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

Brook F. Duerr and Anthony W. Czarnik

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 reversibly 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 $\text{H}^+$ and not $\text{M}^+$ 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.

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 $k_{obs} = 1.0 \times 10^{-6} \text{ s}^{-1}$ ($t_{1/2} = 670,000\text{ s}$). 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 $k_{obs} = 3.9 \times 10^{-6} \text{ s}^{-1}$ ($t_{1/2} = 170,000\text{ s}$) 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 $k_{obs} = 6.2 \times 10^{-3} \text{ s}^{-1}$ ($t_{1/2} = 110\text{ s}$), and addition of 5 eq of Cu(II) gave $k_{obs} = 1.6 \times 10^{-2} \text{ s}^{-1}$ ($t_{1/2} = 64\text{ s}$). 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 $k_{obs} = 6.2 \times 10^{-6} \text{ s}^{-1}$ ($t_{1/2} = 110,000\text{ s}$), 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.)
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Cu(II) CATALYZED HYDROLYSIS OF AN UNACTIVATED ESTER BASED ON REVERSIBLE CONJUGATE ADDITION.1

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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; cyclodextrin6a and micellar6b 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,\(^\text{10}\) can be effected entirely in 0.1 M pH 7.50 buffer.\(^\text{11}\) Compounds 3 and 6 were synthesized independently,\(^\text{12}\) 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.\(^\text{13}\) The reaction of \(\text{N}^\text{\textdegree}\text{-benzyl-2,2-dimethylpropane-1,3-diamine}\) (2) and methyl acrylate (1) proceeds at 23°C \((k = 2.1 \times 10^{-3} \text{ M}^{-1}\text{s}^{-1})\) as expected to give ester 3 as a colorless oil.

Without added metals, the hydrolysis of ester 3 (1.8 mg) to acid 6 proceeded at pH 7.50 and 23°C with \(k_{\text{obs}} = 1.0 \times 10^{-6} \text{ s}^{-1}\) \((t_{1/2} = 670,000 \text{ s})\).\(^\text{15}\) Addition of divalent metal ions\(^\text{16}\) 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 $k_{obs} = 6.2 \times 10^{-6}$ s$^{-1}$ ($t_{1/2} = 110,000$ 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 Cu(ClO$_4$)$_2$ in 0.1 M phosphate buffer.

<table>
<thead>
<tr>
<th>pH</th>
<th>$10^3 \cdot k$ (s$^{-1}$)</th>
<th>$t_{1/2}$ (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.0</td>
<td>0.015</td>
<td>46200</td>
</tr>
<tr>
<td>6.5</td>
<td>0.087</td>
<td>7970</td>
</tr>
<tr>
<td>7.0</td>
<td>0.275</td>
<td>2520</td>
</tr>
<tr>
<td>7.5</td>
<td>0.583</td>
<td>1189</td>
</tr>
<tr>
<td>8.0</td>
<td>1.14</td>
<td>630</td>
</tr>
</tbody>
</table>

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. 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 $\alpha$- to the ester. Significantly, the presence of a single $\beta$-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 $\alpha$-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

1) Presented at the 197th American Chemical Society National Meeting, Dallas, TX, April 1989.


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 'H and 13C NMR, mass spec and the following elemental analysis. Compound 3: Anal. Calcd for C15H24N6O2: 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 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 Cd3OH and 4 parts 0.2 N H3PO4/KOH buffer. The eluant 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-dimethylhydrazine (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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