# Cupric Ion Catalyzed Ester Hydrolysis of *O*-Acetyl-2-pyridinecarboxaldoxime. Nucleophilic Attack by Metal-Bound Water

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**Abstract:** The ester hydrolysis of *O*-acetyl-2-pyridinecarboxaldoxime is catalyzed by $Cu^{2+}$. Thus, apparent rates for the hydroxide path and the water path are enhanced by $2.2 \times 10^7$ and $1.1 \times 10^4$ times, respectively. Detailed analysis indicates that the $Cu^{2+}$-bound hydroxide ion or water molecule reacts with the carbonyl carbon of the complexed ester. Thus, the catalysis includes increases in the effective concentrations of the attacking nucleophiles as well as enhancement in the leaving group ability. Besides, further catalysis in the attack of the coordinated water by general bases is suggested. Implications of the present results on the breakdown of the acyl carboxypeptidase A intermediate are discussed.

Multivalent metal ions catalyze a variety of organic reactions by acting as Lewis acids.[1,2] In the hydrolysis of acyl derivatives (amides, esters, and anhydrides), the rates of hydroxide paths are enhanced by metal ions.[3-7] In these reactions, metal ions polarize the scissile carbonyl bonds by binding the carbonyl oxygens, or metal-coordinated hydroxide ions attack on the carbonyl carbons through template effects. In addition, decreases in the basicity of leaving groups are sometimes involved.

Metal ion catalyzed water attack on the acyl derivatives, however, has rarely been observed. For example, metal ion catalysis of the water path is reported for the hydrolysis of monophenyl esters of 2,6-pyridinedicarboxylate without detailed kinetic analysis.[8]

Metal ion catalysis in the reactions of acyl derivatives also serves as a model for carboxypeptidase A (CPA),[9] a zinc-containing exopeptidase. Catalysis by CPA has been proposed to include an anhydride intermediate formed between the acyl portion of the substrate and the Glu-270 carboxylate of CPA.[10,11] Various shapes (pH-independent, sigmoid, or sigmoid up to pH 9 and then steeply rising) of the pH profiles of $k_{cat}$ for the CPA-catalyzed hydrolysis of ester substrates have been explained in terms of water attack on the anhydride intermediate.[11,12]

In this article, the nucleophilic attack of a metal-bound water molecule on a complexed ester and its implications on the breakdown of the acyl-CPA intermediate are reported.

## Experimental Section

**Materials.** *O*-Acetyl-2-pyridinecarboxaldoxime (**1**) and 2-pyridinecarboxaldoxime (**2**) were prepared according to the literature:[13] mp **1**, 51–52.5 °C (lit.[13] 51–53 °C); **2**, 114 °C (lit.[13] 114 °C). For both of the compounds, syn configurations (the pyridyl ring and the oxime oxygen on the opposite sides) have been established.[13]

Cupric chloride and cupric perchlorate were prepared by dissolving cupric oxide (Aldrich, "Gold Label") with hydrochloric acid and perchloric acid, respectively.

Table I. Rate Data for the $Cu^{2+}$-Catalyzed Hydrolysis of 1[a]

| pH | anion[b] | buffer concn, M | $10^2 k_{cat}$, $s^{-1}$ |
|---|---|---|---|
| 2.00 | $Cl^-$ | | 1.74 ± 0.07 |
| 2.50 | $Cl^-$, $ClAc^-$ | 0.01 | 1.95 ± 0.06 |
| 2.50 | $ClO_4^-$, $ClAc^-$ | 0.01 | 0.935 ± 0.064 |
| 2.50 | $ClO_4^-$, $ClAc^-$ | 0.05 | 0.847 ± 0.039 |
| 3.00 | $Cl^-$, $ClAc^-$ | 0.01 | 1.96 ± 0.03[c] |
| 3.00 | $Cl^-$, $ClAc^-$ | 0.05 | 1.73 ± 0.03[d] |
| 3.00 | $ClO_4^-$, $ClAc^-$ | 0.01 | 1.33 ± 0.07 |
| 3.00 | $ClO_4^-$, $ClAc^-$ | 0.05 | 1.14 ± 0.07 |
| 3.50 | $Cl^-$, $Ac^-$ | 0.01 | 2.46 ± 0.06 |
| 4.01 | $Cl^-$, $Ac^-$ | 0.01 | 4.89 ± 0.12 |
| 4.20 | $Cl^-$, $Ac^-$ | 0.01 | 6.53 ± 0.07[e] |
| 4.20 | $Cl^-$, $Ac^-$ | 0.05 | 6.56 ± 0.18[f] |
| 4.50 | $Cl^-$, $Ac^-$ | 0.01 | 10.8 ± 0.15 |

[a] At 25 °C and $\mu = 0.3$ in the presence of 0.8% (v/v) $CH_3CN$. [b] Chloride and perchlorate ions are added as the anion of the supporting electrolyte, and chloroacetate ($ClAc^-$) and acetate ($Ac^-$) as buffers. [c] $K_f = 75.8 \pm 2.4\ M^{-1}$. [d] $K_f = 72.7 \pm 2.2\ M^{-1}$. [e] $K_f = 50.7 \pm 1.2\ M^{-1}$. [f] $K_f = 45.4 \pm 2.0\ M^{-1}$.

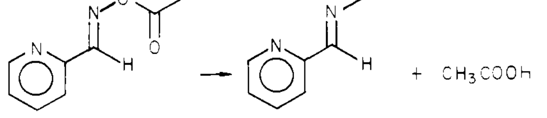
Acetonitrile was purified according to the literature.[14] Water was distilled and deionized before use in kinetic studies. Deuterium oxide (Aldrich) and 20% DCl (Aldrich) solution were 99.8 and 99+ atom %, respectively, enriched.

**Kinetic Measurements.** Reaction rates were measured with a Beckman 5260 UV/vis spectrophotometer. Temperature was controlled to within ±0.1 °C with a Haake E52 circulator. pH measurements were carried out with a Fisher Accumet Model 525 pH meter. Kinetics were performed at an ionic strength of 0.3, which was adjusted with sodium chloride or sodium perchlorate. Buffers used were chloroacetate (pH 2.5–3) and acetate (pH 3.5–4.5). Reaction mixtures contained 0.8% (v/v) acetonitrile. Reaction rates were followed at 310–340 nm with initially added $1 \times 10^{-4}$ M **1**.

Pseudo-first-order rate constants were calculated with infinity absorbance readings measured. Production of **2** in quantitative yields during the hydrolysis of **1** in the presence of $Cu^{2+}$ was evidenced by the product ($Cu\cdot 2^{2+}$) spectra obtained in the presence of $Cu^{2+}$ at all of the pH's investigated.

## Results

The $Cu^{2+}$-catalyzed ester hydrolysis of **1** (eq 1) manifested



(1)

1 2

saturation effects with respect to [$Cu^{2+}$], indicating complex

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[8] Breslow, R.; McAllister, C. *J. Am. Chem. Soc.* **1971**, *93*, 7096.

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[13] Ginsburg, S.; Wilson, I. B. *J. Am. Chem. Soc.*, **1957**, *79*, 481.

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formation between $Cu^{2+}$ and **1** (eq 2). The rate expressions of

$$\mathbf{1}H^+ \xrightleftharpoons{K_a = 10^{-2.29}{}^{4}} \mathbf{1} \xrightleftharpoons{Cu^{2+},\ K_f} Cu\cdot\mathbf{1}^{2+} \xrightarrow{k_{cat}} Cu\cdot\mathbf{2}^{2+} + CH_3COOH \qquad (2)$$

eq 2 are

$$k_0 = \frac{k_{cat}K_f[Cu^{2+}]/(1 + [H^+]/K_a)}{1 + K_f[Cu^{2+}]/(1 + [H^+]/K_a)} \qquad (3)$$

$$\frac{1}{k_0} = \frac{1}{k_{cat}} + \frac{(1 + [H^+]/K_a)}{k_{cat}K_f}\frac{1}{[Cu^{2+}]} \qquad (4)$$

Here, $k_0$ is the pseudo-first-order rate constant. In Figures 1 and 2, rate data obtained at pH 3.00 are plotted according to eq 3 and 4, respectively. A very close fit of theoretical lines based on eq 3 and 4 precludes the possibility of multiple complexation between $Cu^{2+}$ and **1** (i.e., $Cu\cdot[\mathbf{1}]_n{}^{2+}$). In kinetic measurements, emphasis was put on the estimation of $k_{cat}$, and $K_f$ was measured accurately only when the effects of added anions are examined.[15]

The values of $k_{cat}$ and $K_f$ measured under various conditions are summarized in Table I. In this table, the effects of added anions (chloride, perchlorate, chloroacetate, and acetate) as well as the pH dependence of $k_{cat}$ are described. Changes in $k_{cat}$ caused by increases in the concentrations (0.01 to 0.05 M) of chloroacetate and acetate are small, indicating that 0.01 M buffer exerts insignificant effects on $k_{cat}$ values. The pH dependence of $k_{cat}$ measured with 0.01 M buffer is illustrated in Figure 3 and analyzed further according to eq 5 and 6. The values of $k_{cat}{}^{lim}$, $k_{H_2O}{}^{cat}$, and $k_{OH}{}^{cat}$ thus obtained are summarized in Table II.

$$k_{cat} = k_{cat}{}^{lim} + k_{OH}{}^{cat}[OH^-] \qquad (5)$$

$$k_{H_2O}{}^{cat} = k_{cat}{}^{lim}/[H_2O] \qquad (6)$$

From the temperature dependence of $k_{cat}{}^{lim}$, thermodynamic activation parameters are derived and summarized in Table III. The rate data plotted in the Arrhenius plot were the $k_{cat}$ values measured at pH 2, since these are essentially identical with $k_{cat}{}^{lim}$'s. The solvent isotope effect on $k_{cat}{}^{lim}$ was estimated by measuring $k_{cat}$ in $D_2O$ at pD 2.55 (Table IV). The isotope effect is at least 1.72 as $(k_{cat}{}^{lim})_{D_2O}$ is not greater than $k_{cat}$ measured at this pD.

## Discussion

**Mechanism of Catalysis.** The parameter values ($k_{OH}{}^{cat}/k_{OH}{}^{sp}$ and $k_{H_2O}{}^{cat}/k_{H_2O}{}^{sp}$) listed in Table II reveal the remarkable catalysis of the water path ($1.1 \times 10^4$ fold) as well as the hydroxide path ($2.2 \times 10^7$ fold) by $Cu^{2+}$. Possible mechanisms consistent with eq 2 and 5 are illustrated by **3**–**5** (Scheme I). The mechanism of **3** assumes that the catalysis involves only the increased leaving ability of the oximate ion. On the other hand, the mechanism of **4** includes the enhanced electrophilicity of the carbonyl carbon through the polarization of the carbonyl group, and the mechanism of **5** increased effective concentrations of nucleophiles by template effect, in addition to the increased leaving group ability.

Model building indicates that both tetrahedral and planar configurations of Cu(II)[17] are possible for **3**–**5**.[18] For the mechanisms of **3** and **4**, $k_{OH}{}^{cat}$ and $k_{H_2O}{}^{cat}$ represent the reactions of external hydroxide ion and water, respectively. On the other hand, the rate expression becomes eq 5 under the condition of $[H^+] >> K'$ for the mechanism of **5** and then the rate constants for

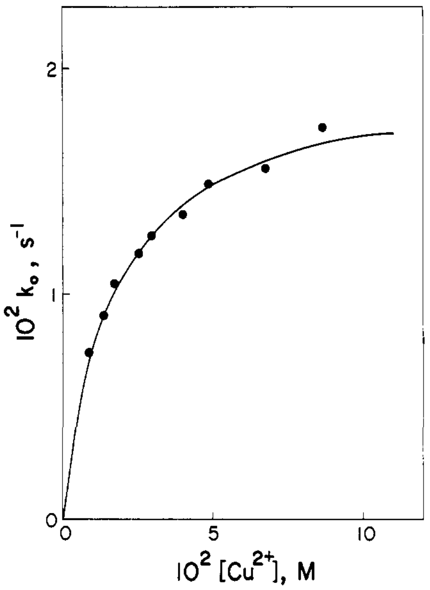

**Figure 1.** Plot of $k_0$ against $[Cu^{2+}]$ measured at pH 3.00 for the $Cu^{2+}$-catalyzed hydrolysis of **1** (0.01 M chloroacetate buffer, $\mu = 0.3$ with NaCl and $CuCl_2$).

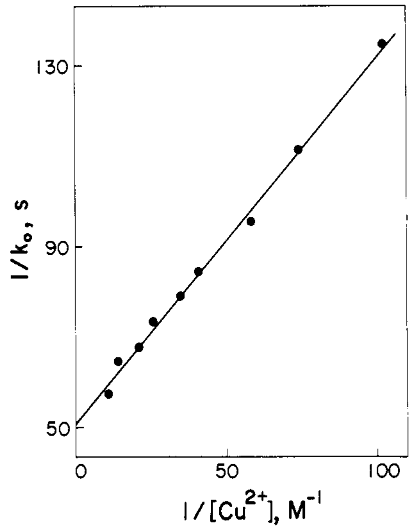

**Figure 2.** Data of Figure 1 plotted according to eq 4.

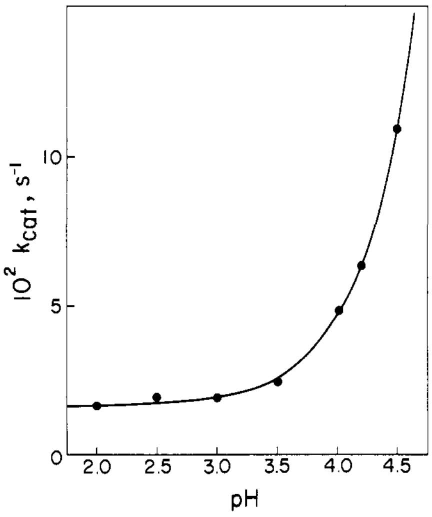

**Figure 3.** Plot of $k_{cat}$ against pH for the $Cu^{2+}$-catalyzed hydrolysis of **1** (0.01 M buffer, $\mu = 0.3$ with NaCl and $CuCl_2$).

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[15] Parameter $k_{cat}$ stands for the reactivity of $Cu\cdot\mathbf{1}^{2+}$ when either the rapid preequilibrium or the steady-state approximation is assumed for the formation of $Cu\cdot\mathbf{1}^{2+}$, while $K_f$ is the formation constant of $Cu\cdot\mathbf{1}^{2+}$ only when the preequilibrium is assumed.

[16] Blanch, J. H. *J. Chem. Soc. B.* **1968**, 167.

[17] Cotton, F. A.; Wilkinson, G. "Advanced Inorganic Chemistry", 4th ed.; Wiley: New York, 1980; p 50.

[18] The model indicates the presence of angular strain for some of the Cu(II) complexes in the ground state, but the strain disappears in the corresponding transition state. Stabilization of the transition state by added metal ions, however, can lead to very efficient catalysis as exemplified by the hydrolysis of nitriles (Breslow, R.; Schmir, M. *J. Am. Chem. Soc.* **1971**, *93*, 4960).

Table II. Kinetic Parameters for the $Cu^{2+}$-Catalyzed and Spontaneous Hydrolysis of 1 at 25 °C

| | $k_{cat}^{lim}$, $s^{-1}$ | $k_{H_2O}^{cat}$ or $k_{H_2O}^{sp}$, $M^{-1}$ $s^{-1}$ | $k_{OH}^{cat}$ or $k_{OH}^{sp}$, $M^{-1}$ $s^{-1}$ | $k_{OH}/k_{H_2O}$ |
|---|---|---|---|---|
| $Cu^{2+}$ catalyzed | $(1.69 \pm 0.06) \times 10^{-2}$ [a]<br>$0.8 \times 10^{-2}$ [b] | $(3.07 \pm 0.10) \times 10^{-4}$ [a] | $(2.98 \pm 0.07) \times 10^{8}$ [a] | $9.7 \times 10^{11}$ [a] |
| spontaneous[c] | | $2.7 \times 10^{-8}$ | $1.34 \times 10^{1}$ | $5.0 \times 10^{8}$ |
| rate enhancement | | $1.1 \times 10^{4}$-fold | $2.2 \times 10^{7}$-fold | |

[a] $\mu = 0.3$ with NaCl and $CuCl_2$. [b] $\mu = 0.3$ with $NaClO_4$ and $Cu(ClO_4)_2$. [c] Reference 16.

Table III. Thermodynamic Activation Parameters of $k_{cat}^{lim}$ for the $Cu^{2+}$-Catalyzed Hydrolysis of 1 at 25 °C[a]

| parameter | value |
|---|---|
| $E_a$ | $14.3 \pm 0.5$ kcal/mol |
| $\Delta H^{\ddagger}$ | $13.7 \pm 0.5$ kcal/mol |
| $\Delta F^{\ddagger}$ | $19.8 \pm 0.01$ kcal/mol |
| $\Delta S^{\ddagger}$ | $-20.6 \pm 0.8$ eu |

[a] $\mu = 0.3$ with NaCl and $CuCl_2$.

Table IV. Deuterium Oxide Isotope Effect on $k_{cat}^{lim}$ for the $Cu^{2+}$-Catalyzed Hydrolysis of 1 at 25 °C[a]

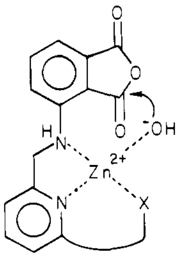
| | |
|---|---|
| $(k_{cat}^{lim})_{H_2O}$ | $(1.69 \pm 0.06) \times 10^{-2}$ $s^{-1}$ |
| $k_{cat}$ at pD 2.55 $\approx (k_{cat}^{lim})_{D_2O}$ | $(0.98 \pm 0.02) \times 10^{-2}$ $s^{-1}$ |
| $(k_{cat}^{lim})_{H_2O}/(k_{cat}^{lim})_{D_2O}$ | $1.72 \pm 0.07$ |

[a] $\mu = 0.3$ with NaCl and $CuCl_2$.

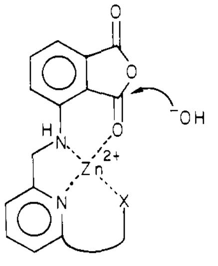
the hydroxide path and the water path are $k_{OH}^{cat}\cdot K_w/K'$[19] and $k_{cat}^{lim}$, respectively.

The spectral titration[20] of $Cu\cdot\mathbf{2}^{2+}$ disclosed the $pK_a$ of $3.2 \pm 0.1$ for the ionization of the oxime group. Enhancement in the acidity of **2** upon complexation with $Cu^{2+}$ ($pK_a$ of **2** = 10.0, $pK_a$ of $Zn\cdot\mathbf{2}^{2+}$ = 6.5)[21,22] indicates that the increased leaving ability of the oximate ion is involved in the catalysis. However, the plot of log $k_{OH}$ against $pK_a$ of the leaving oxime for various acetyl oximes[3] indicates that the rate constant for the reaction of hydroxide ion with $Cu\cdot\mathbf{1}^{2+}$ would be at least $10^3$ times smaller than the observed value of $k_{OH}^{cat}$ if the catalysis is solely due to the enhanced leaving group ability. In order to account for the rate of the hydroxide path, therefore, additional catalytic factors such as those illustrated in the mechanisms of **4** and **5** are needed.

Mechanisms similar to **4** and **5** have been proposed in metal ion catalyzed hydrolysis of several acyl derivatives, but differentiation between them has been not always successful.[4,6] In one instance, Breslow and co-workers supported attack by the complexed hydroxide ion (**6**) against attack on the complexed carbonyl group (**7**) for the $Zn^{2+}$-catalyzed hydrolysis of coordinated anhydrides.[5] This was based on the fact that catalysis was operative only on the hydroxide path. The mechanism of **7** assumes enhanced reactivity of the scissile carbonyl group and, thus, expects decreased preference for a better nucleophile. The failure to observe catalysis on the water path, therefore, favors the mechanism of **6**.



**6** (X = H or $COO^-$)



**7** (X = H or $COO^-$)

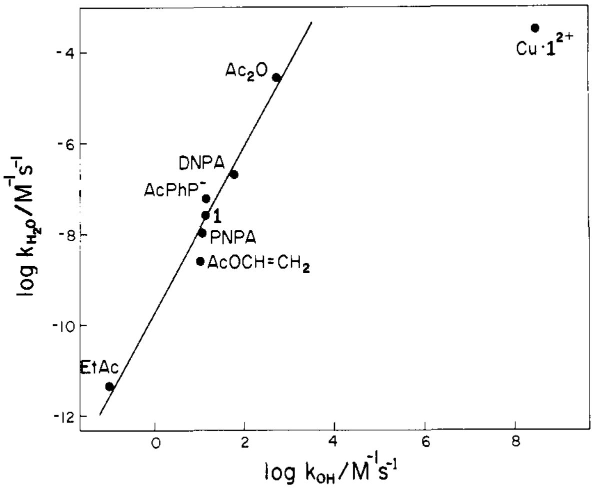
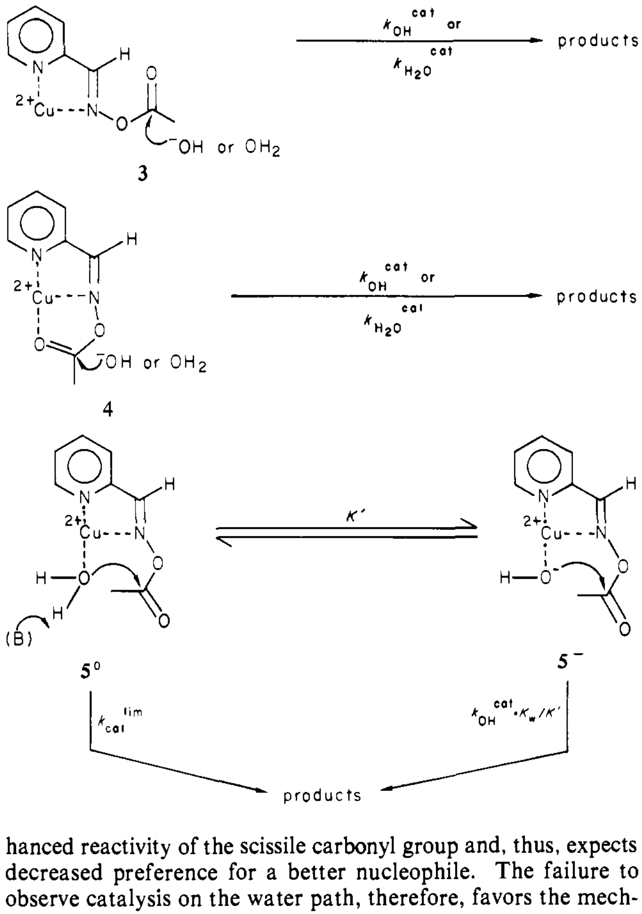


Figure 4. Plot of log $k_{H_2O}$ against log $k_{OH}$ for various acetyl esters including $Cu\cdot\mathbf{1}^{2+}$ and **1**. Other data points are taken from ref 23 (DNPA; 2,4-dinitrophenyl acetate, AcPhP⁻; acetyl phenyl phosphate anion, PNPA, *p*-nitrophenyl acetate).

Scheme I



In the present study, the mechanisms of **4** and **5** would be differentiated with kinetic data obtained at sufficiently high pH's.

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(19) The value of $k_{OH}^{cat}\cdot K_w/K'$ may be estimated as ca. 20 $s^{-1}$, approximating that the $Cu^{2+}$-bound water in $\mathbf{5}^{0}$ is as acidic as the hydrated $Cu^{2+}$ ($pK$ = 6.8: Chaberek, S., Jr.; Courtney, R. C.; Martell, A. E. *J. Am. Chem. Soc.* **1952**, *74*, 5057). Then the ratio of the rates for the hydroxide path and the water path for the mechanism of **5** may be estimated as ca. $10^3$.

(20) Measured in the presence of 3.2% (v/v) acetonitrile at 25 °C with ionic strength maintained at 0.3 ($NaClO_4$ and $Cu(ClO_4)_2$).

(21) Breslow, R.; Chipman, D. *J. Am. Chem. Soc.* **1965**, *87*, 4195.

(22) Much greater Lewis acidity of $Cu^{2+}$ compared with $Zn^{2+}$ is also reflected in the $K_f$'s of $Cu\cdot\mathbf{2}^{2+}$ ($5.36 \times 10^4$ $M^{-1}$)[20] and $Zn\cdot\mathbf{2}^{2+}$ (150 $M^{-1}$)[21] as well as in those of $Cu\cdot\mathbf{1}^{2+}$ (ca. 60 $M^{-1}$) and $Zn\cdot\mathbf{1}^{2+}$ (<<5 $M^{-1}$)[3].

This, however, was hampered by the limited solubility of $Cu^{2+}$ and very fast reaction rates at high pH's. Instead, the mechanism of **5** is chosen on the following grounds.

The rate constant for the hydroxide path of the mechanism of **4**, $k_{OH}^{cat}$, is very close to the diffusion limit while that of **5**, $k_{OH}^{cat} \cdot K_w/K'$, does not require this unusual reactivity.[19] In addition, following Breslow, the carbonyl carbon would become less selective toward external nucleophiles in the presence of $Cu^{2+}$ if the catalysis occurs through the mechanism of **4**. Figure 4 reveals that the selectivity–reactivity relationship holds for a wide range of acetyl derivatives containing oxygen leaving groups. For the acetyl compounds, $k_{H_2O}$ increases by $10^{1.8n}$ times when $k_{OH}$ is enhanced by $10^n$ times as indicated by the slope (1.8) of the linear line. The data point for $Cu \cdot \mathbf{1}^{2+}$ is calculated on the basis of the mechanism of **4**. Very large deviation seen with this data point indicates that the mechanism of **4** is hardly compatible with the experimental data.[24,25]

Nucleophilicity of water would decrease greatly upon metal complexation although this can be compensated for by template effect. However, general bases may assist the attack of the coordinated water as the reactions of esters and anhydrides with neutral oxygen nucleophiles, such as water and alcohols, are subject to catalysis by general bases including solvent molecules.[26] In this regard, $\Delta S^{\ddagger}$ (Table III) and the solvent isotope effect (Table IV) for $k_{cat}^{lim}$ can be related to the general base catalysis. Thus, $\Delta S^{\ddagger}$ of -21 eu is typical of a bimolecular reaction,[27] and $k_H/k_D$ of 1.72 can be compared with those for the acetate-catalyzed hydrolysis of acetic anhydride ($k_H/k_D = 1.65$) and the water reaction of methyl trifluoroacetate ($k_H/k_D = 1.8$), both of which occur through general base mechanisms.[28]

About twofold larger $k_{cat}^{lim}$ in the presence of chloride ion compared with perchlorate ion (Table II) may be attributed in part to specific salt effects.[29] However, the possibility of general base catalysis by chloride ion still exists in spite of its very weak basicity, since the attacking water molecule is bound to $Cu^{2+}$.

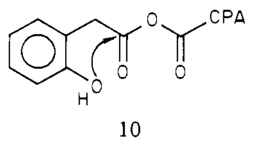
In contrast to chloride ion ($K_f$ for $CuCl^+ = 1.3\ M^{-1}$ at 25 °C and $\mu = 1$),[30] added acetate and chloroacetate ions ($K_f$ for $CuCH_3COO^+ = 180\ M^{-1}$ at 25 °C and $\mu = 0$)[30] mainly bind to $Cu^{2+}$. This would lower the Lewis acidity of the metal ion and block a part of coordination sites available for the attacking water molecule, while small amounts of uncomplexed acetates can act as general bases. A compromise between these conflicting factors appears to be reflected in the small decrease in $k_{cat}$ caused by the addition of more chloroacetate ion. Hydroxide path predominates in the hydrolysis at pH 4.20, and this can be related to the almost identical $k_{cat}$ values in the presence of 0.01 and 0.05 M acetate buffers at pH 4.20. Examination of the effects of general bases was not extended further because of these complications.

In the estimation of $K_f$ values (Table I), only the protonation of **1** was considered (eq 2). However, $K_f$ values measured with chloroacetate and acetate buffers suggest the importance of other factors such as the complexation of buffers and the formation of hydroxo complexes.[15,19]

**Implications on the Breakdown of Acyl–CPA Intermediates.** The $Zn^{2+}$-catalyzed hydrolysis of complexed anhydrides mentioned earlier in this section (**6**) has been proposed as a model for the breakdown of the acyl-CPA intermediate.[5] Metal ion catalysis, however, occurs only on the hydroxide path in the hydrolysis of the model anhydride complexes, while acyl-CPA appears to be hydrolyzed through the water path.[11,12] Water attack on $Cu \cdot \mathbf{1}^{2+}$ can be regarded as a model for that on acyl-CPA in view of the p$K_a$ of $Cu \cdot \mathbf{2}^{2+}$ similar to those of carboxyl groups.

Studies with a space-filling model of CPA indicated that the cleaved alcohol or amine moiety of the substrate remains in the hydrophobic pocket inside the active site until the acid portion leaves the enzyme.[31] As implied by the effects of general bases discussed in the present investigation, the hydroxyl or amine group of the product may assist the attack of the zinc-bound water on acyl-CPA acting as general bases. The general base catalysis can be very efficient as the enzymatic system may provide particularly effective geometry for such interactions. The space-filling model of CPA indicated the absence of any enzyme functional group located suitably for this role in the vicinity of the zinc ion.

Several attempts to trap the acyl-CPA intermediate by transesterification or with externally added trapping reagents have been unsuccessful.[5,32-34] In addition, trapping with intramolecular reagents (**10**[34] and **11**[35])have also failed. Unsuccessful trapping of acyl-CPA can be ascribed in part to the very effective water attack on acyl-CPA catalyzed by the cleaved alcohol or amine moiety of the substrates.



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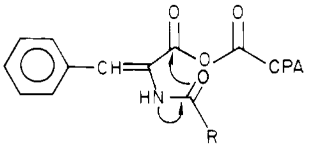

11 (R = Me or Ph)

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**Registry No. 1**, 74231-53-1; **2**, 1193-96-0; $CuCl_2$, 7447-39-4; $Cu(ClO_4)_2$, 13770-18-8.

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[23] Kirsch, J. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1964**, *86*, 837.

[24] Similar reactivity–selectivity relationship is seen in the linear plot (slope 1.2) of log $k_{H_2O}$ against log $k_{OH}$ for *p*-nitrophenyl esters containing various acyl activating groups (Holmquist, B.; Bruice, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 2982). Therefore, the ratio of $k_{H_2O}/k_{OH}$ for **4**, doubly activated in the acyl portion and the leaving group, is expected to be larger than predicted by the linear line of Figure 5.

[25] Electrostatic attraction between hydroxide ion and positively charged $\alpha$ substituents of *p*-nitrophenyl acetates was unimportant (Holmquist, B.; Bruice, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 2982). Such electrostatic interactions, therefore, cannot explain the large deviation seen with the data point of $Cu \cdot \mathbf{1}^{2+}$.

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