

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

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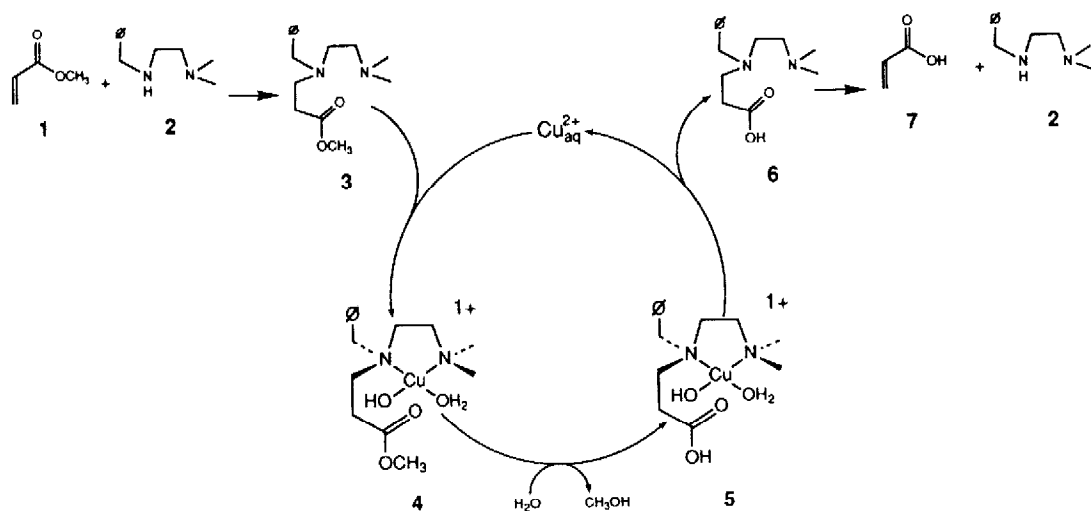
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Summary: Cu(II) catalysis provides a 16,000-fold acceleration in the hydrolysis of methyl acrylate when a removable vicinal diamine ligand is used to increase the stability of the required copper chelate.

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 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. The Cu(II)-catalyzed hydrolysis is also base catalyzed as indicated by the pH profile shown in Table 1.

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	$10^3 \cdot k \text{ (s}^{-1}\text{)}$	$t_{1/2} \text{ (s)}$
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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.

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References and Notes

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- 11) *N*-Hydroxyethylpiperazine-*N'*-2-ethane sulfonic acid (HEPES) was purchased from Unit Biochemical Corporation, Cleveland, Ohio 44128.
- 12) Compounds 3 and 4 each gave suitable ¹H and ¹³C NMR, mass spec and the following elemental analysis. Compound 3: Anal. Calcd for C₁₅H₂₄N₂O₂: C, 68.15; H, 9.15; N, 10.60. Found: C, 67.81; H, 8.94; N, 10.59. Compound 4 was synthesized isolated as the bistrifluoroacetic acid salt: Anal. Calcd for C₁₈H₂₄F₆O₆N₂: 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 and 4 parts 0.2 *N* H₃PO₄/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 Co. Milwaukee, WI, and was purified by making the dihydrobromide salt. The salt w recrystallized to purity (i-PrOH/hexane, 2:1), and then the free amine was obtained 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 G Chemical Co. Columbus, Ohio.
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