Inorganic Chemistry

Article

pubs.acs.org/IC

Cu(II)-Ion-Catalyzed Solvolysis of *N,N*-Bis(2-picolyl)ureas in Alcohol Solvents: Evidence for Cleavage Involving Nucleophilic Addition and Strong Assistance of Bis(2-picolyl)amine Leaving Group Departure

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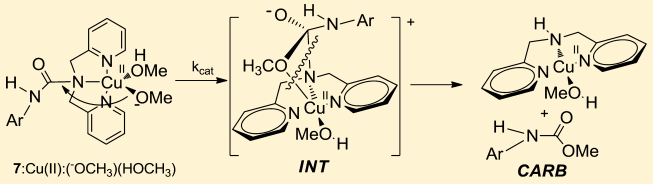
Supporting Information

ABSTRACT: The kinetics and products for solvolysis of *N*-*p*-nitrophenyl-*N*′,*N*′-bis(pyridin-2-ylmethyl) urea (**7a**), *N*-methyl-*N*-*p*-nitrophenyl-*N*′,*N*′-bis(pyridin-2-yl methyl) urea (**7b**), and *N*-phenyl-*N*′,*N*′-bis(pyridin-2-yl-methyl) urea (DPPU) (**7c**) promoted by Cu(II) ion in methanol and ethanol were studied under pH-controlled conditions at 25 °C. Methanolysis and ethanolysis of these substrates proceeds rapidly at a 1:1 ratio of substrate:metal ion, the half-times for decomposition of the Cu(II):**7a** complexes being ∼150 min in methanol and 15 min in ethanol. In all cases, the reaction products are the Cu(II) complex of bis(2-picolyl)amine and the *O*-methyl or *O*-ethyl carbamate of the parent aniline, signifying that the point of cleavage is the bis(2-picolyl)—N—C═O bond. Reactions of the Cu(II):**7b** complexes in each solvent proceed about 3−5 times slower than their respective Cu(II):**7a** complexes, excluding an elimination mechanism that proceeds through an isocyanate which subsequently adds alcohol to give the observed products. The reactions also proceed in other solvents, with the order of reactivity ethanol > methanol >1-propanol >2-propanol > acetonitrile (with 0.2% methanol) > water spanning a range of 150-fold. The mechanism of the reactions is discussed, and the reactivity and mode of cleavage are compared with that of the M(II)-promoted ethanolytic cleavage of a mono-2-picolyl derivative, *N*-*p*-nitrophenyl-*N*′-(pyridin-2-yl-methyl) urea (**4a**), which had previously been shown to cleave at the aniline N−C═O bond. The large estimated acceleration of the rate of attack of ethoxide on **7b** of at least 2×10^{16} provided by associating Cu(II) with the departing group in this urea is discussed in terms of a trifunctional role for the metal ion involving Lewis acid activation of the substrate, intramolecular delivery of a Cu(II)-coordinated ethoxide, and metal-ion-assisted leaving group departure.



I. INTRODUCTION

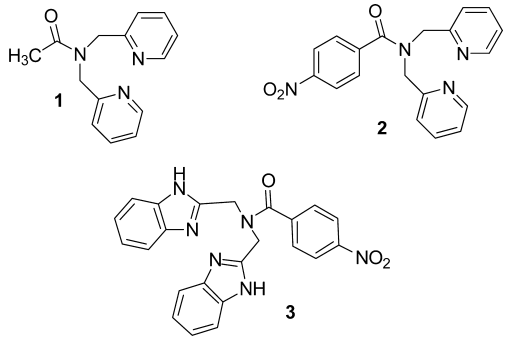
Ureases (EC 3.5.1.5) are Ni(II)-dependent metalloenzymes that functionally belong to the class of amidohydrolases that catalyze the hydrolysis of urea into carbon dioxide and ammonia.[1,2] The widely studied jack-bean urease has a remarkable substrate fidelity since the catalytic efficiency for its second-best urea-type substrate semicarbazide ($NH_2C(=O)NHNH_2$) is 1/1000th that of urea itself.[3] The active sites of all known ureases are highly conserved and contain a bis-μ-hydroxo-bridged dimeric nickel center with a metal−metal ion separation of ∼3.5 Å. The nickel ions are also bridged by an N-carbamylated lysine through its O atoms and by a hydroxide ion. One nickel ion is coordinated to N atoms of histidines residues and one water molecule, while the other is coordinated to two histidines, an aspartic acid, and two water molecules.[4] Urease activity is specific for its metal ion, namely, Ni(II), with the Zn(II)- and Cu(II)-substituted enzymes being inactive.[5]

Urea is resistant toward hydrolysis because of its resonance stabilization estimated at 30−40 kcal/mol.[3] Its pH-independent decomposition in water between 2 and 12 proceeds not by *hydrolysis* involving nucleophilic addition to the C═O unit but by elimination of NH_3 to yield cyanic acid (HN═C═O)[6] with a rate constant from 8.3×10^{-10} to 1.2×10^{-11} s^{-1} at 25 °C.[7,8] The catalytic reaction mediated by urease itself is generally believed to operate via *hydrolytic* nucleophilic addition of water (or hydroxide) to all of its substrates including acetamide, formamide, semicarbazide, and *N*-methyl urea,[9] although recent computational[10] and experimental evidence with small molecule dinuclear complexes[11] indicates that elimination might be a competitive pathway. Whatever its mechanism, the enzyme produces very large rate accelerations since its k_{cat} is estimated to be 10^{14}−10^{15} times greater than the computed spontaneous rate constant for cleavage of urea at pH 7.[12,8] More recent computational studies indicate that the enzymatic acceleration may be as much as 10^{25} times that for the computed rate constant for hydroxide attack on $H_2NC(=O)NH_2$.[10,13]

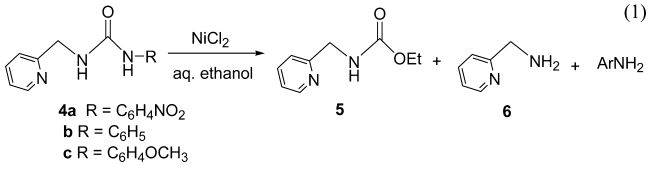
Recent work[14] in our lab has centered on mechanisms by which metal-containing complexes can facilitate cleavage of esters, phosphates, amides, and ureas in alcohol media. The pathways by which metal ions promote acyl and phosphoryl transfer reactions can involve one or more of several roles such as (a) Lewis acid activation, (b) intracomplex delivery of a metal-coordinated lyoxide nucleophile, (c) stabilization of the substrate−nucleophile activated complex, and (d) assistance of the departure of the leaving group (leaving group assistance, LGA).[15,16] Kinetic studies of the methanolysis of *N*-acyl

Received: March 18, 2014
Published: July 23, 2014

derivatives of *N,N*-bis(2-picolyl)amine and *N,N*-bis-(benzimidazol-2-yl-methyl)amine (**1**−**3**)[17−19] catalyzed by various transition metal ions under pH-controlled conditions[20] revealed trifunctional roles for the metal ions. These involved a pre-equilibrium coordination of the metal ion to the bis(2-picolyl)amino or bis(benzimidazol-2-yl)amino portion of the ligand system, intramolecular attack of the bound metal ion's coordinated methoxide on the C═O, and metal-ion-assisted C−N departure. The resulting catalytic effect of the metal ions is striking for Cu(II)-promoted cleavage of **2**, being at least 10^{17} times faster than the reaction involving free methoxide.[19]



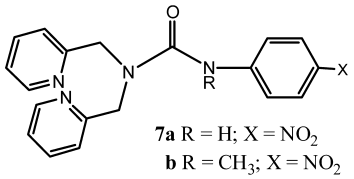
Our attention was drawn recently to two studies[12,21] dealing with transition-metal-ion-promoted ethanolytic cleavage of some substituted ureas bearing an *N*-(2-picolyl)amine portion (**4a,b**). The first[12] reported that **4a**, in aqueous ethanol in the presence of excess $NiCl_2$ at elevated temperature (50−80 °C), produced *O*-ethyl-*N*-(2-picolyl) carbamate (**5**) and by competing hydrolysis gave smaller amounts of (2-picolyl)amine (**6**) as in eq 1. The mechanism was proposed to involve metal binding



(1)

to the C═O unit with subsequent delivery of a Ni(II)-bound lyoxide leading to products. A subsequent report[21] describing the X-ray diffraction structure of the Cu(II) complex of **4a** showed that the metal was actually bidentate bound by both the pyridyl and the urea nitrogens in a five-membered metallocyclic ring. Further infrared spectral studies showed that the Ni(II) complexes of more heavily substituted ureas **4a**−**c** were subject to a similar mode of coordination as the Cu(II) complexes and that these differed in structure from that of the Zn(II) complex of **4a** which was bidentate bound through the pyridyl N and urea C═O in a seven-membered ring. Sczepanski's[22] more detailed results for the Ni(II)-catalyzed ethanolysis reactions indicated that the phenyl- (**4b**) and 4-methoxyphenyl- (**4c**) substituted ureas reacted faster than the 4-nitrophenyl ureas (**4a**) and that the Cu(II) complexes reacted more quickly (by about 7 times) than the Ni(II) complexes. Product studies showed that the primary products of all ethanolysis reactions were the corresponding anilines plus the ethyl carbamate of (2-picolyl)amine (**5**) as in eq 1; no products corresponding to the ethyl carbamate of the anilines could be identified. Finally, Sargeson and co-workers[23] investigated the structure and reactivity of a ligand exchange inert bis(ethylenediamine)Co-(III) adduct of **4**, showing that decomposition of these in aqueous acid at 55 °C led to elimination of the anilines and produced the $(en)_2Co(III)$ complex of (2-picolyl)amine.

In view of the above works and our interest in LGA for cleavage of bis(2-picolyl)-substituted amides, we have undertaken a more detailed study of the $Cu(OTf)_2$-catalyzed alcoholysis of bis(2-picolyl)-substituted ureas **7a**−**c** under $^{s}_{s}$pH-controlled conditions. As will be shown, in contrast to the reported cleavages of **4a**−**c** mediated by Ni(II) (and Cu(II)), which gives the products shown in eq 1, the Cu(II)-promoted methanolyses and ethanolyses of **7a**−**c** proceeds rapidly at 25 °C to give bis(2-picolyl)amine and the *O*-methyl or *O*-ethyl carbamate of the corresponding aniline.



7a R = H; X = NO_2
b R = CH_3; X = NO_2
c R = H; X = H

II. EXPERIMENTAL SECTION

II.a. Materials. Nickel perchlorate hexahydrate (reagent grade) was purchased from GFS Chemicals. Copper(II) trifluoromethanesulfonate (98%), trifluoromethanesulfonic acid (≥99%), phenyl isocyanate (98%), and 4-nitrophenyl isocyanate (98%) were obtained from Aldrich. 2,2′-Dipicolyl amine (97%) was obtained from Pure Chemistry Scientific Inc., while 2,6-lutidine (98%) was obtained from Sigma-Aldrich. 2,4,6-Collidine (98%) was obtained from BDH Laboratory Reagents, and methanol (99.8%, anhydrous) was purchased from EMD Chemicals.

II.b. General Methods. ^{1}H NMR spectra were determined at 400 MHz. $[CH_3OH_2^+]$ and $[C_2H_5OH_2^+]$ were determined potentiometrically using a Fisher Scientific Accumet combination glass electrode (model no. 13-620-292) calibrated with certified standard aqueous buffers (pH 4.00 and 10.00) as described previously.[24] The $^{s}_{s}$pH values in methanol were determined by subtracting a correction constant of −2.24[20] from the electrode readings, and the autoprotolysis constant for methanol was taken to be $10^{-16.77}$ M^2. The $^{s}_{s}$pH values in ethanol were determined by subtracting a correction constant of −2.54[25] from the electrode readings, and the autoprotolysis constant for methanol was taken to be $10^{-19.1}$ 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.

II.c. Synthesis. *II.c.i. Synthesis of N-Phenyl-N′-(pyridin-2-yl-methyl) Urea (PPU), (**4b**).* This was prepared following a previously reported method with some modifications.[22] 2-Picolylamine (0.477 mL, 4.62 mmol) was dissolved in 10 mL of dry CH_2Cl_2 and cooled to 0 °C under Ar. Phenyl isocyanate (0.503 mL, 4.62 mmol) was then added dropwise, giving a clear colorless solution which, after 10 min, turned slightly yellow with formation of white precipitate. The reaction mixture was stirred overnight at room temperature, after which it was filtered under vacuum and the white powder was collected. Mp 127−128 °C. The product was analyzed by ^{1}H NMR in $CDCl_3$, and the resulting spectrum was consistent with the structure and previously reported data[22] and is presented in Figure 8S (Supporting Information).

*II.c.ii. Synthesis of N-4-Nitrophenyl-N′-(pyridin-2-yl-methyl) Urea, (p-nitro-PPU), (**4a**).* This was prepared following the above procedure from 2-picolylamine (0.477 mL, 4.62 mmol) dissolved in 10 mL of dry CH_2Cl_2 cooled to 0 °C under Ar. After addition of 4-nitrophenyl isocyanate (0.76 g, 4.62 mmol) the reaction mixture appeared as a pale yellow cloudy mixture which, with further stirring, gave a pale yellow solid precipitate. The reaction mixture was stirred overnight at room temperature and then filtered under vacuum to give a pale yellow powder. Mp 179−181 °C. The ^{1}H NMR spectrum was consistent with

dx.doi.org/10.1021/ic500620k | Inorg. Chem. 2014, 53, 7916−7925

Table 1. Kinetic $^{s}_{s}pK_a$ and k_{max} Constants for Cleavage of Various 7a,b,c:Cu(II):($^{-}$OR) Complexes Reacting in Methanol or Ethanol at 25 °C[a]

complex	**7a**:Cu(II):($^{-}$OR)	**7b**:Cu(II):($^{-}$OR)	**7c**:Cu(II):($^{-}$OR)
methanol			
kinetic $^{s}_{s}pK_a$	7.16 ± 0.10	<6.7	6.24 ± 0.06
k_{max} (s^{-1})	(7.5 ± 1.3) × 10^{-5}	(2.9 ± 0.3) × 10^{-5}	(1.9 ± 0.14) × 10^{-5}
ethanol			
kinetic $^{s}_{s}pK_a$	6.25 ± 0.09	6.47 ± 0.06	6.39 ± 0.08
k_{max} (s^{-1})	(7.0 ± 0.7) × 10^{-4}	(1.3 ± 0.1) × 10^{-4}	(6.2 ± 0.5)x10^{-4} s^{-1}

[a]Complexes are generated in situ and assumed to be fully formed at 1:1 concentrations of ligand and metal ion.

the structure and previously reported data[22] and is presented in Figure 7S, Supporting Information.

II.c.iii. Synthesis of N-p-Nitrophenyl-N′,N′-bis(pyridin-2-ylmethyl) Urea, (4-nitro-DPPU), ***7a.*** 2,2′-Dipicolylamine (0.287 g, 1.51 mmol) was dissolved in 7 mL of dry CH_2Cl_2 and cooled to 0 °C under Ar. 4-Nitrophenyl isocyanate (0.237 g, 1.44 mmol) was dissolved in 5 mL of dry CH_2Cl_2, which was then added dropwise to the reaction mixture. The bright yellow solution was stirred overnight at room temperature, after which a portion of the reaction mixture was purified by MPLC (silica stationary phase, ethyl acetate/methanol, 50:50 v/v ratio) to give yellow solid which was analyzed by ^{1}H and ^{13}C NMR in d^4-methanol. ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ 8.57 (d, 2H, J = 4.4 Hz), 8.21 (m, 2H; AA′), 7.77 (td, 2H, J = 7.78 Hz, J = 1.77), 7.69 (m, 2H; BB′), 7.36−7.30 (m, 4H), 4.75 (s, 4H). ^{13}C NMR (100.58 MHz, CD_3OD, 25 °C): δ 158.55, 158.16, 150.05, 147.92, 143.56, 138.98, 125.80, 124.28, 123.92, 120.00, 53.81. These spectra can be found in Figures 3S and 4S, Supporting Information. The FTIR-IR spectrum of **7a** showed a C═O absorbance at 1680 cm^{-1} as well as NO_2 symmetrical and asymmetrical stretches at 1329 and 1507 cm^{-1}. UV−vis: ε_{326} = 3.53 × 10^4 M^{-1} cm^{-1}. EI-MS: $C_{19}H_{17}N_5O_3$; m/z calcd 363.1331 (+); found 363.1319 (+). Mp 142−144 °C

II.c.iv. Synthesis of N-Methyl-N-p-nitrophenyl-N′,N′-bis(pyridin-2-yl-methyl) Urea, ***7b.*** *N-p*-Nitrophenyl-*N*′,*N*′-bis(pyridin-2-yl methyl) urea (0.72 g, 1.98 mmol) was mixed with 6 mL of dry acetone with stirring at room temperature to give a pale yellow slurry, after which potassium hydroxide (0.12 g, 2.18 mmol) was added in one portion, causing the slurry to turn bright orange. The mixture was stirred for 10 min under argon, and dimethyl sulfate (0.28 mL, 2.97 mmol) was added in one portion by a syringe to the reaction mixture. The reaction mixture was then heated to reflux under Ar for 2 h, after which it was hot filtered, and the solvent was removed by rotatory evaporation. Part of the mixture was purified by MPLC (silica gel stationary phase, methanol/ethyl acetate, gradient elution from 0:100 to 50:50 v/v ratio). ^{1}H NMR analysis of the eluted fraction showed the presence of both the nonmethylated and the *N*-methylated *N-p*-nitrophenyl-*N*′,*N*′-bis(pyridin-2-yl methyl) urea. The product was further purified by dissolving the mixture in methanol followed by addition of water until the solution became turbid, after which it was placed in a freezer (−11 °C) overnight. The liquid was separated from the crystals by filtration, and the solvent was removed by rotary evaporation followed by further evaporation under reduced pressure provided by a vacuum pump. The product was analyzed by ^{1}H NMR and ^{13}C NMR in $CDCl_3$. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.59 (d, 2H, J = 4.48 Hz), 8.12 (m, 2H; A^{phenyl}), 7.65 (td, 2H, J = 7.75 Hz, J = 1.77 Hz), 7.25−7.10 (m, 6H), 4.59 (s, 4H) 3.25(s, 3H). ^{13}C NMR (100.58 MHz, $CDCl_3$, 25 °C): δ 160.92, 156.62, 151.20, 149.61, 141.85, 136.64, 125.24, 122.51, 122.21, 118.61, 53.74, 37.52. These spectra can be found in the Supporting Information (Figure 5S and 6S). The FTIR-IR spectrum of **6** showed a C═O absorbance at 1667 cm^{-1} as well as NO_2 symmetrical and asymmetrical stretches at 1311 and 1504 cm^{-1}. UV−vis: ε_{337} = 1.25 × 10^4 M^{-1} cm^{-1} at 337 nm. EI-MS: $C_{20}H_{19}N_5O_3$; m/z calcd 377.1488 (+); found 377.1475 (+). Mp 184−186 °C.

II.c.v. Synthesis of N-Phenyl-N′,N′-bis(pyridin-2-yl-methyl) Urea (DPPU), ***7c.*** 2,2′-Dipicolyl amine (0.172 g, 0.861 mmol) was dissolved in 10 mL of dry CH_2Cl_2 and cooled to 0 °C under Ar. Phenyl isocyanate (93.6 μL, 0.861 mmol) was then added slowly, and the yellow-orange reaction mixture was stirred for 72 h at room temperature. The product mixture was purified by MPLC (silica gel stationary phase). The first elution using a 50:50 ratio of hexanes and ethyl acetate removed unreacted phenyl isocyanate. Subsequent elution using a 50:50 ratio of ethyl acetate/methanol yielded the desired product as an oil. The purified product was analyzed by ^{1}H NMR and ^{13}C NMR in $CDCl_3$. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 10.11 (bs, 1H), 8.58 (d, 2H, J = 4.74 Hz), 7.60 (td, 2H, J = 7.64 Hz, J = 1.77 Hz), 7.51 (m, 2H), 7.30 (m, 2H), 7.24−7.18 (m, 4H), 7.00 (tt, 1H, J = 7.45 Hz, J = 1.1 Hz), 4.64 (s, 4H). NMR (100.58 MHz, $CDCl_3$, 25 °C): δ 157.55, 156.84, 148.56, 140.14, 136.92, 128.52, 122.81, 122.51, 121.97, 119.15, 52.82. ^{1}H NMR and ^{13}C NMR spectra can be found in the Supporting Information (Figure 1S and 2S). The ATR-IR spectrum showed a C═O absorbance at 1663 cm^{-1}. UV−vis: ε_{240} = 2.72 × 10^4 M^{-1} cm^{-1} at 240 nm. EI-MS: $C_{19}H_{18}N_4O$; m/z calcd 318.1481 (+); found 318.1469 (+).

II.d. General UV−Vis Kinetics. $Cu(CF_3SO_3)_2$-catalyzed methanolyses and ethanolyses of ureas **7a−c** were followed by monitoring the rate of disappearance of the starting materials at 360 nm using a UV−vis spectrophotometer with the cell compartment thermostated at 25.0 ± 0.1 °C. Reaction mixtures were buffered using 2,6-lutidine or 2,4,6-collidine, both partially neutralized with HOTf in various ratios, and by ytterbium triflate partially neutralized by tetrabutylammonium methoxide to maintain the constant $^{s}_{s}$pH.

A typical kinetic experiment for determining the $^{s}_{s}$pH dependence of the Cu(II)-catalyzed cleavage of the NR(C═O) bond in methanol was performed as follows. Three cells with concentrations of $Cu(OTf)_2$ at 0.2, 0.4, and 0.6 mM, using aliquots of a 50 mM stock solution in methanol, were prepared in methanol containing 4 mM of buffer. A 50 μL amount of a 10 mM acetonitrile stock solution of substrates **7a−c** (0.2 mM) was added to each cell, and the reactions were allowed to run until completion. The total cell volume was 2.5 mL.

Kinetic experiments in ethanol were performed as follows. Two cells with concentrations of $Cu(OTf)_2$ at 0.1 and 0.2 mM were prepared in ethanol containing 4 mM of buffer. A 50 μL amount of 10 mM stock solution of substrates **7a−c** in acetonitrile was added to each cell to give a substrate concentration of 0.1 mM (total cell volume was 2.5 mL). Duplicates of each cell were run to obtain two averaged data points at each $^{s}_{s}$pH value and for each [Cu^{2+}].

The first-order rate constants for the disappearance of the starting material were calculated from the Abs vs time kinetic curves collected at 360 nm or using the initial rate method at 360 nm when necessary. The Abs vs time data were fit to a standard first-order exponential equation to obtain the k_{obs} values. Data collected at various $^{s}_{s}$pH values generated a full $^{s}_{s}$pH profile for cleavage of ureas **7a−c** catalyzed by Cu^{2+} at 25 °C. The so-obtained rate constants are presented in Table 1, located in the Results and Discussion section.

II.d.I. Kinetic Experiments for Cleavage of ***7a*** *in Various Solvents.* The effect of various solvents on the Cu^{2+}-catalyzed cleavage of *N-p*-nitrophenyl-*N*′,*N*′-bis(pyridin-2-yl methyl) urea (**7a**) was studied at 25 °C. Since the maximum activity was shown to occur at a 1:1:1 ratio of Cu(II):substrate:alkoxide (vide infra), cells were charged with 1-propanol, 2-propanol, or acetonitrile followed by 0.1 mM each of $Cu(OTf)_2$ (5 μL aliquot of a 50 mM stock solution in acetonitrile), 0.1 mM $NaOCH_3$ in methanol (5 μL of a 50 mM stock solution of

dx.doi.org/10.1021/ic500620k | Inorg. Chem. 2014, 53, 7916−7925

$NaOCH_3$ in methanol), and **7a** (25 μL of a 10 mM stock solution in acetonitrile) to give a total cell volume of 2.5 mL.

The kinetics for decomposition of **7a** were monitored as described above.

II.e. Product Analysis. Following completion of the kinetic runs for the alcoholysis reactions of the ureas **7a**–**c** run in each type of buffer, solutions were combined and all solvent was removed in vacuo. The residue was redissolved in d^4-methanol and then analyzed by ^{1}H NMR. The Cu(II)-bound *N*′,*N*′-bis(2-picolyl)amine leaving group was not detected in the sample due to the paramagnetic effect of the Cu(II) ion, but the presence of a carbamate product was detected, and its concentration was determined from integration of characteristic ^{1}H NMR peaks for each product.

The preparative product analysis in ethanol was conducted in a vial with a total volume of 15 mL containing 0.1 mM of ureas, 0.1 mM $Cu(OTf)_2$, and 4 mM of buffer. The reaction mixture was left at room temperature for 2 days, after which the solvent was removed in vacuo and the residue was redissolved in d^4-methanol and analyzed by ^{1}H NMR. As was the case with the reaction in methanol the Cu(II)-bound *N*′,*N*′-bis(2-picolyl)amine leaving group was not detected due to the paramagnetic effect of the Cu(II) ion, but the presence of carbamate products was.

A product analysis for cleavage of **4b** was performed as follows. A vial with a total volume of 15 mL of ethanol, containing 0.1 mM of **4b**, 0.5 mM $Ni(ClO_4)_2$, and 0.1 mM (20% molar equivalence per $Ni(ClO_4)_2$) of NaOEt base was prepared. It was heated at 80 °C for 2 days, after which the solvent was removed and the residue redissolved in d^4-methanol and analyzed by ^{1}H NMR and high-resolution EI-MS.

III. RESULTS AND DISCUSSION

III.a. Kinetics of Cu(II)-Promoted Alcoholysis of *N*-4-Nitrophenyl-*N*′,*N*′-bis(pyridin-2-yl-methyl) Urea (7a). Our initial studies involved Ni(II)-catalyzed methanolysis and ethanolysis of ureas **7**; however, these were far slower than the reactions with Cu(II), exhibiting very small spectral changes with **7a** and none with **7c**, so further studies with Ni(II) were discontinued.

Cu(II)-promoted methanolyses of 0.2 mM solutions of **7a** in methanol were studied over a ^s_spH range of 5.6–8.2 under buffered conditions in the presence of varying $[Cu(OTf)_2]$ between 0.2 and 0.6 mM. In all cases the maximal rate of reaction occurred at $[Cu^{2+}] = [\mathbf{7a}]$ with a slight decrease in rate being observed with increasing $[Cu(OTf)_2]$. These observations are consistent with strong 1:1 binding of the metal ion to **7a** as has been previously observed in the cases of Cu^{2+}-promoted cleavage of *N*′,*N*′-bis(pyridin-2-yl-methyl) amides.[17,18] (The diminution of rate with added $Cu(OTf)_2$ will be shown later to result from an inhibitory effect of a second metal ion.) NLLSQ (nonlinear least-squares) fits of the maximum experimentally observed first-order rate constants (k_{obs}^{max}) for decomposition of **7a** in the presence of equimolar Cu^{2+} vs ^s_spH to eq 2, derived for a one-proton dissociation model, gave a kinetic $^s_s pK_a$ of 7.16 ± 0.10 and a maximum rate constant (k_{max}) of (7.5 ± 1.3) × 10^{-5} s^{-1}. These constants are presented in Table 1 along with the values for cleavage of other complexes in methanol and ethanol (vide infra).

$$\log(k_{obs}^{max}) = \log\left(\frac{k_{max}\,{}^s_sK_a}{{}^s_sK_a + [H^+]}\right) \quad (2)$$

The appearance of the ^s_spH rate profile in Figure 1 suggests that the active form of the complex is **7a**:Cu(II):($^-$$OCH_3$).

Cu(II)-promoted ethanolysis of **7a** was studied under similar conditions (a ^s_spH range of 5.6–7.7 with small variations outlined in the Experimental Section. The k_{obs}^{max} values for decomposition of **7a**:Cu(II) in ethanol in the presence of 1 equiv of $Cu(OTf)_2$ were NLSSQ fit to eq 2 to give a kinetic $^s_s pK_a$ value of 6.25 ± 0.09 and a maximum rate constant (k_{max}) of (7.0 ± 0.7) × 10^{-4} s^{-1}, (log (k_{obs}^{max}) vs ^s_spH profile shown in Figure 16S, Supporting Information).

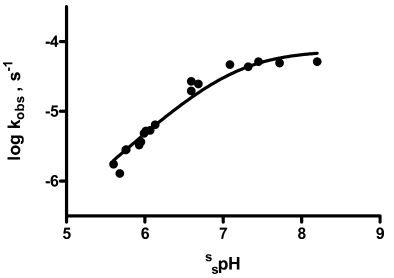


Figure 1. Plot of log(k_{obs}^{max}) vs ^s_spH for cleavage of **7a**:Cu(II) (0.2 mM each of Cu(II) triflate and *p*-nitro-DPPU (**7a**)) in anhydrous methanol under buffered conditions at T = 25 °C. Data were NLLSQ fit to eq 2 to give a kinetic $^s_s pK_a$ of 7.16 ± 0.10 and a maximum rate constant (k_{max}) for decomposition of **7a**:Cu(II):($^-$$OCH_3$) of (7.5 ± 1.3) × 10^{-5} s^{-1}.

To better understand the stoichiometric requirements for the metal ion we determined the initial rates of the decomposition of 0.1 mM **7a** as a function of increasing $[Cu(OTf)_2]$ in ethanol at ^s_spH 7.6, where **7a**:Cu(II):($^-$OEt) is essentially completely formed. The plot of the initial rate vs $[Cu^{2+}]$ shown in Figure 2

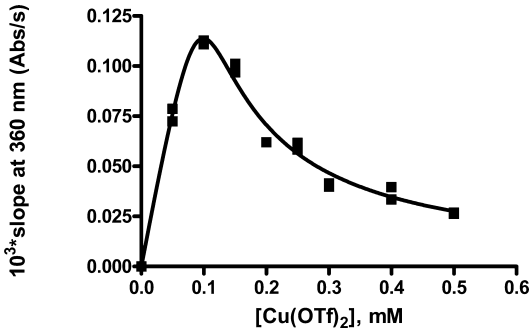
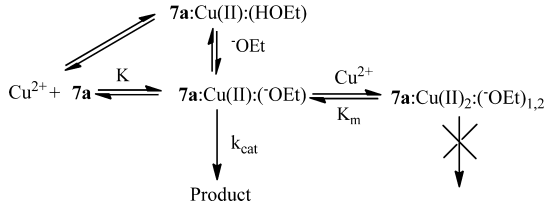


Figure 2. Plot of the initial rate of decomposition of 0.1 mM **7a** in ethanol as a function of $[Cu(OTf)_2]$ at ^s_spH 7.6, T = 25 °C.

maximizes at a 1:1 ratio and then asymptotically diminishes with increasing metal-ion concentration. These observations are consistent with binding of a second Cu(II) (with or without an associated ethoxide) to a reactive **7a**:Cu(II):($^-$OEt) complex, resulting in formation of a less reactive or nonreactive complex of proposed stoichiometry **7a**:$Cu(II)_2$:($^-$$OEt)_{1,2}$ as is depicted in Scheme 1. This seems to be a common feature for such complexes as we observed a similar behavior for the Cu(II)-catalyzed cleavage of *N*,*N*-bis(2-picolyl) carbamates.[26]

Scheme 1. Hypothetical Process Rationalizing the Concentration Effects of Cu^{2+} for Decomposition of 7a:Cu(II) Shown in Figure 2



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On the basis of Scheme 1 an equation was derived[27] defining the relationship between $[Cu^{2+}]$ and the observed rate of the reaction. NLLSQ fitting of the rate vs $[Cu^{2+}]$ data to eq 3[27] provided the line through the data in Figure 2; the derived k_{max} and ${}^{s}_{s}pK_a$ are given in Table 1.

*III.a.i. Kinetics of the Cu(II)-Promoted Cleavage of N-Methyl-N-p-nitrophenyl-N′,N′-bis(pyridin-2-yl methyl) Urea (**7b**) in Methanol and Ethanol.* The k_{max} for decomposition of **7a**:Cu(II):($^{-}OCH_3$) in methanol is 7.5×10^{-5} s^{-1}, 50 times less than that for cleavage of **2**:Cu(II):($^{-}OCH_3$) (3.9×10^{-3} s^{-1}).[18,19] Ureas are notoriously inert to solvolytic attack on their C═O unit as it is flanked by two nitrogen atoms. However, an alternative explanation for the rate reduction relative to that of the corresponding amide might be the presence of the relatively labile N−H proton in **7a** which, when abstracted, reduced the electrophilicity of the N^{-}—C═O unit similar to what is observed for Cu(II)-promoted hydrolysis of secondary amides.[28,29]

The rate of the Cu(II)-promoted methanolysis of the *N*-methyl analogue, **7b**, was studied as a function of ${}^{s}_{s}pH$ under conditions similar to those used for **7a**:Cu(II). The first-order rate constants were obtained in the presence of 1, 2, and 4 equiv of $Cu(OTf)_2$ relative to that of the substrate (0.1 mM). Contrary to what was observed for Cu(II):**7a**, the observed rate constants increased slightly with the increase in $[Cu(OTf)_2]$ (Figure 19S, Supporting Information). NLLSQ fits of these experimental first-order rate constants to a strong binding equation[30] yielded k_{obs}^{max} values (Supporting Information) for decomposition of **7b**:Cu(II) indicative of a plateau in the ${}^{s}_{s}pH$ range of 6.8−8.0, so the anticipated kinetic ${}^{s}_{s}pK_a$ would be <6.7. The average k_{max} value of $(2.9 \pm 0.3) \times 10^{-5}$ s^{-1} for cleavage of **7b**:Cu(II):($^{-}OCH_3$) in this ${}^{s}_{s}pH$ range is about 3 times slower than that for **7a**:Cu(II):($^{-}OCH_3$), the small rate reduction perhaps resulting from a steric encumbrance of intramolecular nucleophilic addition of the coordinated Cu(II):($^{-}OCH_3$) to the C═O unit. Nevertheless, that the rates of decomposition of these two complexes are so similar suggests that N−H deprotonation of the complex of **7a**, followed by nucleophilic attack of the Cu(II):($^{-}OCH_3$), is not a reasonable mechanism for methanolysis of the latter, further suggesting that the N−H deprotonation and elimination of the Cu(II):bis(2-picolyl) amine is not the preferred pathway for production of the *O*-methyl carbamate of *p*-nitroaniline.

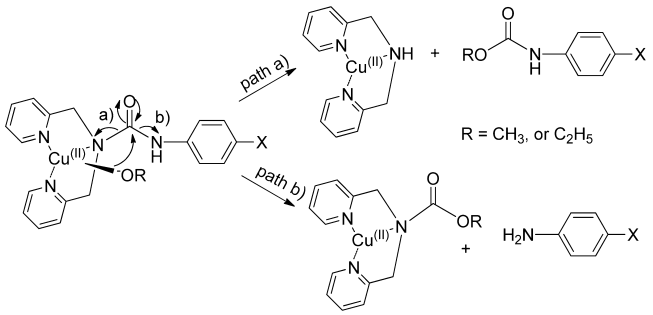
The ${}^{s}_{s}pH$ dependence of the rate of cleavage of 0.1 mM **7b**:Cu(II):($^{-}OCH_2CH_3$) was also studied at 25 °C at the two concentrations of 0.1 and 0.2 mM $Cu(OTf)_2$ in ethanol containing 4 mM of buffer. Duplicate kinetics were run to obtain averaged data points at each ${}^{s}_{s}pH$ value and for each $[Cu^{2+}]$. The maximal rate constants (k_{obs}^{max}) were observed at a 1:1 ratio of **7b**:Cu(II). A full ${}^{s}_{s}pH$ profile for its ethanolysis at 25 °C was constructed (Figure 17S, Supporting Information) by fitting of the rate constant vs ${}^{s}_{s}pH$ data to eq 2, yielding a kinetic ${}^{s}_{s}pK_a$ of 6.47 ± 0.06 and k_{max} of $(1.3 \pm 0.1) \times 10^{-4}$ s^{-1}. Cleavage of **7b**:Cu(II):(^{-}OR) is about 5 times faster in ethanol than methanol.

*III.a.ii. Kinetics of the Cu(II)-Promoted Cleavage of N-Phenyl-N′,N′-bis(pyridin-2-yl methyl) Urea (**7c**) in Methanol and Ethanol.* The ${}^{s}_{s}pH$ dependence of the Cu(II)-catalyzed cleavage of 0.2 mM **7c** in methanol was determined at T = 25 °C using 0.2, 0.4, and 0.6 mM concentrations of Cu^{2+} in buffered solutions. Above ${}^{s}_{s}pH$ 6 the k_{obs}^{max} was obtained at a 1:1 ratio of **7c**:Cu(II) with further increases in $[Cu(OTf)_2]$ leading to a slight inhibitory effect. Below ${}^{s}_{s}pH$ 6 the observed rate constants increased slightly with increasing $[Cu^{2+}]$. In these cases the experimental data were fitted using a universal binding equation[30] at each ${}^{s}_{s}pH$ to provide a rate constant at saturation, taken to be the k_{obs}^{max} for decomposition of Cu(II):**7c** complex at a given ${}^{s}_{s}pH$. The $\log(k_{obs}^{max})$ vs ${}^{s}_{s}pH$ data for decomposition of Cu(II):**7c** were subsequently fit to eq 2 to yield the kinetic ${}^{s}_{s}pK_a$ and k_{cat} values in Table 1.

Cu(II)-promoted ethanolysis of **7c** was studied similarly to the case of **7a**, and at all ${}^{s}_{s}pH$ values the k_{obs}^{max} values were obtained at a 1:1 ratio of $[Cu^{2+}]$ and [**7c**]. Subsequent data fitting to eq 2 gave a kinetic ${}^{s}_{s}pK_a$ of 6.25 ± 0.09 and k_{max} = (6.2 ± 0.5) × 10^{-4} s^{-1}; **7c**:Cu(II) reacts about 30 times faster in ethanol than in methanol, while **7a**:Cu(II) reacts ∼10 times faster in ethanol.

III.b. Product Analysis of the Cleavage Reaction of 7a−c in Methanol and Ethanol. Depicted in Scheme 2 are two sets of products that may result from Cu(II)-assisted cleavage of **7**. Cleavage pathways were probed by ^{1}H NMR analysis of the products after completion of the alcoholysis reactions of **7** in the various buffers, after removal of the solvents and redissolution of the residues in d^4-methanol. The *O*-methyl and *O*-ethyl carbamate products were identified by characteristic chemical shifts of the CH_3O singlet at δ = 3.75 ppm and CH_3CH_2O signals at δ = 4.25 d (J = 7.07 Hz) and 1.32 t (J = 7.07 Hz) (Figures 9S and 10S, Supporting Information) showing that these reactions proceeded by path a in Scheme 2. No traces of aniline, the product formed by path b, were found by ^{1}H NMR analysis or using UV−vis spectoscopy.

Scheme 2. Cleavage Pathways for the Cu(II)-Promoted Alcoholysis of Ureas 7a,c, X = H, NO_2



^{1}H NMR analysis of the combined product mixtures from the kinetic experiments showed that cleavage of **7b** and **7c** also produced only the corresponding *O*-methyl or *O*-ethyl carbamates following path a in Scheme 2. No traces of the corresponding anilines were observed; UV−vis scanning kinetic studies with **7a** also confirm that reaction proceeds only by path a since the presence of *p*-nitroaniline would result in a significant increase of absorbance at 380 nm which was not observed.

III.c. Medium Effects on the Rate of Solvolysis of 7a Catalyzed by Cu(OTf)$_2$. From Table 1 the respective solvolyses of **7a,b,c**:Cu(II):(^{-}OR) are, respectively about 10, 5, and 30 times faster in ethanol than methanol. Solvolyses of **7a**:Cu(II) were also investigated in water, 1-propanol, 2-propanol, and acetonitrile containing 0.2% methanol or ethanol by volume, these amounts being contributed by the stock solutions containing base. In these solvents, by analogy with the methanol and ethanol cases, the active forms are considered to

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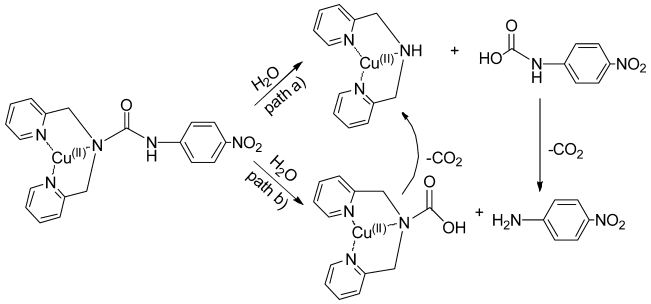
involve Cu(II):($^-$OR) bound to **7a**, solvolyzing by a mechanism analogous to what occurs in the two former alcohols.

*III.c.i. Hydrolysis of **7a** Catalyzed by Cu(OTf)$_2$.* Reaction of **7a** in water was studied at concentrations of 0.01 mM for each of Cu(OTf)$_2$, urea **7a**, and NaOH base.[31] Kinetic traces were obtained at 390 nm, the wavelength of maximum change under these conditions, corresponding to the appearance of *p*-nitroaniline (see below). The fit of the Abs vs time traces to a standard exponential equation gave a k_{cat} of 4.8×10^{-6} s^{-1} at pH of 7.0, T = 25 °C, which is about 15- and 150-times, respectively, slower than the reactions in methanol and ethanol. Increasing [Cu^{2+}] to 0.2 mM led to only a slight increase in the rate constant, and further increases in [Cu^{2+}] led to formation of a yellow-brown solid, surmised to be oligomeric Cu(II) hydroxide.

The product mixture from the hydrolysis reaction of **7a** was analyzed by ^{1}H NMR and UV−vis spectrometry with the only product observed[32] being *p*-nitroaniline. This is consistent with the cleavage reaction proceeding in the same fashion as the methanolysis or ethanolysis via path a (Scheme 3), where the initial product is the carbamic acid of *p*-nitroaniline which spontaneously decarboxylates to give aniline. It is also consistent with reaction proceeding via path b, where aniline is directly formed along with the carbamic acid of the Cu(II):bis(2-picolyl)amine complex which spontaneously loses CO$_2$.

Scheme 3. Proposed Pathways for Hydrolytic Decomposition of 7a:Cu(II):($^-$OH) in Water



*III.c.ii. Solvolysis of **7a** Catalyzed by Cu(OTf)$_2$ in Various Organic Solvents.* Solvolyses of **7a**:Cu(II) in 1- or 2-propanol should also have the metal-bound alkoxides acting as the intramolecular nucleophiles. Methanol cannot be avoided given that a small amount (0.2% by volume) arises from addition of 1 equiv of NaOCH$_3$ base solution in methanol. Solvolysis of Cu(II):**7a** in neat acetonitrile does not occur unless there is added alcohol and base.

The reactions were conducted in the above solvents along with 0.1 mM each of **7a**, Cu^{2+}, and NaOCH$_3$ or TBAE base. These were monitored by an initial rate method at 360 nm for the disappearance of **7a**:Cu(II). Controls confirming that a reaction actually occurred with **7a**:Cu(II) were run under identical conditions observing no changes in the spectrum of 0.1 mM of dipicolylamine or Cu^{2+} alone in the different solvents. The observed rate constants given in Table 2 span a range of ~150-fold, following the order ethanol > methanol >1-propanol >2-propanol > acetonitrile > water.

Observation of a hydrolysis reaction in the aqueous solution containing **7a**:Cu(II) is notable relative to the attempted hydrolyses of the Cu(II) complexes of structurally related amides **1**−**3**,[17−19] which have limited solubility and stability in water with no noticeable cleavage reaction being observed. General retardation of the metal-ion catalysis of acyl and phosphoryl transfer reactions one often sees in water stems from many sources such as limited complex solubility, weaker binding of the metal ion and substrate, and oligomerization/precipitation of the metal-ion:hydroxo species. Notably, water heavily solvates the metal ion which, when coupled with a weaker electrostatic association of metal ion and substrate in a high dielectric constant solvent, reduces the binding energy of the ensuing complex. In addition, relative to less polar alcohols, an aqueous solvent tends to raise the activation energy for metal-ion-promoted cleavages where charge is being dispersed in the transition states relative to ground state.[33] The fact that **7**:Cu(II) complexes undergo hydrolysis indicates that the effect of the Cu(II) ion in promoting solvolytic cleavage is not limited to light alcohols but is effective in water for this system. Presumably this is aided by the very tight binding of the metal ion provided by the bis(2-picolyl) portion of the substrate and the solubility characteristics of the urea complex. The unusual ability of Cu(II) to provide powerful leaving group assistance for hydrolysis of a specially designed set of phosphate mono-, di-, and triesters has been noted,[16b] which may signify a far more general process for accelerating hydrolysis of such processes where the leaving groups are poor.

Table 2. Comparison of First-Order Rate Constants for the Solvolysis of 7a at 25 °C in Various Solvents Containing a 1:1:1 Mixture of 7a, Cu(OTf)$_2$, and NaOCH$_3$ or TBAE, each at 0.1 mM

solvents	10^3 k_{max}, s^{-1}
H_2O	0.0046
MeOH	0.075
EtOH	0.70
1-PrOH[a]	0.057
2-PrOH[a]	0.021
acetonitrile[a]	0.011

[a]In the presence of 0.2% v/v MeOH.

III.d. Ni(II)-Promoted Cleavage of N-(2-Picolyl)-N′-aryl Ureas 4a,b in Ethanol. We confirmed and expanded upon the previous results for the metal-ion-catalyzed ethanolysis of the *N*-(2-picolyl)-*N*′-aryl ureas.[22] A series of experiments with **4a,b** (respective aniline substituents, *p*-NO$_2$ and *p*-H) was performed in ethanol with ^s_spH control in the presence of a noninhibitory perchlorate counterion. We could not use Cu^{2+} with **4a,b** since their complexes were sparingly soluble in ethanol, which precluded accurate kinetic determination of the rate constants, although the mode of cleavage of the Cu(II) complexes could be determined.

Since the available evidence indicates that metal-ion-promoted cleavage of bis(2-picolyl) ureas and amides[17−19] involves an active form containing a ligand-complexed M(II):($^-$OR), our experiments were conducted in the presence of 20% molar equivalents of tetrabutylammonium ethoxide relative to the concentration of Ni(ClO$_4$)$_2$ to hold the ^s_spH constant. These conditions were chosen to avoid precipitation of M(II) alkoxides that can occur at high [alkoxide]. The plot of the k_{obs} for cleavage of **4a** as a function of [Ni(ClO$_4$)$_2$] was linear over a range of 0.0−1.0 mM, and from the gradient we obtained a k_2^{obs} of $(0.87 \pm 0.05) \times 10^{-2}$ M^{-1} s^{-1} at 58.4 °C and $(1.45 \pm 0.03) \times 10^{-2}$ M^{-1} s^{-1} at 68.1 °C. In the same fashion, k_2^{obs} values were obtained for the Ni(II)-promoted decom-

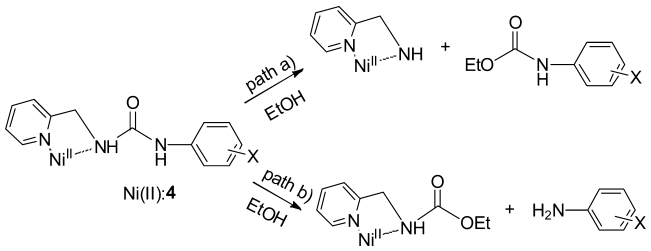
dx.doi.org/10.1021/ic500620k | Inorg. Chem. 2014, 53, 7916−7925

position of **4b** of 5.2×10^{-2} and 14×10^{-2} M^{-1} s^{-1} at 58.4 and 68.1 °C.

These k_2^{obs} values for **4a** and **4b** obtained at 68 °C are larger by ∼18 and 3 times, respectively, than was previously[22] observed for these substrates at 80 °C. Given that only 20% molar equivalents of base were used here for the reasons stated above, our experimental numbers are suboptimal by at least a factor of 5, meaning that the rate constants for the fully active Ni(II):**4a,b**:($^-$OEt) complexes are ∼100 and 15 times larger than what was reported previously.[22] This is likely due to our use of $Ni(ClO_4)_2$ with its non or poorly inhibitory counterion rather than $NiCl_2$ where the chloride is known to form complexes with transition-metal ions, particularly in solvents with lower polarity such as alcohols.[34] Contrary to what we observe for the metal-ion-catalyzed cleavage of the bis(2-picolyl)amine containing ureas **7** (where the presence of the NO_2 group accelerates the rate of the reaction), the presence of an electron-withdrawing $-NO_2$ group in **4a** slows the rate of the reaction down by approximately 1 order of magnitude relative to that observed with the phenyl derivative, **4b**.

Our product results also confirm that both Ni(II)- and Cu(II)-catalyzed ethanolysis of **4a,b** in the presence of a noninhibiting counterion gives the corresponding aniline and *O*-ethyl-*N*-(2-picolyl) carbamate, following path b in Scheme 4.

Scheme 4[a]

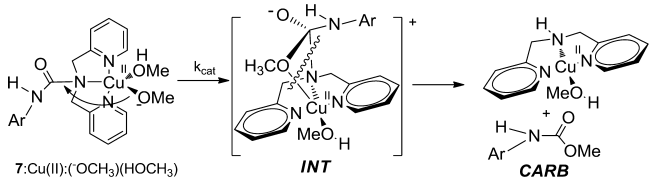


[a]X = H, NO_2.

This mode of cleavage of Ni(II):**4b** in ethanol is also supported by MS experiments, where peaks attributable to both *O*-ethyl-*N*-(2-picolyl)carbamate ($C_9H_{12}N_2O_2$; *m*/*z* calcd 180.0899; found 180.0908) and aniline (C_6H_7N; *m*/*z* calcd 93.0578; found 93.0574) were detected.

III.e. Mechanistic Aspects and Differences between the Cleavage Pathways for the Bis(2-picolyl) and Mono(2-picolyl) Ureas. Each of the ligands in **7a**:Cu(II):($^-$OR) and **7c**:Cu(II):($^-$OR) binds metal ion sufficiently strongly that saturation is observed in the k_{obs} vs $[Cu^{2+}]$ plots, and decomposition of these complexes exclusively produces bis(2-picolyl)amine:Cu(II) and an *O*-methyl or *O*-ethyl carbamate (***CARB***) of the parent aniline (path a in Scheme 2). Although we have not performed detailed calculations on the Cu(II)-mediated cleavage of **7a−c**, the available experimental evidence, by analogy with decomposition of amide complexes such as **2**:Cu(II):($^-$$OCH_3$),[17−19] points to the mechanism presented in Scheme 5 involving a 3-fold role for the metal ion. Following initial binding to **7**, Cu^{II}:(HOR) is deprotonated to form a kinetically active **7**:Cu^{II}:($^-$OR)(HOR) complex. The metal ion activates the urea via complexation (or partial complexation) of the bis(2-picolyl)amino nitrogen, which allows a subsequent intramolecular delivery of the metal-bound alkoxide to the C=O to give a tetrahedral intermediate (***INT***, suggested to be fleeting), which then

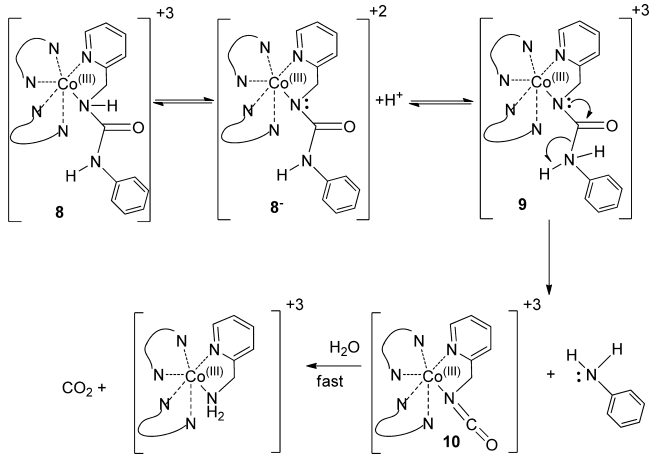
Scheme 5. Proposed Pathway for the Cu(II)-Mediated Methanolysis of 7



decomposes to products. The latter cleavage step involves a simultaneous, or nearly so, fracturing of the Cu−OR and N−CO bond (identified by the corrugated line in the ***INT*** in Scheme 5) to yield the *O*-methyl *N*-anilino carbamate (***CARB***) and is highly dependent on the metal-ion-facilitated departure of the bis(2-picolyl)amide portion through increasingly strong Cu(II) coordination of the emerging N. Once free, or nearly so, from ***INT*** the Cu(II)-coordinated bis(2-picolyl) amide anion is protonated by the medium or buffer components therein.[35]

The Cu(II)- and Ni(II)-promoted ethanolyses of mono(2-picolyl)ureas **4a−c** have been shown by prior studies[21,22] and the current work to exclusively produce aniline and *O*-ethyl-*N*-(2-picolyl) carbamate, suggesting that, if there is a tetrahedral intermediate comparable to ***INT*** in Scheme 5, the Cu(II)-coordinated mono(2-picolyl)amide(amine) is either a poorer leaving group than aniline or there is a different mechanism for cleavage of the metal-ion complexes of **4a−c**. While more work would be required to ascertain this, an obvious possibility is that the Cu(II)- and Ni(II)-promoted reactions of **4** involve an elimination of aniline through deprotonation of the NH of the picolyl amine coordinated to the metal ion. Roecker and Sargeson[23] studied the decomposition of a Co(III) complex of ureas **4** for which the structure (**8**) and mechanism for hydrolysis in acidic media are shown in Scheme 6. An

Scheme 6. Proposed Pathway for Decomposition of Co(III) Complexes of *N*-(2-Picolyl) *N*′-Aryl Ureas (8)[23a]



[a]Ethylene diamine ligands represented as two N's connected by curved line for clarity.

important feature of the mechanism is the proposed formation of a chelated isocyanate ligand (**10**) that rapidly decomposes to the final products. The pathway is consistent with other literature examples[36] and with the fact that free phenyl isocyanate, the initial product if cleavage had occurred at the 2-picolyl N−C(=O) linkage, is not observed. The mechanism

dx.doi.org/10.1021/ic500620k | Inorg. Chem. 2014, 53, 7916−7925

is driven by the fact that the Co(III)-coordinated N−H is quite acidic and therefore easily deprotonated to form 8^- with a potential equilibrium formation of a zwitterionic form (**9**)[37] which decomposes to **10**.

IV. CONCLUSIONS

Despite our systems being mononuclear in Cu(II) or Ni(II) and as such cannot be considered as models of the dinuclear Ni(II) site of urease, the results of the above study may have both direct and indirect implications for enzymatic cleavage of urea. The roles of the metal ions in urease (designated as Ni_1(II) and Ni_2(II)) have been postulated to involve urea coordination by Ni_1(II) followed by nucleophilic delivery of a metal-bound hydroxide to the Ni_1(II)-coordinated C═O unit by the second Ni_2(II). There is experimental[11d,23] and computational[10] support for a possible enzymatic elimination mechanism, but more favored are hydrolytic mechanisms for which there are three current variants.[38] These differ in whether the urea is coordinated to one or two metal ions (the latter via an Ni_1(II)--O═N-NH_2--Ni_2(II)) bridge and whether the nucleophilic hydroxide is bound terminally to one metal ion or bridged between the two Ni ions. All involve formation of a tetrahedral intermediate from which the NH_3 departs aided by general acid catalysis from an active site His-H^+ or from the di-Ni-bridged hydroxide. These hydrolytic variants have been discussed[38] alongside the enzymatic alternative of general-base−general-acid-promoted elimination of ammonia to yield cyanic acid, which hydrates and then eliminates CO_2. There are instances where Ni(II) complexes are shown to accelerate ethanolysis of ureas,[12,21,22,39] but as far as we are aware, none of these has ruled out the possibility of an elimination reaction giving a transient isocyanate followed by addition of ethanol to form a carbamate. In fact, there have been calls to re-evaluate the hydrolytic mechanism postulated for the enzyme to consider elimination.[11d,23,10,40]

An important contribution bearing upon the possible role of metal coordination of the urea N in a solvolytic process has been provided by Kostić and co-workers, who have shown that Pd(II) complexes like (en)$Pd(OH_2)_2$ can promote hydrolysis and alcoholysis of urea through a mechanism that involves initial C═O coordination, subsequent rearrangement to a Pd-NH_2-bound form, and apparent nucleophilic attack by a metal-bound hydroxide or alkoxide.[41] In none of the Kostić studies nor any of the currently favored enzymatic[42] or model processes is one, or both, of the metal ions (Pd(II) or Ni(II)) postulated or demonstrated to assist the departure of the NH_2 group either from a decomposing tetrahedral intermediate or in an elimination mechanism, although under special circumstances this phenomenon can impart very large accelerations to remove leaving groups that are difficult to displace in solvolytic processes[17−19] including hydrolysis.[16a,b]

The present results indicate that the Cu(II)-promoted and in all likelihood, the Ni(II)-promoted cleavages of **7a,b** in methanol proceed with very similar rates, giving the respective *O*-methyl carbamates of *p*-nitroaniline and *N*-methyl *p*-nitroaniline. This excludes an elimination mechanism, at least for these mononuclear complexes. That the reaction is also prominent in ethanol and water suggests that these solvolyses also proceed by nucleophilic addition, followed by metal-ion-promoted departure of the leaving amine. In terms of reaction rate, there is a very large acceleration of the cleavage of **7a−c** relative to solvent-induced reactions, and although the exact amount of acceleration is difficult to quantify, a lower limit can be estimated as follows. The k_{obs} for decomposition of **7a**:Cu(II):($^-OCH_3$) in methanol is 7.5×10^{-5} s^{-1} ($t_{1/2}$ = 150 min), which is 50 times less than that for cleavage of **2**:Cu(II):($^-OCH_3$).[18,19] The rate of decomposition of **7a**:Cu(II):($^-OCH_2CH_3$) complex in ethanol is about 10 times faster, giving a $t_{1/2}$ of ∼15 min at 25 °C. The acceleration of the alkoxide reactions of amide **2** produced by complexation to the Cu(II) is at least 10^{17} in methanol and 10^{20} in ethanol.[19]

Due to the fact that solvolysis of ureas is very slow there are only a limited number of kinetic data available for the rate of hydrolysis[6,8,13b,43] and to the best of our knowledge no kinetic data for the rate of ethanolysis. Therefore, several assumptions are needed in order to calculate the acceleration achieved by the presence of Cu(II) ions for decomposition of **7** in ethanol. The reactivity of hydroxide and ethoxide in the simple reaction of cleavage of *p*-nitrophenyl acetate is measured by their relative second-order rate constants of 9.5[44a] and 107 M^{-1} s^{-1}.[44b] Extrapolation of the experimental data[13b] for the alkaline hydrolysis of urea to 25 °C gives a second-order rate constant of 10^{-8} M^{-1} s^{-1}, and considering that alkaline hydrolysis of tetramethyl urea is ∼4 times slower than that of urea[43] one might estimate a rate constant for its hydrolysis at 25 °C of 2.5×10^{-9} M^{-1} s^{-1}. Coupling the latter with an assumed 10-fold increase in activity gives an estimated 2.5×10^{-8} M^{-1} s^{-1} for ethoxide attack on tetramethylurea. The $^s_spK_a$ and log k_{max} data from Figure 17S, Supporting Information, for the Cu(II)-promoted ethanolysis of **7b** allows one to calculate[45] a second-order rate constant for ethoxide attack on **7b**:Cu(II) of 5×10^8 M^{-1} s^{-1}. By this analysis, the acceleration provided by the Cu(II) for ethoxide attack on **7b** corresponds to about 2×10^{16} times.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectral data for **7a−c**, plots of rate constant vs metal-ion concentration or ^s_spH, NMR data for products arising from cleavage of **7a−c** in methanol and ethanol. 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.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the generous support of the Natural Sciences and Engineering Research Council of Canada (NSERC) and Queen's University. M.-N.B. also thanks the NSERC for an Undergraduate Summer Research Assistant award (2013).

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$$\delta\mathrm{Abs}/\delta t = \Delta\varepsilon k_{obs}((1 + K[\mathbf{7a}] + [\mathrm{Cu(OTf)_2}]K - (1 + 2K[\mathbf{7a}] + 2[\mathrm{Cu(OTf)_2}]K + (K)^2[\mathbf{7a}]^2 - 2(K)^2[\mathrm{Cu(OTf)_2}][\mathbf{7a}] + [\mathrm{Cu(OTf)_2}]^2(K)^2)^{0.5})/(2K))K_m/(K_m + [\mathrm{Cu(OTf)_2}] - (1 + K[\mathbf{7a}] + [\mathrm{Cu(OTf)_2}]K - (1 + 2K[\mathbf{7a}] + 2[\mathrm{Cu(OTf)_2}]K + (K)^2[\mathbf{7a}]^2 - 2(K)^2[\mathrm{Cu(OTf)_2}][\mathbf{7a}] + [\mathrm{Cu(OTf)_2}]^2(K)^2)^{0.5})/(2K)) \quad (3)$$

where δAbs/δt is the initial reaction rate and $\Delta\varepsilon$ is the differential extinction coefficient at 360 nm; K_m is the dissociation constant for **7**:$(\mathrm{Cu(II)})_2 \leftrightarrow$ Cu(II) + **7**, Cu(II); K is an effective association constant for formation of **7**:Cu(II):($^-$OR), which incorporates acid dissociation of **7**:Cu(II):(HOR) so is pH dependent; k_{obs} is the observed first-order rate constant for decomposition of the **7**:Cu(II) complex at a given pH. (b) Equation 3 was obtained from the equations for equilibrium binding and conservation of mass using the commercially available MAPLE software: *Maple 9.00*, June 13, 2003, Built 136194; Waterloo Maple Inc.: Waterloo, Ontario, Canada.
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