Metal Ion Effects in Intramolecular Reactions. Effects of Divalent Metal Ions on Intramolecular Acetamido Group Participation in Ester Hydrolysis

Thomas H. Fife,* Theodore J. Przystas, and Mahesh P. Pujari[1]

Contribution from the Department of Biochemistry, University of Southern California, Los Angeles, California 90033. *Received February 17, 1988*

Abstract: The hydrolysis reactions of a series of esters of α-acetamidocinnamic acid proceed with formation of an oxazolinone intermediate. In 50% dioxane–H_2O (v/v) at 50 °C, an oxazolinone can be observed spectrophotometrically in the OH^--catalyzed cyclization reactions of the α-acetamido-substituted esters with leaving groups of pK_a 12.4 or less. In comparison with the OH^--catalyzed hydrolysis of the corresponding cinnamate esters, the rate enhancement due to the presence of the acetamido group is a factor of 200 with the trifluoroethyl ester and increases to 2×10^6 with the *p*-nitrophenyl ester. The plot of log k_{OH} vs σ, the Hammett substituent constant, is linear and has a slope (ρ) of 2.7 (1.8 when σ^- is employed) for the cyclization reactions of the phenolic esters, but the ρ value is only 1.4 for the OH^--catalyzed hydrolysis of the corresponding cinnamates. The slope of log k_{OH} vs the pK_a of the leaving group for the cyclization of the α-acetamidocinnamic acid derivatives, β_{lg}, is −0.9. Thus, there must be considerable C–O bond breaking in the critical transition state for oxazolinone formation. In H_2O as the solvent, 6-carboxy-2-pyridylmethyl α-(*N*-acetylamino)cinnamate and the corresponding 2-pyridylmethyl derivative cyclize rapidly to the oxazolinone with k_{OH} (5×10^4)-fold larger than that for hydrolysis of 2-pyridylmethyl cinnamate, even though the leaving group is an aliphatic alcohol. There is significant metal ion catalysis in the cyclization reactions with Cu^{2+}, Ni^{2+}, Co^{2+}, or Zn^{2+}. The binding of the metal ions to the 6-carboxy-substituted derivative is very strong, and saturation occurs at metal ion concentrations less than 0.01 M. A saturating concentration of Cu^{2+} (0.001 M) enhances the rate of cyclization by a factor of 5×10^4. Thus, the total rate enhancement provided by bifunctional catalysis (Cu^{2+} and the neighboring acetamido group) is $>10^9$-fold. Metal ion binding to 2-pyridylmethyl α-(*N*-acetylamino)cinnamate is weak, but nevertheless, the second-order rate constants k_{OH} are similar to those of the 6-carboxy-substituted ester at equal metal ion concentrations. The metal ions must exert their catalytic effect by stabilizing the leaving group alcohol in the transition state. This appears to be a general mechanism for metal ion catalysis of reactions in which C–O bond breaking is the rate-determining step.

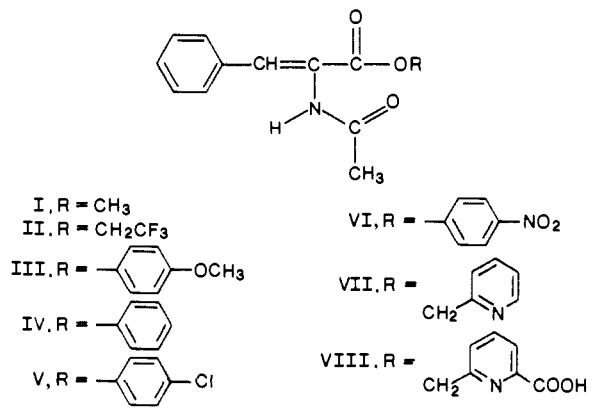
Chemical intramolecular reactions have been extensively studied because of their analogy with enzyme-catalyzed reactions, which proceed through an enzyme–substrate complex.[2,3] However, the effects of metal ions on intramolecular processes have scarcely been studied even though a large percentage of known enzymes are metalloenzymes.[4-6] Therefore, it is of major importance to determine the general effect of chelated metal ions in intramolecular reactions to further understanding of both enzymatic and chemical catalysis.

One severe problem in demonstrating metal ion effects in chemical intramolecular nucleophilic reactions of esters is that the metal ion promoted hydroxide ion catalyzed reactions are so facile,[5-10] and these reactions are in competition with the intramolecular nucleophilic reaction. For example, rate enhancements due to the presence of metal ion of 10^8 have been observed in the OH^--catalyzed hydrolysis of 8-(2-carboxy)quinolyl esters,[7,8] and participation by a neighboring carboxyl group cannot then be observed, although such participation is quite efficient in the absence of metal ions.[7] Consequently, in order to determine the mechanisms and magnitudes of metal ion effects in intramolecular reactions, it is clearly necessary to employ intramolecular nucleophiles with which the pK_a of the conjugate acid is greater than that of a carboxyl group. By employing a more powerful nucleophile, the nucleophilic reaction should be better able to compete with the metal ion promoted OH^--catalyzed hydrolysis.

Neighboring amide[11-13] and ureido[14,15] groups have been found to be highly effective intramolecular nucleophiles in reactions of esters. The intramolecular attack of the neighboring benzamido group of *p*-nitrophenyl hippurate in which an oxazolinone is formed is hydroxide ion catalyzed and occurs with considerable facility ($k_{OH} = 1.05 \times 10^4$ M^{-1} s^{-1} at 30 °C).[13] Although a neighboring amide group appears to be among the best of intramolecular nucleophiles, there is still little known of the detailed mechanism of its reaction with esters, and the effects of metal ions on these reactions have not previously been investigated. Knowledge of the mechanism of neighboring amide group reactions with esters is also of fundamental importance in enzymology because of the frequent use of N-acylated esters of α-amino acids as substrates for esterolytic enzymes, e.g., α-chymotrypsin[16,17] or carboxypeptidase A,[18,19] a Zn(II) metalloenzyme. The oxazolinone that would be produced in the cyclization of esters of α-acetamidocinnamic acid has strong characteristic absorbance at 340 nm.[19] Consequently, the formation of an oxazolinone can be easily detected in the hydrolysis reactions of such esters if indeed cyclization occurs. An understanding of the mechanism of an intramolecular reaction is necessary before metal ion effects can be properly interpreted. We have therefore investigated the hydrolysis reactions of α-acetamidocinnamic acid esters I–VIII with which the leaving group has been varied over a wide range in the alcohol pK_a so that the effect of the leaving group can be de-

(1) Postdoctoral fellow, University of Southern California.
(2) (a) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969. (b) Bruice, T. C.; Benkovic, S. *Bioorganic Mechanisms*; W. A. Benjamin: New York, 1966.
(3) Bruice, T. C. *Enzymes (3rd Ed.)* **1970**, *2*, 217.
(4) Lehninger, A. L. *Biochemistry*; Worth: New York, 1975.
(5) Fife, T. H.; Przystas, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 7297. Metal ion catalysis occurs in the neighboring carboxyl nucleophilic reactions of esters with poor leaving groups.
(6) Fife, T. H.; Przystas, T. J. *J. Am. Chem. Soc.* **1982**, *104*, 2251.
(7) Fife, T. H.; Przystas, T. J.; Squillacote, V. L. *J. Am. Chem. Soc.* **1979**, *101*, 3017.
(8) Hay, R. W.; Clark, C. R. *J. Chem. Soc., Dalton Trans.* **1977**, 1866, 1993.
(9) Wells, M. A.; Bruice, T. C. *J. Am. Chem. Soc.* **1977**, *99*, 5341.
(10) Fife, T. H.; Przystas, T. J. *J. Am. Chem. Soc.* **1986**, *108*, 4631.
(11) Shafer, J. A.; Morawetz, H. *J. Org. Chem.* **1963**, *28*, 1899.
(12) Behme, M. T.; Cordes, E. H. *J. Org. Chem.* **1964**, *29*, 1255.
(13) (a) de Jersey, J.; Willadsen, P.; Zerner, B. *Biochemistry* **1969**, *8*, 1959. (b) de Jersey, J.; Kortt, A. A.; Zerner, B. *Biochem. Biophys. Res. Commun.* **1966**, *23*, 745.
(14) Hegarty, A. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1970**, *92*, 6575.
(15) Bruice, T. C.; Hegarty, A. F. *Proc. Natl. Acad. Sci. U.S.A.* **1970**, *65*, 805. Hegarty, A. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1970**, *92*, 6561.
(16) Fersht, A. *Enzyme Structure and Mechanism*; W. H. Freeman: San Francisco, 1977; and references therein.
(17) Bender, M. L. *Mechanisms of Homogeneous Catalysis from Protons to Proteins*; Wiley Interscience: New York, 1971; and references therein.
(18) Ludwig, M. L.; Lipscomb, W. N. In *Inorganic Biochemistry*; Eichhorn, G., Ed.; Elsevier: New York, 1973; Vol. 1, pp 438–487.
(19) Suh, J.; Cho, W.; Chung, S. *J. Am. Chem. Soc.* **1985**, *107*, 4530.

0002-7863/88/1510-8157$01.50/0



termined, and for comparison purposes we have measured rate constants for hydrolysis of the corresponding cinnamate esters. The esters VII and VIII possess metal ion chelating functional groups, and with VIII, the metal ion binding will be very strong.

Experimental Section

Materials. The esters of cinnamic acid were synthesized by stirring 0.02 mol of freshly distilled cinnamoyl chloride, triethylamine, and the appropriate alcohol in 100 mL of ethyl acetate for 2 h. The triethylamine hydrochloride was removed by filtration, and the solvent was then removed by rotary evaporation. The remaining ester was vacuum distilled or recrystallized from methanol. Methyl cinnamate: bp 68 °C (0.05 mm); mp 35–36 °C (lit.[20] mp 34 °C). 2,2,2-Trifluoroethyl cinnamate: bp 63 °C (0.05 mm); n^{22}_D = 1.5062. Anal. Calcd for $C_{11}H_9F_3O_2$: C, 57.39; H, 3.91. Found: C, 57.23; H, 4.01. 4-Methoxyphenyl cinnamate: mp 100–102 °C. Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.59; H, 5.51. Found: C, 75.52; H, 5.57. Phenyl cinnamate: mp 77–78 °C (lit.[21] mp 75–76 °C). 4-Chlorophenyl cinnamate: mp 104–105 °C (lit.[22] mp 104–105 °C). 4-Nitrophenyl cinnamate: mp 145–147 °C (lit.[23] mp 146.5–147.5 °C).

The methyl (I) and 2,2,2-trifluoroethyl (II) esters of α-acetamidocinnamic acid were prepared by refluxing 2 g of 2-methyl-4-benzylideneoxazolin-5-one[24] in 30 mL of alcohol for ~16 h. The excess alcohol was removed by rotary evaporation, and the ester was recrystallized several times from ethyl acetate. Methyl α-(*N*-acetylamino)-cinnamate: mp 123–125 °C (lit.[25] mp 125 °C). 2,2,2-Trifluoroethyl α-(*N*-acetylamino)cinnamate: mp 156–158 °C. Anal. Calcd for $C_{13}H_{12}F_3NO_3$: C, 54.35; H, 4.18; N, 4.87. Found: C, 54.32; H, 4.20; N, 4.83.

The phenyl esters of α-acetamidocinnamic acid (III–VI) were prepared by mixing 0.02 mol of 2-methyl-4-benzylideneoxazolin-5-one and 0.04 mol of phenol in a round-bottom flask. The solid mixture was warmed gently until it liquified. It was kept in the liquid state for 2–3 h and then cooled to room temperature. The solid residue was recrystallized several times from ethyl acetate. 4-Methoxyphenyl α-(*N*-acetylamino)cinnamate: mp 139–141 °C. Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.45; H, 5.46; N, 4.50. Found: C, 69.27; H, 5.55; N, 4.51. Phenyl α-(*N*-acetylamino)cinnamate: mp 135–137 °C. Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.60; H, 5.34; N, 4.98. Found: C, 72.62; H, 5.39; N, 4.99. 4-Chlorophenyl α-(*N*-acetylamino)cinnamate: mp 140–141 °C. Anal. Calcd for $C_{17}H_{14}ClNO_3$: C, 64.62; H, 4.44; N, 4.44. Found: C, 64.62; H, 4.47; N, 4.46. 4-Nitrophenyl α-(*N*-acetylamino)cinnamate: mp 147–149 °C. Anal. Calcd for $C_{17}H_{14}N_2O_5$: C, 62.58; H, 4.29; N, 8.59. Found: C, 62.50; H, 4.38; N, 8.48. The dioxane used in the kinetic studies was refluxed with sodium borohydride and freshly distilled prior to use.

2-Pyridylmethyl α-(*N*-acetylamino)cinnamate (VII) was prepared by refluxing a mixture of 2-(hydroxymethyl)pyridine (3 g, 0.028 mol; obtained from Sigma) and 5.15 g (0.028 mol) of 2-methyl-4-benzylideneoxazolin-5-one in dry benzene for 6 h. The benzene was removed by rotary evaporation at reduced pressure, and the residue was recrystallized from dry chloroform. The compound melted at 139–140 °C. Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.92; H, 5.41; N, 9.46. Found: C, 69.04; H, 5.41; N, 9.53.

6-Carboxy-2-(hydroxymethyl)pyridine was prepared by the method reported by Fife and Przystas.[6] 6-Carboxy-2-pyridylmethyl α-(*N*-acetylamino)cinnamate (VIII) was prepared by the same method as VII: mp 162–163 °C. Anal. Calcd for $C_{18}H_{16}N_2O_5$: C, 63.53; H, 4.71; N, 8.24. Found: C, 63.78; H, 4.70; N, 8.16.

2-Pyridylmethyl cinnamate was prepared by adding dropwise 1 equiv of cinnamoyl chloride in ether to 2 equiv of 2-(hydroxymethyl)pyridine in ether. The mixture was stirred for 2 h. After filtration, the ether was removed by rotary evaporation. The residual material was vacuum distilled and boiled at 136 °C (0.02 mm). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.38; H, 5.50; N, 5.79.

Kinetic Measurements. The rates of hydrolysis of the esters were measured at 30 or 50 °C in 50% dioxane–H_2O (v/v) or H_2O with a Pye-Unicam SP8-100 recording spectrophotometer or a Durrum D110 stopped-flow apparatus equipped with a Hewlett-Packard Model 1207B storage oscilloscope. A 50% dioxane–H_2O mixture was utilized as the solvent in the hydrolysis of I–VI because of limited water solubility of some of the esters. Hydrolysis of the cinnamate esters was followed by monitoring the disappearance of reactant at 310 nm, except in the case of the nitrophenyl ester, with which nitrophenol appearance at 400 nm was followed. The reactions of the substituted phenyl α-acetamidocinnamate esters (III–VI) were monitored at 340 nm. With the *p*-nitrophenyl ester (VI), nitrophenol appearance at 400 nm was also followed when possible. The hydrolysis of the methyl ester (I) was monitored by the disappearance of the reactant at 310 nm, while with the 2,2,2-trifluoroethyl derivative (II), appearance and disappearance of the oxazolinone intermediate at 340 nm was followed. The reactions of VII and VIII were studied in H_2O by following the absorbance changes at 330 nm. The hydrolysis of 2-methyl-4-benzylideneoxazolin-5-one was followed by measuring the disappearance of reactant at 340 nm.

In a typical experiment, 10–30 μL of the ester stock solution (5×10^{-3} M in THF) was injected into 3 mL of reactant solution maintained at the desired temperature. The reactions [with the exception of that of 2,2,2-trifluoroethyl α-(*N*-acetylamino)cinnamate] followed excellent pseudo-first-order kinetics for at least 4 half-lives. Rate constants and subsequent kinetic parameters were evaluated by a least-squares computer program. The rates were measured in 0.01–0.02 M buffer solutions; the buffer concentration did not have a significant effect on the reaction rates except with the oxazolinone. The rate constants for oxazolinone hydrolysis were obtained by extrapolation to zero buffer concentration in dilution experiments. The buffers used were acetate, *N*-ethylmorpholine, morpholine, butylamine, 2,6-dimethylpiperidine, and carbonate. Addition of 5×10^{-5} M of an appropriate alcohol corresponding to the leaving group, e.g., trifluoroethanol, has no effect on the rate of the cyclization reaction. Reaction solution pH values were measured with a Beckman Model 3500 digital pH meter standardized with aqueous buffers according to Bates.[26] The glass electrode gives the correct pH reading in concentrated dioxane–water mixtures.[27]

The trifluoroethyl ester (II) gave first an absorbance increase at 340 nm and then a decrease. Thus, the reaction is of the type A → B → C. The kinetics are greatly simplified by the fact that only the oxazolinone intermediate (B) absorbs at 340 nm. Thus, $A_{340nm} = \epsilon_B[B]$. The extinction coefficient of the oxazolinone, 2-methyl-4-benzylideneoxazolin-5-one (B), was carefully measured and found to be 2.6×10^4 M^{-1} cm^{-1} under the experimental conditions. The concentration of [B] is given by[28]

$$[B] = \frac{[A_0]k_1}{k_2 - k_1}(e^{-k_1 t} - e^{-k_2 t}) \quad (1)$$

and

$$A_{340} = \frac{2.6 \times 10^4 [A_0]k_1}{k_2 - k_1}(e^{-k_1 t} - e^{-k_2 t}) \quad (2)$$

A known amount of II was injected into 3 mL of buffer solution. The exact zero time was noted, and the absorbance was continuously monitored. The rate constant k_2 can be obtained independently with a prepared sample of B; the value of k_1 was then determined from a computer fit of the experimental data to the analytical expression. An excellent fit of the data was obtained.

The substituted phenyl esters III–VI cyclize rapidly with release of phenol and formation of a derivative having an absorbance spectrum identical with that of the 2-methyl-4-benzylideneoxazolin-5-one plus the

(20) Stobbe, H. *Ber. Dtsch. Chem. Ges.* **1925**, *58B*, 2859.
(21) Womack, E. B.; McWhirter, J. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, 714.
(22) Speroni, G. *Chim. Ind.* (Milan) **1952**, *34*, 391; *Chem. Abstr.* **1953**, *47*, 2924.
(23) Bender, M. L.; Schonbaum, G.; Zerner, B. *J. Am. Chem. Soc.* **1962**, *84*, 2540.
(24) Herbst, R. M.; Shemin, D. In *Organic Synthesis*; Wiley: New York, 1943; Collect. Vol. II, 1.
(25) Cook, A.; Harris, G.; Heilbron, I. *J. Chem. Soc.* **1948**, 1060.
(26) Bates, R. G. *Determination of pH. Theory and Practice*; Wiley: New York, 1965.
(27) Marshall, H. P.; Grunwald, E. *J. Chem. Phys.* **1953**, *21*, 2143.
(28) Frost, A. A.; Pearson, R. G. *Kinetics and Mechanism*; Wiley: New York, 1953; p 153.

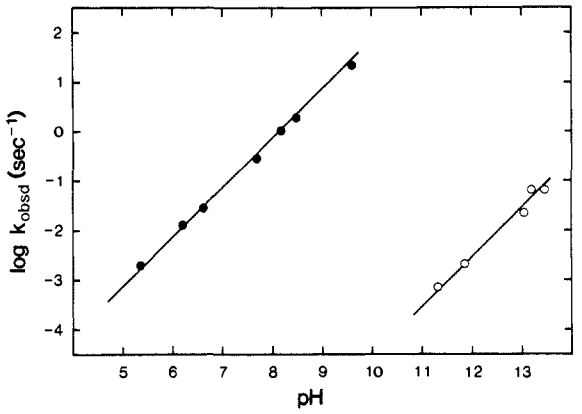


Figure 1. Plots of log k_{obsd} vs pH for the hydrolysis of *p*-nitrophenyl cinnamate (○) and for the cyclization of *p*-nitrophenyl α-(*N*-acetylamino)-cinnamate (●) in 50% dioxane–H_2O (v/v) at 30 °C and μ = 0.1 M (with KCl).

Table I. Second-Order Rate Constants for Hydrolysis of Esters of Cinnamic Acid at 50 °C in 50% Dioxane–H_2O (v/v) and μ = 0.1 M with KCl

ester	k',[a] M s^{-1}	k_{OH},[b] M^{-1} s^{-1}
methyl	4.7×10^{-16}	0.95
trifluoroethyl	5.7×10^{-15}	11.0
p-methoxyphenyl	1.4×10^{-15}	2.8
phenyl	2.3×10^{-15}	4.6
p-chlorophenyl	4.6×10^{-15}	9.2
p-nitrophenyl	4.1×10^{-14}	82.0
	2.2×10^{-15} [c]	16.8

[a] $k' = k_{OH}K_w$. [b] Employing pK_w = 15.299 at 50 °C and 15.882 at 30 °C.[29] [c] At 30 °C.

phenol. Likewise, the reactions of the (hydroxymethyl)pyridine derivatives VII and VIII proceed with formation of an intermediate whose spectrum is quantitatively identical with that of an authentic sample of the oxazolinone plus alcohol. These cyclization reactions could be followed to completion without complication from the much slower hydrolysis of the oxazolinone. The derivative formed in the initial reaction (cyclization) hydrolyzes with rate constants that are identical with those of a separately prepared authentic sample of 2-methyl-4-benzylideneoxazolin-5-one. Thus, the identity of the intermediate has been established by both spectral and kinetic measurements.

Results

The hydrolysis reactions of the esters of cinnamic acid are hydroxide ion catalyzed. A typical plot of log k_{obsd} vs pH is shown in Figure 1 for hydrolysis of the *p*-nitrophenyl ester. The plot is linear with a slope of 1.0. Rate constants are given in Table I for OH^--catalyzed hydrolysis of the series of cinnamate esters at 50 °C in 50% dioxane–H_2O (v/v). The values of k' in Table I are equal to $k_{obsd}a_H$, i.e., $k' = k_{OH}K_w$, where k_{OH} is the true second-order rate constant and K_w is the ion product of water in 50% dioxane–H_2O. The value of pK_w in 50% dioxane–H_2O (wt/wt) has been measured at 50 °C and is 15.299.[29] This value of pK_w was employed in calculating the second-order rate constants k_{OH} in Table I, since the difference in solvent composition between 50% dioxane–H_2O (v/v) and (wt/wt) is slight.

The reactions of the esters of α-acetamidocinnamic acid I–VI are also OH^- catalyzed. The rate constants for these reactions are given in Table II. The second-order rate constant for hydrolysis of the methyl ester is only 4-fold larger than that for hydrolysis of methyl cinnamate. The formation of the oxazolinone could be directly observed with esters II–VI at 340 nm, and rate constants were the same for oxazolinone formation as for appearance of phenol (measured at 400 nm in the case of VI at pH >7). The plot of log k_{obsd} vs pH in Figure 1 for reaction of the *p*-nitrophenyl ester VI is linear with a slope of 1.0 at pH values as low as 5. As the leaving group is improved the difference in rate constants k_{OH} for corresponding esters in the two series becomes larger. With the trifluoroethyl ester the difference is a factor of 200, and with the *p*-nitrophenyl esters it is 2×10^6. The value of k_{OH} for cyclization of the *p*-nitrophenyl ester VI at 30 °C in H_2O is 4.4×10^6 M^{-1} s^{-1}.

The hydrolysis of the oxazolinone produced from the esters was studied separately in 50% dioxane–H_2O at 50 °C. The plot of log k_{obsd}, obtained by extrapolation to zero buffer concentration, vs pH is shown in Figure 2. The slope of the plot is 1.0, indicating that the reaction is OH^- catalyzed. The value of k' is 2.2×10^{-12} M s^{-1} ($k_{OH} = 4.4 \times 10^3$ M^{-1} s^{-1}).

(29) Elsemongy, M. M.; Elnader, H. M. *J. Ind. Chem. Soc.* **1977**, *54*, 1055.

Table II. Second-Order Rate Constants for Reactions of Esters of α-Acetamidocinnamic Acid at 50 °C in 50% Dioxane–H_2O (v/v) and μ = 0.1 M with KCl

ester	k',[a] M s^{-1}	k_{OH},[b] M^{-1} s^{-1}
methyl	1.9×10^{-15}	3.8
trifluoroethyl	1.2×10^{-12}	2.4×10^3
p-methoxyphenyl	1.5×10^{-10}	3.0×10^5
phenyl	3.7×10^{-10}	7.4×10^5
p-chlorophenyl	1.5×10^{-9}	3.0×10^6
p-nitrophenyl	9.5×10^{-8}	1.9×10^8
	7.5×10^{-9} [c]	5.7×10^7 [c]

[a] $k' = k_{OH}K_w$. [b] Employing pK_w = 15.299 at 50 °C and 15.882 at 30 °C.[29] [c] At 30 °C.

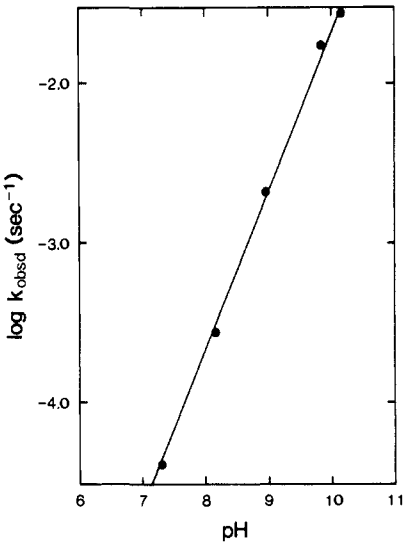


Figure 2. Plot of log k_{obsd} vs pH for hydrolysis of the oxazolinone produced by cyclization of the substituted phenyl esters of α-acetamidocinnamic acid (III–VI) in 50% dioxane–H_2O (v/v) at 50 °C and μ = 0.1 M (with KCl).

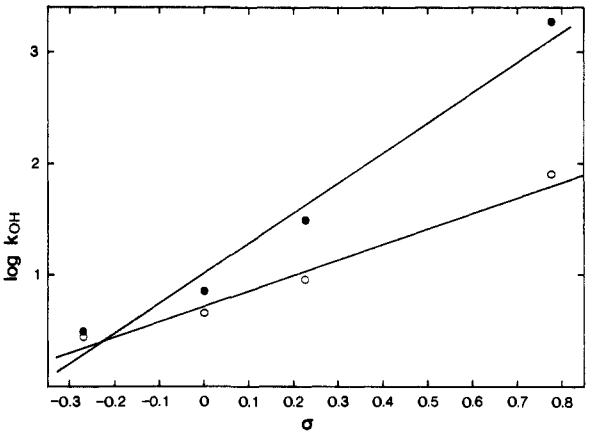


Figure 3. Plots of log k_{OH} (M^{-1} s^{-1}) vs σ, the Hammett substituent constant, for hydrolysis of substituted phenyl cinnamate esters (○) and plots of log k_{OH} − 5 (M^{-1} s^{-1}) vs σ for cyclization of the substituted phenyl esters of α-acetamidocinnamic acid (III–VI) (●) in 50% dioxane–H_2O (v/v) at 50 °C and μ = 0.1 M.

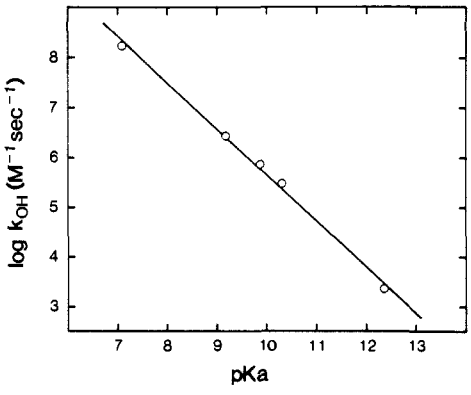


Figure 4. Plot of log k_{OH} vs the pK_a of the leaving group for the cyclization of the esters of α-acetamidocinnamic acid (II–VI) in 50% dioxane–H_2O at 50 °C and μ = 0.1 M.

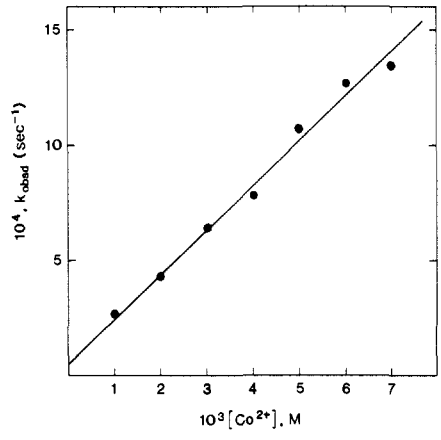


Figure 5. Plot of k_{obsd} for cyclization of 2-pyridylmethyl α-(*N*-acetylamino)cinnamate (VII) vs the concentration of Co^{2+} at pH 6.25 in H_2O and 30 °C (μ = 0.1 M with KCl).

In Figure 3 are presented plots of log k_{OH} vs σ, the Hammett substituent constant,[30] for the hydrolysis of the cinnamate esters and the cyclization reactions of the α-acetamidocinnamate esters III–VI. The slopes of these plots, ρ, are 1.4 ± 0.2 (r = 0.988) and 2.7 ± 0.4 (r = 0.989), respectively. In Figure 3, a σ value of 0.778 was employed for the *p*-NO_2 substituent. Only a slightly better fit was obtained with σ^- (σ^- = 1.27 for *p*-NO_2) in the cyclization of the α-acetamidocinnamate esters. The value of ρ is then 1.8 ± 0.2 (r = 0.998). Thus, there is a much larger dependence of the reactions of the α-acetamidocinnamate esters on electron withdrawal in the leaving group. This is also seen in Figure 4, where log k_{OH} is plotted vs the pK_a of the alcohol or phenol leaving group (in H_2O) in the cyclization of esters II–VI. The slope β_{lg} is −0.9 with the α-acetamidocinnamate esters. A similar plot of log k_{OH} vs the pK_a of the leaving group for OH^--catalyzed hydrolysis of the corresponding cinnamate esters had a slope of −0.4.

Plots of log k_{obsd} vs pH for cyclization of 2-pyridylmethyl α-(*N*-acetylamino)cinnamate (VII) and 6-carboxy-2-pyridylmethyl α-(*N*-acetylamino)cinnamate (VIII) in H_2O to 2-methyl-4-benzylideneoxazolin-5-one are again linear with slopes of 1.0. Thus, the reactions are hydroxide ion catalyzed, and k_{OH} values at 30 °C and μ = 0.1 M are 8000 and 10000 M^{-1} s^{-1}, respectively. In contrast, k_{OH} for OH^--catalyzed hydrolysis of 2-pyridylmethyl cinnamate at 30 °C in H_2O is 0.16 M^{-1} s^{-1}. The hydrolysis of 2-methyl-4-benzylideneoxazolin-5-one in H_2O at 30 °C has k_{OH} = 1000 M^{-1} s^{-1}.[31]

(30) Hammett, L. P. *Physical Organic Chemistry*; McGraw-Hill: New York, 1940; Chapter 7. Wells, P. R. *Chem. Rev.* **1963**, *63*, 171.

(31) The second-order rate constant for alkaline hydrolysis of 2-methyl-4-benzylidene-oxazolin-5-one has been previously reported to be 221.7 M^{-1} s^{-1} at 25 °C in 3% aqueous acetone with μ = 1.0 M NaCl: Suh, J.; Lee, E.; Myoung, Y. C.; Kim, M.; Kin, S. *J. Org. Chem.* **1985**, *50*, 977.

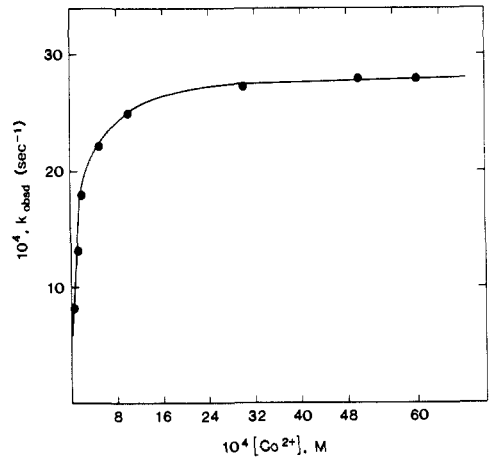


Figure 6. Plot of k_{obsd} for cyclization of 6-carboxy-2-pyridylmethyl α-(*N*-acetylamino)cinnamate (VIII) vs the concentration of Co^{2+} at pH 6.25 in H_2O and 30 °C (μ = 0.1 M with KCl).

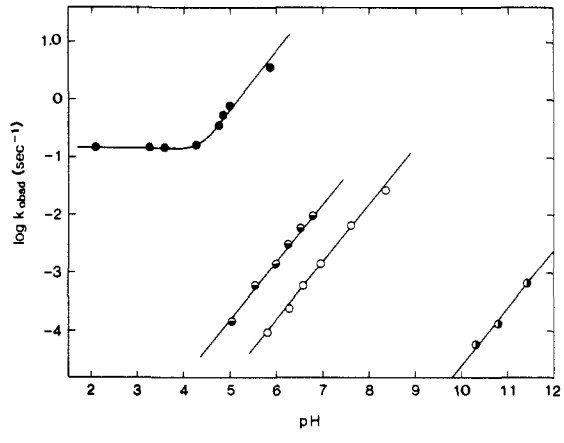


Figure 7. Plots of log k_{obsd} vs pH for cyclization of 6-carboxy-2-pyridylmethyl α-(*N*-acetylamino)cinnamate at 30 °C (μ = 0.1 M) in H_2O in the presence of saturating concentrations of Cu^{2+} (0.001 M) (●) and Ni^{2+} (0.004 M) (◒) and in the absence of metal ion (○). Also shown is the plot of log k_{obsd} vs pH for hydrolysis of 2-pyridylmethyl cinnamate (◑). The ester concentration was 2 × 10^{-5} M.

Table III. Rate Constants for Cyclization of Esters of α-Acetamidocinnamic Acid in H_2O at 30 °C (μ = 0.1 M with KCl)

compd	metal ion	$k_{OH'}$ M^{-1} s^{-1}	compd	metal ion	$k_{OH'}$ M^{-1} s^{-1}
VII[a]	none	8.05 × 10^3	VIII[b]	none	1.0 × 10^4
	Cu^{2+}	6.8 × 10^7		Cu^{2+}	5.2 × 10^8
	Ni^{2+}	4.5 × 10^4		Ni^{2+}	1.1 × 10^5
	Co^{2+}	5.1 × 10^4		Co^{2+}	1.1 × 10^5
	Zn^{2+}	4.1 × 10^4		Zn^{2+}	8.1 × 10^4

[a] Metal ion concentrations in the pH variation studies were Cu^{2+} 1 × 10^{-3} M, Ni^{2+} 4 × 10^{-3} M, Co^{2+} 5 × 10^{-3} M, and Zn^{2+} 6 × 10^{-3} M. [b] Saturating concentrations of metal ions were employed: Cu^{2+} 1 × 10^{-3} M, Ni^{2+} 4 × 10^{-3} M, Co^{2+} 5 × 10^{-3} M, and Zn^{2+} 6 × 10^{-3} M.

The divalent metal ions Cu^{2+}, Ni^{2+}, Co^{2+}, and Zn^{2+} have a significant effect on the rates of cyclization of both VII and VIII. Plots of k_{obsd} vs metal ion concentration in the reactions of VII were linear even at high metal ion concentrations (0.01 M). A typical example is shown in Figure 5, where k_{obsd} is plotted vs the concentration of Co^{2+} at pH 6.25. Low concentrations of the metal ions (<0.005 M) produce saturation effects in the reactions of VIII. In Figure 6, the plot of k_{obsd} vs the concentration of Co^{2+} is presented. Thus, metal ion binding to VIII is quite strong, and eq 3 is followed where K_M is the metal ion binding constant and

$$k_{obsd} = k_M K_M[M^{2+}]/(1 + K_M[M^{2+}]) \quad (3)$$

k_M is the limiting rate constant for metal ion catalysis at a specified pH value. The association constants K_M are as follows: Cu^{2+}, 6.4 × 10^5 M^{-1} at pH 5.26; Ni^{2+}, 9.6 × 10^3 M^{-1} at pH 6.55; Co^{2+},

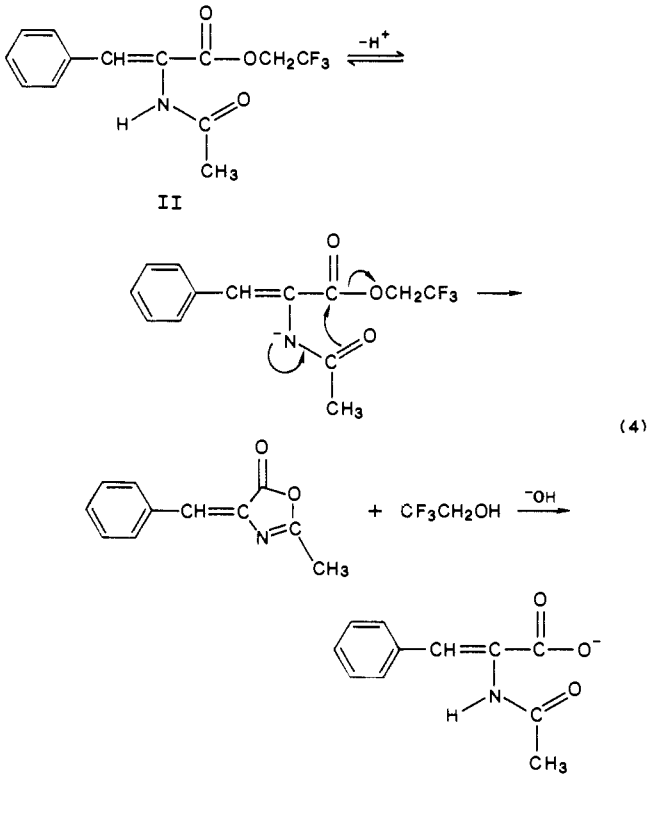
8.4×10^3 M^{-1} at pH 6.25; Zn^{2+}, 3.5×10^3 M^{-1} at pH 6.25. These constants were calculated at the given pH and are uncorrected for protonation of the substrate. At a constant concentration of metal ion, saturating in the case of VIII but nonsaturating with VII, plots of log k_{obsd} for cyclization vs pH were linear with slopes of 1.0 as seen in Figure 7. The values of the second-order rate constants k_{OH}' are given in Table III. The Cu^{2+}-catalyzed reaction of VIII becomes pH independent at pH <4. The metal ion catalyzed reactions could not be studied at pH >7 because of precipitation of the metal ion. The metal ions Ni^{2+}, Co^{2+}, and Zn^{2+} have little effect on the hydrolysis of the oxazolinone intermediate, which was identified spectrophotometrically in each case. For example, in the presence of 0.004 M Ni^{2+} k_{OH}' is 1.09×10^3 M^{-1} s^{-1} at 30 °C. A 0.001 M concentration of Cu^{2+}, however, accelerates the rate of hydrolysis of the oxazolinone by a factor of 200 ($k_{OH}' = 2 \times 10^5$ M^{-1} s^{-1} at 30 °C in H_2O).

The metal ion catalyzed reactions of VII and VIII were not further accelerated by increasing the buffer concentration at constant pH. For example, increasing the concentration of cacodylate buffer at pH 6.28 had no effect on the cyclization reactions in the absence of metal ions and increased k_{obsd} by only ~3% in the presence of 0.004 M Ni^{2+}. Likewise, similarly increasing the concentration of *N*-ethylmorpholine at pH 7.51 in the absence of metal ion and at pH 6.75 with 0.004 M Ni^{2+} has no effect.

Discussion

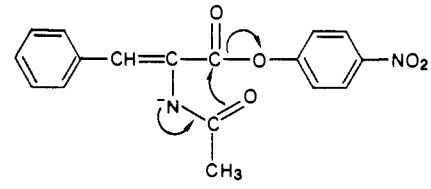
Only hydroxide ion catalysis was observed in the hydrolysis of the series of cinnamate esters and cyclization of the corresponding α-acetamidocinnamate esters. The methyl esters in the two series have very similar values of k_{OH}, the second-order rate constant for OH^--catalyzed hydrolysis (4-fold difference). Therefore, the neighboring acetamido group of I is not significantly enhancing the rate of the reaction. The leaving group of the methyl ester is, of course, very poor (pK_a = 15.5). However, extrapolation of the plot of Figure 4 to the pK_a of methanol gives a value of k_{OH} that is in reasonable agreement with the experimental value. As a consequence, the hydrolysis reaction may be proceeding in part via oxazolinone formation even with the methyl ester.

When the pK_a of the alcohol leaving group is improved to 12.4 with the trifluoroethyl esters, then the difference in the rate constants increases to a factor of 200. The neighboring group of II must then be participating in the reaction. It was possible



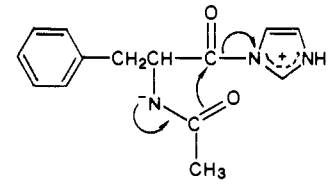
to observe an oxazolinone intermediate at 340 nm, although it hydrolyzes rapidly in a reaction that is also OH^- catalyzed. Formation of the intermediate is rate determining in the sequence of reactions, but the difference in the rate constants is not large. In terms of the leaving group, the cutoff point for the spectrophotometric observation of intramolecular participation by a neighboring acetamido group lies between trifluoroethanol (pK_a = 12.4) and methanol (pK_a = 15.5).[32]

When the leaving group is further improved to phenol (pK_a = 10), then the oxazolinone intermediate can be observed spectrophotometrically, and both its formation and decomposition can be easily monitored in successive reactions at 340 nm. The rate enhancement for cyclization in comparison with hydrolysis of phenyl cinnamate is then 10^5. The *p*-nitrophenyl ester VI cyclizes very rapidly to the oxazolinone, and the rate enhancement in comparison to hydrolysis of *p*-nitrophenyl cinnamate is 2×10^6. Again only OH^- catalysis IX was observed even at pH values as



IX

low as 5. Likewise, Zerner and his co-workers found only OH^- catalysis in the cyclization reaction of *p*-nitrophenyl esters of *N*-acyl amino acids.[13] In contrast, a pH-independent reaction was found in the cyclization of *N*-acylimidazoles of *N*-acetyl amino acids,[33] but in these cases, in addition to the possibility of a neutral species reaction, there is also the possibility of a favorable kinetic equivalent involving attack of the anionic species on the protonated *N*-acylimidazole (X). It is clear that with esters the favored



X

pathway is that in which the acetamido anion is the nucleophile. Thus, the efficiency of the intramolecular anion nucleophilic reaction increases greatly as the leaving group of the ester is improved, although the intramolecular reaction will still occur with aliphatic esters.[34]

The Hammett ρ value in the plot of log k_{OH} vs σ (σ = 0.778 for *p*-NO_2) for the OH^--catalyzed cyclization of the substituted phenyl esters of α-acetamidocinnamic acid is 2.7, which shows quantitatively the large effect of electron withdrawal in the leaving group in the cyclization reaction. In contrast, the ρ value is only 1.4 in the OH^--catalyzed hydrolysis of the corresponding cinnamate esters. The fit was slightly improved for the acetamido-substituted esters when σ^- was employed (σ^- = 1.27 for *p*-NO_2), and ρ^- is then 1.8. Correlation of the logarithms of the rate constants with σ would occur if formation of a tetrahedral intermediate was rate determining, as would be expected in the OH^--catalyzed hydrolysis of phenyl esters.[2] However, the rate constants for intramolecular nucleophilic reactions of phenyl esters have often been found to be dependent on σ^- when the nucleophile is much less basic than hydroxide ion, as for example in intramolecular aminolysis reactions.[35] These reactions, which show a large dependence of the rate on electron withdrawal in the leaving group, are either concerted, with both C–O bond breaking and bond formation with the nucleophile occurring in the transition

(32) Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795.
(33) Kogan, R. L.; Fife, T. H. *J. Org. Chem.* **1984**, *49*, 5229.
(34) Effects due to changes in the amide pK_a should be small.[14]

state, or they involve rate-determining breakdown of a tetrahedral intermediate. In either case there will be C–O bond breaking in the critical transition state.

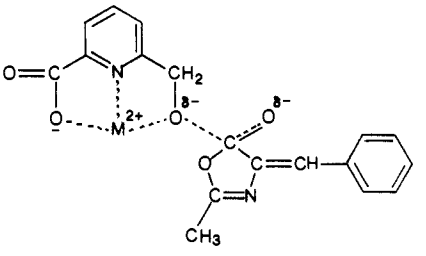
That C–O bond breaking must be occurring in the transition state of the intramolecular acetamido group reactions is shown by the large dependence of the rate constants on the pK_a of the leaving group. The slope of the plot of log k_{OH} vs pK_a in Figure 4, β_{lg}, is −0.9.[36] Similar large β_{lg} values in other reactions have been considered previously to indicate rate-limiting breakdown of a tetrahedral intermediate.[2,37] In contrast, the β_{lg} in the OH^--catalyzed hydrolysis of the cinnamate esters is only −0.4. The β_{lg} of −0.3 found in the alkaline hydrolysis of acetate esters was considered to indicate rate-determining attack of OH^- at the ester carbonyl.[2,37,38]

Metal Ion Catalysis. Metal ion promoted OH^- catalysis in ester hydrolysis is markedly dependent on leaving group ability.[6] This reaction, of course, will be in competition with reactions involving metal ion catalysis of neighboring group reactions. Thus, the best opportunity for demonstrating metal ion catalysis of intramolecular reactions is with esters having poor aliphatic alcohol leaving groups and intramolecular nucleophiles that are highly basic so that they can displace the poor leaving group. The results with I and II show that indeed a neighboring acetamido group can enhance the decomposition of aliphatic esters via intramolecular nucleophilic attack, even in 50% dioxane–H_2O as the solvent. The cyclization reactions are more favorable in H_2O,[39] and this is in accord with a transition state that is quite polar. Therefore, the esters VII and VIII, which possess metal ion chelating functional groups in addition to a neighboring acetamido group, are ideally suited for a study of metal ion effects in such reactions.

The esters VII and VIII cyclize rapidly to 2-methyl-4-benzylideneoxazolin-5-one in H_2O. These reactions can be easily monitored by following the appearance of the oxazolinone. The pK_a values of the leaving group alcohols of VII and VIII are very likely 1–2 pK_a units greater than 12.4; the spectrophotometric observation of oxazolinone formation must then reflect in large part the favorability of the cyclization reaction in H_2O as compared with 50% dioxane–H_2O. As is the case with II–VI, the cyclization reactions of VII and VIII show apparent OH^- catalysis. The second-order rate constants k_{OH} for VII and VIII are $>10^4$ larger than that for OH^--catalyzed hydrolysis of the reference compound 2-pyridylmethyl cinnamate.

The metal ions Cu^{2+}, Ni^{2+}, Co^{2+}, and Zn^{2+} have a significant effect on the rate of cyclization of VII, even though metal ion binding to the ester must be weak. Plots of k_{obsd} vs metal ion concentration were still linear at the high metal ion concentration of 0.01 M. The enhancements in the second-order rate constant k_{OH} then range from (8×10^3)-fold with 0.001 M Cu^{2+} to 5-fold with 0.006 M Zn^{2+}. These rate enhancements will, of course, increase with increasing metal ion concentration until saturation is achieved.

The carboxyl group in the 6-position of the pyridine ring of VIII has little effect on the rate of cyclization. The values of k_{OH} are very similar for VII and VIII in the absence of metal ions. However, the second metal ion chelating group of VIII permits very strong metal ion binding to the ester.[40] Saturation effects are observed at low metal ion concentrations (<0.005 M) as seen in Figure 6, but the rate enhancements produced by these saturating concentrations are about the same as those produced by the nonsaturating concentration of 0.01 M in the reactions of VII. Cupric ion is the best catalyst in the series of metal ions, and this could be due in part to its greater strength of binding to the ester (as reflected in the association constants K_M for binding to VIII). Furthermore, the pH-independent Cu^{2+}-catalyzed reaction at pH <4 must represent cyclization of the neutral species and/or a water-catalyzed reaction, i.e., Cu^{2+} can bring about a mechanism change at low pH. Nevertheless, the comparable effect of each metal ion in the OH^--catalyzed cyclization of VII and VIII shows that it is not the strength of binding to the ester that is of major importance in regard to catalytic efficiency,[41] but rather the most important factor must be strength of binding in the transition state.[42] Binding of a metal ion to the carbonyl oxygen of the reactant would not be sterically favorable because a seven-membered ring would be required. Stabilization of a tetrahedral intermediate by the metal ion is therefore not a likely mechanism, because binding to the oxygen anion of the intermediate would also be sterically unfavorable.[43] Furthermore, such binding would markedly reduce the driving force necessary for C–O bond breaking. Metal ion binding to the leaving group oxygen in the reactant would involve a five-membered chelate ring but would also be quite weak. However, as the C–O bond breaks in the rate-determining step negative charge would be generated on oxygen so that binding in the transition state would be strong. In the transition state XI binding of the metal ion to oxygen would



XI

enhance the reaction by stabilizing the leaving group. Such an interpretation is consistent with the effect on the rate of cyclization of the pK_a of the leaving group with II–VI (Figure 4), which indicates that C–O bond breaking is part of the rate-determining step.

General-acid catalysis by a metal ion bound water molecule is unlikely because a seven-membered ring would be required. Note also that the rate constants for the Ni^{2+}, Co^{2+}, and Zn^{2+}-catalyzed reactions are comparable, even though Ni^{2+}-complexed water is a much weaker acid than are the aquo complexes of the other metal ions.[44] Complexation of the metal ions

(35) (a) Bruice, T. C.; Benkovic, S. J. *J. Am. Chem. Soc.* **1963**, *85*, 1. (b) Fife, T. H.; Hutchins, J. E. *J. Am. Chem. Soc.* **1981**, *103*, 4194.

(36) Anhydrides of α-acetamidocinnamic acid could not be prepared in the present work, presumably because of their great reactivity. Extrapolation of the plot of Figure 4 to $pK_a = 5.0$ (assumed as the pK_a of a typical carboxyl leaving group) gives a k_{OH} value of 2×10^{10} M^{-1} s^{-1} in 50% dioxane–H_2O at 50 °C. The value of k_{obsd} at pH 7.5 would then be 318 s^{-1}, and the half-life for cyclization would be 0.002 s. Employing $\beta_{lg} = -0.9$ and the value of k_{OH} for the *p*-nitrophenyl ester VI at 30 °C gives $k_{OH} = 4.6 \times 10^9$ M^{-1} s^{-1} for cyclization of an α-acetamidocinnamic acid derivative at 30 °C with a leaving group of $pK_a = 5.0$. The value of k_{obsd} at pH 7.5 and 30 °C would be 19 s^{-1}, and the half-life for cyclization would be 0.04 s. See ref 19 for a discussion of carboxypeptidase A reactions with an ester of α-acetamidocinnamic acid.

(37) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622. Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7018.

(38) Bruice, T. C.; Fife, T. H.; Bruno, J. J.; Brandon, N. E. *Biochemistry* **1962**, *1*, 7.

(39) The half-life for cyclization of the *p*-nitrophenyl ester VI at pH 7 and 30 °C is ~1 s in H_2O.

(40) The binding constants of the metal ions to the product alcohol 2-(hydroxymethyl)picolinic acid are Cu^{2+} 5×10^6 M^{-1}, Ni^{2+} 2×10^5 M^{-1}, Co^{2+} 2×10^4 M^{-1}, and Zn^{2+} 2×10^4 M^{-1}: Green, R. W.; Ooi, G. K. S. *Aust. J. Chem.* **1962**, *15*, 786. The major chelating groups must be the carboxyl group and the pyridine nitrogen.

(41) Note that the k_{OH}' values in Table III for VII and VIII are not directly comparable since k_{OH}' for VIII is equal to $k_M/[OH^-]$, whereas that for VII is $k_M K_M [M^{2+}]/[OH^-]$; see eq 3. The k_{OH}' values will only be directly comparable when $K_M[M^{2+}] > 1$, i.e., at higher metal ion concentrations than could be employed in the study of VII. However, since the k_{OH}' values for VII and VIII are very similar at the concentrations employed (they will be equal at 0.01 M M^{2+}), it is clear that at higher metal ion concentrations the k_{OH}' for VII will be equal to or *greater* than that of VIII. Thus, the magnitude of the rate enhancements is not dependent on the strength of metal ion binding to the reactant as determined by K_M.

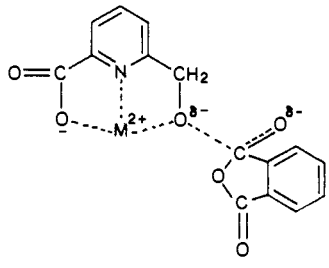
(42) This would be reflected in an association constant K_M^* for metal ion binding in the transition state to the leaving group oxygen. Coordination of a carboxylate anion will reduce the effective charge of the metal ion.

(43) There have been a number of studies of metal ion catalyzed ester and amide hydrolysis reactions that could reflect metal ion stabilization of a tetrahedral intermediate: Hay, R. W. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, 1987; p 411. See also ref 2b, Vol. 1, p 110.

to VII and VIII should be pH independent at pH values above the pK_a of the pyridine nitrogen.[45] Therefore, the most likely mechanism in the metal ion catalyzed cyclization reactions is XI.

Strong binding of a metal ion will stabilize the reactants. Consequently, a rate enhancement will only be obtained if the transition state is stabilized to an even greater extent. Any additional stabilization of the transition state provided by metal ion chelation due to the liganding carboxyl group of VIII is clearly not sufficient to offset the stabilization of the reactants in comparison with VII. The rate enhancements will be maximized when metal ion binding to the reactant is weak but binding in the transition state is very strong. A rate enhancement of 5×10^4 with Cu^{2+} in the apparent OH^--catalyzed reaction of VIII is only moderately large, but when this is multiplied by the factor of 5×10^4 due to acetamido group participation in the absence of metal ion, then the total rate enhancement due to bifunctional catalysis is $>10^9$-fold.

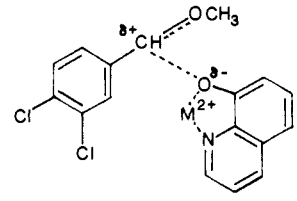
We have previously found metal ion catalysis in the pH-independent intramolecular carboxylate anion nucleophilic reactions of phthalate monoesters of aliphatic alcohols in cases where there is a chelating functional group in the molecule.[5,6] These reactions must also involve metal ion stabilization of the leaving group in the transition state for breakdown of the tetrahedral intermediate to products (XII). As with VII and VIII, the strength of metal



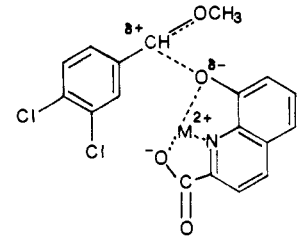
XII

ion binding to the reactant is not a factor of importance in regard to the magnitude of the rate enhancements. At a nonsaturating metal ion concentration of 0.005 M, the rate enhancement displayed by the ester without a carboxyl group substituent in the 6-position of the pyridine ring is comparable to that of a saturating concentration of metal ion in the hydrolysis of the ester with a second chelating functional group (10^4 with Cu^{2+} and $\sim 10^2$ with Ni^{2+}, Co^{2+}, and Zn^{2+}). Again it is the strength of metal ion binding in the transition state that is of predominant importance. Thus, the effects of metal ions are similar regardless of whether the nucleophile is carboxyl or the much more powerful acetamido anion. Transition states XI and XII then represent a general mechanism for metal ion catalysis of intramolecular nucleophilic reactions in which C–O bond breaking is the rate-determining step.

The same general type of transition-state effect was also found in the metal ion catalyzed hydrolysis of substituted benzaldehyde methyl 8-quinolyl acetals (XIII and XIV).[46] Metal ion binding



XIII



XIV

to the 8-quinolyl acetal (XIII) is weak (saturation does not occur at metal ion concentrations as high as 0.01 M), but nevertheless, rate enhancements greater than 10^5 at pH 7 are achieved. The reactions at constant metal ion concentrations are pH independent at pH >4. A carboxyl group in the 2-position of the quinoline ring (XIV) allows strong metal ion binding to the reactant with saturation effects at low metal ion concentration, but this does not additionally facilitate the rate of hydrolysis in comparison with XIII at metal ion concentrations greater than 0.01 M. Thus, the acetal hydrolysis reactions, in which C–O bond breaking occurs in the transition state, are quite analogous to the intramolecular reactions of esters with aliphatic alcohol leaving groups proceeding with rate-determining breakdown of a tetrahedral intermediate. In all of these cases, the metal ion effects are produced by strong binding in the transition state to stabilize the leaving group. This mechanism occurs then in diverse reactions that have C–O bond breaking as part of the rate-determining step.

Acknowledgment. This work was supported by a research grant from the National Science Foundation.

Registry No. I, 52386-78-4; II, 116212-73-8; III, 116212-74-9; IV, 116212-75-0; V, 116212-76-1; VI, 116212-77-2; VII, 116212-78-3; VIII, 116212-79-4; $C_6H_5CH{=}CHCOOCH_3$, 103-26-4; $C_6H_5{=}CHCOOCH_2CF_3$, 23094-31-7; $C_6H_5CH{=}CHCOOC_6H_4$-*p*-OCH_3, 22867-46-5; $C_6H_5CH{=}CHCOOC_6H_5$, 2757-04-2; $C_6H_5CH{=}CHCOOC_6H_4$-*p*-Cl, 73789-34-1; $C_6H_5CH{=}CHCOOC_6H_4$-*p*-NO_2, 18736-43-1; Cu^{2+}, 15158-11-9; Ni^{2+}, 14701-22-5; Co^{2+}, 22541-53-3; Zn^{2+}, 23713-49-7; $C_6H_5CH{=}CHCOCl$, 102-92-1; CF_3CH_2OH, 75-89-8; $C_6H_5CH{=}C(NHCOCH_3)CO_2^-$, 116212-81-8; 2-methyl-4-benzylideneoxazolin-5-one, 881-90-3; 2-(hydroxymethyl)pyridine, 586-98-1; 6-carboxy-2-(hydroxymethyl)pyridine, 1197-10-0; 2-pyridylmethyl cinnamate, 116212-80-7.

(44) The pK_a values for acid ionization of the aquo complexes of the metal ions at 25 °C are Cu^{2+} 6.8, Zn^{2+} 8.8, Co^{2+} 8.9, and Ni^{2+} 10.6: Basolo, F.; Pearson, R. G. *Mechanisms of Inorganic Reactions*, 2nd ed.; Wiley: New York, 1967; p 32.

(45) Water replacement in the aquo complexes of the metal ions occurs with rate constants of Cu^{2+} 5×10^8 s^{-1}, Zn^{2+} 3×10^7 s^{-1}, Co^{2+} 5×10^5 s^{-1}, and Ni^{2+} 3×10^4 s^{-1}: Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1972; p 656.

(46) Przystas, T. J.; Fife, T. H. *J. Am. Chem. Soc.* **1980**, *102*, 4391.