Divalent Metal Ion Catalysis of Acetal Hydrolysis; Effects of Oxycarbocation Stability and Leaving Group Basicity

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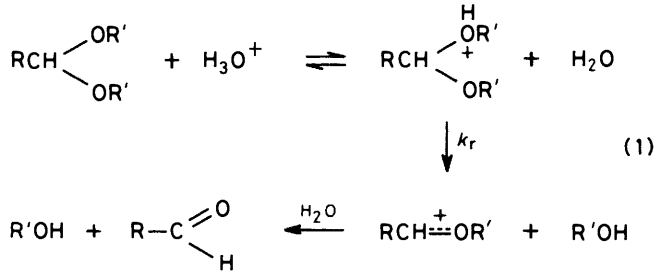
Large catalytic effects by low concentrations of Ni^{2+}, Co^{2+}, and Zn^{2+} were observed in the hydrolysis of 2-(8-quinolyloxy)tetrahydropyran, 6-(8-quinolyloxy)tetrahydropyran-2-carboxylic acid, and ethyl 6-(8-quinolyloxy)tetrahydropyran-2-carboxylate in H_2O at 50 °C (μ 0.1 M), even though metal ion binding to the acetals is weak. Plots of k_{obs} *vs.* metal ion concentration are linear even at metal ion concentrations as high as 0.01 M. At constant metal ion concentration the reactions are pH-independent at pH >5. The minimum rate enhancement with these compounds at 0.01 M-Ni^{2+} is more than 10^4 at pH 7.0; Co^{2+} and Zn^{2+} are three-fold less effective than Ni^{2+}. The rate constants for oxonium ion catalysis and metal ion catalysis are affected alike by changes in basicity and oxycarbocation stability in 8-quinolyl acetals; these features vary over a wide range (from substituted benzaldehyde methyl 8-quinolyl acetals to 8-quinolyl β-D-glucopyranoside). With each acetal the second-order rate constants for oxonium ion and metal ion catalysis are similar, which indicates that the large rate enhancements observed in the metal-ion-catalysed reactions are due to relative concentration effects of the metal ions in comparison with oxonium ion. Metal ion catalysis was not observed in the hydrolysis of acetals of 2-hydroxymethylpyridine nor in the hydrolysis of *m*-methoxybenzaldehyde 6-carboxy-2-pyridylmethyl methyl acetal. As in the case of general-acid-catalysed reactions, metal ion catalysis in acetal hydrolysis is highly dependent on leaving group ability; it does not occur when the leaving group is an aliphatic alcohol even in cases where the intermediate oxycarbocation is quite stable (a methoxybenzyl ion) and metal ion binding to the acetal is strong. There are striking mechanistic similarities between intramolecular metal ion catalysis and general acid catalysis in acetal hydrolysis because both reactions involve stabilization of the leaving group in the transition state of the pH-independent C–O bond-breaking reaction.

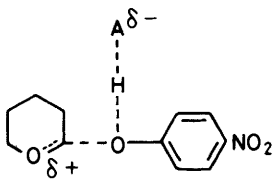
Oxonium-ion-catalysed hydrolysis of simple acetals of aliphatic alcohols has generally been considered [1,2] to proceed *via* an *A*-1 mechanism [equation (1)] in which pre-equilibrium protonation of the acetal is followed by rate-determining breakdown of the



(1)

conjugate acid to an alcohol and a resonance-stabilized oxycarbocation. General acid catalysis will occur in cases in which C–O bond breaking is easy [3,4] because of a good leaving group (a phenol) and a moderately stable oxycarbocation intermediate,[5–8] or, if the leaving group is poor (an aliphatic alcohol), because of a highly stabilized oxycarbocation intermediate (an oxytropylium ion).[9] In such reactions proton transfer and C–O bond breaking occur in a concerted process [see (1)], as shown by values of Brønsted α-coefficients between 0.5 and 0.7,[4,6,8] *i.e.* proton transfer is taking place in the transition state of the reaction.

Metal ion catalysis has not been reported in the hydrolysis of acetals in which metal-ion-chelating functional groups are absent. However, a significant metal ion catalysis has been observed in the hydrolysis of 8-quinolyl β-D-glucopyranoside [10] and substituted benzaldehyde methyl 8-quinolyl acetals.[11] In the latter case, minimum rate enhancements of 10^5—10^6 were found at 0.01 M (non-saturating) concentrations of Ni^{2+}, Co^{2+}, and Zn^{2+}. The metal-ion-catalysed reactions of the latter compounds are pH-independent at constant metal ion concentration. It is clear that the metal ions are exerting their catalytic effect by enhancing the pH-independent unimolecular decomposition of these acetals,[11] a reaction that is always detected in the hydrolysis of acetals subject to general acid catalysis.[3–6] Thus, the metal ions and general acids may be catalysing the hydrolysis reactions in the same manner. The clear elucidation of mechanistic similarities in these reactions would lead to an increased understanding of both types of catalysis. It is therefore important to discover the effect of changes in structure of the acetal on metal ion catalysis and to determine whether there is a correlation with the effects of similar structural changes in general acid catalysis.[3,4] Consequently, we have studied the



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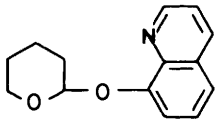

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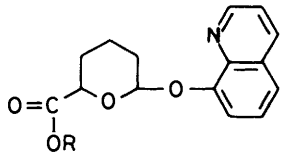
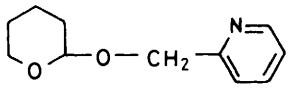


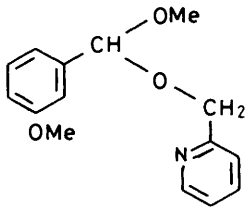
(3) R = H
(4) R = Et

metal-ion-catalysed hydrolysis reactions of the tetrahydropyranyl acetals (**2**)—(**4**), since the hydrolysis of phenolic acetals of tetrahydropyran is catalysed by general acids.[5] The oxycarbocation intermediate is considerably less stable than that derived from substituted benzaldehyde methyl 8-quinolyl acetals but is much more stable than the glucosyl ion derived from glycosides. Thus, in conjunction with those reported in the literature,[10,11] a series of 8-quinolyl acetals is available which give oxycarbocation intermediates of widely varying stability.

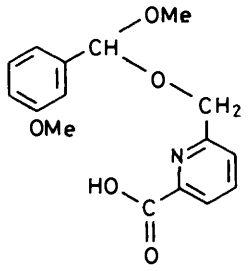
To determine whether metal ion catalysis will occur in these systems when the leaving group is an aliphatic alcohol (general acid catalysis is *not* then detected), we have also studied the hydrolysis of the acetals (**5**)—(**7**). Metal ion binding to (**7**) is



(**5**)



(**6**)



(**7**)

quite strong and the intermediate oxycarbocation produced in the hydrolysis reactions is reasonably stable.

The glycosidase enzyme α-amylase requires the presence of Ca^{2+}.[12] The metal ion appears to be important for structural reasons, but could also exert a catalytic effect. Likewise, it has been reported that Mn^{2+} and Mg^{2+} activate β-galactosidase.[13] Thus, the determination of the effect of structure on metal ion catalysis in acetal hydrolysis could lead to increased understanding of the manner in which such enzymes function.

Experimental

Materials.—2-(8-Quinolyloxy)tetrahydropyran (**2**) and 2-(6-quinolyloxy)tetrahydropyran were synthesized by adding 2-chlorotetrahydropyran[14] (0.01 mol) to the sodium salt of 6- or 8-hydroxyquinoline (0.01 mol) in dry dimethylformamide (DMF) (35 ml) as previously described.[15] 2-(8-Quinolyloxy)-tetrahydropyran had b.p. 126 °C (0.02 mmHg), n_D^{24} 1.5967 (Found: C, 73.1; H, 6.8; N, 6.0. Calc. for $C_{14}H_{15}NO_2$: C, 73.4; H, 6.55; N, 6.1%). The corresponding 6-quinolyl derivative boiled at 130 °C (0.02 mmHg). The compound crystallized from hexane; m.p. 58—60 °C (Found: C, 73.3; H, 6.5; N, 6.1. Calc. for $C_{14}H_{15}NO_2$: C, 73.4; H, 6.55; N, 6.1%). 2-(2-Pyridylmethoxy)-tetrahydropyran (**5**) was also synthesized by the same procedure as (**2**) and had b.p. 125 °C (2.0 mmHg), n_D^{25} 1.5058 (Found: C, 68.3; H, 7.9; N, 7.4. Calc. for $C_{11}H_{15}NO_2$: C, 68.4; H, 7.8; N, 7.25%).

Ethyl 6-(8-quinolyloxy)tetrahydropyran-2-carboxylate (**4**) was prepared by adding ethyl 6-chlorotetrahydropyran-2-carboxylate (obtained by bubbling dry HCl gas through ethyl 3,4-dihydro-2*H*-pyran-2-carboxylate)[16] to the sodium salt of 8-hydroxyquinoline (0.01 mol) in dry DMF (35 ml) as with (**2**). The compound was a viscous oil (b.p. 170 °C at 0.005 mmHg) which partially decomposed upon distillation. The i.r. spectrum was consistent with the structure, and the u.v. spectrum of the hydrolysis products with and without metal ion was the same as the spectrum of an equal concentration of 8-hydroxyquinoline or that of its metal ion complex, *i.e.* the release of 8-hydroxyquinoline in the hydrolysis reaction is quantitative.

m-Methoxybenzaldehyde methyl 2-pyridylmethyl acetal (**6**) was prepared by the reaction of α-chloro-3-methoxybenzyl methyl ether with the sodium salt of 2-pyridylmethanol by methods previously described;[15] b.p. 128—130 °C (0.005 mmHg), n_D^{24} 1.5458 (Found: C, 69.4; H, 6.8; N, 5.3. Calc. for $C_{15}H_{17}NO_3$: C, 69.5; H, 6.6; N, 5.4%).

m-Methoxybenzaldehyde 6-ethoxycarbonyl-2-pyridylmethyl methyl acetal was prepared by adding triethylamine (0.01 mol), ethyl 6-hydroxymethylpicolinate, and α-chloro-3-methoxybenzyl methyl ether to dry tetrahydrofuran (THF) (50 ml). The solution was stirred for 2 h and then filtered to remove the precipitated triethylamine hydrochloride. The THF was removed under reduced pressure, and the residue was dissolved in dry benzene (100 ml) and treated as previously described.[15] The compound was a clear oil which did not crystallize; b.p. 180 °C at 0.05 mmHg, n_D^{23} 1.5356 (Found: C, 64.9; H, 6.3; N, 4.2. Calc. for $C_{18}H_{21}NO_5$: C, 65.2; H, 6.3; N, 4.2%).

The dioxane used in the solvent for kinetic studies (50% dioxane–water) was spectroscopic grade (Mallinckrodt) and was refluxed over sodium borohydride for at least 3 h and freshly distilled prior to use.

Kinetic Methods.—The rates of hydrolysis of the acetals were measured spectrophotometrically with a Beckman 25 or Pye-Unicam SP8-100 recording spectrophotometer. Stock solutions of the acetals were 10^{-2}M in THF or 5×10^{-3}M in 80:20 EtOH–H_2O containing NaOH (0.2M) [(**3**) and (**7**)]. The latter stock solution was used to hydrolyse the esters to the corresponding carboxylates. At least 2 h was allowed for the ester hydrolysis to proceed to completion. To initiate a kinetic run, the stock solution (15—30 μl) was injected into the reaction solution (3 ml) maintained at the desired temperature. The reactions followed good pseudo-first-order kinetics for at least four half-lives. The values of k_{obs}, the pseudo-first-order rate constant, were evaluated using a non-linear least-squares computer program. Reaction mixture pH values were measured with a Beckman 3500 pH meter.

The hydrolysis of the acetals (**2**)—(**4**) and 2-(6-quinolyloxy)-tetrahydropyran was followed by measuring the appearance of 8-hydroxyquinoline or 6-hydroxyquinoline at 260 nm. With the *m*-methoxybenzaldehyde acetals (**6**) and (**7**) the reactions were followed by measuring the rate of appearance of aldehyde at 315 nm. The rates of hydrolysis of 2-(2-pyridylmethoxy)tetrahydropyran (**5**) could not be followed by spectrophotometric techniques because the absorbance changes were only small. The appearance of the aldehyde addition compound with semicarbazide could be detected at 225 nm by employing the procedure reported by Jensen and Wuhrman[17] for measuring the rates of hydrolysis of 2-alkoxytetrahydropyrans. In order to test the accuracy of this method, the rates of hydrolysis of 2-(8-quinolyloxy)tetrahydropyran (**2**) were also followed in the presence and in the absence of semicarbazide. In the absence of semicarbazide, the rate of 8-hydroxyquinoline appearance at 260 nm was the same as that for acetal disappearance at 225 nm. When semicarbazide (0.01M) was added, the rate of appearance of 8-hydroxyquinoline at 260 nm was unaffected, but the small absorbance decrease seen at 225 nm was replaced by a much larger absorbance increase due to semicarbazone formation. At all pH values and metal ion concentrations the rates of phenol and semicarbazone appearance were identical. Thus, the semicarbazide method gives accurate rate measurements in the hydrolysis of the tetrahydropyran acetal (**2**), and it is therefore a reasonable assumption that this is also the case with (**5**).

The ionic strength was 0.1M, maintained with KCl, and the

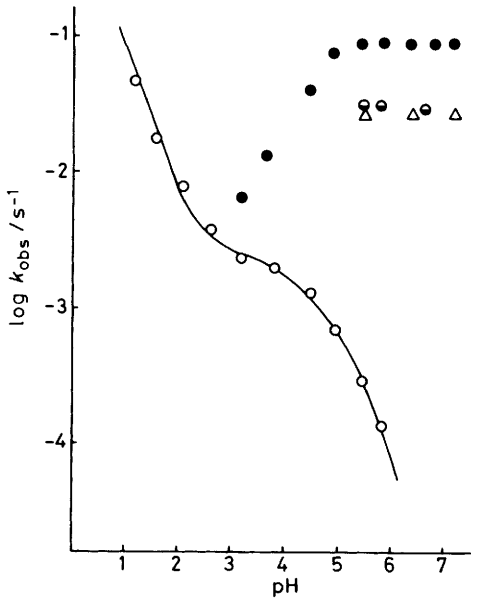
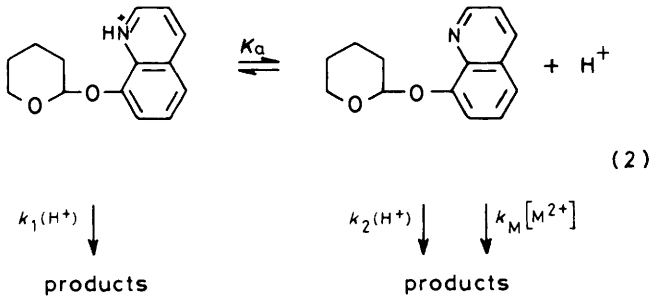


Figure 1. Plots of log k_{obs} *vs.* pH for hydrolysis of 2-(8-quinolyloxy)-tetrahydropyran (**2**) in H_2O at 50 °C with μ 0.1M in the presence of 0.002M-Ni^{2+} (●), -Co^{2+} (△), or -Zn^{2+} (◒), or in the absence of metal ions (○)

solutions used for the studies in the absence of metal ion contained 2 × 10^{-5}M-ethylenedinitrilotetra-acetic acid (EDTA) as a precaution against trace metal ion in the buffer or salt. In the pH range 1—3 HCl solutions were employed. The buffers employed in studies in H_2O were formate (pH 3—4.5), acetate (pH 4.5—5.5), and dimethylarsinate (cacodylate) (pH 5.5—6.5). In 50% dioxane–H_2O (v/v), the buffers were chloroacetate (pH 3—4.5), and formate (pH 4.5—5.8). No corrections were made for buffer–metal ion complexation. The buffer concentration was always 0.02M. Such low concentrations of buffer do not have an experimentally significant catalytic effect on the observed rate constants.

Results

Figure 1 shows the plot of log k_{obs} *vs.* pH for hydrolysis of 2-(8-quinolyloxy)tetrahydropyran (**2**) in H_2O at 50 °C with μ 0.1M (KCl). The plot for hydrolysis in the absence of metal ions shows two regions in which the logarithms of the rate constants increase with decreasing pH, with limiting slopes of −1.0 (at pH < 2 and again at pH > 5). These two regions in the log k_{obs} *vs.* pH profile must represent the oxonium-ion-catalysed reactions of the species with the quinoline nitrogen protonated and unprotonated, respectively, as shown in equation (2). The equation for k_{obs} that is followed in the hydrolysis of (**2**) in the absence of metal ions is equation (3), where K_a is the



(2)

Table 1. Second-order rate constants for oxonium-ion-catalysed acetal hydrolysis in H_2O (μ 0.1M)

Compd.	k_1/l mol^{-1} s^{-1}	k_2/l mol^{-1} s^{-1}	k_3/l mol^{-1} s^{-1}	pK_{app}
(**2**)[a]	0.68	93.0		4.6
(**3**)[a]		9.8	106	3.3, 5.0
(**4**)[a]	0.0042			
(**5**)[b]		39		
(**6**)[a]	11.1	100		4.2
(**7**)			140[a]	
			46[c]	
2-(6-Quinolyloxy)-tetrahydropyran[a]	1.1	16.8		4.2

[a] At 50 °C. [b] At 70 °C. [c] At 70 °C in 50% dioxane–H_2O (v/v) (μ 0.1M).

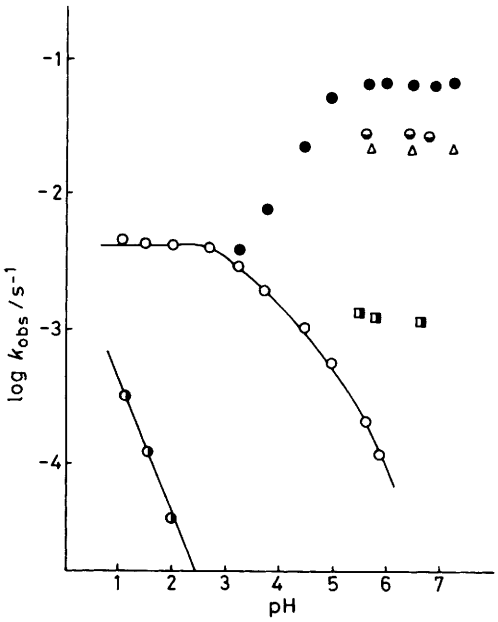


Figure 2. Plot of log k_{obs} *vs.* pH for hydrolysis of 6-(8-quinolyloxy)-tetrahydropyran-2-carboxylic acid (**3**) in H_2O at 50 °C with μ 0.1M in the presence of 0.002M-Ni^{2+} (●), -Co^{2+} (△), or -Zn^{2+} (◒), or in the absence of metal ions (○). Also shown is a plot of log k_{obs} *vs.* pH for hydrolysis of the corresponding ethyl ester (**4**) in H_2O at 50 °C with μ 0.1M in the presence of 0.01M-Ni^{2+} (◨) and in the absence of metal ions (◑)

$$k_{obs} = k_1 a_H \left[\frac{a_H}{K_a + a_H}\right] + k_2 a_H \left[\frac{K_a}{K_a + a_H}\right] \quad (3)$$

dissociation constant of the quinoline nitrogen conjugate acid, k_1 and k_2 are the second-order rate constants for oxonium-ion-catalysed hydrolysis of the monocation and the neutral species, respectively, and a_H is the activity of hydrogen ion. The theoretical line in Figure 1 was drawn by employing equation (3) and the constants in Table 1.

Plots of log k_{obs} *vs.* pH are shown in Figure 2 for the hydrolysis in H_2O at 50 °C (μ 0.1M) of ethyl 6-(8-quinolyloxy)-tetrahydropyran-2-carboxylate (**4**) and the corresponding acid (**3**) obtained by alkaline hydrolysis. The ester (**4**) was hydrolysed slowly in comparison with (**2**) and (**3**); an oxonium-ion-catalysed reaction was observed at pH < 2 with a second-order rate constant (k_H) of 4.2 × 10^{-3} l mol^{-1} s^{-1}. Oxonium-ion-catalysed hydrolysis of the protonated species of the acid (**3**) (k_1)

Table 2. Second-order rate constants (l mol^{-1} s^{-1}) for divalent metal ion catalysis in the hydrolysis of 2-(8-quinolyloxy)tetrahydropyran (**2**) and 6-(8-quinolyloxy)tetrahydropyran-2-carboxylic acid (**3**) in H_2O at μ 0.1M[a]

Compd.	T/°C	pH	k'_{Ni}[b]	k'_{Co}[b]	k'_{Zn}[b]
(2)	50	7.08	48.9		
	30	7.50	6.91	1.33	
	30	6.60			1.7
(3)	50	7.18	39.4		
	30	7.46	3.43	0.67	
	30	6.65			0.91

[a] Calculated as the slope of k_{obs} *vs.* metal ion concentration. [b] The rate constants equal $k_M K_M$ where k_M is the limiting rate constant for metal ion catalysis and K_M is the metal ion association constant.

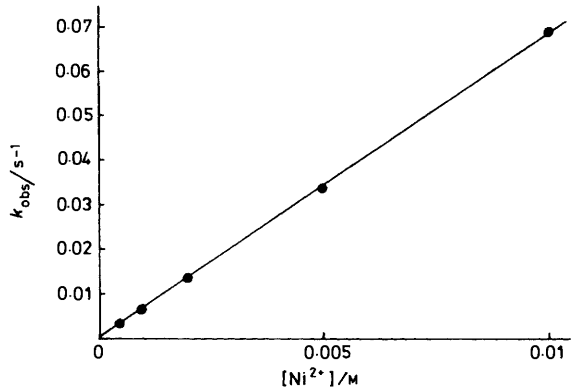


Figure 3. Plot of k_{obs} *vs.* [Ni^{2+}] in the hydrolysis of 2-(8-quinolyloxy)-tetrahydropyran (**2**) in H_2O at 30 °C with μ 0.1M and at pH 7.51

is not evident at pH values greater than 1.0. The hydrolysis reaction is pH-independent from pH 1 to 3 with k_{obs} 4.5 × 10^{-3} s^{-1}. However, in the pH range 3—6 the values of k_{obs} for (**2**) and (**3**) are nearly identical. The equation for k_{obs} in the hydrolysis of (**3**) at pH 1—6 is equation (4), where K_a' and K_a are the first and second acid dissociation constants, and k_3 is the second-order

$$k_{obs} = \frac{k_2 a_H^2 K_a' + k_3 a_H K_a K_a'}{a_H^2 + K_a' a_H + K_a K_a'} \quad (4)$$

rate constant for oxonium-ion-catalysed hydrolysis of the monoanion (ionized carboxy group). Computer-estimated values of pK_a' and pK_a are 3.3 and 5.0, respectively. Values of the constants are given in Table 1.

The hydrolysis reactions of the acetals (**2**)—(**4**) are strongly catalysed by low concentrations of divalent metal ions. The plot of k_{obs} for the hydrolysis of (**2**) *vs.* the concentration of Ni^{2+} at pH 7.50 and 30 °C (Figure 3) is linear, which shows that saturation is not occurring even at a metal ion concentration of 0.01M. Similar linear plots were also found with Co^{2+} and Zn^{2+}. Second-order rate constants for metal ion catalysis of the hydrolysis of (**2**) and (**3**), calculated as the slopes of the plots of k_{obs} *vs.* metal ion concentration, are given in Table 2. Since k_{obs} at pH >5 is given by equation (5) in the metal-ion-catalysed

$$k_{obs} = \frac{k_M K_M [M^{2+}]}{1 + K_M [M^{2+}]} \quad (5)$$

acetal hydrolysis reactions, where K_M is the metal ion association constant and k_M is the limiting rate constant for

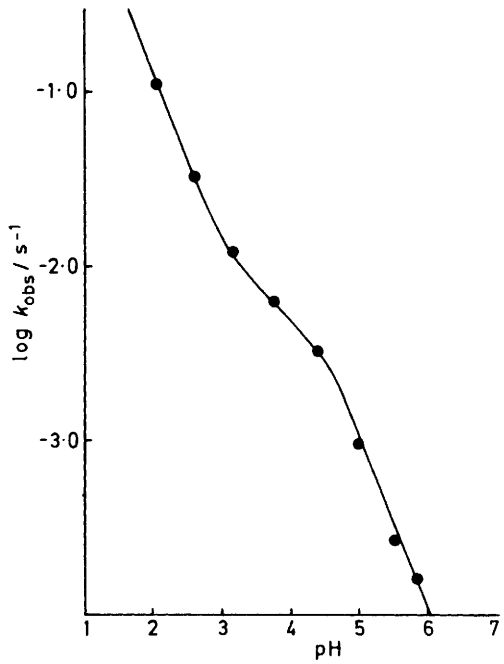


Figure 4. Plot of log k_{obs} *vs.* pH for the hydrolysis of *m*-methoxybenzaldehyde methyl 2-pyridylmethyl acetal (**6**) in H_2O at 50 °C with μ 0.1M

metal ion catalysis, equation (6) is obtained for the reactions of

$$k_{obs} = k_M K_M [M^{2+}] \quad (6)$$

acetals with which metal ion binding is very weak, *i.e.* K_M is small. The second-order rate constants then are equal to $k_M K_M$.

At constant metal ion concentration (0.002M) the values of k_{obs} increase with increasing pH in the range pH 3—5. Thereafter the metal-ion-catalysed reactions are pH-independent, with k_{obs} 9 × 10^{-2} s^{-1} for (**2**) and 7 × 10^{-2} s^{-1} for (**3**) when Ni^{2+} is the catalyst. Plots of log k_{obs} *vs.* pH for the metal-ion-catalysed hydrolysis reactions at 50 °C are shown in Figures 1 and 2. Likewise, k_{obs} in the presence of 0.01M-Ni^{2+} in the hydrolysis of the ester (**4**) is pH-independent in the pH range 5—7 (k_{obs} 1.2 × 10^{-3} s^{-1}). Rate measurements could not be carried out at pH values greater than 7.5 with any of the acetals because of precipitation of the metal ion. The hydrolysis of 2-(6-quinolyloxy)tetrahydropyran is not catalysed by Ni^{2+}; 0.01M-Ni^{2+} had no effect on k_{obs} at pH 4.86 (50 °C).

The plot of log k_{obs} *vs.* pH for hydrolysis of *m*-methoxybenzaldehyde methyl 2-pyridylmethyl acetal (**6**) in H_2O at 50 °C (μ 0.1M) is shown in Figure 4. As in the case of (**2**) there are two regions of increasing values of k_{obs} with decreasing pH, with a small plateau between. The data fit well to equation (3) with k_1 11 l mol^{-1} s^{-1}, k_2 100 l mol^{-1} s^{-1}, and pK_a 4.2; the line in Figure 4 is theoretical. The hydrolysis of (**6**) is not catalysed by the divalent metal ions. For example, the rate constants were unchanged in the presence of 0.01M-Ni^{2+} at pH 5.9 and 50 °C, and at pH 6.9 and 70 °C. Likewise the hydrolysis of (**5**) is not significantly affected by 0.01M-Ni^{2+}.

The hydrolysis of *m*-methoxybenzaldehyde 6-carboxy-2-pyridylmethyl methyl acetal (**7**) in 50% dioxane–H_2O at 70 °C gives the plot of log k_{obs} *vs.* pH shown in Figure 5. The second-order rate constants for oxonium ion catalysis are given in Table 1. The kinetic measurements were made in 50% dioxane–H_2O because in H_2O at 50 °C addition of 0.0005—0.005M-Cu^{2+}, -Ni^{2+}, or -Zn^{2+} resulted in precipitation. No solubility problems were encountered in 50% dioxane–H_2O. As

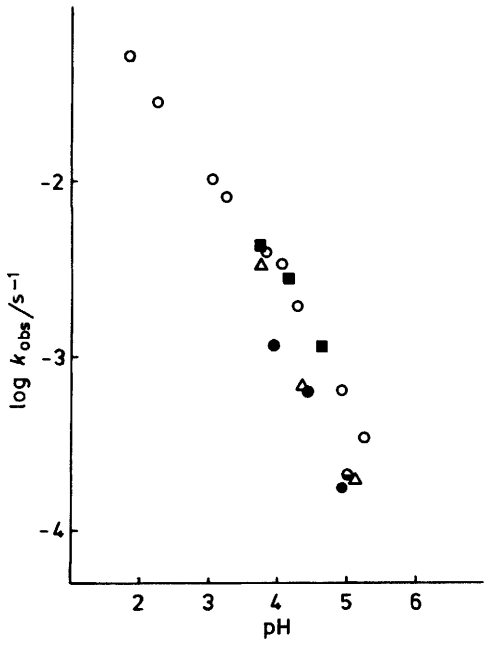
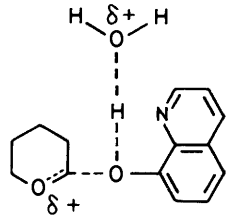


Figure 5. Plot of log k_{obs} *vs.* pH for the hydrolysis of *m*-methoxybenzaldehyde 6-carboxy-2-pyridylmethyl methyl acetal (**7**) in 50% dioxane–H_2O (v/v) at 70 °C in the presence of 0.01M-Ni^{2+} (●), 0.01M-Co^{2+} (△), 0.01M-Zn^{2+} (◒), or 0.001M-Cu^{2+} (■), or in the absence of metal ions (○)

seen in Figure 5, metal ion catalysis is not observed in the hydrolysis of (**7**); at concentrations of 0.01M with Co^{2+} and Ni^{2+} a small inhibition occurs.

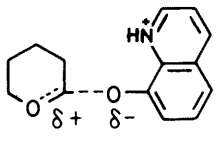
Discussion

Oxonium Ion Catalysis.—Kinetic equivalents exist for the apparent oxonium-ion-catalysed reaction of the neutral species of 2-(8-quinolyloxy)tetrahydropyran (**2**) depicted in (**8**). For

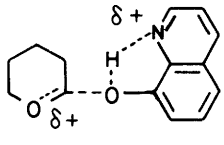


(**8**)

example, the reaction might be considered to involve unimolecular decomposition of the protonated species (**9**) or intramolecular general acid catalysis by the protonated quinoline nitrogen as in (**10**). Tetrahydropyran acetals having



(**9**)



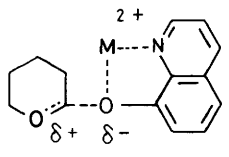
(**10**)

phenolic leaving groups are subject to both bimolecular and intramolecular general acid catalysis in their hydrolytic reactions,[3–6] and the protonated nitrogen would be properly positioned sterically to transfer the proton partially to the leaving group in the transition state. However, the corresponding 6-quinolyl derivative, with which such proton transfer cannot occur, is hydrolysed only five-fold more slowly than (**2**) at pH >5. Therefore, if any intramolecular general acid catalysis of that type is occurring, its effect on the observed rate of hydrolysis is small. The lack of intramolecular general acid catalysis in the hydrolysis of (**2**), in contrast with the pronounced intramolecular general acid catalysis by a neighbouring carboxy group in the hydrolysis of 2-(*o*-carboxyphenoxy)tetrahydropyran,[14] may be due in part to the large unfavourable change in the inductive effect as the proton is transferred from nitrogen. This change in electron withdrawal in the leaving group would reduce the kinetic advantage of intramolecular proton transfer to oxygen to a far greater extent with the protonated quinoline nitrogen of (**2**) than with the carboxy group substituent of the corresponding salicyl acetal.

The rate constants for hydrolysis of 6-(8-quinolyloxy)tetrahydropyran-2-carboxylic acid (**3**) are nearly identical with those of (**2**) at pH >5. Consequently, it is clear that the neighbouring carboxy group in the 2-position of the tetrahydropyran ring is not participating in the reaction of the neutral species. In contrast with (**2**) the values of k_{obs} for hydrolysis of (**3**) at pH <3 become pH-independent. This must be partly due to the electron-withdrawing inductive effect of the un-ionized carboxy group in retarding the step governed by k_1. However, an oxonium-ion-catalysed reaction is observed in the hydrolysis of the corresponding ethyl ester (**4**), and the inductive effect of the substituent ethoxycarbonyl group (σ_I = 0.34) is similar to that for CO_2H (σ_I = 0.39).[18] The ester has a value of k_{obs} for hydrolysis at pH 1.0 that is ten-fold less than the k_{obs} value at pH 1.0 in the pH-independent hydrolysis of (**3**). Therefore, the lack of apparent oxonium ion catalysis at low pH in the hydrolysis of (**3**) is not only because of inductive electron withdrawal by the un-ionized carboxy group; it must also reflect the rapidity of the pH-independent reaction of the monocation. The pH-independent reaction of (**3**) at low pH must involve either an oxonium-ion-catalysed reaction of a zwitterionic species in which the carboxy group is ionized and the quinoline nitrogen is protonated (k_2), or a kinetically equivalent unimolecular reaction of the monocation species.

Metal Ion Catalysis.—Pronounced metal ion catalysis by Ni^{2+}, Co^{2+}, and Zn^{2+} takes place in the hydrolysis of the acetals (**2**)—(**4**), even though binding of the metal ions to the acetals is weak. As can be seen in the typical example of Figure 3, plots of k_{obs} *vs.* metal ion concentration are still linear at 0.01M-metal ion. As shown in Figures 1 and 2, at constant metal ion concentration k_{obs} increases with increasing pH to pH 5, which corresponds roughly with the pK_a of the conjugate acid (protonated quinoline nitrogen). This occurs because there is competition between the metal ions and oxonium ion for binding to the quinoline nitrogen at pH values below the pK_a. At pH values greater than 5, k_{obs} is independent of pH. The rate enhancements produced by the metal ions are quite large: 0.002M-Ni^{2+} enhances k_{obs} in the hydrolysis of (**2**) and (**3**) at pH 7 by close to 10^4. These are, of course, minimum rate enhancements. Simply increasing the concentration of metal ion will increase k_{obs} [note in Figure 3 that in the hydrolysis of (**2**) k_{obs} in the presence of 0.01M-Ni^{2+} is five-fold larger than with 0.002M-Ni^{2+}]. Likewise, in view of the shapes of the plots of log k_{obs} *vs.* pH in the presence and absence of metal ions, each increase in pH of 1 pH unit would increase the rate enhancements by a factor of 10 if that were experimentally possible.

It is clear from the pH independence of k_{obs} in the metal-ion-catalysed reactions that the metal ions are enhancing the unimolecular decomposition reactions of the acetals as in (**11**).



(11)

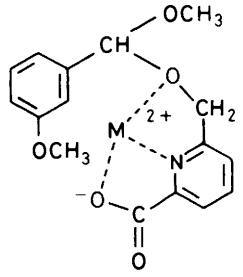
Water molecules will also be ligated to the metal ion and will be moderately acidic (the pK_a values for acid ionization of aquo complexes of the metal ions at 25 °C are: Zn^{2+} 8.8; Co^{2+} 8.9; Ni^{2+} 10.6).[19] Therefore, intramolecular general acid catalysis by metal-ion-bound water might occur if the steric situation was favourable for proton transfer to the leaving group oxygen. However, with the acetals of 8-hydroxyquinoline a seven-membered-ring transition state would be required. Only small rate enhancements have been observed in acetal hydrolysis reactions involving a seven-membered-ring transition state when a carboxy group is the intramolecular general acid.[15] Consequently, it is unlikely that general acid catalysis by complexed water could produce the large rate enhancements observed in the hydrolysis of (**2**)—(**4**). Note also that the rate constants for the Ni^{2+}-catalysed reactions are larger than with Co^{2+} and Zn^{2+}, even though Ni^{2+}-complexed water is a much weaker acid than are the aquo complexes of the other metal ions. Replacement of a water ligand on the metal ion must occur during the chelation process. Water replacement in the aquo complexes of Zn^{2+}, Co^{2+}, and Ni^{2+} occurs with rate constants of 3×10^7, 5×10^5, and 3×10^4 s^{-1}, respectively.[20] Therefore dissociation of ligated water cannot be the rate-determining step in the metal-ion-catalysed reactions of (**2**)—(**4**). The reactions of Ni^{2+} with neutral ligands have second-order rate constants of *ca.* 4×10^3 l mol^{-1} s^{-1} at 25 °C.[21] The most likely mechanism in the metal-ion-catalysed reactions is therefore that shown in (**11**).

Although metal ion binding to the acetal is weak, mechanism (**11**) would be effective, because as the C–O bond breaks partial negative charge will be generated on oxygen, thereby allowing strong metal ion binding in the transition state.* The greater catalytic effect of Ni^{2+} than of Co^{2+} or Zn^{2+} could be due to greater strength of binding to the quinoline nitrogen; the association constant for Ni^{2+} binding to pyridine is approximately eight-fold larger than the constants for binding of Co^{2+} or Zn^{2+}.[22] However, the association constants of Ni^{2+} and Zn^{2+} are similar for binding to 8-methoxyquinoline.[22] That a chelation effect of the type depicted in (**11**) is important is shown by the lack of significant metal ion catalysis in the hydrolysis of 2-(6-quinolyloxy)tetrahydropyran with which chelation cannot occur in a 1:1 complex. Whether bidentate binding also occurs in the reactant state cannot be ascertained. However, an acetal oxygen is very weakly basic; the conjugate acids of acetals of aliphatic alcohols have dissociation constants of 10^5—10^6 mol l^{-1}.[23,24] and phenolic acetals will be still less basic. If binding of the metal ions to the acetal oxygen is not significant in the reactant, then the lack of saturation effects with (**2**) and (**3**) at high metal ion concentrations would be explained; metal ion binding to oxygen would then be concerted with C–O bond breaking.

Metal-ion-catalysed reactions that are pH-independent were previously observed in the hydrolysis of substituted benzaldehyde methyl 8-quinolyl acetals,[11] and rate enhancements were similar to those with (**2**) and (**3**) (10^5 with 0.01M-Ni^{2+} at pH 7). Incorporation of a carboxy group into the 2-position of the quinoline ring brought about strong metal ion binding with saturating effects at low concentration. However, that did not lead to an increase in the rate enhancement in comparison with that produced by 0.01M-metal ion with the acetal in which binding is weak. The strength of binding in the transition state must be of critical importance with regard to the magnitude of the metal ion catalysis. In the hydrolysis of the substituted benzaldehyde acetals and the tetrahydropyran acetals (**2**)—(**4**), the metal ions must be exerting their effects in the same manner by stabilizing the leaving group in the pH-independent unimolecular decomposition reaction.

The rate constants for the Ni^{2+}-catalysed hydrolysis of the ethyl ester of (**3**) are also pH-independent at pH 5—7 when the metal ion concentration is held constant (Figure 2). However, the rate constants are approximately 60-fold less than those with (**3**) even though the concentration of Ni^{2+} was 0.01M in hydrolysis of the ester as compared with 0.002M in the hydrolysis of (**3**). Thus, the actual rate difference is 3×10^2. This is similar to the difference in k_2 for these compounds [estimated in the case of the ester by assuming that the log k_{obs} *vs.* pH profile is the same shape as that of (**2**)]. The experimentally measured difference in k_1 for ethyl 6-(8-quinolyloxy)tetrahydropyran-2-carboxylate and (**2**) is 160. These rate differences can be attributed to the electron-withdrawing inductive effect of the ethoxycarbonyl group in the 2-position which will decrease the basicity of the acetal and will decrease the stability of the developing oxycarbocation in the transition state.

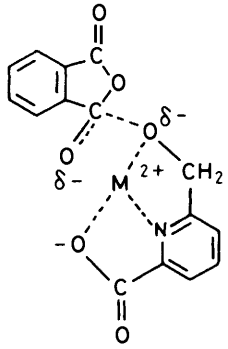
Acetals of Aliphatic Alcohols.—In contrast with the strong metal ion catalysis of the hydrolysis of (**2**)—(**4**) there is no detectable catalysis of the hydrolysis of the acetals (**5**)—(**7**) which have an aliphatic alcohol leaving group. In these cases the metal ion can form a five-membered chelate ring with the leaving group. The increased strength of metal ion binding to the corresponding acid (**7**) produces a small inhibition. The presence of the positively charged metal ion may make protonation of the leaving group oxygen by oxonium ion more difficult, a situation analogous to that when there is a proton on nitrogen. With (**7**) there is no doubt that the metal ion is strongly chelated to the acetal in a position that would be sterically favourable for binding to the leaving group [see (**12**)].



(12)

It is clear that such binding will not produce a catalytic effect when the leaving group is poor (an aliphatic alcohol) even when the oxycarbocation intermediate is as stable as a methoxybenzyl ion. In contrast, significant catalysis by divalent metal ions occurs in the hydrolysis of the ester 2-pyridylmethyl hydrogen phthalate[25] and the corresponding 6-carboxy compound[26] by the stabilization of the leaving group in the transition state (**13**) for decomposition of the tetrahedral intermediate. In that reaction C–O bond breaking is facilitated by the 'push' provided by the negatively charged oxygen of the tetrahedral intermediate, and metal ion binding in the transition state will be strong. The α-methoxy group of the acetals (**6**) and (**7**) evidently cannot facilitate C–O bond breaking to such an extent; spontaneous C–O bond breaking will therefore not occur when

* Values of the logarithms of the stability constants at 25 °C for complexation of various metal ions with 8-hydroxyquinoline are: Ni^{II} 9.27; Co^{II} 8.65; and Zn^{II} 8.52.[22]



(13)

the leaving group is an aliphatic alcohol, and consequently, metal ion catalysis is not observed.

A consideration of mechanism (**11**) might lead to the conclusion that metal ion catalysis should enhance the rates of hydrolysis of *all* types of acetals, not just those with relatively good leaving groups. However, if kinetically significant metal ion binding only occurs in the transition state of the pH-independent unimolecular decomposition reaction, then only those acetals in which C–O bond breaking is reasonably easy will have their reactions catalysed, *i.e.* a good leaving group will be a requirement. Acetals of aliphatic alcohols do not normally give rise to observable pH-independent reactions. Metal ion chelation to the reactant will necessarily involve binding to the pyridine nitrogen, which will in turn further decrease the basicity of the acetal oxygens. Therefore, it is likely that significant chelation of the very weakly basic acetal oxygen is not occurring even though the steric situation is very favourable. In that case, metal ion catalysis would not take place since the C–O bond of acetals of aliphatic alcohols hydrolysed by an *A*-1 mechanism cannot begin to break unless it is protonated or complexed with a comparable positive species, *i.e.* only oxonium ion catalysis would then be observed. An *A*-1 mechanism in the hydrolysis of acetals of aliphatic alcohols is in accord with a large amount of experimental evidence,[1–4] *e.g.* values of ΔS^{*}, the D_2O solvent isotope effect, and the lack of observable general acid catalysis. As previously pointed out,[27] there is only one reliable criterion for a concerted A_{SE}-2 mechanism and that is the observation of significant general acid catalysis; the absence of such catalysis strongly supports an *A*-1 mechanism. Thus, it is the difference in transition-state structure for hydrolysis of the phenolic acetals (**2**)—(**4**) and the acetals of aliphatic alcohols (**5**)—(**7**) that is responsible for the different effects of metal ions.

Comparison of Oxonium Ion and Metal Ion Catalysis.—The rate constants for hydrolysis of the 8-quinolyl acetals of substituted benzaldehydes[11] are considerably larger than those of (**2**)—(**4**), whereas the rate constants for hydrolysis of 8-quinolyl β-D-glucopyranoside[10] are much less than those of (**2**)—(**4**). The k_2 values for oxonium-ion-catalysed hydrolysis of the neutral species in H_2O are: 8-quinolyl β-D-glucopyranoside, 1.6×10^{-2} l mol^{-1} s^{-1} (89.8 °C); ethyl 6-(8-quinolyloxy)tetrahydropyran-2-carboxylate, 7×10^{-1} l mol^{-1} s^{-1} (estimated; 50 °C); 2-(8-quinolyloxy)tetrahydropyran, 93 l mol^{-1} s^{-1} (50 °C); *p*-chlorobenzaldehyde methyl 8-quinolyl acetal, 7×10^{3} l mol^{-1} s^{-1} (30 °C).[11] There is a parallel change in the rate constants for divalent metal ion catalysis. For example, second-order rate constants for Co^{2+} catalysis in the hydrolysis of these compounds are 7.2×10^{-5} (70.1 °C), 2.3×10^{-2} (50 °C), 1.3 (30 °C), and 302 l mol^{-1} s^{-1} (30 °C), respectively. While there are large differences in the absolute magnitudes of the rate constants with these compounds, the enhancements in k_{obs} due to metal ion catalysis in comparison with the oxonium-ion-catalysed reaction at a given pH are quite similar in view of the temperature differences. Thus, oxonium ion catalysis and divalent metal ion catalysis are affected in very similar manners by changes in basicity and oxycarbocation stability. It should be noted that the second-order rate constants for oxonium ion catalysis and Co^{2+} catalysis do not differ greatly, and the rate constants for Co^{2+} catalysis are somewhat less than those for H_3O^{+} catalysis. The sizeable enhancements in k_{obs} in the metal-ion-catalysed reactions are therefore due in large part to the relative concentration effects, *e.g.* at pH 7 one may employ 10^{-2}M-Co^{2+}, whereas the concentration of H_3O^{+} is then only 10^{-7}M. Since a pH-independent unimolecular decomposition reaction would be expected to occur at progressively higher pH values as the oxycarbocation becomes less stable, the actual rate enhancement produced by metal ion catalysis would be larger with the less reactive compounds if that comparison could be made.

Comparison of General Acid and Metal Ion Catalysis.—In a unimolecular decomposition reaction the C–O bond must begin to break without the assistance of a proton or metal ion. As a consequence, there should be a strong dependence on the leaving group in both general acid and metal ion catalysis. General acid catalysis is observed only in cases where the leaving group is good or in cases where the intermediate oxycarbocation is exceedingly stable.[3–9] A significant dependence on leaving group ability also exists in metal-ion-catalysed reactions, as shown by the lack of metal ion catalysis in the hydrolysis of the 2-pyridylmethyl acetals (**5**)—(**7**) in which the leaving group is an aliphatic alcohol. Thus, metal ion catalysis and general acid catalysis in acetal hydrolysis are quite similar in regard to the leaving group requirement, and very likely for the same reason, *i.e.* binding of both species to the leaving group oxygen occurs in the transition state of the pH-independent, unimolecular breakdown reaction.

Intramolecular general acid catalysis by a neighbouring carboxy group in acetal hydrolysis has, with one exception,[28] been observed only with phenolic acetals,[14,15,28–33] and generally with a salicylic acid leaving group.[14,28–33] In the exceptional case of benzaldehyde bis-(*cis*-2-carboxycyclohexyl) acetal[28] the presence of a second carboxy group allows bifunctional catalysis and thereby facilitates C–O bond breaking. The salicyl acetals that have been studied encompass a series ranging from benzaldehyde methyl salicyl acetal[14] to *o*-carboxyphenyl β-D-glucopyranoside,[29,30] *i.e.* oxycarbocation stability varies greatly. There is no doubt that the mechanism of the intramolecular reaction of benzaldehyde methyl salicyl acetal involves proton transfer in the transition state from the neighbouring carboxy group since the kinetically equivalent possibilities can be ruled out.[14] With *o*-carboxyphenyl β-D-glucopyranoside[29,30] other possibilities remain open, and in the case of methoxymethoxybenzoic acid the mechanism is in dispute.[29,31,32] Nevertheless, it is noteworthy that, as with metal ion catalysis, enhancements in k_{obs} due to carboxy participation in comparison with oxonium-ion-catalysed hydrolysis of suitable reference compounds are reasonably similar within the series. In H_2O these rate enhancements range from 2×10^{5} with benzaldehyde methyl salicyl acetal[14] and 10^{4} with 2-(*o*-carboxyphenoxy)tetrahydropyran[14] to 10^{3}—10^{4} with *o*-carboxyphenyl β-D-glucopyranoside.[29,30] Thus, the rate enhancements achieved by intramolecular general acid catalysis are not greatly affected by changes in oxycarbocation stability. The similarities in the effects of metal ion catalysis and intramolecular general acid catalysis in acetal hydrolysis are thus striking. Likewise, intramolecular general acid catalysis is not observed in the hydrolysis of ketone acetals when the leaving group is an aliphatic alcohol.[34] With a good leaving

group and in the presence of a chelated metal ion or an intramolecular general acid the developing oxycarbocation is not a factor of great importance with regard to the magnitude of the rate enhancements. The comparison of metal ion catalysis with intramolecular general acid catalysis is appropriate because of the requirement for a metal ion binding site within the molecule before catalysis can be achieved. Thus both types of catalysis can be explained within a common interpretive framework.

Acknowledgements

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