Facile Metal-Assisted Hydrolysis of a Urethane
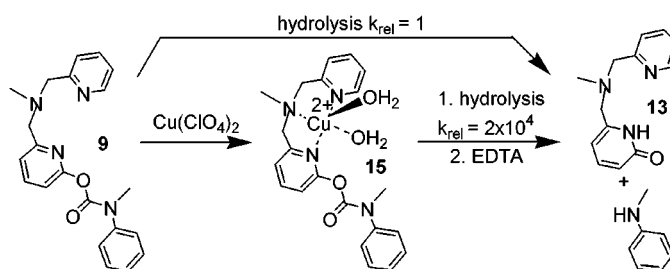
T. Ross Kelly,* Marta Cavero, and Yajun Zhao

E. F. Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467

ross.kelly@bc.edu

ABSTRACT

Kinetic studies demonstrate that it is possible to achieve large rate enhancements (2×10^4) for the hydrolysis of a urethane group by using metal-bound water or hydroxide as the nucleophile.

We recently reported a prototype of the first rationally designed, chemically powered molecular motor.[1] The operation of the prototype is summarized in Scheme 1. Addition of the fuel (phosgene) to **1** initiates a cascade of events resulting, after cleavage of the urethane (carbamate) in **4**, in the unidirectional 120° rotation of **1** to **5**.

With a functioning prototype in hand, the new goal is to extend the original system so that the sequence of events in Scheme 1 can be achieved repeatedly. A continually rotating molecular motor would then be the result.

To accomplish that aim, three subgoals must be achieved (Figure 1): (i) **1** must be modified so that each blade of the triptycene is ready to be selectively armed at the appropriate time; there must also be included within the system units that, with the appropriate spatial positioning and timing, (ii)

can capture and deliver $Cl_2C{=}O$ and (iii) can cleave the urethane. Efforts in all three directions are underway; we now provide a partial solution to the third objective: cleavage of the urethane under reaction conditions compatible with the operation and analysis of the system as a whole.

Urethanes are typically similar to amides in reactivity.[2] Thus, hydrolysis for most urethanes normally requires exposure to refluxing aqueous acid or base for several hours. For instance, pseudo-first-order rate constants for the hydrolysis of *N,N*-dimethylbenzamide[3] and phenyl *N,N*-dimethylcarbamate[4] at pH 7.00 in water were found to be 6.9×10^{-9} min^{-1} ($t_{1/2} = 69\,000$ days, 72 °C) and 6.0×10^{-10} min^{-1} ($t_{1/2} = 80\,000$ days, 34 °C), respectively. Although the values were determined at different temperatures, these figures provide a clear indication of the high stability to hydrolysis

---

Scheme 1. Operation of a Prototype of the First Rationally Designed Chemically Powered Molecular Motor
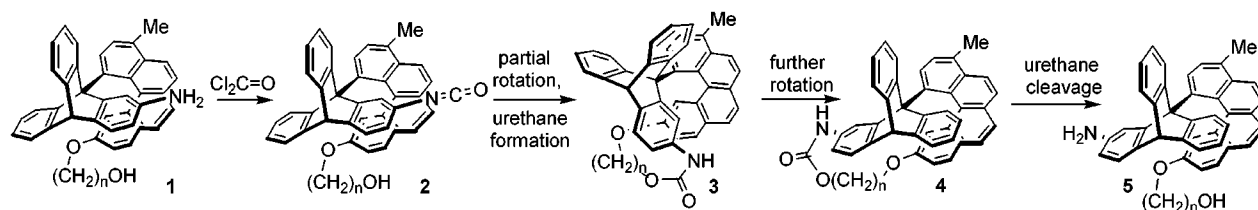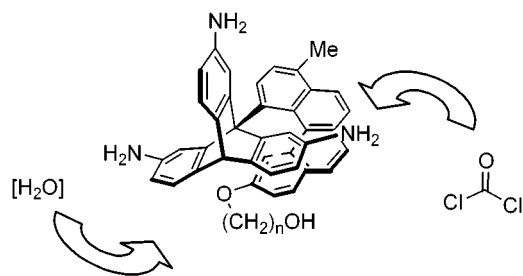
Figure 1. Schematic representation of the concepts underlying the design of a continually rotating motor (see text).

of both functional groups for similar substrates. The usual cleavage conditions are incompatible with the present work (Scheme 1) since the experimentally determined barrier to rotation around the triptycyl−helicene bond in **1** is approximately 25 kcal/mol, meaning that at 100 °C once the constraint of the urethane is removed, **1** would rapidly ($t_{1/2}$ = 38 s) convert to an equilibrium mixture of the three atropisomers **1**, **5**, and **6** (not shown, in which the benzene ring bearing the amine is the top one). Practically speaking, urethane cleavage must be achieved at room temperature or below in order to preserve atropisomer integrity.

In the original system this limitation was overcome by using $NaBH_4$ in ethanol at 0 °C over 8 h, but the yield is low (much **4** is recovered) and the reaction time too long for the present purposes. Accordingly, other methods of urethane cleavage were considered.

Metal ion promoted cleavage of amides, particularly in intramolecular settings, can result in enormous rate accelerations. For example, Groves[5] has reported rate accelerations of up to 10^8 in the cobalt-promoted hydrolysis of **7** relative to the metal-free system **8**. A mechanism involving intramolecular nucleophilic attack by metal-bound hydroxide or water onto the carbonyl group was proposed for this system.
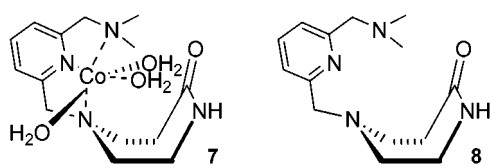
In the context of enzyme mimics, similar effects have been studied in systems containing nitriles, esters, and phosphate esters.[6] To our knowledge, however, no examples of metal-accelerated hydrolysis of a urethane have been described. We now report that metal-assisted hydrolysis of urethane **9** is complete within less than 5 min at 25 °C and pH 7.5 and that the hydrolysis occurs 2×10^4 times faster than it does in the same system but in the absence of the metal ion.

(1) (a) Kelly, T. R.; de Silva, H.; Silva, R. A. *Nature* **1999**, *400*, 150. (b) Kelly, T. R.; Silva, R. A.; de Silva, H.; Jasmin, S.; Zhao, Y. *J. Am. Chem. Soc.* **2000**, *122*, 6935. (c) Kelly, T. R. *Acc. Chem. Res.* **2001**, *34*, 514.
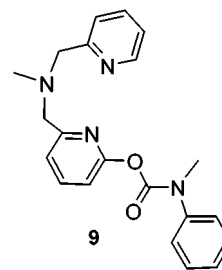
Metal-catalyzed hydrolysis of the carbamate moiety in buffered solutions proceeded over a period of a few minutes to several hours depending on the pH and metal ion concentration. Because the free ligand and complex are insoluble in pure water, acetonitrile was added as a cosolvent in a 50% v/v relation, thus allowing for solution of all the components in the hydrolysis mixture.

Carbamate substrate **9** was prepared as shown in Scheme 2.[7]

Scheme 2. Synthesis of Carbamate Ligand **9**
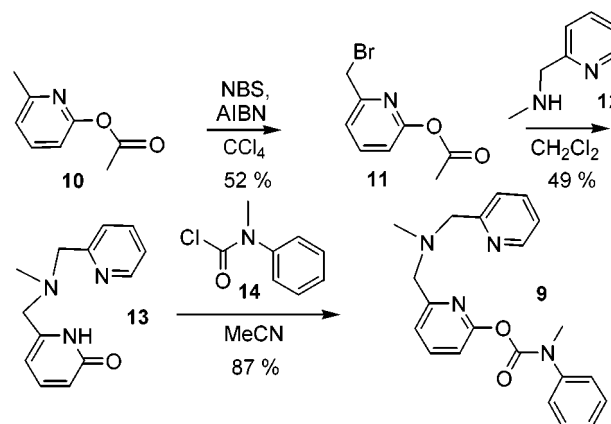
Reactions were followed by reverse-phase HPLC (C18).[8,9] To confirm that the reaction being monitored was hydrolysis and that no side reactions were taking place, products of some of the reactions were also isolated and characterized by proton NMR. Only the expected aniline and pyridone **13** were found in all final reaction mixtures.

(2) (a) Hegarty, A. F. In *Derivatives of Carbon Dioxide*, *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D. Eds.; Pergamon Press: Oxford, 1979; Vol. 2, p 1067. (b) Heywang, G.; Petersen, U. In *Kohlensaure-Derivative, Methoden der Organischen Chemie (Houben-Weyl)*; Georg Thieme Verlag: Stuttgart, 1983; Vol. E4, p 1. (c) Adams, P.; Baron, F. A. *Chem. Rev.* **1965**, *65*, 567.
(3) Brown, R. S.; Bennet, A. J.; Slebocka-Tilk, H. *Acc. Chem. Res.* **1992**, *25*, 481.
(4) Dittert, K. W.; Higuchi, T. *J. Pharm. Sci.* **1963**, *52*, 852.
(5) Groves, J. T.; Baron, L. A. *J. Am. Chem. Soc.* **1989**, *111*, 5442.
(6) For instance, see reviews: (a) Reichwein, A. M.; Verboom, W.; Reinhoudt, D. N. *Rec. Trav. Chim. Pays-Bas* **1994**, *113*, 343. (b) Chin, J. *Acc. Chem. Res.* **1991**, *24*, 145 and references therein.
(7) See Supporting Information for experimental details and spectral characterization.
(8) For additional details on procedures employed during kinetic studies, see Supporting Information.
(9) Direct analysis by ^{1}H NMR was precluded due to the paramagnetism of Cu(II).

In a typical kinetic run, a 2.0 mM solution of the carbamate **9** in 1:1 acetonitrile:aqueous buffer was prepared. The solution had a final concentration of 50 mM buffer and 50 mM NaClO$_4$. Aliquots (200 μL) were placed in a series of small vials, and these were equilibrated to 25 °C prior to addition of 4.0 μL (1 equiv) of a 0.10 M solution of Cu-(ClO$_4$)$_2$·6H$_2$O in water. At appropriate times, the catalyzed reaction was stopped in one of the small vials by removing the metal from the complex by addition of a large excess of solid EDTA (ca. 50 equiv). Aliquots (10 μL) of the resulting mixtures were then injected onto an analytical HPLC column. Consecutive injections confirmed that EDTA is effective at removing the metal from the reacting complex and that no appreciable hydrolysis takes place after its addition and during the course of the analysis.

In the absence of any added metal, carbamate **9** was found to be quite stable at room temperature. In solutions between pH 6.0 and 9.5 at 25 °C, it was almost unchanged after 2 or 3 days. At pH 7.5 the pseudo-first-order rate constant k_{obs} (Table 1) for the hydrolysis was determined to be 3×10^{-5}

Table 1. Relative Rate Constants of Hydrolysis of **9** and Its Copper Complex at pH 7.5

	k_{obs} (min^{-1}) ^{a}	$t_{1/2}$	k_{rel}
noncatalyzed reaction	3×10^{-5} ^{b}	16 days	1
copper-catalyzed reaction	0.56	1.2 min	2×10^4

^{a} Measured at pH 7.5 and 25 °C. The k_{obs}s are the average of the values obtained for at least two kinetic runs which agreed within a 10% experimental error. ^{b} Pseudo-first-order rate constant.

min^{-1}, which corresponds to a half-life of approximately 16 days. In comparison, the value of k_{obs} at the same pH and temperature in the presence of 1 equiv of copper(II) was determined to be 0.56 min^{-1} which corresponds to a half-life of only 1.2 min and an acceleration factor of 2×10^4.

A pH−rate profile of the copper-catalyzed reaction (Figure 2) revealed an 18-fold variation of the rate between pH 6.0
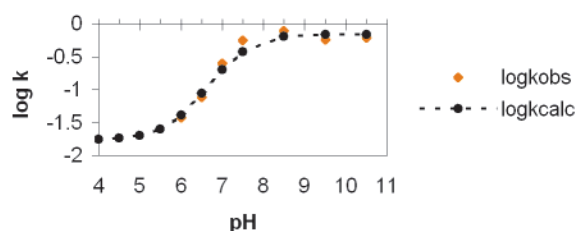

Figure 2. pH profile for the hydrolysis of the copper(II) complex of **9**. Reactions were carried out in mixtures of acetonitrile:aqueous buffer 1:1 and all k_{obs}s are the average of the values obtained for at least two kinetic runs. k_{calc}s correspond to the values calculated using eq 2.

and 10.5 with a leveling off for pHs above 7.5 and an inflection point around pH 7, which indicates that the

deprotonation of some important group is taking place in this region. A plausible mechanism consistent with these data involves the intramolecular nucleophilic attack of a metal-bound water or hydroxide molecule onto the carbonyl group as the rate-determining step.[10] The reaction would involve the two forms schematically represented in Figure 3. In form
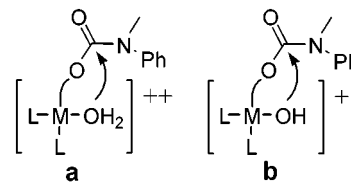

Figure 3. Schematic representation of the two reactive forms involved in the hydrolysis process.

a, a metal-complexed water molecule is the active nucleophile. In form **b**, the nucleophile is a metal-bound hydroxyl. The proportion of these two species present in the reaction mixture depends on the pH and the pK_a for the metal-bound water.[11] Equation 1 is the rate equation in terms of these two processes and eq 2 can be derived[11] from eq 1 and relates k_{obs} with the pH. By a suitable choice of the constants k_{OH}, k_{H_2O}, and K_a, eq 2 can be closely fitted to the observed rate constants ($r^2 = 0.987$). The line shown in Figure 2 has been fitted using the following values: $k_{OH} = 0.685$, $k_{H_2O} = 0.017$, and p$K_a = 7.4$.

$$k_{obs}[\text{carbamate}] = k_{OH}[\text{M(OH)}] + k_{H_2O}[\text{M(H}_2\text{O)}] \quad (1)$$

$$[\text{H}^+] = K_a(k_{OH} - k_{obs})/(k_{obs} - k_{H_2O}) \quad (2)$$

For an 85:15 aqueous acetonitrile solution we obtained a pK_a value of 5.4 for the complex formed between Cu^{2+} and **9**.[12] The apparent disagreement between the value determined by us and that obtained from Figure 2 can be explained in terms of an organic-solvent effect on the pK_a. This increase of the pK_a values of organic acids in partially organic mixtures with increasing proportions of the organic solvent is well documented in the literature.[13] For instance, it has been found that in 50% aqueous acetone mixtures pK_a values can increase by up to 2.5 units with respect to the values in water.[14]

In agreement with the proposed mechanism, the initial rate for the reaction was found to depend on the concentration

(10) The competitive mechanism known for carbamate hydrolysis via formation of an isocyanate intermediate by initial loss of the nitrogen proton could be ruled out in this system since the proton has been substituted by a methyl group. See ref 4.

(11) Zuman, P.; Patel, R. C. *Techniques in Organic Reaction Kinetics*; John Wiley & Sons: New York, 1984; pp 145−192.

(12) Determination of the ionization constants was performed using the minimum amount of organic solvent possible in order to avoid damage to the electrode.

(13) Suh, J.; Son, S. J.; Myunghyun, P. S. *Inorg. Chem.* **1998**, 37, 4872.

(14) Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*; Chapman and Hall: London, 1984; 3rd ed., p 31 and references therein.
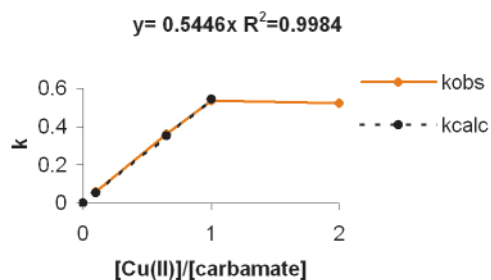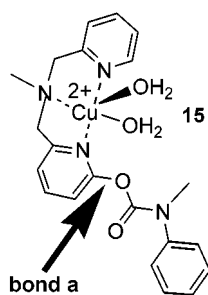
Figure 4. Rate vs $[Cu^{2+}]$/[carbamate] ratio. Reaction carried out at pH 7.5 and 25 °C under conditions described in the text and in the Supporting Information section. k_{calc}s correspond to the values calculated by linear regression.

of copper present in the solution (Figure 4). A linear plot could be obtained for k_{obs} vs $[Cu^{2+}]$/[carbamate] for $0 < [Cu^{2+}]$/[carbamate] ≤ 1, and there is no additional rate acceleration for values >1, at which point enough Cu^{2+} has been added to complex all the ligand.

While other mechanisms involving intramolecular delivery[15] of H_2O/OH^- are possible (such as ones involving activation of the carbonyl by intramolecular coordination to the metal ion), we believe that reaction is occurring via a complex such as **15**. It was expected that in solution tridentate carbamate ligand **9** would form a stable monomeric complex with divalent metals. In water, this dicationic complex could adopt a square pyramidal shape such as **15**, with two solvent molecules bound to the metal center, one occupying the vacant equatorial position and the second the apical position.[16] The equatorial water, being closer to the metal center, was expected[16] to be more acidic.

bond a

Molecular modeling calculations (Spartan, PM3) on **15** show that in the equilibrium geometry the equatorial water and the carbamate carbonyl carbon are situated at a distance of 3.4 Å. However, by rotating around bond **a**, it is possible

for the molecule to adopt conformations in which these two groups are situated at distances as short as 2.9 Å,[17] in conformations readily accessible at 25 °C. An analogous analysis can be applied to the motor system.

These geometric considerations are in agreement with rate acceleration for hydrolysis via a mechanism in which a metal-bound water (or hydroxide) molecule acts as an internal nucleophile attacking the carbamate moiety.

For comparison, the catalyzed reaction was also studied for two other divalent metals, namely, Zn^{2+} and Co^{2+}. In both cases the reaction was found to be slower than when Cu^{2+} was used (Table 2) but still much faster than the

Table 2. Comparison of Ionization and Hydrolysis Constants of $Metal^{2+}$ Complexes

	copper	zinc	cobalt
$pK_a^{titr\ a}$	5.4	7.1	7.0
$pK_a^{app\ b}$	7.4		
k_{obs} (min^{-1}) pH 7.5	0.56	0.19	0.30
k_{obs} (min^{-1}) pH 8.5	0.78	0.31	0.73

[a] Calculated by titration of a 0.01 M solution of the complex in 85:15 aqueous acetonitrile with a 0.1 M aqueous NaOH solution. Ionic strength was not controlled. A combination glass electrode was used. [b] Derived by calculating the regression curve for experimental data in Figure 3.

noncatalyzed reaction. At pH 7.5 the reaction catalyzed by Zn^{2+} is 2.9 times slower than the reaction catalyzed by Cu^{2+}. Co^{2+} was found to be 1.9 times slower than copper. For both cobalt and zinc, the values of the potentiometrically determined pK_as for the metal-bound water molecule were found to be higher than that obtained for the Cu^{2+} complex, and these values are expected to be even higher in a 1:1 acetonitrile:buffer mixture.[14] At pH 8.5 the reaction catalyzed by Zn^{2+} is 2.5 times slower than the reaction catalyzed by Cu^{2+}, whereas the reaction catalyzed by Co^{2+} has approximately the same rate as the copper-promoted reaction. However, for the reaction in the presence of Co^{2+}, side reactions seem to take place at this pH.

In conclusion, the results of this model study show that it is possible to achieve substantial rate enhancements (2×10^4) for the hydrolysis of a carbamate group by using a metal salt as a catalyst. Incorporation of this system into a molecular motor is currently under examination.

Supporting Information Available: Experimental procedures and characterization data for all new compounds; additional details of experimental procedures used during kinetic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016867Z

(15) In principle, one might also consider alternative structures for the complex in which the carbonyl oxygen is coordinated to the metal. However, for those complexes, *intermolecular* attack by water/hydroxide would display a pH profile with increasing pk_{obs} values for higher pHs instead of the observed leveling off (Figure 2; see also ref 11 and Breslow, R.; Schepartz, A. J. *J. Am. Chem. Soc.* **1987**, *109*, 1814). On the other hand, intramolecular attack of metal−bound water/hydroxide onto the coordinated carbonyl would be disfavored on the basis of geometric constraints.

(16) For similar complexes and a detailed description of their structure, see, for example: Young, M. J.; Wahnon, D.; Hynes, R. C.; Chin, J. *J. Am. Chem. Soc.* **1995**, *117*, 9441.

(17) Menger has proposed an "optimal" distance for intramolecular carbonyl addition to be a value close to 2.8 Å: Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128.