Birmingham, England, 1969; p 105.
(5) The function minimized was $\Sigma w(|F_o| - |F_c|)^2$. Mean atomic scattering factors (neutral atoms except for I^-) were taken from ref 4, Vol. IV, 1974, pp 72–78. When applied, real and imaginary dispersion corrections for all atoms except hydrogen were taken from the same source, pp 149–150.
(6) GOF = goodness of fit = $\Sigma w(|F_o| - |F_c|)^2/(N_o - N_v)$. N_o = number of observations = 3421, N_v = number of variables = 181.
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Transition-State Effects in the Divalent Metal Ion Catalysis of Acetal Hydrolysis

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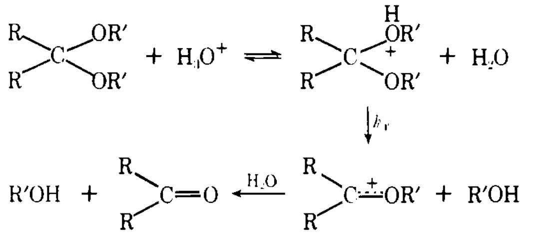
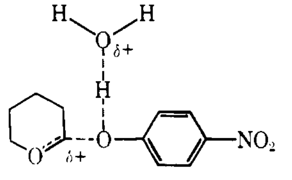
Abstract: The rates of hydrolysis of a series of substituted benzaldehyde methyl 8-quinolyl acetals have been determined in 50% dioxane–H_2O (v/v) at 30 °C. The reactions involve hydronium ion catalyzed hydrolysis of the neutral and protonated species. Hammett ρ values are −3.1 and −2.6, respectively. These acetals are also subject to general acid catalysis. Divalent metal ions (Cu^{2+}, Co^{2+}, Ni^{2+}, Mn^{2+}, and Zn^{2+}) exert a large catalytic effect even though binding to the reactant is very weak. For example, a 0.02 M concentration of Ni^{2+} (1000-fold excess) at pH 7.2 produces a 2×10^5 enhancement in k_{obsd} for hydrolysis of 3,4-dichlorobenzaldehyde methyl 8-quinolyl acetal, but there is no indication of saturation effects. The rate constants for metal ion catalysis of the hydrolysis of the substituted benzaldehyde methyl 8-quinolyl acetals vary with changing substituents in the same manner as those for the hydronium ion catalyzed reactions. At constant metal ion concentration k_{obsd} is pH independent at pH values above the pK_a of the quinoline nitrogen. Metal ion catalysis must be due to a transition-state effect in which the leaving group is stabilized. Incorporation of a second functional group which can chelate the metal ion, as in 3,4-dichlorobenzaldehyde 8-(2-carboxyquinolyl) methyl acetal, leads to strong binding to the reactant; i.e., saturation effects are observed at low metal ion concentrations (10^{-2}–10^{-3} M), but catalytic effects at >0.01 M metal ion concentration are slightly less than with the 8-quinolyl acetals where reactant binding is weak. This emphasizes the importance of transition-state binding in these reactions.

The mechanism of hydronium ion catalyzed hydrolysis of simple acetals has been well established as the classical A-1 mechanism (eq 1) in which there is preequilibrium protonation



of the acetal followed by rate-determining breakdown of the conjugate acid to an alcohol and a resonance-stabilized carbonium ion.[2,3] In this mechanism protonation facilitates departure of the leaving group. In the light of eq 1, it might be expected that metal ions would also effectively catalyze the reactions if they could bind to the reactant. Apparently, simple acetals without metal ion coordinating functional groups are not subject to metal ion catalyzed hydrolysis. However, Clark and Hay[4] found that hydrolysis of 8-quinolyl β-D-glucopyranoside is catalyzed by metal ions. Binding to the substrate was found to be weak, and saturation effects could not be achieved.

General acid catalysis and partially rate-determining protonation by hydronium ion occur in cases where C–O bond breaking is facile,[5,6] owing to a good leaving group (a phenol) in combination with a moderately stable carbonium ion intermediate,[7-9] or to a highly stabilized carbonium ion when the leaving group is poor.[10,11] In those reactions, protonation and C–O bond breaking occur in a concerted manner, as, for example, in I.[5-7] A metal ion should participate similarly; i.e., its effect would be a transition-state effect. A transition-state effect in which the leaving group is stabilized has been regarded as a possibility in metal ion catalyzed ester and amide hydrolysis,[12-15] but evidence is lacking. In order to determine the effectiveness of metal ions in reactions in which C–O bond breaking is part of the rate-determining step, we have studied the hydrolysis of substituted benzaldehyde methyl 8-quinolyl acetals such as II, and, to determine the effects of strong metal ion binding to the reactant, the hydrolysis reactions of 3,4-dichlorobenzaldehyde 8-(2-carboxyquinolyl) methyl acetal (III) have been investigated. Mixed methyl phenyl acetals of substituted benzaldehydes have been shown to be subject to general acid catalysis in their hydrolysis reactions.[9,16]



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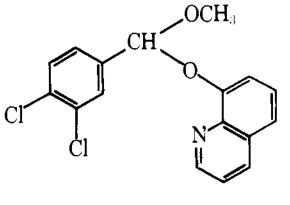

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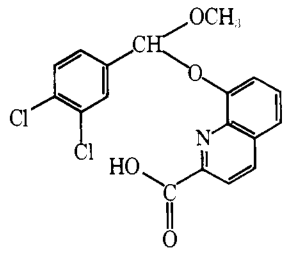

III

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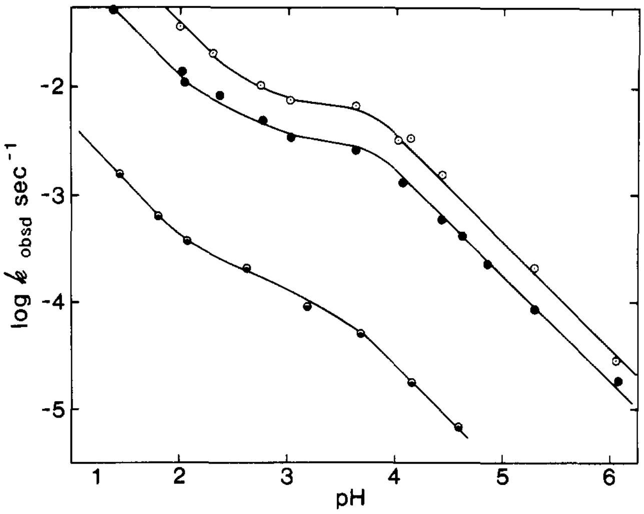


Figure 1. Plots of log k_{obsd} vs. pH for hydrolysis of benzaldehyde methyl 8-quinolyl acetal (⊙), *p*-chlorobenzaldehyde methyl 8-quinolyl acetal (●), and *p*-nitrobenzaldehyde methyl 8-quinolyl acetal (◒) in 50% dioxane-H_2O (v/v) at 30 °C and $\mu = 0.05$ with $LiClO_4$.

Table I, Rate Constants for Hydrolysis of Substituted Benzaldehyde Methyl 8-Quinolyl Acetals at 30 °C in 50% Dioxane-H_2O (v/v), $\mu = 0.05$ (with $LiClO_4$)

substituent	pK_{app}	k_{NH}, $M^{-1} s^{-1}$	k_N, $M^{-1} s^{-1}$	$k_0 \times 10^4$, s^{-1}
H	3.71	2.86	42.9	
H[a]			96.0	
p-Cl	3.71	1.07	19.1	
p-Cl[a]		1.77	35.5	
p-Cl[b]	5.20	198	6990	3.12
p-NO_2	3.29	0.0356	0.289	
3,4-diCl	3.58	0.206	2.48	

[a] In 50% dioxane-D_2O (v/v). [b] In H_2O.

Experimental Section

Materials, 8-Hydroxyquinoline-2-carboxylic acid was prepared as previously described[17] except that 8-hydroxyquinoline *N*-oxide was obtained from Aldrich Co. The acid was esterified by refluxing overnight in methanol saturated with dry HCl. After the methanol was removed by rotary evaporation, the ester hydrochloride was suspended in a small volume of water which was neutralized to pH 5 by the addition of sodium acetate. The precipitated free base form of methyl 8-hydroxyquinoline-2-carboxylate was then recrystallized from dry chloroform-hexane (mp 84-86 °C). Hay and Clark[14] have reported a melting point of 105-106 °C for the ester hemihydrate.

The syntheses of the mixed acetals were accomplished by the general method described earlier.[18] The acetals which were solids were recrystallized from chloroform-hexane.

Benzaldehyde methyl 8-quinolyl acetal had bp 140 °C (0.03 mm), n_D^{24} 1.6172. Anal. Calcd for $C_{17}H_{15}NO_2$: N, 5.28. Found: N, 5.26.

4-Chlorobenzaldehyde methyl 8-quinolyl acetal had bp 155 °C (0.04 mm), n_D^{24} 1.6178. Anal. Calcd for $C_{17}H_{14}ClNO_2$: C, 68.13; H, 4.68; N, 4.68. Found: C, 67.59; H, 4.82; N, 4.50.

3,4-Dichlorobenzaldehyde methyl 8-quinolyl acetal had bp 175 °C (0.02 mm), n_D^{24} 1.6261. Anal. Calcd for $C_{17}H_{13}Cl_2NO_2$: C, 61.11; H, 3.89; N, 4.19. Found: C, 61.10; H, 4.07; N, 4.10.

4-Nitrobenzaldehyde methyl 8-quinolyl acetal hydrate had mp 48-50 °C. Anal. Calcd for $C_{17}H_{14}N_2O_4 \cdot H_2O$: C, 62.19; H, 4.87; N, 8.53. Found: C, 61.78; H, 4.58; N, 8.39. The infrared spectrum conclusively showed the presence of the hydrated form.

3,4-Dichlorobenzaldehyde methyl 8-(2-carbomethoxyquinolyl) acetal had mp 127-129 °C. Anal. Calcd for $C_{19}H_{15}NO_4Cl_2$: C, 58.19; H, 3.83; N, 3.57. Found: C, 57.84; H, 3.96; N, 3.39. The ester was hydrolyzed to its carboxylate salt by adding equal volumes of a solution of 4 × 10^{-3} M ester in MeOH to a solution of 0.4 M NaOH in 80/20 v/v EtOH/H_2O and allowing the solution to stand for at least 1 h.

The dioxane used in these studies was spectral grade (Mallinckrodt) and was refluxed over sodium borohydride for 3 h and distilled prior to use.

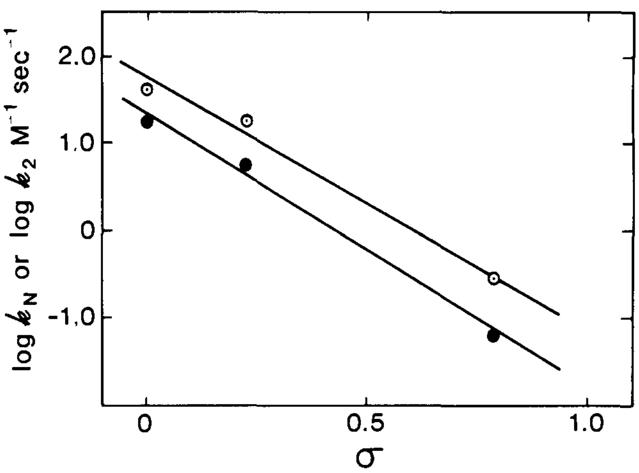


Figure 2, Plots of log k_N (⊙) and log k_2 (Co^{2+}) (●) vs. σ for hydrolysis of para-substituted benzaldehyde methyl 8-quinolyl acetals in 50% dioxane-H_2O (v/v) at 30 °C and $\mu = 0.05$ with $LiClO_4$.

Kinetic Measurements, The rates of hydrolysis of the acetals were measured with a Beckman Model 25 recording spectrophotometer or a Durrum D110 stopped-flow apparatus equipped with a Hewlett-Packard Model 1207B storage oscilloscope. With the 8-hydroxyquinolyl acetals, the non-metal-ion-catalyzed reactions were followed by monitoring appearance of phenol at 260 nm, and the metal-ion-assisted reactions were measured by following appearance of metal ion-phenol complex at 260 or 252 nm. In the case of the 8-(2-carboxyquinolyl) acetal (III), all rates were measured by following appearance of phenol or metal ion-phenol complex at 265 nm. In a typical experiment where the half-life of the reaction was 10 s or greater, 10-50 μL of a stock solution of acetal (1 × 10^{-2} M in MeOH) was added to 2-3 mL of reactant solution maintained at the desired temperature. Reaction rates with half-lives of 5 s or less were measured using the stopped-flow spectrophotometer. One drive syringe contained 40 μL of the acetal stock solution in 0.001 M *N*-ethylmorpholine buffer (pH 8). The other drive syringe contained metal ion and the reaction buffer (0.02 M).

Noncomplexing buffers were used whenever possible, and the total buffer concentration was only 0.02 M. Therefore, no corrections were made for any possible metal ion-buffer complexation. In addition, the solutions contained 2 × 10^{-5} M EDTA as a precaution against trace metal ion effects from buffer or salts. However, reactant solutions which did not contain EDTA but which were extracted with 0.001 M dithizone in carbon tetrachloride[19] gave exactly the same results with the 8-hydroxyquinolyl acetals. Good first-order kinetics were obtained for at least 4 half-lives. Pseudo-first-order rate constants and subsequent kinetic parameters were evaluated using a nonlinear least-squares program. Reaction solution pH values were measured with a Beckman Model 3500 or a Radiometer Model 22 pH meter.

Results

The pH-log (rate constant) profiles in Figure 1 for hydrolysis of substituted benzaldehyde methyl 8-quinolyl acetals at 30 °C in 50% dioxane-H_2O, $\mu = 0.05$, show hydronium ion catalysis at low pH, a plateau as the pK_a of the quinoline nitrogen is approached, and a hydronium ion catalyzed hydrolysis of the neutral species at higher pH values. The values of k_{obsd} follow the equation

$$k_{obsd} = \frac{k_{NH}a_H^2 + k_N K_a a_H}{K_a + a_H} \qquad (2)$$

where k_{NH} and k_N are second-order rate constants for hydronium ion catalyzed hydrolysis of the protonated and neutral species, respectively, and K_a is the apparent dissociation constant of the quinoline conjugate acid. Values of these constants are given in Table I. The Hammett σ*p* plots[20] for the substituent groups H, *p*-Cl, and *p*-NO_2 are linear as shown for k_N in Figure 2. The values of ρ for k_{NH} and k_N are −2.60 and −3.07,

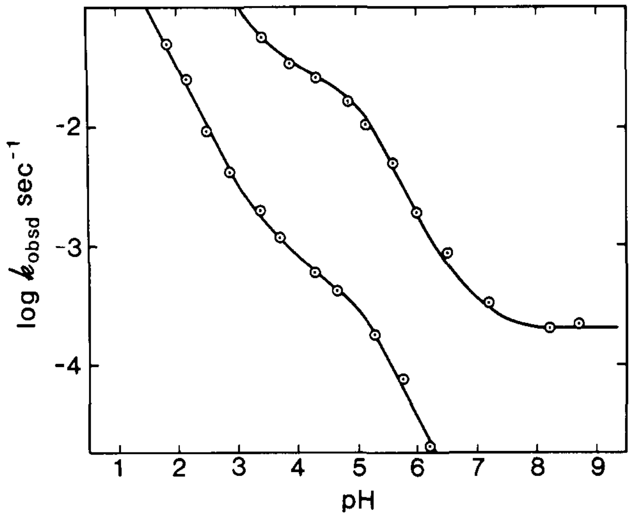


Figure 3. Plots of log k_{obsd} vs. pH for hydrolysis of 3,4-dichlorobenzaldehyde 8-(2-carboxyquinolyl) methyl acetal in H_2O (top curve) and 50% dioxane-H_2O (v/v) (bottom curve) at 30 °C and μ = 0.05 with $LiClO_4$.

Table II. Rate Constants for Hydrolysis of 3,4-Dichlorobenzaldehyde 8-(2-Carboxyquinolyl) Methyl Acetal at 30 °C in H_2O and 50% Dioxane-H_2O (v/v), μ = 0.05 (with $LiClO_4$)

solvent	pK_{app}	k_{NH}, $M^{-1}\,s^{-1}$	k_N, $M^{-1}\,s^{-1}$	$k_O \times 10^4$, s^{-1}
H_2O	4.83	75.2	2090	2.04
50% dioxane-H_2O	4.79	3.11	39.6	

respectively. In H_2O as the solvent a pH-independent reaction was observed in hydrolysis of the *p*-chloro-substituted compound ($k_O = 3.12 \times 10^{-4}\,s^{-1}$).

It has been well established that hydrolysis of benzaldehyde methyl phenyl acetals is general acid catalyzed.[9,16] A small catalytic effect by buffer was also observed with the present series of acetals. For example, the second-order rate constant for chloroacetic acid catalysis of the hydrolysis of *p*-chlorobenzaldehyde methyl 8-quinolyl acetal in 50% dioxane-H_2O at 30 °C is 0.035 $M^{-1}\,s^{-1}$, while that for formic acid catalysis (pH 4.22, μ = 0.25 M with $LiClO_4$) is 0.018 $M^{-1}\,s^{-1}$. The second-order rate constant for formic acid catalysis of the hydrolysis of II at 30 °C in 50% dioxane-H_2O (pH 4.22, μ = 0.25 M with $LiClO_4$) is 0.0017 $M^{-1}\,s^{-1}$. Rate constants at pH >3 were therefore routinely obtained in 0.02 M total buffer where buffer effects are negligible.

The pH-log (rate constant) profiles for hydrolysis of 3,4-dichlorobenzaldehyde 8-(2-carboxyquinolyl) methyl acetal in H_2O and 50% dioxane-H_2O at 30 °C, μ = 0.05, are presented in Figure 3. In dioxane-H_2O eq 2 is followed, but in H_2O an additional term k_O for pH-independent hydrolysis is required:

$$k_{obsd} = \frac{k_{NH}a_H^2 + k_N K_a a_H + k_o K_a}{K_a + a_H} \qquad (3)$$

Values of the constants are given in Table II.

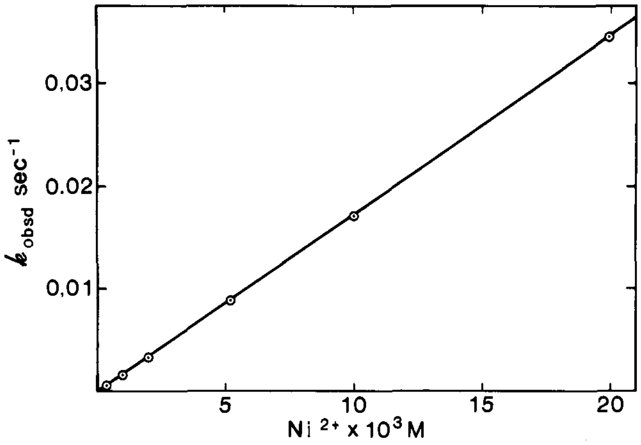


Figure 4. Plot of k_{obsd} vs. Ni^{2+} concentration for hydrolysis of 3,4-dichlorobenzaldehyde methyl 8-quinolyl acetal at pH 7.2 in 50% dioxane-H_2O (v/v) at 30 °C and μ = 0.05 with $LiClO_4$.

Table III. Second-Order Rate Constants for Metal Ion Catalysis of the Hydrolysis of Substituted Benzaldehyde Methyl 8-Quinolyl Acetals at 30 °C in 50% Dioxane-H_2O (v/v), μ = 0.05 (with $LiClO_4$)

compd	metal ion	pH	k_2, $M^{-1}\,s^{-1}$
benzaldehyde methyl 8-quinolyl acetal	Ni^{2+}	6.5	34.0
	Co^{2+}	6.5	17.7
	Co^{2+}	6.9	21.8[a]
	Mn^{2+}	6.5	0.318[a]
p-chlorobenzaldehyde methyl 8-quinolyl acetal	Ni^{2+}	6.8	17.8
	Co^{2+}	6.8	5.63
3,4-dichlorobenzaldehyde methyl 8-quinolyl acetal	Ni^{2+}	7.2	1.67
	Co^{2+}	6.1	0.752
	Zn^{2+}	5.4	1.54
	Cu^{2+}	6.1	3020
p-nitrobenzaldehyde methyl 8-quinolyl acetal	Ni^{2+}	6.4	0.364
	Ni^{2+}	7.2	12.5[b]
	Co^{2+}	7.4	0.0632
	Co^{2+}	7.2	3.32[b]
	Co^{2+}	6.5	3.41[c]
	Cu^{2+}	5.9	200
	Cu^{2+}	5.2	17 800[b,21]
	Mn^{2+}	6.5	0.0384[c]

[a] In 50% dioxane-H_2O, μ = 0.1, with KCl. [b] In H_2O. [c] In H_2O, μ = 0.1, with KCl.

The rate of hydrolysis of the substituted benzaldehyde methyl 8-quinolyl acetals in 50% dioxane-H_2O and H_2O[21] is markedly catalyzed by low concentrations of divalent metal ions (Cu^{2+}, Co^{2+}, Ni^{2+}, Mn^{2+}, and Zn^{2+}). However, saturation effects were not observed at metal ion concentrations as high as 0.02 M (1000-fold excess over substrate). In Figure 4 is shown the linear plot of k_{obsd} vs. Ni^{2+} concentration for hydrolysis of 3,4-dichlorobenzaldehyde methyl 8-quinolyl acetal at pH 7.2. Similar linear plots were obtained with the other metal ions in the series at various pH values. The second-order rate constants k_2 (slope of k_{obsd} vs. Me^{2+}) are given in Table III, and in Figure 2 is shown a plot of log k_2 vs. σ for Co^{2+} catalysis. The order of reactivity is $Cu^{2+} > Ni^{2+} \sim Zn^{2+} \sim Co^{2+} > Mn^{2+}$. The metal ion catalyzed reactions are pH independent at pH >4 as shown in Figure 5 where the pH-log (rate constant) profiles are presented for hydrolysis of 3,4-dichlorobenzaldehyde methyl 8-quinolyl acetal in the presence of 0.005 M Ni^{2+} and in the absence of metal ion. The decrease in k_{obsd} at pH <4 must reflect an increased difficulty of metal ion binding when the quinoline nitrogen is protonated.

The hydrolysis of 3,4-dichlorobenzaldehyde 8-(2-carboxyquinolyl) methyl acetal is also catalyzed by divalent metal ions, and saturation effects are observed at low concentrations of metal ion. Figure 6 is a plot of k_{obsd} at pH 7.3 vs. the concentration of Ni^{2+}. Since spontaneous hydrolysis is negligible the equation

$$k_{obsd} = \frac{k_{Me}K_{Me}[Me^{2+}]}{1 + K_{Me}[Me^{2+}]} \qquad (4)$$

is followed, where k_{Me} is the limiting value of k_{obsd} and K_{Me} is the metal ion association constant. Similar saturation plots for the other metal ions at various pH values allowed determination of the constants in Table IV. The metal ion dilution

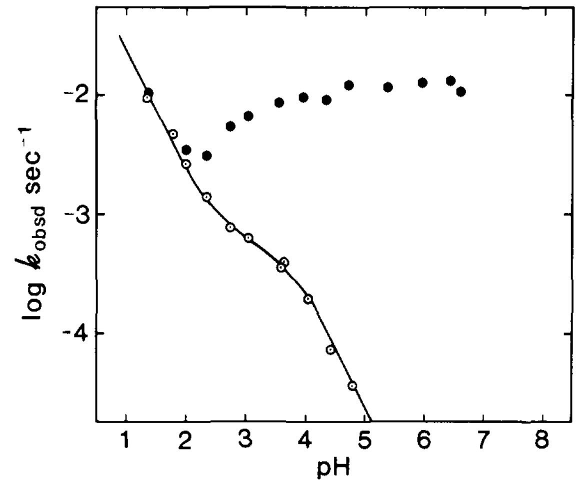


Figure 5. Plot of log k_{obsd} vs. pH for hydrolysis of 3,4-dichlorobenzaldehyde methyl 8-quinolyl acetal in 50% dioxane-H_2O at 30 °C and μ = 0.05 with $LiClO_4$ in the absence of metal ion (⊙) and in the presence of 0.005 M Ni^{2+} (●).

Table IV. Metal Ion Effects in the Hydrolysis of 3,4-Dichlorobenzaldehyde 8-(2-Carboxyquinolyl) Methyl Acetal at 30 °C in H_2O and 50% Dioxane-H_2O (v/v), μ = 0.05 (with $LiClO_4$)

metal ion	pH	solvent	k_{Me}, s^{-1}	$K_{Me} \times 10^{-3}$, M^{-1}
Ni^{2+}	7.30	H_2O	1.36	1.10
Co^{2+}	7.20	H_2O	1.33	0.740
	6.30	H_2O	1.34	0.768
	5.30	H_2O	1.56	0.514
	6.40	50% dioxane-H_2O	0.0212	3.70
Zn^{2+}	6.30	H_2O	0.74	1.67
	5.30	H_2O	0.705	1.55
	6.40	50% dioxane-H_2O	0.0278	2.16
Cu^{2+}	6.09	H_2O	23.4	>10[a]
	5.23	H_2O	21.1	>10[a]
	4.09	H_2O	23.4	>10[a]
	6.40	50% dioxane-H_2O	1.03	>10[a]

[a] Cu^{2+} shows a saturating effect at a concentration of 2×10^{-4} M.

data obtained in 50% dioxane-water are less satisfactory than those obtained in water. The value of k_{obsd} increases more than expected at high metal ion concentrations, perhaps due to a medium effect because of replacement of unipositive lithium ions by dipositive metal ions at low ionic strength in the dioxane-H_2O medium. This trend was observed to a much lesser extent in water. To test whether a medium effect was indeed the cause, several kinetic runs in 50% dioxane-water (v/v) were followed with ionic strength μ = 0.5 M. The data obtained were significantly improved at the higher ionic strength; at pH 7.2, the values of k_{Me} and K_{Me} are 3.85×10^{-2} s^{-1} and 1.16×10^3 M^{-1}, respectively, for Co^{2+}.

In hydrolysis of III catalyzed by Mn^{2+} at pH 7.2 in H_2O (μ = 0.1 with KCl), saturation effects were not observed at metal ion concentrations as high as 0.005 M. The value of k_2 is 26.5 M^{-1} s^{-1}. At Mn^{2+} concentrations greater than 0.005 M the points fall below the straight line in the plot of k_{obsd} vs. metal ion concentration, and at 2×10^{-2} M Mn^{2+} k_{obsd} is almost 50% below the line, thus indicating that K_{Me} for binding is ~50 M^{-1} and the limiting rate constant k_{Me} is ~6×10^{-1} s^{-1}.

Discussion

The hydrolysis of the substituted benzaldehyde methyl 8-quinolyl acetals proceeds in an analogous manner to the corresponding benzaldehyde methyl phenyl acetals which have been extensively studied.[9,16] Thus, the Hammett ρ value for hydronium ion catalyzed hydrolysis of para-substituted benzaldehyde methyl phenyl acetals is −2.26.[16] The ρ values for hydronium ion catalyzed hydrolysis of the neutral and protonated species of the substituted benzaldehyde methyl 8-quinolyl acetals are −3.1 and −2.6, respectively. These large negative values reflect the unfavorable effect of electron withdrawal in the aldehyde portion of the molecule on basicity and on the ease of stabilization of the developing carbonium ion. The benzaldehyde methyl phenyl acetals are subject to general acid catalysis in their hydrolytic reactions with Brønsted coefficients of 0.5–0.9.[9,16] General acid catalysis arises in these reactions because of the ease of C–O bond breaking due to the good leaving group (a phenol) in combination with a moderately well stabilized carbonium ion in the transition state. Likewise, the benzaldehyde methyl 8-quinolyl acetals, possessing the same structural features, also undergo general acid catalysis in their hydrolytic reactions. The D_2O solvent isotope effects for hydronium ion catalyzed hydrolysis of substituted benzaldehyde methyl 8-quinolyl acetals (Table I) are comparable to those obtained with electronically similar methyl phenyl acetals.[16] Consequently, the acetals hydrolyze by identical mechanisms which undoubtedly involve partial proton transfer from hydronium ion or general acids to the leaving group oxygen in the transition state (IV).

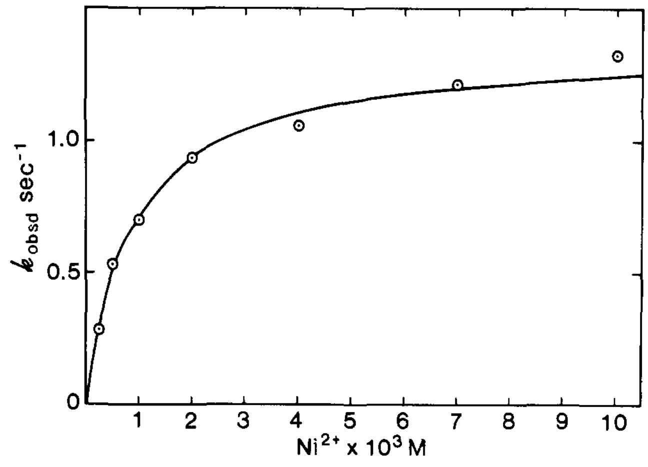
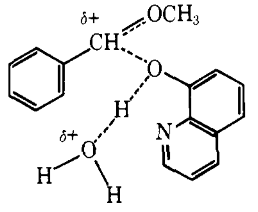


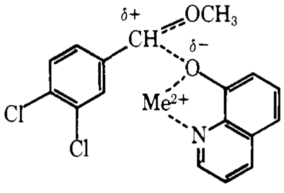
Figure 6. Plot of k_{obsd} vs. Ni^{2+} concentration for hydrolysis of 3,4-dichlorobenzaldehyde 8-(2-carboxyquinolyl) methyl acetal at pH 7.3 in H_2O at 30 °C and μ = 0.05 with $LiClO_4$. The solid line was constructed from eq 4 and the constants of Table IV.



IV

In reactions proceeding via transition states similar to IV it might be expected that metal ions would duplicate or enhance the effect of acids by binding to the leaving group in the transition state. However, for this to occur it is necessary that a functional group be present so that the metal ion can be chelated; metal ion catalysis is not observed in the hydrolysis of simple acetals, although heavy metal ions will catalyze hydrolysis of thioacetals by binding to sulfur.[22] Divalent metal ions are very effective catalysts in the hydrolysis of the benzaldehyde methyl 8-quinolyl acetals. Large rate enhancements are observed at low metal ion concentrations. For example, in hydrolysis of 3,4-dichlorobenzaldehyde methyl 8-quinolyl acetal a 0.02 M concentration of Ni^{2+} enhances k_{obsd} at pH 7.20 by a factor of 2.2×10^5.[23] The other metal ions in the series Cu^{2+}, Co^{2+}, Zn^{2+}, and Mn^{2+} are also highly effective catalysts, the order of reactivity being $Cu^{2+} > Ni^{2+} \sim Co^{2+} \sim Zn^{2+} > Mn^{2+}$. This catalysis is associated with the ability of a metal ion to chelate the quinoline nitrogen and the oxygen leaving group at some point in the reaction, since benzaldehyde methyl 6-quinolyl acetals are not subject to metal ion catalyzed hydrolysis.[24] The second-order rate constants for metal ion catalyzed hydrolysis roughly parallel the binding constants to the product 8-hydroxyquinoline.[25] Since the second-order rate constant k_2 is actually $k_2'K_{Me}$, the product of a binding constant and a rate constant, the parallel with the product binding constants suggests that the values of k_2' are similar.

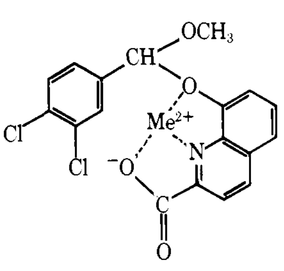
The catalytic effects exerted by the divalent metal ions are obtained in spite of the fact that binding of metal ion to the reactant is very weak. In Figure 4 it can be seen that there is no indication of any saturation effect in the Ni^{2+}-catalyzed reaction at 0.02 M metal ion concentration. The metal ion must therefore be exerting its large effect in the transition state. The metal ions bind strongly to the product 8-hydroxyquinoline,[25] and accordingly binding in the transition state should be much stronger than binding to reactant. As the C-O bond begins to break negative charge will be generated on oxygen, thereby allowing the metal ion to bind strongly in the transition state as in V. The metal ion binding to the quinoline nitrogen and the leaving group would increase the ease of unimolecular C-O bond breaking. Metal ion catalysis can therefore be properly viewed as an enhancement in the pH-independent unimolecular decomposition, just as hydronium ion and general acid catalysis, in which concerted proton transfer and C-O bond breaking occur, can be similarly viewed. All acetals subject to general acid catalysis have been found to give rise to a unimolecular decomposition reaction because of the great ease of bond breaking.[5,6] It will be noted in Figure 5 that the metal ion catalyzed reaction is pH independent at pH >4. Further evidence that the metal ion is functioning analogous to hydronium ion is afforded by the similar changes in the rate constants for the two reactions as the substituent groups in the aldehyde portion of the molecule are varied (Figure 2). It can be seen in Tables I and III that k_N and k_2 for Ni^{2+} are quite similar for all the 8-quinolyl acetals.



V

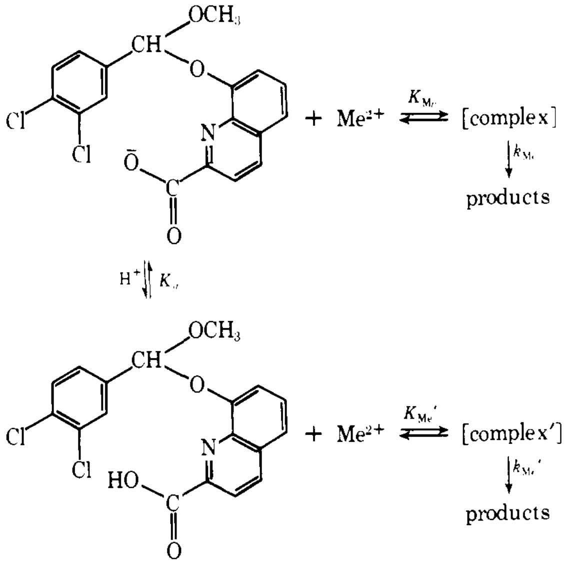
The hydrolysis of 8-quinolyl-β-D-glucopyranoside is also metal ion catalyzed,[4] but in that case catalysis may be due to binding of the metal ion to the reactant. Glycoside hydrolysis proceeds by an A-1 mechanism or perhaps may be solvent assisted (A-2).[26,27] In those mechanisms, which occur because of the relative instability of the glycosyl carbonium ion, a proton is completely donated to oxygen by hydronium ion in a preequilibrium process. Before the C-O bond can begin to break in such cases, a proton must be completely transferred to the leaving group. Therefore, it would be expected that metal ion catalysis would be analogous and would depend upon binding to the reactant.

Incorporation of a carboxyl group into the 2 position of the benzaldehyde methyl 8-quinolyl acetals has little influence (~tenfold rate enhancement) on the non-metal-ion-catalyzed hydrolysis reaction. Thus, the pH-log (rate constant) profiles for II and III are quite similar in shape. However, the second functional group in position to bind a metal ion in III leads to strong metal ion chelation to the reactant (VI). In contrast with II, saturation effects are now observed at low metal ion concentrations. Figure 6 shows a typical plot of k_{obsd} vs. metal ion concentration illustrating this saturation effect. However, strong binding to the reactant does not increase the effectiveness of metal ion catalysis over that with the benzaldehyde methyl 8-quinolyl acetals. In fact, at equal concentrations of metal ion (>0.01 M), the rate-enhancing effect in hydrolysis of II is greater than that of III. It is likely that strong binding to the reactant does not produce a further rate enhancement because such binding does not appreciably facilitate the ease of metal-ion binding in the transition state. The smaller catalytic effect of metal ions in hydrolysis of III may in fact reflect an increased difficulty of binding to the transition state; i.e., the geometrical constraints imposed by binding to the reactant may be less favorable for the reaction. The limiting rate at high metal ion concentration is almost the same for Ni^{2+}, Co^{2+}, and Zn^{2+}, and only ~tenfold larger for Cu^{2+}. This is again very likely because binding to the phenolic oxygen of the leaving group in the transition state is the critical factor. The rate ratios are therefore similar to those encountered with the 8-hydroxyquinoline acetals with small variations in the series.



VI

One complexity encountered in the 2-carboxyquinolyl system, which does not occur with the acetals of 8-hydroxyquinoline, is that addition of one proton to the quinoline portion of the molecule will not necessarily inhibit metal ion catalysis. Thus, the scheme of eq 5 is possible.



(5)

Assuming that the non-metal-ion-catalyzed reaction can be neglected

$$k_{obsd} = \frac{k_{Me}'a_H K_{Me}'[Me^{2+}] + k_{Me}K_{Me}K_a[Me^{2+}]}{a_H(1 + K_{Me}'[Me^{2+}]) + K_a(1 + K_{Me}[Me^{2+}])} \tag{6}$$

Since $K_{Me} > K_{Me}'$

$$k_{obsd} = \frac{(k_{Me}'a_H K_{Me}' + k_{Me}K_{Me}K_a)[Me^{2+}]}{a_H + K_a(1 + K_{Me}[Me^{2+}])} \tag{7}$$

Evidence for a significant contribution to k_{obsd} of the k_{Me}' pathway would be an acid dependence of the limiting rate at high metal ion concentration. However, this is not observed.

The rate constants give a satisfactory fit to the equation

$$k_{\text{obsd}} = \frac{k_{\text{Me}}K_{\text{Me}}K_{\text{a}}[\text{Me}^{2+}]}{a_{\text{H}} + K_{\text{a}}(1 + K_{\text{Me}}[\text{Me}^{2+}])} \tag{8}$$

and are nearly pH independent at pH >5.

α-Amylase, an enzyme catalyzing the hydrolysis of the polysaccharide α-amylose, requires the presence of Ca^{2+}.[28] It is not known whether the metal ion is necessary for catalytic purposes, although it is important for structural reasons. However, it is clear that a properly positioned metal ion could play a large catalytic role in such enzymatic reactions. It has recently been reported[29] that Mn^{2+} and Mg^{2+} activate β-galactosidase. A catalytic effect of Mn^{2+} was observed in hydrolysis of the substituted benzaldehyde methyl 8-quinolyl acetals, but it is small in comparison with the other metal ions in the series. For example, at pH 6.5 (30 °C) the second-order rate constant for Mn^{2+} catalysis of the hydrolysis of *p*-nitrobenzaldehyde methyl 8-quinolyl acetal (0.0384 $M^{-1}\ s^{-1}$) is 100-fold less than that for Co^{2+} (3.41 $M^{-1}\ s^{-1}$). However, the catalytic effect of Mn^{2+} in hydrolysis of III is comparable to that for Ni^{2+}, Co^{2+}, and Zn^{2+}. Binding to oxygen ligands is favored over nitrogen by Ca^{2+}, Mn^{2+}, and Mg^{2+}.[30] With the benzaldehyde methyl 8-quinolyl acetals, where catalysis occurs through binding in the transition state, preferred binding to oxygen should confer little or no advantage over the other metal ions, because binding is taking place to an incipient oxygen anion and the quinoline nitrogen. On the other hand, Ca^{2+}, Mn^{2+}, and Mg^{2+} might have an advantage when strong binding to the reactant is required, i.e., in cases where the acetal hydrolyzes by an A-1 or A-2 mechanism (preequilibrium protonation by hydronium ion), as in glycoside hydrolysis, and the other ligand is an oxygen base (carboxylate anion, etc.).

Metal Ion Enhancement of C–O Bond Breaking. The finding of marked catalytic transition state effects with the present series of compounds shows conclusively that metal ions can greatly enhance the ease of C–O bond breaking by stabilization of the leaving group. This type of catalysis might also be effective in the hydrolysis of esters in cases where breakdown of a tetrahedral intermediate is rate determining. Such an effect has in fact been considered in certain metal ion promoted OH^--catalyzed reactions of 8-hydroxyquinoline esters.[13,14] However, in hydrolysis reactions of phenolic esters involving attack of hydroxide ion it would be expected that formation of a tetrahedral intermediate would be rate determining,[31] and therefore metal ion stabilization of the leaving group would be of little consequence.[32] A transition-state effect has also been suggested as a mechanistic possibility for the zinc metalloenzyme carboxypeptidase A.[12] A mechanism in which a metal ion stabilizes the leaving group in the transition state might be a favorable possibility when the leaving group is poor and the rate-determining step is breakdown of the tetrahedral intermediate.

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