(II)-Catalyzed Methanolysis of 4a between $^{s}_{s}$pH 6.7 and 7.8 in Anhydrous Methanol at T = 25 °C[a]

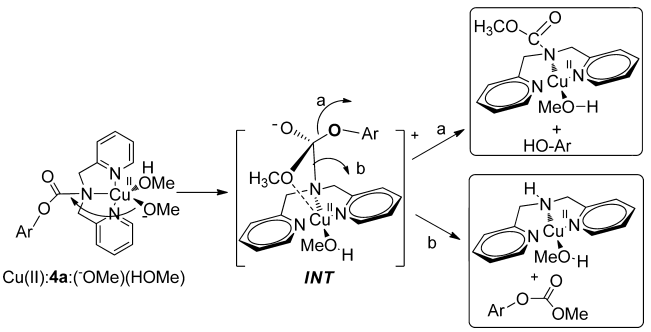
$^{s}_{s}$pH	k_{cat} (s^{-1})	$1/K$ (M)	K_m (M)
7.8	$(1.7 \pm 0.2) \times 10^{-2}$	$(4.0 \pm 1.3) \times 10^{-5}$	9.5×10^{-5}[c]
7.4	$(1.2 \pm 0.08) \times 10^{-2}$	$(4.1 \pm 0.8) \times 10^{-5}$	1.35×10^{-4}[c]
6.7	$(2.7 \pm 0.6) \times 10^{-3}$	$(1.2 \pm 0.4) \times 10^{-4}$	$(7.2 \pm 2.3) \times 10^{-4}$
6.2	$(5.1 \pm 0.4) \times 10^{-4}$	$(2.2 \pm 0.8) \times 10^{-4}$[b]	NA
5.5	$(1.9 \pm 0.1) \times 10^{-4}$	$(7.4 \pm 1.0) \times 10^{-4}$[b]	NA
5.2	$(1.1 \pm 0.2) \times 10^{-4}$	$(1.7 \pm 0.5) \times 10^{-3}$[b]	NA

[a]Data obtained at $^{s}_{s}$pH < 6.5 obtained by NLLSQ fits of k_{obs} vs $[Cu^{2+}]$ to a standard 1:1 binding model. [b]Data fitted to standard 1:1 binding equation. [c]Due to the heavy correlation between k_{cat}, K and K_m, the errors of the fit were excessively high. In order to obtain realistic error parameters the values of K_m were fixed to ones obtained by unrestricted fit.

Scheme 2. Hypothetical Process Consistent with the Observed Concentration Effects of Cu^{2+} on the Rate of the Decomposition of 4a Shown in Figure 2



Scheme 3. Cleavage Pathways for the Cu(II)-Promoted Methanolysis of Cu(II):4a:$^{-}$OCH$_3$



was monitored at 335 nm at a $^{s}_{s}$pH of 7.9 under buffered conditions at 25 °C. The k_{obs} vs $[Cu^{2+}]$ plot exhibits a rise/fall behavior similar to that observed with **4a** (see Figure 18S, Supporting Information), which maximizes at 4.3×10^{-3} s^{-1} at [**4b**] = $[Cu^{2+}]$ = 0.08 mM. The initial product released was 3-nitrophenol (λ_{max} = 335 nm) followed by a slower process resulting in the formation of the Cu(II) complex of bis(2-picolyl)amine and dimethyl carbonate.

(b) Cu(II)-Promoted Methanolysis of *N,N*-Bis(2-picolyl)-carbamates 4c–e. All of the substrates follow a kinetic behavior similar to that of **4a** with respect to the appearance of the k_{obs} vs $[Cu^{2+}]$ plots at high $^{s}_{s}$pH (as an example, see Figure 17S, Supporting Information, for the plot with **4d** at $^{s}_{s}$pH 6.3). Since the rise/fall nature of the plots stems from an intersection of two processes, formation of a $^{s}_{s}$pH-dependent active Cu(II):**4**:($^{-}$OCH$_3$) form and inhibition due to involvement of a second Cu(II):($^{-}$OCH$_3$) in the solution, we opted for a simpler method to compare the efficacy of the Cu(II)-promoted decomposition of all members of series **4**. This involved determining the maxima of the k_{obs} vs $[Cu^{2+}]$ profiles at a common set of conditions by observing the rate of disappearance of **4c–e** (0.5 mM) at 362 nm, $^{s}_{s}$pH = 7.9 (10 mM of a 2,4,6-collidine/HOTf buffer; 3:1) in the presence of equimolar $Cu(OTf)_2$ at 25 °C as described in the Experimental Section. These k_{obs} constants can be compared with those obtained for **4a** and **4b** that were obtained as described above. That the apex of the k_{obs} vs $[Cu^{2+}]$ plot can provide comparative rate data rests on the assumption that the binding constants of the first and second Cu(II):($^{-}$OCH$_3$) components that provide the activation and inhibition for methanolysis are roughly the same for all substrates. Another complication arises due to the slow rate and significant inhibition of the reaction **4c–e** by one of the products, (bis(2-picolyl)-amine),[8] so that the latter reactions had to be followed using an initial rate method. This rate was obtained as the slope of Abs vs time plot for the first ~10% of the reaction, and the pseudo-first-order rate constants were calculated using the overall change in absorbance after the reaction was completed.[9] The so-obtained rate constants are given in Table 2 along with the $^{s}_{s}pK_a$ values for

Table 2. Pseudo-First-Order Rate Constants for the $Cu(OTf)_2$-Catalyzed Methanolysis of *N,N*-Bis(2-picolyl)carbamates 4a–e at $^{s}_{s}$pH 7.9 in Anhydrous Methanol at T = 25 °C

	$10^5 k_{obs}$ (s^{-1})				
	4a	**4b**	**4c**	**4d**	**4e**
C–N bond cleavage	*c*	*c*	12.3	3.0	0.9
C–O bond cleavage	630[b]	430	26.7	*c*	*c*
$^{s}_{s}pK_a$ HOR[a]	11.30	12.49	15.36	18.13	19.72

[a]$^{s}_{s}pK_a$ values in methanol from ref 10. Reported k_{obs} values have estimated errors at 10% on the basis of assumptions described in the text. [b]Rate constant for reaction of **4a** determined at $^{s}_{s}$pH 7.8. [c]No observed products from the specified pathway.

the parent alcohols,[10] and the analogous data for **4a** and **4b** as well as modes of cleavage which will be dealt with subsequently. The k_{obs} values here are estimated to have a 10% uncertainty which is conditional on the assumptions made above. This limits detailed interpretation beyond a conclusion that the log(k_{obs}) values are linearly dependent on the $^{s}_{s}pK_a$ of the parent alcohols.[11a]

(c) ^{1}H NMR Studies of the Mode of Cu(II)-Promoted Cleavage of 4d,e. NMR samples were prepared in buffered d_4-methanol and subjected to ^{1}H NMR analysis as described in the Experimental Section. The signal corresponding to the CH_3– groups of 2,6-lutidine buffer (δ = 2.57) provided an internal standard calibrated to 600 units (1 unit per 0.01 mM). Due to the paramagnetic nature of Cu(II) ions the NMR signals corresponding to the starting material complexed to them were not observed. With **4d** the productive pathway results from C–N bond cleavage leading to ($CD_3OC(=O)OCH_3$) appearing at δ = 3.76. The gradient of the plot (see Figure 13S, Supporting Information) of appearing [$CD_3OC(=O)OCH_3$)] vs time was found to be $(4.2 \pm 0.2) \times 10^{-8}$ M s^{-1}, corresponding to a pseudo-first-order rate constant of $(1.4 \pm 0.1) \times 10^{-5}$ s^{-1}. This rate

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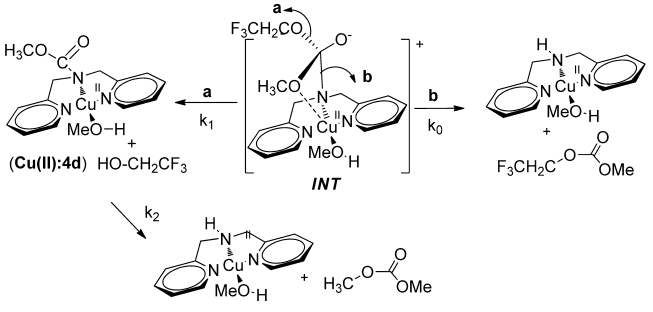
constant is about half of what was determined from the UV/vis kinetic studies under UV/visible monitoring of the second process in the reaction of **4a** presented in section a above and is attributable to the fact that the latter was obtained at $^{s}_{s}$pH 7.9 at lower concentrations of metal ion and substrate, while the lutidine-buffered NMR conditions have higher concentrations and a lower $^{s}_{s}$pH to prevent precipitation. The rate of the putative nonproductive pathway (resulting from C−OCH_3 bond cleavage) could have been observed (if it occurred) by integration of the peak for a nondeuterated methanol which would be released from the Cu(II)-bound starting material. No increase in [CH_3OH] was detected during the course of the reaction (41 h), indicating that Cu(II)-catalyzed methanolysis of *O*-methyl *N*,*N*-bis(2-picolyl)carbamate proceeds, within experimental error, exclusively by cleavage of the C−N bond.

The progress of the Cu(II)-promoted cleavage of *O*-isopropyl *N*,*N*-bis(2-picolyl)carbamate (**4e**) was monitored by ^{1}H NMR after 48 h. The sole product was isopropyl methyl carbonate characterized by the signal at δ = 1.25, (d, J = 6.31 Hz) corresponding to the $(CH_3)_2$CH− protons. No signals characteristic of isopropyl alcohol were observed (δ = 1.50 ppm, doublet and δ = 3.92 ppm, septet[12]) indicating exclusive C−N bond cleavage.

(d) Cu(II)-Promoted Methanolysis of *O*-(2,2,2-Trifluoroethyl) *N*,*N*-Bis(2-picolyl)carbamate (4c). After 48 h at 25 °C, the reaction of equimolar (3 mM) **4c** and $Cu(OTf)_2$ was analyzed by ^{19}F NMR (see Figure 14S, Supporting Information), and products resulting from C−O and C−N cleavage pathways were observed: 2,2,2-trifluoroethanol (δ = −78.81 triplet, J = 8.93 Hz) and 2,2,2-trifluoroethyl methyl carbonate (δ = −76.20 triplet, J = 8.51 Hz). The ^{19}F signal at δ = −80.02 originates from the $Cu(OTf_2)$ and was used as an internal standard. The relative intensities of the two product signals were found to be 2.17:1 indicating that the reaction proceeded predominantly with C−O cleavage. Comparison of the integration of the triflate signal of 6.31 units with the sum of the signal intensities of both products (1.00 + 2.17= 3.17 units) confirmed that the reaction was complete at 48 h.

Since both products of C−O and C−N cleavage are observed, there is a very small free energy difference for the two product-forming transition states leading from the tetrahedral intermediate, with that resulting from C−O cleavage being 0.6 kcal/mol lower in energy than the one proceeding via C−N cleavage, paths a and b, respectively, in Scheme 4. A similar product analysis of the Cu(II)-promoted cleavage reaction of **4c** was conducted at 55 °C. In this case, there is an inversion of the product ratio, with *less* 2,2,2-trifluoroethanol being produced than 2,2,2-trifluoroethyl methylcarbonate, the product ratio now being 0.88:1. A calculation based on the relative amounts of C−N and C−O cleavage products shows that at 55 °C the free energy of C−N cleavage TS is 0.07 kcal/mol lower than that for C−O cleavage.

Scheme 4. Bond Cleavage Pathways for the Cu(II)-Promoted Methanolysis Reaction of 4c



(e) Additional Kinetic Studies of the $Cu(OTf)_2$-Catalyzed Methanolysis of 4c. Since the Cu(II)-promoted methanolysis of **4c** gives an appreciable amount of the Cu(II) complex of **4d** via pathway a (Scheme 4) as a result of C−O cleavage, a more detailed kinetics study was undertaken using UV/vis spectroscopy to attempt to detect the subsequent reaction of Cu(II):**4d**:($^-OCH_3$). The kinetic curves for this process monitored at 362 nm at 25 and 55 °C, $^{s}_{s}$pH 7.9, are given in Figures 15S and 16S, Supporting Information. These Abs vs time profiles are more complicated than a simple first-order process requires and are more indicative of a process with two or more observable competing reactions. Therefore, eq 2 was derived for the kinetic process depicted in Scheme 4 as monitored by changes in absorbance using UV−vis spectroscopy, where k_0, k_1, and k_2 are rate constants and Abs_o, ΔAbs_1, and ΔAbs_2 are initial absorbance and absorbance changes during the first and second phase of the process.

$$\mathrm{Abs} = \mathrm{Abs_0} + \Delta\mathrm{Abs_1}e^{-(k_0+k_1)t} + \frac{\Delta\mathrm{Abs_2}(k_1+k_0)}{(k_2-(k_1+k_0))}\left(e^{-(k_0+k_1)t} - e^{-k_2t}\right) \quad (2)$$

Due to the number of variables, an unrestricted NLLSQ fitting of the Abs vs time data to eq 2 was not possible. However, since the product ratio determined by ^{19}F analysis of the products of cleavage of **4c** is known (Figure 14S, Supporting Information) a value of 2.17:1 can be set for the ratio of k_1 and k_0. This restriction allowed a satisfactory fit of the experimental data (presented in Figure 16S, Supporting Information) with the computed values for the rate constants being $k_0 = 1.2 \times 10^{-4}$ s^{-1}, $k_1 = 2.77 \times 10^{-4}$ s^{-1}, and $k_2 = 3.5 \times 10^{-5}$s^{-1}. In this analysis, k_2 corresponds to the pseudo-first-order rate constant for the cleavage of the Cu(II):**4d** formed as an intermediate during the methanolysis of **4c** (Scheme 4). This value correlates well with the independently obtained k_{cat} for the Cu(II)-promoted methanolysis of authentic **4d** under similar experimental conditions (3.0×10^{-5} s^{-1}, see Table 2)

The kinetic trace determined at 55 °C was also non-first order (Figure 16S, Supporting Information), but NLLSQ fitting of these experimental data to eq 2 produced the theoretical line in Figure 16S correlating well with the experimental data. The calculated rate constants, $k_0 = 7.7 \times 10^{-3}$ s^{-1}, $k_1 = 5.8 \times 10^{-3}$ s^{-1}, and $k_2 = 1.5 \times 10^{-3}$s^{-1}, are in good agreement with the product analysis data. The kinetic data predict that the ratio between the 2,2,2-trifluoroethyl methyl carbonate and 2,2,2-trifluoroethanol produced at 55 °C should be 1:0.76, while the product analysis using experimental ^{19}F NMR data provides a ratio of 1:0.88.

DISCUSSION

Our previous studies of LGA of the catalyzed alcoholysis of amides[1] and ureas[2] containing a bis(2-picolyl)amido unit showed that the Cu(II)-promoted reactions were 10^{16} times faster than the respective alkoxide-promoted reactions. A DFT computational analysis of the Cu(II)-promoted methanolysis of a series of substituted *N*-benzoyl-*N*,*N*-bis(2-picolyl)amides[1b] indicated that the reactions for substrates having both electron-donor and -acceptor substituents proceeded by rate-limiting addition of the Cu(II)-coordinated methoxide to the C═O unit with formation of a tetrahedral intermediate. The latter

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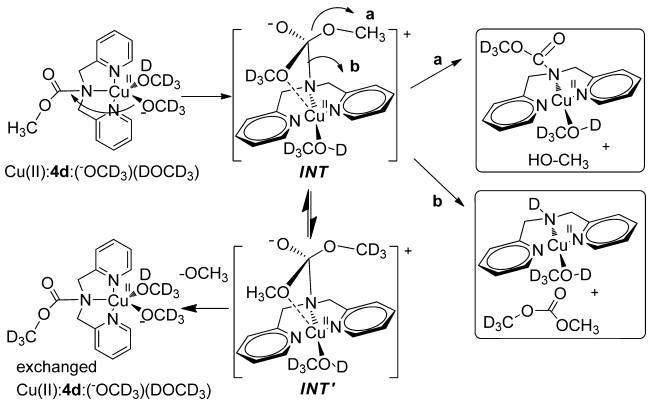
decomposes by an enforced concerted[13] C−N cleavage without a significant barrier meaning the intermediate is too unstable to exist. The product-forming routes of these sorts of amides and ureas are biased because the scissile Cu(II)-coordinated N-containing portion is always the best leaving group in the system so there was no experimental information about the formation of a tetrahedral intermediate. The present study with **4a−e** allows one to determine whether partitioning of the putative tetrahedral intermediates (***INT***) in Schemes 3 and 4 changes as a function of the increase in ${}^{s}_{s}pK_a^{HOR}$ of the carbamates' parent alcohols. Moreover, the present case of the methanolysis of **4d** allows one to determine whether the CH_3O group can be replaced by a CD_3O group from methanol-d_4, thus providing evidence for reversible formation of a tetrahedral intermediate.

The data compiled in Table 2 indicate that with good *p*-nitro- and *m*-nitrophenoxy leaving groups the reactions of **4a**,**b** proceed exclusively via C−O cleavage, giving *O*-methyl-*N*,*N*-bis(2-picolyl)carbamate (**4d**), which is observed to decompose about 200 times more slowly to yield dimethyl carbonate and the Cu(II) complex of bis(2-picolyl)amine. When Cu(II)-promoted decomposition of **4d** is conducted in methanol-d_4 there is no indication of formation of CH_3OH (based on ^{1}H NMR spectrum of the reaction mixture) and, correspondingly, the CD_3O isotopomer of **4d**, thus signifying that if a tetrahedral intermediate (such as ***INT*** in Scheme 5) is formed it does not revert back to exchanged starting material. By microscopic reversibility the CH_3O unit can only be removed from the starting material through its coordination with the Cu(II) as in ***INT***′ followed by collapse to exchanged Cu(II):**4d**:($^-$OCD$_3$)(DOCD$_3$). The lack of exchange could result from a high barrier for exchange of the CH_3O and CD_3O groups on the Cu(II) or simply from a low barrier for C−N cleavage: in either event, the formation of ***INT*** would be rate-limiting.[11b]

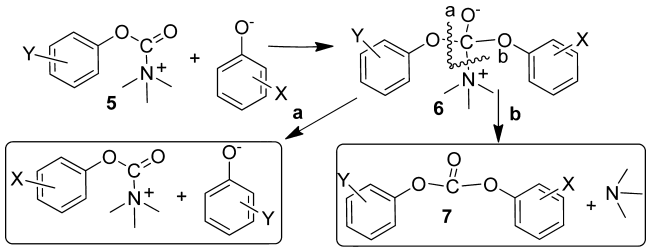
Scheme 5. Hypothetical Pathways for the Formation and Decomposition of Intermediate Formed during Cu(II)-Promoted Methanolysis of 4d in Methanol-d_4



With **4c** one sees products arising from competitive C−OCH_2CF_3 and C−N cleavage in a 2.17:1 ratio at 25 °C. This suggests that the tetrahedral intermediate produces these observed products via pathways separated in free energy by 0.6 kcal/mol. Based on the relative free energy differences of the C−O and C−N cleavage transition states at 25 and 55 °C, we calculated a difference in entropy of activation between those transition states of 22.3 cal/mol deg with the C−N cleavage transition state having a more positive entropy of activation and, correspondingly, a less entropically restricted transition state. The difference may stem from the fact that C−N bond cleavage is assisted by the Cu(II) ion and may not require much additional stabilization by the solvent, while the $CF_3CH_2O^-$ anion should require H-bonding stabilization and more restriction of degrees of freedom of the surrounding solvent to assist its departure.

It is sometimes useful to evaluate the relative leaving ability of different groups departing competitively from a common intermediate in terms of their relative pK_a values. Gresser and Jencks used this approach to compare the relative leaving abilities of alcohols and amines from tetrahedral intermediate **6** formed from attack of an X-substituted phenoxide on **5**, the breakdown of which can yield two sets of products formed by expulsion of the trialkylamine or a Y-substituted phenoxide as in Scheme 6.[5]

Scheme 6. Breakdown of Tetrahedral Intermediate Formed from Carbamates Involving Two Competing Pathways[5]



In this specific reaction, equal partitioning of a tetrahedral intermediate (**6**) containing the 3,4-dinitrophenoxide leaving group, departing via path **a**, occurs with amines (via path **b**) that are 4.4 p*K* units more basic. In this case, the pK_a values in question are those for the parent phenol and the protonated ammonium ion of the amine.

With the Cu(II) complexes of **4a−e**, the relevant values are ${}^{s}_{s}pK_a^{HOR}$ for the parent alcohols and the ${}^{s}_{s}pK_a^{H-N}$ for the Cu(II) complex of bis(2-picolyl)amine, a value which is not experimentally obtainable. This is due to difficulties in determining the ${}^{s}_{s}pK_a^{H-N}$ by titration with methoxide in methanol which extracts the Cu(II) to form an insoluble oligomer of Cu(OCH$_3$)$_2$. Nevertheless, considering the nearly equivalent C−O and C−N partitioning of the tetrahedral intermediate with Cu(II):**4c** and the ${}^{s}_{s}pK_a^{HOR}$ of 2,2,2-trifluoroethanol (15.36) an "effective" ${}^{s}_{s}pK_a^{H-N}$ of the latter complex can be estimated to be approximately 15.6.[14] There are no data available for the pK_a values of amines dissociating to amide ions in methanol of which we are aware. However, relationships are available that convert the aqueous pK_a values of aromatic[15a] and aliphatic[16b] alcohols to methanol values. If we are allowed to approximate the ${}^{s}_{s}pK_a$ of bis(2-picolyl)amine as being the same as, or slightly higher than[15c], the pK_a of NH_3 in water (38[16]), the coordinated Cu(II) provides a reduction of ~23 ${}^{s}_{s}pK_a$ units or ~36 kcal/mol for N−H deprotonation. This estimate is somewhat higher than a previously experimentally derived value of 21.3 kcal/mol that we observed in the case of Cu(II) promoted cleavage of a 2-aryloxyphenanthroline leaving group during the methanolysis of a series of phosphate mono-, di-, and triesters.[17] The apparently more impressive stabilization of the departing amide perhaps relates to the stronger "soft/soft" interaction between Cu(II) and amide anion versus a weaker "soft/hard" interaction between Cu(II) and a 2-phenathroline aryloxy anion.

As a final speculation, the demonstration of such large metal ion stabilizations of anionic amide leaving groups departing from intermediates in the acyl-transfer reactions from carbamates, carboxamides, and ureas to alcohols and water[1,2] gives some credence to the thesis that LGA may be of fundamental

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importance for metallo-enzymatic acyl- and phosphoryl-transfer processes involving the replacement of poor leaving groups of normally difficult-to-solvolyze species.

EXPERIMENTAL SECTION

(a) Materials. Copper(II) trifluoromethanesulfonate (98%), ytterbium(III) trifluoromethanesulfonate (99.9%), trifluoromethylsulfonic acid (≥99%), methyl chloroformate (99%), isopropyl chloroformate (98%), triphosgene (98%), and 2,2′-bis(2-picolyl)amine (97%) were commercially available and used as obtained.

(b) General Methods. NMR spectra were recorded at 400 MHz. $[CH_3OH_2^+]$ and $[C_2H_5OH_2^+]$ concentrations were determined potentiometrically using a combination glass electrode (Accumet model no. 13-620-292) calibrated with certified standard aqueous buffers (pH 4.00 and 10.00) as described previously.[18] The $^{s}_{s}$pH values in methanol were determined by subtracting a correction constant of −2.24[3] from the electrode readings and the autoprotolysis constant for methanol was set at $10^{-16.77}$ M^2. The $^{s}_{s}$pH values for the kinetic experiments were measured postreaction to avoid the possibility of inhibitory effects of KCl leaching from the electrode.

(i) Synthesis of O-p-Nitrophenyl-2,2′-bis(2-picolyl)carbamate, ***4a****.* *O-p*-Nitrophenyl-2,2′-bis(2-picolyl)carbamate was synthesized by mixing 300 μL (1.67 mmol) of 2,2′-bis(2-picolyl)amine and 370 mg (1.1 equiv) of 4-nitrophenyl chloroformate in 20 mL of CH_2Cl_2 at room temperature with stirring. Approximately 1 g of solid sodium bicarbonate was added to the mixture as a base. The reaction progress was followed by TLC (30% hexane−70% ethyl acetate) and was completed after 60 min after which time it was washed with water, aqueous ammonia, and dilute HCl. The product HCl salt[19] was obtained after solvent removal as a yellowish crystalline material (154 mg, 0.35 mmol, 21%). ^{1}H NMR (400 MHz, D_2O, 25 °C): δ 8.73−8.60 (bm, 2H), 8.60−8.45 (bm, 2H), 8.14−7.85(bm, 6H), 7.24−7.14 (bm, 2H), 5.27 (bs, 2H), 5.11(bs, 2H). ^{13}C NMR (100.6 MHz, D_2O, 25 °C): δ [154.6(broad), 154.5 (broad)], 150.6, 150.1, [147.8 (broad), 147.7 (broad)], 145.1, [141.5 (broad), 141.4], 126.6, [126.0 (broad), 125.7(broad)], 125.2, 122.5, [49.9 (broad), 49.8 (broad)]. ^{1}H NMR and ^{13}C NMR spectra can be found in the Supporting Information (Figures 1S and 2S). UV−vis: $\varepsilon_{262\ nm}$ = 24263 ± 88 M^{-1} cm^{-1}. HRMS: ESI-Orbitrap Velos Pro $C_{19}H_{17}N_4O_4$, *m/z* calcd 365.12443(+), *m/z* found 365.12412 (+), PPM −0.845. Mp = 43 °C dec.

(ii) Synthesis of O-m-Nitrophenyl-2,2′-bis(2-picolyl)carbamate, ***4b****.* Triphosgene (675 mg (2.27 mmol)) was dissolved in 30 mL of dry toluene followed by cooling to 0 °C, after which 994 μL (6.25 mmol) of diethylaniline was added with stirring over 15 min. Subsequently, 791 mg (5.69 mmol) of 3-nitrophenol was slowly added over 5 min. The resulting reaction mixture was allowed to warm to room temperature for 2 h. after which it was washed with 2 × 50 mL of ice-cold water and dried over magnesium sulfate for 20 min. Following filtration, the solvent was removed to give 900 mg of a yellow oil (82% yield based on 3-nitrophenol) which was used without further purification in the next step.

3-Nitrophenyl chloroformate (272 mg, 1.35 mmol) was dissolved in 30 mL of dry CH_2Cl_2, followed by the addition of 243 μL (1.35 mmol) of bis(2-picolyl)amine with stirring at room temperature. Solid sodium bicarbonate (500 mg) was added to the reaction mixture, which was allowed to stir for 150 min. Approximately half of the reaction mixture was filtered from its solid precipitate and was used for product purification with an MPLC Biotage SP1 instrument. The solvent gradient system comprised ethyl acetate and hexane; 2 CV of hexane; 10 CV 0% ethyl acetate progressing to 100% ethyl acetate; and then 4 CV of 100% ethyl acetate. Elution of the product was monitored at 280 and 310 nm with a flow rate of 20 mL/min. The acquired fractions (9 mL) containing the product were combined, and the dissolved material was converted into an HCl salt by the gradual addition of concentrated HCl. This yielded a white precipitate; the organic layer was decanted and the residual white solid dried under vacuum to give 35 mg of product, 0.08 mmol, 6%.[19] ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C): δ 8.85 (bs, 2H), 8.45 (bm,1H) 8.38 (bm,1H) 8.12−8.07 (bm, 2H), 8.05−7.95 (m, 2H), 7.88 (t,1H) 7.82 (t,1H), 7.72−7.62 (m,2H) 5.26 (bs, 2H), 5.11(bs, 2H). ^{13}C NMR (125. MHz, d_6-DMSO, 25 °C): δ 153.7, [153.5(broad), 152.9 (broad)], 151.0, 148.0, [144.5 (broad), 143.9 (broad)], [143.6 (broad), 142.9 (broad)], 130.5, 128.8, [125.2 (broad), 124.9 (broad)], [125.0 (broad), 124.5(broad)], 120.6, 117.2, [50.7 (broad), 50.4 (broad)]. ^{1}H NMR and ^{13}C NMR spectra can be found in the Supporting Information (Figures 10S and 11S). UV−vis: $\varepsilon_{262\ nm}$ = 14800 ± 40 M^{-1} cm^{-1}. HRMS: ESI-Orbitrap Velos Pro $C_{19}H_{17}N_4O_4$, *m/z* calcd 365.12443(+), *m/z* found 365.12419 (+), PPM-0.6571. Mp = 108−110 °C dec.

*(iii) Synthesis of O-Methyl-2,2′-bis(2-picolyl)carbamate (****4d****).* Dipicolylamine (DPA) (1.36 mL (7.55 mmol)) was dissolved in 30 mL of dry CH_2Cl_2 followed by the addition of 1.58 mL of triethylamine. Immediately, 613 μL of methylchloroformate was added to the solution by syringe under argon, and the reaction mixture was heated to reflux for 5 h after which it was allowed to cool to room temperature and stirred overnight. It was washed with 2 × 50 mL portions of deionized water followed by 2 × 50 mL of saturated KCl and finally a 50 mL portion of deionized water. The separated organic layer was dried over anhydrous Na_2SO_4 and filtered and the solvent evaporated under vacuum. The resulting crude dark brown oil was purified by MPLC (Biotage). On the basis of TLC results (90% ethyl acetate/10% methanol; R_f = 0.37), the following gradient system of ethyl acetate and methanol was chosen: 2 column volumes (CV) of 2% MeOH/98% ethyl acetate; 10 CV 2% methanol progressing to 20% methanol; and 4 CV of 20% methanol. Elution of the product was monitored at 280 and 310 nm with a flow rate of 20 mL/min. The acquired fractions (9 mL) were scanned for product peaks and then evaporated under vacuum to retrieve the purified product as yellowish oil (224 mg, 0.87 mmol, 12%). ^{1}H NMR (400 MHz, CD_3CN, 25 °C): δ 8.48 (d, 2H, *J* = 4.42 Hz), 7.69 (td, 2H, *J* = 7.70 Hz, *J* = 1.64) 7.33−7.18 (m, 4H), 4.60 (bs, 4H), 3.65 (s,3H). ^{13}C NMR (100.58 MHz, CD_3CN, 25 °C): δ 158.7, 158.1, 150.2, 137.6, 123.2, [122.6 broad), 122.2 (broad)], 53.3, [53.6 (broad), 53.2 (broad)]. The ^{1}H NMR and ^{13}C NMR spectra can be found in the Supporting Information (Figures 3S and 4S). The FTIR-IR spectrum of **4d** showed a C═O absorbance at 1699 cm^{-1}. UV−vis: $\varepsilon_{260\ nm}$ = 6760 M^{-1} cm^{-1}. HRMS: EI-Orbitrap Velos Pro $C_{14}H_{15}N_3O_2$, *m/z* calcd 257.1155(+), *m/z* found 257.1164(+), PPM +3.50.

*(iv) Synthesis of O-Isopropyl-2,2′-bis(2-picolyl)carbamate (****4e****).* To an oven-dried 100 mL round-bottom flask containing 20 mL of CH_2Cl_2 was added bis(2-picolyl)amine (0.678 mL, 3.76 mmol). The flask was fitted with a condenser and placed in an oil bath. Triethylamine (0.733 mL, 5.264 mmol) was added, and the solution was allowed to stir under argon for 15 min. Isopropyl chloroformate (4.55 mL, 4.55 mmol) was added dropwise to the flask, and the oil bath was heated to 40 °C for 4.5 h, after which the solution was allowed to stir while returning to room temperature overnight. The solvent was removed by rotary evaporation, and the crude product was dried under vacuum via an oil pump to give a brown oil. Approximately half of the material was redissolved in the minimum amount of dichloromethane (∼5 mL), and the solution was used to prepare a sample for Biotage MPLC purification with the parameters required for separation being determined from TLC trials. Ultimately, an R_f value of 0.31 in a solvent mixture of 50:50 hexanes/ethyl acetate was used to select the solvent gradient program (hexane/ethyl acetate gradient elution starting 88:12 for 45 mL; ramp to 0:100% over 350 mL; maintain 0:100% for 200 mL; fractions: 9 mL; flow rate: 25 mL/min. The UV−vis absorbance of the eluting fractions was followed at 270 and 310 nm. Fractions corresponding to the peaks on elution profiles were analyzed by ^{1}H NMR, and those containing the desired product were combined and solvent removed using rotary evaporation to yield a colorless oil (187 mg, 0.66 mmol, 17%). ^{1}H NMR (400 MHz, CD_3CN, 25 °C): δ 8.47 (d, 2H, *J* = 4.42 Hz), 7.70 (td, 2H, *J* = 7.70 Hz, *J′* = 1.65 Hz) 7.33−7.17 (m, 4H), 4.86 (septet, 1H, *J* = 6.22 Hz), 4.63 (bs, 2H) 4.57 (bs, 2H), 1.13 (d, 6H *J* = 6.31 Hz). ^{13}C NMR (100.58 MHz, CD_3CN, 25 °C): δ [158.9(broad),158.8(broad)], 157.1, 150.0, 137.6, 123.1, [122.5(broad),122.2 (broad)], 69.7, [53.5(broad), 53.1 (broad)], 22.2. ^{1}H NMR and ^{13}C NMR spectra can be found in the Supporting Information (Figures 5S and 6S). The FTIR-IR spectrum of **4d** showed a C═O absorbance at 1693 cm^{-1}. UV−vis: $\varepsilon_{260\ nm}$ = 7799 M^{-1} cm^{-1}. HRMS:EI-Orbitrap Velos Pro $C_{16}H_{19}N_3O_2$, *m/z* calcd 285.1477(+), *m/z* found 285.1468(+), PPM −3.3.

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(v) Synthesis of O-Trifluoroethyl-2,2′-bis(2-picolyl)carbamate (4c). This was prepared by a variation of the procedure reported previously.[20] Into a 50 mL round-bottom flask cooled in ice bath at 0 °C containing a suspension of triphosgene (1.00 g, 3.4 mmol) in CH_2Cl_2 (6 mL) were sequentially added 2,2,2-trifluoroethanol (1.00 g, 0.72 mL, 9.96 mmol), dimethylformamide (20 μL), and triethylamine (1.01 g, 1.39 mL, 9.8 mmol). The mixture was allowed to stir at 0 °C for 1 h and then stirred for another 3 h at rt.

The resulting reaction solution was pale yellow and was stored in a −11 °C freezer overnight. The next day, one-fourth of the reaction mixture prepared as above was added dropwise to a 50 mL round-bottom flask containing bis(2-picolyl)amine (452 μL, 2.5 mmol) and triethylamine (0.284 mL, 2.75 mmol) in acetonitrile (4 mL). The reaction mixture was allowed to stir for 2 h at room temperature (reaction turned dark green and opaque). The mixture was filtered, and the collected solid was washed with ethyl ether. This and the organic fractions were combined and evaporated. TLC analysis for the residue (100% ethyl acetate) demonstrated good separation and complete reaction of starting material. Part of the crude product was purified by MPLC (Biotage) using the following parameters: column size, medium 25+; monitoring wavelength, 275 and 300 nm; fraction size, 9 mL; flow rate, 20 mL/min; gradient, ethyl acetate/hexanes (20:80, 4 CV; 20:80 to 100:0 10 CV; 100:0 4 CV).

The fractions containing pure **4c** were combined and solvent evaporated, and the pale brown oil residue was collected (163 mg, 0.50 mmol, 20%). ^{1}H NMR (400 MHz, CD_3CN, 25 °C): δ 8.50 (d, 2H, J = 4.3 Hz), 7.71 (t, 2H, J = 7.7 Hz,) 7.32−7.18 (m, 4H), 4.67 (bs, 2H) 4.63 (bs, 2H), 4.59 (quad., 2H, J = 8.7 Hz). ^{13}C NMR (100.58 MHz, CD_3CN, 25 °C): δ [158.1 (broad), 158.0 (broad)], 155.8, 150.2, 137.7, [123.4 (broad), 123.3 (broad)], [122.7 (broad), 122.3 (broad)], 62.1 (quad. J = 35.9 Hz), [54.2 (broad), 53.3 (broad)]. ^{19}F NMR (376.5 MHz, CD_3CN, 25 °C) δ = −75.97 (t, J = 8.7 Hz). ^{1}H, ^{19}F, and ^{13}C NMR spectra can be found in the Supporting Information (Figures 7S, 8S, and 9S). UV−vis: $\varepsilon_{260\ nm}$ = 7556 $M^{-1}cm^{-1}$. HRMS: EI-Orbitrap Velos Pro $C_{15}H_{14}N_3O_2F_3$, m/z calcd 325.1038(+), m/z found 325.1031(+). PPM: −2.2

(c) Kinetic Studies. *(i) Cu(II)-Catalyzed Methanolysis of (4a,b).* The Cu(II)-promoted methanolyses of **4a,b** were studied over a ^{s}pH range of 5.2−7.8 under buffered conditions (2,6-lutidine, ^{s}pH = 6.2−6.7; 2,4,6-collidine, ^{s}pH = 7.4−7.8 (^{s}pH = 7.9 for **4b**); ytterbium(III) trifluoromethanesulfonate, ^{s}pH = 5.2−5.5) in the presence of varying [$Cu(OTf)_2$] at 25 °C in methanol. Duplicate kinetic runs were performed at [**4a**] = 0.05 mM ([**4b**] = 0.08 mM), and the reaction progress was followed by observing the rate of formation of 4-nitrophenol at 330 nm (3-nitrophenol at 335 nm in the case of **4b**). Reaction solutions having a total volume of 2.50 mL were prepared by sequential addition of methanol, and the appropriate amount of a stock solution of the buffer in methanol was partially neutralized by triflic acid in the case of amine buffers and sodium methoxide in the case of $Yb(OTf)_3$ so that the total [buffer] was 10 mM. To these were added the appropriate amounts of a methanol stock solution (50 mM) of $Cu(OTf)_2$ to give final concentrations that varied from 0.025 to 2 mM. The reaction was initiated by the addition of a 25 μL aliquot of stock solution (5 mM) of **4a** in acetonitrile (83.3 μL of 2.4 mM solution of **4b**). The Abs vs time traces followed first-order behavior for at least five half-times and were fitted to a standard first-order kinetic exponential equation yielding first-order rate constants, k_{obs}. Kinetic data presented in Tables 1 and 2 are averages of duplicate sets of experiments.

(ii) Kinetics of Cu(II)-Promoted Methanolysis of Carbamates 4c−e. The Cu(II)-promoted methanolyses of **4c−e** were studied at ^{s}pH = 7.9 (10 mM of a 2,4,6-collidine/HOTf buffer; 3:1) in the presence of various [$Cu(OTf)_2$] at 25 °C in methanol. Duplicate kinetic runs were performed at a [**4c−e**] = 0.5 mM, and the progress of the reaction was followed by observing the disappearance of the starting material at 362 nm. Reaction solutions were prepared by sequential addition of methanol and the appropriate amount of stock solution of the buffer in methanol partially neutralized by triflic acid followed by the addition of corresponding amounts of methanol stock solution (50 mM) of $Cu(OTf)_2$. The reaction was initiated by the addition of a 25 μL aliquot of stock solution (50 mM) of the substrate (**4c−e**) in acetonitrile. Initial rates of the reaction were obtained as the slope of Abs vs time plot for the first ∼10% of the reaction, and first-order rate constants were calculated using the overall change in absorbance after the reaction was completed. Kinetic data presented in Table 2 are averages of duplicate sets of experiments.

(iii) Product Analysis of the Metal Ion Catalyzed Methanolysis of Carbamates 4c−e. Aliquots of the stock solutions of **4c−e** (25 mM), 2,6-lutidine (50 mM), and $Cu(OTf)_2$ (50 mM) prepared in methanol-d_4 were added to 600−1000 μL of methanol-d_4 in an NMR tube. The concentrations in the final preparations were **4c−e** (3 mM), 2,6-lutidine (6 mM), and $Cu(OTf)_2$ (3 mM). The 2,6-lutidine was added as an internal standard and buffer. The progress of the reaction was followed by ^{1}H NMR at 25 °C with multiple spectra taken at various time periods over the course of several days with the NMR tube being placed into thermostated bath at 25 °C when not under NMR observation. Each spectrum was phase and baseline corrected before the integration procedure. The internal standard signal corresponding to the CH_3− groups of 2,6-lutidine (δ = 2.57) was calibrated to 600 (1 unit per 0.01 mM). Due to the paramagnetic nature of the Cu(II), the NMR signals corresponding to complexed **4c−e** are severely broaden and were not observed under these experimental conditions. The productive pathway (resulting from C−N bond cleavage) was evident from the appearance of the methoxy peak corresponding to dimethylcarbonate ($CD_3OC(O)OCH_3$) at δ = 3.70. No production of nondeuterated methanol or $(CH_3)_2CHOD$ resulting from C−O bond cleavage was observed under experimental conditions.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectral data for **4a−e**, ^{19}F NMR spectral data for the Cu(II)-promoted cleavage of **4c** and UV/vis Abs vs time profiles for the Cu(II)-promoted decomposition of **4b** at 25 °C, **4c** in methanol at 25 and 55 °C, and initial rate data for methanolysis of **4d** at 25 °C. 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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(3) The designation of pH in nonaqueous solvents is based on that recommended by the IUPAC: IUPAC. *Compendium of Analytical Nomenclature. Definitive Rules 1997*, 3rd ed.; Blackwell: Oxford, U.K., 1998. The pH meter reading for an aqueous solution determined with

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an electrode calibrated with aqueous buffers is designated as ${}^{w}_{w}$pH; if the electrode is calibrated in water and the "pH" of the neat buffered alcohol solution is then measured, the term ${}^{s}_{w}$pH is used; and if the electrode is calibrated in the same solvent in which the "pH" reading is made, then the term ${}^{s}_{s}$pH is used; acid dissociation constants are designated as ${}^{s}_{s}pK_a$ values. In methanol, ${}^{s}_{s}$pH = ${}^{s}_{w}$pH − (−2.24), and since the autoprotolysis constant of methanol is $10^{-16.77}$ M^2, neutral ${}^{s}_{s}$pH is 8.4.

(4) Broxton, T. J.; Deady, L. W.; Lim, R. H. K. *Aust. J. Chem.* **1981**, *34*, 1993.

(5) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6970.

(6) (a) This behavior has been observed before and previously discussed for the Cu(II)-promoted decomposition of bis(2-picolyl) ureas (**2**)[2] and for the La^{3+}-promoted cleavage of 2-hydroxypropyl-*p*-nitrophenyl phosphate: Tsang, J. S. W.; Neverov, A. A.; Brown, R. S. *J. Am. Chem. Soc.* **2003**, *125*, 1559. (b) The first ${}^{s}_{s}pK_a$ of methanol bound to Cu(II) was determined by half neutralization at ($^{-}OCH_3$)/Cu(II) = 0.5 to be 6.86. Neverov, A. A.; Brown, R. S. *Org. Biomol. Chem.* **2004**, *2*, 2245.

(7) Equation 1 was derived using a strong binding equation as presented in ref 6a and material balance for $Cu(OTf)_2$.

(8) We have noted before that there is a slight deviation from first-order kinetics for the decomposition of Cu(II) complexes of bis(2-picolyl)amides[1a−c] and ureas[2] studied at a 1:1 ratio of Cu^{2+}:substrate. This probably stems from the fact that the C═O-containing amide or urea substrate binds the metal ion worse than does the immediate cleavage product, bis(2-picolyl)amine, meaning that as the reaction progresses some free Cu^{2+} is being removed from the mixture. This is not a problem with substrates **4a**,**b** where the initial cleavage produces the aryloxy group but becomes a problem with **4c**−**e** where alkoxy cleavage is suppressed (**4d**,**e**) or competes with C−N cleavage (**4c**).

(9) The overall kinetic dependences for **4d**,**e** were similar to those obtained for the decomposition of **4a**,**b** vs [Cu^{2+}] with trends analogous to those described above (rate of the reactions, binding and inhibition constants being ${}^{s}_{s}$pH-dependent; as an example, see Figure 18S, Supporting Information). However, as an additional complication, the change in absorbance during the course of the reaction was also ${}^{s}_{s}$pH-dependent (as this originates from the presence of Cu(II):**4d**,**e**: ($^{-}OCH_3$) complex). These additional complications precluded us from making a detailed analysis of the concentration dependences for this reaction. The situation with **4c** is further complicated by the fact that the actual disappearance of starting material is channeled into C−O and C−N cleavage pathways.

(10) Maxwell, C. I.; Neverov, A. A.; Mosey, N. J.; Brown, R. S. *J. Phys. Org. Chem.* **2014**, *27*, 419.

(11) (a) A Brønsted plot (not shown) of the five data points of log(k_{obs}) vs ${}^{s}_{s}pK_a^{HOR}$ data in Table 2 gives a gradient of −0.34 ± 0.02, r^2 = 0.9934. A linear plot with a small negative gradient is most simply interpreted as arising from a common rate-limiting transition state of nucleophilic attack with some build-up of negative charge on the ArO/OR groups. (b) A change from rate of formation of intermediate to its breakdown would have been evident as a change in mechanism with substrates having poor leaving groups such as methoxide or isopropoxide. If this occurred it would appear as an upward break in the Brønsted plot with a less negative, or possibly zero or slightly positive gradient, since now the leaving group departing is a common one of the Cu(II) coordinated amido unit and not the alkoxide. That this is not observed most likely indicates that that the change in mechanism occurs after the rate-limiting step of formation of the intermediate..

(12) Gottlieb, H. E.; Kotlyar, V.; Nudekman, A. *J. Org. Chem.* **1997**, *62*, 7512.

(13) IUPAC. *Compendium of Chemical Terminology*, 2nd ed. (the "Gold Book"); Compiled by McNaught, A. D., Wilkinson, A.; Blackwell Scientific Publications: Oxford, 1997. XML on-line corrected version:Nic, M.; Jirat, J.; Kosata, B. 2006, http://goldbook.iupac.org updates compiled by Jenkins, A. ISBN 0-9678550-9-8. Doi: 10.1351/goldbook.

(14) (a) What is termed here as the "effective" ${}^{s}_{s}pK_a^{H-N}$ of 15.6 for the departing Cu(II):bis(2-picolyl)amide anion from the tetrahedral intermediate **6** is conditional for this specific case. The departure of any leaving group from a nonsymmetric tetrahedral intermediate depends not only on how good the electron attraction of the departing group is but also on the electron push provided by the remaining groups during the former's departure. See ref 5 and related works by Jencks for examples of this. (b) The Gresser and Jencks study of the breakdown of tetrahedral intermediates formed from the attack of aryloxides on carbamates containing trialkylamines allowed them to vary both the leaving groups according to their pK_a values. This and the fact that the amines used in their study left as neutral amines, where the appropriate pK_a would be that of H^+-$NR_1R_2R_3$. In the present work, since we cannot vary the amine structure and the amine leaves as a Cu(II)-coordinated amido unit, we cannot ascertain the consequences on leaving ability of the OR groups due to varying the structure of the amine portion..

(15) (a) An estimate of 44.5 for the in methanol comes from the relationship converting the pK_a values for aromatic alcohols in water to methanol; ${}^{s}_{s}pK_a^{MeOH} = (1.08 \pm 0.03)pK_a^{HOH} + (3.50 \pm 0.20)$. Neverov, A. A.; Liu, C. T.; Bunn, S. E.; Edwards, D.; White, C. J.; Melnychuk, S. A.; Brown, R. S. *J. Am. Chem. Soc.* **2008**, *130*, 6639. (b) An estimate of 35 for the ${}^{s}_{s}pK_a$ of bis(2-picolyl)amine comes from the relationship ${}^{s}_{s}pK_a^{MeOH} = 0.75pK_a^{HOH} + 6.53$ derived from a limited set of aliphatic alcohols; see: Neverov, A. A.; Sunderland, N. E.; Brown, R. S. *Org. Biomol. Chem.* **2005**, *3*, 65. (c) The relationship for amines will not necessarily follow those for the alcohols; however, the amine → amide ionization process will produce a charged anion which should be destabilized in methanol relative to water, increasing the pK_a relative to that determined in water..

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(17) Liu, C. T.; Neverov, A. A.; Maxwell, C. I.; Brown, R. S. *J. Am. Chem. Soc.* **2010**, *132*, 3561.

(18) Gibson, G.; Neverov, A. A.; Brown, R. S. *Can. J. Chem.* **2003**, *81*, 495.

(19) Our initial attempts to obtain *O*-aryl *N*,*N*-bis(2-picolyl) carbamates **4a**,**b** in a free base form demonstrated that these materials are very unstable even for short-term storage as the first-obtained product rapidly turned into a dark brown oil. As such, we have prepared these substrates in a stable hydrochloride salt form. Further kinetic experiments demonstrated that the addition of 2 equiv of chloride ions does not affect the rate of the reaction.

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