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Form Approved
OMB No. 0704-0188

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2b. DECLASSIFICATION/DOWNGRADING SCHEDULE

1b. RESTRICTIVE MARKINGS

3. DISTRIBUTION/AVAILABILITY OF REPORT
approved for public release;
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4. PERFORMING ORGANIZATION REPORT NUMBER(S)

5. MONITORING ORGANIZATION REPORT NUMBER(S)

Technical Report #3

6a. NAME OF PERFORMING ORGANIZATION

6b. OFFICE SYMBOL
(If applicable)

7a. NAME OF MONITORING ORGANIZATION

Ohio State University

OSU

Office of Naval Research

6c. ADDRESS (City, State, and ZIP Code)

7b. ADDRESS (City, State, and ZIP Code)

Department of Chemistry
120 W. 18th Avenue
Columbus, Ohio 43210-1173

Arlington, VA 22217

8a. NAME OF FUNDING/SPONSORING
ORGANIZATION8b. OFFICE SYMBOL
(If applicable)

9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER

Office of Naval Research

ONR

N00014-88-K-0309

8c. ADDRESS (City, State, and ZIP Code)

10. SOURCE OF FUNDING NUMBERS

800 N. Quincy Street
Arlington, VA 22217-5000

PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO.
61153N	RR1309	413P	413P003

11. TITLE (Include Security Classification)

Cu(II) Catalyzed Hydrolysis of an Unactivated Ester Based on Reversible Conjugate Addition.

12. PERSONAL AUTHOR(S)

Brook F. Duerr and Anthony W. Czarnik

13a. TYPE OF REPORT

13b. TIME COVERED

14. DATE OF REPORT (Year, Month, Day)

15. PAGE COUNT

reprint

FROM TO

1990, May 1

4

16. SUPPLEMENTARY NOTATION

published in: Tetrahedron Letters 1989, 30, 6951.

Copper (II)

17. COSATI CODES

18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)

FIELD GROUP SUB-GROUP

07

03

ORGANIC Chemistry, Metalloenzymes, Ethylenediamine,
Chelation, Metals, Nonmetals (TG)

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

Summary: Cu(II) catalysis provides a 16,000-fold acceleration in the hydrolysis of methyl acrylate when a removable vicinal diamine ligand is used to increase the stability of the required copper chelate.

The early work of Kroll, Bender, and Westheimer on metal ion-promoted hydrolyses of α -amino acid esters and amides has provided the impetus for numerous studies of metal ion promoted and catalyzed ester hydrolysis. Enzyme models of metalloesterase activity possess both the ester and the metal ligand covalently and irreversibly connected; cyclodextrin and micellar systems have served as noncovalent enzyme mimics. Despite the early successes using methyl esters of α -amino acids, little work has been directed toward the hydrolysis of unactivated substrates. Co(III) catalysis of methyl acetate hydrolysis described by Chin stands as a notable exception. Of course, metalloenzymes utilize M^{2+} and not M^{3+} catalytic centers,

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT

21. ABSTRACT SECURITY CLASSIFICATION

☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS

Unclassified

22a. NAME OF RESPONSIBLE INDIVIDUAL

22b. TELEPHONE (Include Area Code)

22c. OFFICE SYMBOL

Harold E. Guard

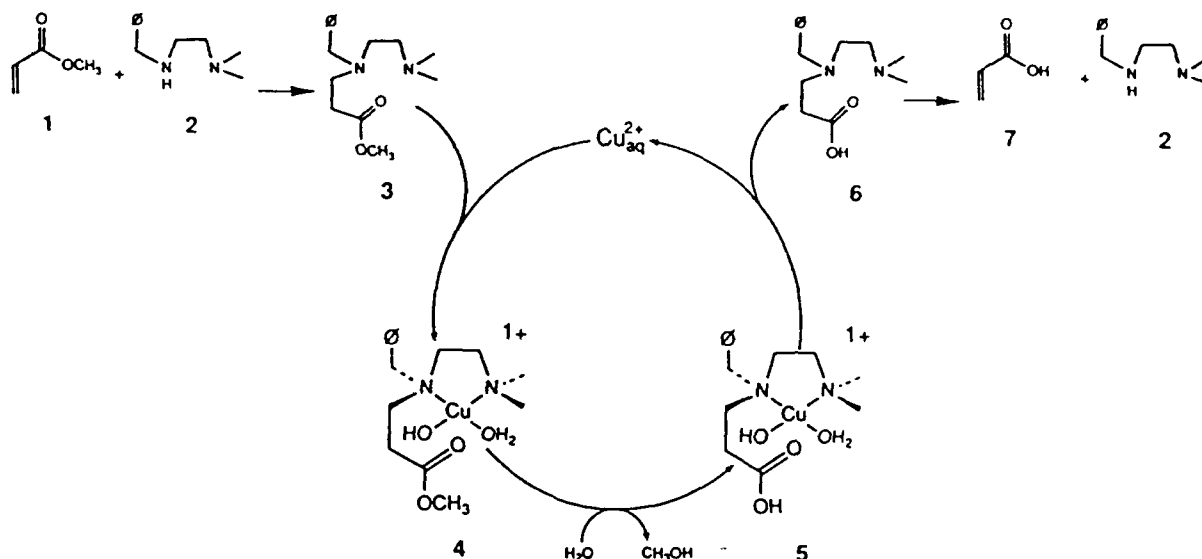
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but without a suitable ligand to bind M^{2+} ions in a proper orientation near the substrate divalent ions do not accelerate the hydrolysis of unactivated esters, which is slow at neutral pH.

The reactions shown in Scheme I, including the well-known reversible conjugate addition of amines to enones, can be effected entirely in 0.1 M pH 7.50 buffer.

Scheme I



Without added metals, the hydrolysis of ester 3 (1.8 mM) to acid 6 proceeded at pH 7.50 and 23°C with $k_{\text{obs}} = 1.0 \times 10^{-6} \text{ s}^{-1}$ ($t_{1/2} = 670,000 \text{ s}$). Addition of divalent metal ions accelerated the rate of the hydrolysis by varying extents. The addition of 1 eq of Co(II) or Ni(II) accelerated the hydrolysis, yielding $k_{\text{obs}} = 3.9 \times 10^{-6} \text{ s}^{-1}$ ($t_{1/2} = 170,000 \text{ s}$) and $1.2 \times 10^{-5} \text{ s}^{-1}$ ($t_{1/2} = 57,000 \text{ s}$), respectively. The use of copper ion led to the largest accelerations; addition of 1 eq of Cu(II) gave $k_{\text{obs}} = 6.2 \times 10^{-3} \text{ s}^{-1}$ ($t_{1/2} = 110 \text{ s}$), and addition of 5 eq of Cu(II) gave $k_{\text{obs}} = 1.6 \times 10^{-2} \text{ s}^{-1}$ ($t_{1/2} = 44 \text{ s}$). Therefore, the hydrolysis rate for the fully complexed ester is 16,000-times faster than the same reaction without added metal. Significantly, the reaction was catalytic with respect to copper ion; 0.01 eq of Cu(II) gave $k_{\text{obs}} = 6.2 \times 10^{-6} \text{ s}^{-1}$ ($t_{1/2} = 110,000 \text{ s}$), and the reaction proceeded to >90% completion while following first order kinetics. As we did not observe product inhibition, it must be inferred that the complexation of Cu(II) to acid 6 is readily reversible and largely incomplete at the lower Cu(II) concentrations.

(This work, while supported principally by the NSF, has direct overlap with the goals of our ONR project.)

OFFICE OF NAVAL RESEARCH

Contract N00014-88-K-0309

R&T Code 413p002

Technical Report No. 3



Cu(II) Catalyzed Hydrolysis of an Unactivated Ester Based on
Reversible Conjugate Addition

by

Brook F. Duerr and Anthony W. Czarnik

Published in

Tetrahedron Letters

Ohio State University
Department of Chemistry
Columbus, OH

May, 1990

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Cu(II) CATALYZED HYDROLYSIS OF AN UNACTIVATED ESTER BASED ON REVERSIBLE
CONJUGATE ADDITION.¹

Brook F. Duerr and Anthony W. Czarnik*

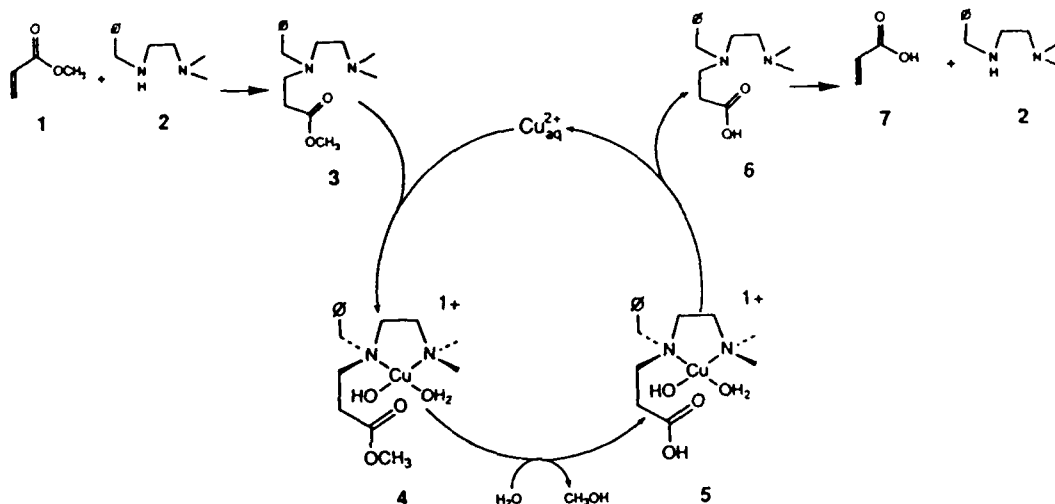
Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Summary: Cu(II) catalysis provides a 16,000-fold acceleration in the hydrolysis of methyl acrylate when a removable vicinal diamine ligand is used to increase the stability of the required copper chelate.

The early work of Kroll,² Bender,³ and Westheimer⁴ on metal ion-promoted hydrolyses of α -amino acid esters and amides has provided the impetus for numerous studies of metal ion promoted and catalyzed ester hydrolysis.⁵ Enzyme models of metalloesterase activity possess both the ester and the metal ligand covalently and irreversibly connected; cyclodextrin^{6a} and micellar^{6b} systems have served as noncovalent enzyme mimics. Despite the early successes using methyl esters of α -amino acids, little work has been directed toward the hydrolysis of unactivated substrates; Co(III) catalysis of methyl acetate hydrolysis described by Chin stands as a notable exception.⁷ Of course, metalloenzymes utilize M^{2+} and not M^{3+} catalytic centers, but without a suitable ligand to bind M^{2+} ions in a proper orientation near the substrate divalent ions do not accelerate the hydrolysis of unactivated esters, which is slow at neutral pH.⁸ Our research group has described work utilizing reversible covalent bond formation as a means of transiently associating a metal complex with unactivated substrates.⁹ In this paper we report that the vicinal diamine group serves as a convenient ligand for transient association with Cu(II) ion in aqueous solution; the ensuing hydrolysis of an unactivated β -ester group is therefore metal ion catalyzed, not promoted.

The reactions shown in Scheme I, including the well-known reversible conjugate addition of amines to enones,¹⁰ can be effected entirely in 0.1 M pH 7.50 buffer.¹¹ Compounds 3 and 6 were synthesized independently,¹² and each step of the reaction sequence was studied separately. The presence of the UV-active benzyl group in diamine 2 allowed us to obtain kinetic measurements using reverse-phase HPLC.¹³ The reaction of *N'*-benzyl-*N,N*-dimethylethylenediamine¹⁴ (2) and methyl acrylate (1) proceeds at 23°C ($k_2 = 2.1 \times 10^{-3} \text{ M}^{-1}\text{s}^{-1}$) as expected to give ester 3 as a colorless oil.

Scheme I



Without added metals, the hydrolysis of ester 3 (1.8 mM) to acid 6 proceeded at pH 7.50 and 23°C with $k_{\text{obs}} = 1.0 \times 10^{-6} \text{ s}^{-1}$ ($t_{1/2} = 670,000 \text{ s}$).¹⁵ Addition of divalent metal ions¹⁶ accelerated the rate of the hydrolysis by varying extents. The addition of 1 eq of $\text{Co}(\text{II})$ or $\text{Ni}(\text{II})$ accelerated the hydrolysis, yielding $k_{\text{obs}} = 3.9 \times 10^{-6} \text{ s}^{-1}$ ($t_{1/2} = 170,000 \text{ s}$) and $1.2 \times 10^{-5} \text{ s}^{-1}$ ($t_{1/2} = 57,000 \text{ s}$), respectively. The use of copper ion led to the largest accelerations; addition of 1 eq of $\text{Cu}(\text{II})$ gave $k_{\text{obs}} = 6.2 \times 10^{-3} \text{ s}^{-1}$ ($t_{1/2} = 110 \text{ s}$), and addition of 5 eq of $\text{Cu}(\text{II})$ gave $k_{\text{obs}} = 1.6 \times 10^{-2} \text{ s}^{-1}$ ($t_{1/2} = 44 \text{ s}$). Therefore, the hydrolysis rate for the fully complexed ester is 16,000-times faster than the same reaction

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Table 1. Effect of pH on the hydrolysis of 1.8 mM 3 with 0.45 mM $\text{Cu}(\text{ClO}_4)_2$ in 0.1 M phosphate buffer.

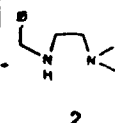
pH	$10^3 \cdot k \text{ (s}^{-1}\text{)}$	$t_{1/2} \text{ (s)}$
6.0	0.015	46200
6.5	0.087	7970
7.0	0.275	2520
7.5	0.583	1189
8.0	1.14	630

We have surveyed the ability of various metals to accelerate the hydrolysis of 3 to 6.

A solution of ester 3 in pH 7.5 HEPES buffer containing one equivalent of the following metal perchlorates showed the following % reaction after 12 days at 25°C: Cu(II), 100%; Ni(II), 98%; Zn(II), 75%; Pb(II), 71%; Cd(II), 67%; Gd(III), 65%; Co(II), 61%. Under the same conditions, uncatalyzed reactions had undergone 40% hydrolysis. While the accelerating effects of Cu(II), Ni(II), Zn(II), and Co(II) have been long recognized, catalysis by Pb(II) and Cd(II) has been reported only rarely.¹⁷ Our observation of accelerated ester hydrolysis by Gd(III) is apparently novel.

In summary, we have found that the metal catalyzed hydrolysis of an unactivated ester can be accomplished in the presence of a chelating ethylenediamine unit β - to the ester. Significantly, the presence of a single β -amine group, such as obtained by the conjugate addition of *n*-butylmethylamine to ethyl acrylate, does not result in metal ion accelerated hydrolysis. This stands in contrast to the well-known metal ion promotion of α -amino ester hydrolysis as reported initially by Kroll and Bender. Apparently, the ester group of complex 4 is sufficiently near the metal-bound hydroxide for intracomplex reaction, but the product's carboxylate group does not participate strongly in chelation of the metal. The result is metal ion catalysis, rather than metal ion promotion, of the hydrolysis reaction.

Acknowledgment. We wish to thank the National Science Foundation for financial support of this work. FT-NMR spectra were obtained using equipment funded in part by NIH Grant #1 S10



at pH 7.50
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RR01458-01A1. AWC thanks the A. P. Sloan Foundation for support in the form of a Fellowship and Eli Lilly and Company for support in the form of a Granteeship.

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- 10) Johnson, M. R. *J. Org. Chem.* 1986, 51, 833.
- 11) N-Hydroxyethylpiperazine-N'-2-ethane sulfonic acid (HEPES) was purchased from United States Biochemical Corporation, Cleveland, Ohio 44128.
- 12) Compounds 3 and 4 each gave suitable ^1H and ^{13}C NMR, mass spec and the following elemental analysis. Compound 3: *Anal.* Calcd for $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_2$: C, 68.15; H, 9.15; N, 10.60. Found: C, 67.81; H, 8.94; N, 10.59. Compound 4 was synthesized and isolated as the bistrifluoroacetic acid salt: *Anal.* Calcd for $\text{C}_{18}\text{H}_{24}\text{F}_6\text{O}_6\text{N}_2$: C, 45.19; H, 5.06; N, 5.86. Found: C, 45.38; H, 4.65; N, 5.77.
- 13) For HPLC analysis an acidic buffered solvent system was used consisting of 7 parts CH_3OH and 4 parts 0.2 N $\text{H}_3\text{PO}_4/\text{KOH}$ buffer. The elutant was monitored at 254 nm, and the solvent system listed above gave separation of 2 first, 6 second, and 3 third.
- 14) N'-Benzyl-N,N-dimethylethylenediamine (technical grade) was purchased from Aldrich Chemical Co. Milwaukee, WI, and was purified by making the dihydrobromide salt. The salt was recrystallized to purity (i-PrOH/hexane, 2:1), and then the free amine was obtained by extracting from basic aqueous solution.
- 15) This control reaction contained 0.2 mM EDTA added to the buffer solution.
- 16) All metal ions utilized were hydrated perchlorate salts, and were purchased from GFS Chemical Co. Columbus, Ohio.
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(Received in USA 23 June 1989)