Metal-ion Assisted Catalysis of Nucleophilic Attack. Part II.[1] The Pathway of Zinc–Base Co-operation in Aldehyde Hydration

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A path for acetaldehyde hydration in which zinc and acetate or pyridine act as co-operative catalysts is described. Comparison with pyridine-2-carboxylate shows that the zinc ion and the base are not bound to each other when acting as co-catalysts. In the presence of chloride ions a different type of co-operative catalysis is seen. The rates observed in the zinc–pyridine and –acetate co-operative catalysis of the hydration are analysed in terms of the concentrations of complex species present in solution. The only effect of a base bound to the metal ion appears to be to block some of the metal's catalytic co-ordination sites.

THE enzyme carbonic anhydrase [2] catalyses a variety of reactions, each of which involves at some stage nucleophilic attack by oxygen at carbon and, perhaps, at sulphur. These include the hydration of carbon dioxide and aldehydes, and the hydrolysis of certain esters. In the non-enzymic reactions of carbon dioxide [3] and of aldehydes [4] the nucleophilic addition is rate limiting; this is also true of esters,[5] unless the alkoxy-leaving group is a particularly poor one. It has already been shown [1] that in the attack on acetaldehyde the rate equation contains, in addition to the familiar [6] water, specific acid or base, and buffer catalysis, terms such as $k[Zn^{2+}][MeCHO]$, $k[Zn^{2+}][MeCO_2^-][MeCHO]$, and $k[Zn^{2+}][OH^-][MeCHO]$.

EXPERIMENTAL

The kinetic apparatus and procedure were as previously described.[1] In addition, runs were carried out using a new digital data logger, built by S. H. Palmstrøm of these laboratories.[7] This was attached to a Gilford SP 2400 spectrophotometer. The wavelength used to follow the reaction should ideally be 275 nm, the u.v. absorption maximum for the acetaldehyde carbonyl group. Because of the strong absorbance of the pyridine (py) and pyridine-2-carboxylate (pc) buffers, these systems were observed respectively at 285 (path length 5 mm) and 300 nm (2 mm). All rates were measured at 0 ± 0.2 °C. Ionic strength (I) was maintained at a value of 1.4 mol l^{-1} by addition of sodium perchlorate, nitrate, or chloride as inert salts.

Materials were analytical grade where possible; deionised distilled water was used. Buffers were prepared by mixing solutions of the metal salt, stock buffer, and neutral salt with water to total *ca.* 9 cm^3. The pH was then adjusted with sodium hydroxide or the appropriate acid (perchloric, nitric, or hydrochloric) to the required value and final correction made of the solution's volume. Where possible the pH value before adjustment was on the alkaline side; this prevented precipitation of zinc hydroxide on addition

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[1] R. H. Prince and P. R. Woolley, *J.C.S. Dalton*, 1972, 1548. We wish to apologise for two errors in this paper: equations 3 and 4 should have appeared as 4 and 3 respectively, and the factor 20/19 in equations 2—4 as 19/20.

[2] S. Lindskog, L. E. Henderson, K. K. Kannan, A. Liljas, P. O. Nyman, and B. Strandberg in 'The Enzymes,' vol. 5, ed. P. Boyer, Academic Press, 1971, p. 587.

[3] M. M. Sharma and P. Dankwerts, *Trans. Faraday Soc.*, 1963, **59**, 386.

[4] W. P. Jencks, 'Catalysis in Chemistry and Enzymology, McGraw-Hill, 1969, pp. 211—215.

[5] Ref. 4, pp. 508—517.

[6] R. P. Bell, *Adv. Phys. Org. Chem.*, 1966, **4**, 1.

[7] S. H. Palmstrøm, Ph.D. Thesis, University of Cambridge, 1973.

of alkali. Adjustment of pH was carried out at room temperature (*ca.* 20 °C), as it was impracticable to adjust each buffer at 0 °C. There is therefore a small uncertainty in the final pH. Thus pH-dependent constants derived separately in py and acetate systems may have different values. Control experiments showed that, whereas the pH of an acetate buffer ($I = 1.4$ mol l^{-1}, $NaClO_4$) is invariant between room temperature and 0 °C, that of a similar py buffer increases by *ca.* 0.27 units. Allowance is made for this in comparing values of k_{Zn} in the two systems (see Kinetic Analysis section).

All reactions were first order in the concentration of acetaldehyde. The observed rate constant quoted, $k_{obs.}$, is $-d[MeCHO]/[MeCHO]dt$ and this is the sum of the rate constants of the hydration and dehydration reactions as equilibrium is reached.[1] Since the proportional change in these is the same in the presence of any catalyst, the rate constants given in this paper are $k_{obs.}$ uncorrected.

Invariant initial and final optical densities were taken as confirmation that no reaction occurred between acetaldehyde and the py or pc buffers (contrast the case of imidazole [1]).

RESULTS

(a) *Pyridine and Pyridine-2-carboxylate Buffers.*—The rate of hydration of acetaldehyde was measured in pyridine (py) buffers of various concentrations with py : Hpy^+ ratios of 1 : 3 (pH 5.09 ± 0.05) and 3 : 1 (pH 6.1 ± 0.1). From these rates the catalytic constants of the buffer species, defined in equation (1), were obtained. At a given pH

$$k_{obs.} = k_0 + k_H[H^+] + k_{OH}[OH^-] + k_A[A] + k_{AH}[HA^+] \quad (1)$$

value the first three terms are constant and the remainder is written as $\Delta k_{obs.}$. The same experiments were carried out for pyridine-2-carboxylate (pc) and -2-carboxylic acid (Hpc) buffers, the conjugate base : acid ratio being 1 : 4 (pH 4.72 ± 0.05) and 4 : 1 (pH 6.00 ± 0.05). The catalytic constants are presented in Table 1.

TABLE 1

Catalysis of acetaldehyde hydration by buffer species [see k_A and k_{AH} in equation (1)]

Catalyst	Rate constant/ l mol^{-1} s^{-1}	
py	0.032	±0.001
Hpy^+	0.024	
pc^-	0.015	
Hpc	0.012	

(b) *Zinc Ions in Pyridine Buffers.*—The hydration was studied in solutions at pH 6.0 containing py as buffer and zinc ions. A co-operative effect was observed (Figures 1 and 2). The buffer concentration was varied from 0.1 to 0.5 mol l^{-1}. In a more concentrated buffer, 1.0 mol l^{-1}, a suspension, possibly of $[Zn(py)_n(ClO_4)_2]$, was formed at the start of the reaction except at zinc concentrations exceeding 0.2 mol l^{-1}. Precipitation was presumably induced either by the addition of the acetaldehyde or by the stirring.

The co-operative effect could be due to the interaction of Zn^{2+} and Hpy^+, rather than Zn^{2+} and py, but this is ruled out by the experiment at pH 4 (Figure 3). Here the proton-catalysed hydration was faster and the errors correspondingly larger, but there was no sign of the co-operativity which one would expect, *viz.* much greater than in Figure 1 as Hpy^+ now predominates over py, if the protonated form of py were the active one.

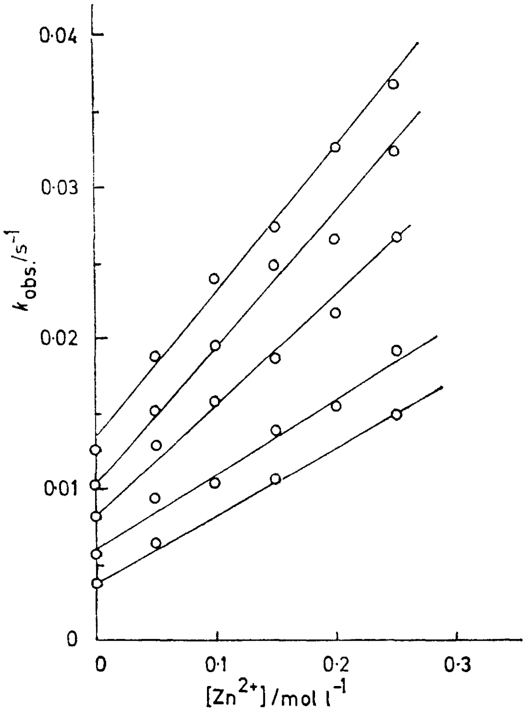

FIGURE 1 Co-operative catalysis between zinc ions and py buffer at pH 6.0, buffer concentrations from 0.5 (upper curve) to 0. mol l^{-1} (lowest curve), 0 °C, and $I = 1.4$ mol l^{-1} (perchlorate)

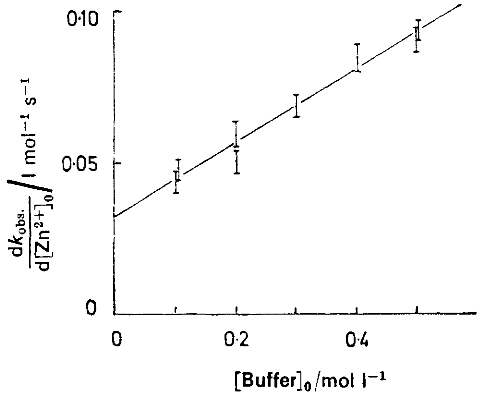

FIGURE 2 Gradients from Figure 1 plotted against buffer concentration

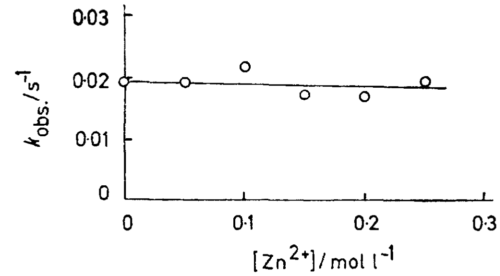

FIGURE 3 Lack of co-operative catalysis between zinc and pyridinium ions at pH 4.0, [acetate buffer] = 0.05 mol l^{-1}, $[Hpy^+]$ = 0.2 mol l^{-1}, 0 °C, and $I = 1.4$ mol l^{-1} (perchlorate)

(c) *Zinc Ions with Pyridine-2-carboxylate.*—Systems containing pyridine-2-carboxylatozinc complexes in the presence of perchlorate were difficult to handle when the pc : zinc concentration ratio was less than 3 : 1. Below this value either $[Zn(pc)_2]$ or else $[Zn(pc)ClO_4]$ was precipitated. To avoid this almost all the experiments with pc were carried out using sodium nitrate rather than sodium perchlorate as an 'inert' salt: to a 0.2 mol l^{-1} solution of zinc nitrate, with sodium nitrate and a weak acetate buffer, was added sodium pyridine-2-carboxylate up to 0.15 mol l^{-1}. The effect of pc on the reaction rate was very small [Figure 4(*a*)]. The addition of zinc ions to a 0.15 mol l^{-1} pc buffer reduced the catalysis more strongly [Figure 4(*b*)].

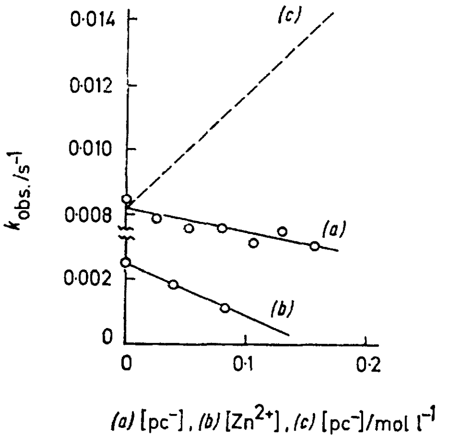

FIGURE 4 (*a*) Effect of adding pc ions to a solution containing 0.2 mol l^{-1} zinc ions supported by 0.05 mol l^{-1} acetate buffer at pH 5.5, 0 °C, and I = 1.4 mol l^{-1} (nitrate); (*b*) effect of adding zinc ions to pc buffer at [Buffer] = 0.15 mol l^{-1}, pH 6.0, 0 °C, and I = 1.4 mol l^{-1} (nitrate); (*c*) curve which would have been expected in the case of (*a*) if the co-operative mechanism were to involve a metal-bound rather than a free carboxylate group, gradient = +0.036 l mol^{-1} s^{-1} (see text)

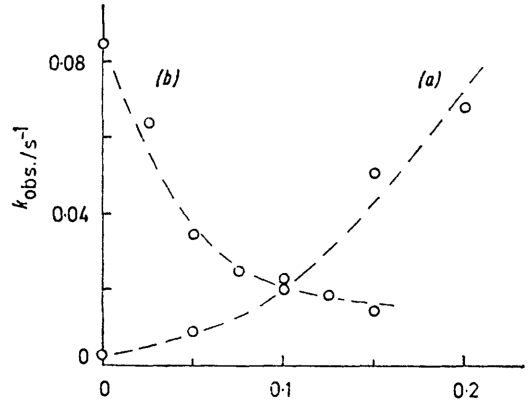

FIGURE 5 (*a*) Acetaldehyde hydration catalysed by zinc ions in the presence of chloride at pH 6.0, [acetate buffer] = 0.05 mol l^{-1}, 0 °C, and I = 1.4 mol l^{-1} (chloride); (*b*) effect of added pc on the catalysis by zinc ions in the presence of chloride at pH 6.0, [acetate buffer] = 0.05 mol l^{-1}, 0 °C, and I = 1.4 mol l^{-1} (chloride). The broken lines indicate the form of the curve but do not correspond to any theoretical model

(d) *Zinc Ions in the Presence of Chloride.*—The attempt to use chloride as an 'inert' ion where perchlorate was unsuitable [(c) above] revealed a new kind of co-operative catalysis. Rates were very much greater for Zn^{2+} alone [Figure 5(*a*)] and were drastically reduced on addition of pc [Figure 5(*b*)]. Furthermore, as the Figure shows, the rate was no longer first order in zinc concentration but of higher order. Chloride is therefore not an inert ion; control experiments, however, showed that there is no such effect with nitrate under the conditions of section (c). It is therefore safe to use sodium nitrate as an inert salt.

DISCUSSION

Table 1 shows the catalytic constants for the protonated and deprotonated forms of the buffers. The figure for Hpc is of interest, since the Hpc zwitterion possesses an acidic NH^+ and a basic CO_2^- group. This might therefore be expected to show simultaneous acid and base catalysis, as many protonated anions may for CO_2 [3] and as phosphate may for acetaldehyde.[8] Clearly it does not; in fact pc and Hpc are both poorer catalysts than molecules possessing only one of their potentially active groups.

The co-operative catalysis by zinc and py is shown clearly in Figure 2, where the gradients $dk_{obs.}/d[Zn^{2+}]_0$ are plotted against buffer concentration. Assuming (*cf.* Figure 3) that the pyridinium ion is inactive in the co-operative catalysis, and using a pK_a value of 5.6 [9] for py, the rate is therefore expressed by equation (2).

$$dk_{obs.}/d[Zn^{2+}]_0 = 0.0324\ l\ mol^{-1}\ s^{-1} + 0.172\ l^2\ mol^{-2}\ s^{-1}\ [py]_0 \quad (2)$$

The subscript 0 refers to total concentration. Thus the expression is empirical, ignoring complex formation.

The behaviour of zinc ions in the presence of pc ions is quite different. At the pH used, 5.5, pc is virtually 100% co-ordinated to the zinc. The rate of acetaldehyde hydration, catalysed by zinc, decreases as pc is added to the system (Figure 4). The decrease is only slight, 0.008 l mol^{-1} s^{-1}, suggesting that the inhibition of catalysis is due simply to blockage of available zinc co-ordination sites. The loss of two out of six such sites per zinc ion gives an expected gradient of −0.006 l mol^{-1} s^{-1}. The fact that the rate does not increase shows that there can be no intramolecular co-operativity available in the $[Zn(pc)]^+$ ion. This would have been expected if the co-operative catalysis with zinc ions came from **bound** py or carboxylate groups, as a simple calculation shows: taking acetate as an example, although py would give a similar answer, equation (3) is

$$dk_{obs.}/d[Zn^{2+}]_0 = k[MeCO_2], \quad \text{where}^{1}\ k = 0.15\ l^2\ mol^{-2}\ s^{-1} \quad (3)$$

obtained. Replacing $[Zn^{2+}]$ with $[Zn(pc)^+]$ and using the figure * of 4.2 l mol^{-1} to convert the third- to a second-order rate constant, the rate constant expected if intramolecular co-operativity were to occur is $dk_{obs.}/d[pc^-]_0 = dk_{obs.}/d[Zn(pc)^+] = +0.036$ l mol^{-1} s^{-1} as opposed to the value of −0.008 l mol^{-1} s^{-1} observed.

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* The Zn^{2+}–$MeCO_2^-$ association constant; this work.

[8] Y. Pocker and J. E. Meaney, *J. Phys. Chem.*, 1967, **71**, 3113.

[9] L. Sillén and A. E. Martell, 'Stability Constants of Metal–Ion Complexes,' *Chem. Soc. Special Publ.*, (*a*) no. 17, 1964; (*b*) no. 25, 1971.

The same conclusion follows from Figure 4(*b*), where each zinc ion added removes three pc ions from solution, giving a gradient of *ca.* -0.03 l mol^{-1} s^{-1}. It follows that in zinc–carboxylate (if one may generalise from acetate and pc) and in zinc–pyridine systems the co-operative catalytic path involves an *outer*-sphere base acting in conjunction with the metal. This confirms our suggestion [1] based on the hydration rates, rather lower than expected, observed with zinc in very strong acetate buffers.

The surprising co-operative phenomenon seen in media containing chloride ions (Figure 5) clearly has a different origin from that of zinc–pyridine co-operativity, since (*i*) py is an uncharged base whereas chloride has charge but negligible proton affinity, (*ii*) the order in zinc concentration is no longer first. It is also interesting that the reduction by pc of the zinc-induced hydration rate is correspondingly much greater in the presence than in the absence of chloride. These features of the chloride catalysis suggest a mechanism involving ionic aggregation, so that an aldehyde molecule is subjected to simultaneous influences from more than one zinc ion, for example, simultaneous Lewis-acid and hydroxide donor functions (*cf.* ref. 1 and below). Nitrate and perchlorate do not encourage aggregation as chloride does,[9] so they behave as genuinely inert counter-ions; chelation by pc, reducing the net charge on the zinc ion, apparently prevents aggregation in the presence of chloride ions, giving the result shown in Figure 4(*b*).

FURTHER KINETIC ANALYSIS

On the assumption that the co-operative effect involves zinc and an unbound base, it is possible to reanalyse the data based on acetate [1] and py buffers in more detail. To do this one must know the approximate magnitudes of the stability constants for the binding of zinc by py and by the acetate ion. Values of the first binding constants were estimated at 0 °C and $I = 1.4$ mol l^{-1} by titrating 0.1 mol l^{-1} solutions of these bases with perchloric acid in the presence of an excess of zinc ions. Association constants, K_L, measured under these conditions were: for Zn^{2+} and acetate, 4.2 l mol^{-1}; for Zn^{2+} and py, 20 l mol^{-1}. No values are available in the literature for these constants at 0 °C; in the range 20—30 °C comparable values have been reported, *e.g.* 4.0 l mol^{-1} for acetate (25 °C, $I = 1.0$ mol l^{-1}) [10] and 28 l mol^{-1} (20 °C, $I = 1.0$ mol l^{-1}) [11] for py; however other authors propose higher values [12,13] under slightly different conditions.

(a) *The Zinc–Acetate System.*—The general kinetic equation including zinc–base co-operation at a fixed pH is as in (4). Here A = acetate ion or py. The first term

$$\Delta k_{obs.} = k_B[B] + k_{Zn}[Zn^{2+}] + k_2[Zn^{2+}][A] + k_{ZnA}[ZnA^{2+}] + k_{2A}[ZnA^{2+}][A] \quad (4)$$

represents catalysis by the buffer. The second and third terms embody two kinds of catalysis, one by the metal ion alone and the other by the metal ion acting co-operatively with unbound A. In either case the catalysis is unaffected by bound A, except inasmuch as the accessibility of the metal ion's surface is reduced, so that the fourth and fifth terms of equation (4) appear, in which k_{ZnA} is expected to be less than k_{Zn} and k_{2A} to be less than k_2.

In equation (4), k_B and [B] are composite terms; [B] is the sum of the concentrations of the free deprotonated and protonated buffer species while k_B is the linear combination of their catalytic constants appropriate to the pH in question. The other rate constants at fixed pH may also in principle be composite; for instance k_{Zn} is already known to increase with increasing hydroxide concentration.[1] Terms three and four are kinetically indistinguishable, and $[Zn^{2+}][A]$ may be replaced with $[ZnA^{2+}]/K_L$. Furthermore, if the initial analytical concentrations of zinc and buffer are $[Zn^{2+}]_0$ and $[B]_0$, and these concentrations are reduced by the formation of the $[ZnA]^{2+}$ complex, the equation becomes (5).

$$\Delta k_{obs.} = k_B[B]_0 + k_{Zn}[Zn^{2+}]_0 + [ZnA^{2+}]\{-k_B - k_{Zn} + k_{ZnA} + (k_2/K_L) + k_{2A}[A]\} \quad (5)$$

In the Job's plot experiment carried out previously,[1] the linear terms A and B are related to the first two terms in equation (5); k_{Zn} (0.017 l mol^{-1} s^{-1}) is in good agreement with the other values at pH 6, but k_B (0.026 l mol^{-1} s^{-1}) is lower than expected (0.03 l mol^{-1} s^{-1}). The quadratic and higher terms in the Job's plot do not bear exactly on equation (5) as the assumption of no complex formation was made at that time. The parameters in equation (5) were, therefore, found for the zinc–acetate system by plotting the function $(\Delta k_{obs.} - k_B[B]_0 - k_{Zn}[Zn^{2+}]_0)/[ZnA^{2+}]$ against [A] with data taken from ref. 1. To do this, the concentrations of the species in solution (A, HA^+, Zn^{2+}, and $[ZnA]^{2+}$) were evaluated using a computer program, assuming the pK_a of acetic acid to be 4.6 and K_L to be 4.2 l mol^{-1}. This yielded a set of points (Figure 6) regressing to a straight line without noticeable curvature. The gradient is k_{2A} and the intercept is $[-k_B - k_{Zn} + k_{ZnA} + (k_2/K_L)]$. From the latter, $[k_{ZnA} + (k_2/K_L)]$ may be calculated as k_B and k_{Zn} are known.

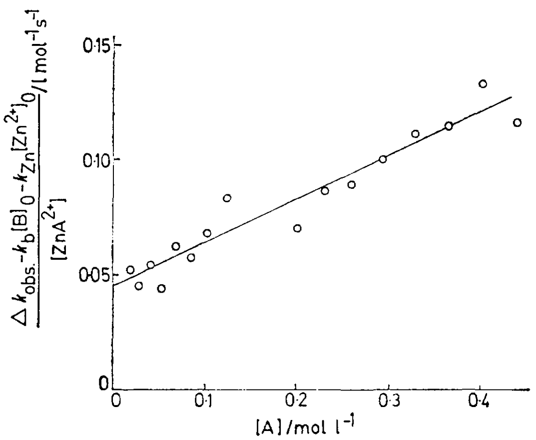

FIGURE 6 Analysis of rate equation in acetate [see equation (5) and text]

The omission of the complex $[ZnA_2]$ from consideration in these equilibria is based on the assumption that the second association constant K_{L_2} is fairly small ($\ll K_L$).

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[10] M. H. Hutchinson and W. C. E. Higginson, *J.C.S. Dalton*, 1973, 1247.

[11] Ya. D. Fridman and M. G. Levina, *Russ. J. Inorg. Chem.*, 1967, **12**, 1425.

[12] G. Atkinson and J. E. Bauman, *Inorg. Chem.*, 1963, **2**, 64.

[13] H. Matsuda, Y Ayabe, and K. Adachi, *Ber. Bunsengesellschaft Phys. Chem.*, 1963, **67**, 593.

Under all conditions where K_{L_2} has been estimated it has been shown to be considerably less than K_L (*i.e.* 30% of K_L or less).[13-15] Under the conditions of our experiments the effect of $[ZnA_2]$ on the concentrations of other species was calculated to be negligible for $K_{L_2} \leqslant 0.3K_L$.

In order to differentiate between the kinetically equivalent terms containing k_{ZnA} and k_2 one further assumption is needed. Bearing in mind the derivation of equation (4), one would expect the effect of a bound molecule of A in reducing the substrate accessibility of the zinc ion to be the same for unco-operative as for co-operative paths. Thus $k_{ZnA}/k_{Zn} = k_{2A}/k_2 < 1$. (This simple picture is backed up by the results with pc.) However, we also know the value of $[k_{ZnA} + (k_2/K_L)]$ from the intercept of Figure 6. These equations combine to give a quadratic expression soluble for k_{ZnA} and k_2; one of the two roots gives a value of k_{ZnA}/k_{Zn} greater than unity and is therefore rejected. The parameters extracted from equation (5) are in Table 2.

TABLE 2

Rate constants for the co-operative catalysis, calculated from equations (5) (acetate) and (7) (py). Non-significant figures used in the calculation to avoid rounding errors are not shown

Rate constant	AcO⁻	py
k_o/s^{-1}	0	0.001
$k_B/l\ mol^{-1}\ s^{-1}$	0.026	0.024
k_{Zn} */$l\ mol^{-1}\ s^{-1}$	0.017	0.032
$k_{ZnA}/l\ mol^{-1}\ s^{-1}$	0.0097	0.018
$k_2/l^2\ mol^{-2}\ s^{-1}$	0.33	1.3
$k_{2A}/l^2\ mol^{-2}\ s^{-1}$	0.19	0.72

* These two values should be the same, as terms containing k_{Zn} do not involve A. The discrepancy is brought about by the pH used (see text).

(b) *The Zinc–Pyridine System.*—Application of the same procedure to the zinc–pyridine system gave a poor fit to the data until additional allowance had been made for the presence of $[Zn(py)_2]^{2+}$ in the metal–buffer equilibrium. A value for the binding constant K_{L_2} was taken as approximately one sixth that of K_L, in accordance with most literature values[9b] for various conditions. The modified forms of equations (4) and (5) are (6) and (7), whence (8) is obtained.

$$\Delta k_{obs.} = k_B[B] + k_{Zn}[Zn^{2+}] + k_2[Zn^{2+}][A] + k_{ZnA}[ZnA^{2+}] + k_{2A}[ZnA^{2+}][A] + k_{ZnA_2}[ZnA_2{}^{2+}] + k_{2A_2}[ZnA_2{}^{2+}][A] \quad (6)$$

$$\Delta k_{obs.} = k_B[B]_0 + k_{Zn}[Zn^{2+}]_0 + [ZnA^{2+}][-k_B - k_{Zn} + k_{ZnA} + (k_2/K_L)] + [ZnA_2{}^{2+}]\{-2k_B - k_{Zn} + k_{ZnA_2} + (k_{2A}/K_{L_2}) + k_{2A_2}[A]\} \quad (7)$$

$$(\Delta k_{obs.} - k_B[B]_0 - k_{Zn}[Zn^{2+}]_0)/[ZnA^{2+}] = [(-k_B - k_{Zn} + k_{ZnA} + (k_2/K_L)] + \{k_{2A} + (-2k_B - k_{Zn} + k_{ZnA_2} + k_{2A_2}[A])K_{L_2}\}[A] \quad (8)$$

The parameters were extracted as before (Figure 7), assuming values: $(k_{obs.} - \Delta k_{obs.})$, 0.00106 s^{-1}, extrapolated from the intercepts of Figure 1; k_B, 0.0244 l mol^{-1} s^{-1}, again from the intercepts of Figure 1; and k_{Zn}, 0.0324 l mol^{-1} s^{-1}, from the intercept of Figure 2. The value adopted for K_{L_2} is not critical as the term containing K_{L_2} is small (−0.27) compared with k_{2A} (0.72). It is necessary to assume that the rates due to terms containing k_{ZnA_2} and k_{2A_2} are negligible; this is justified below.

Values of k_{Zn} measured in acetate and in py buffers were unequal, owing to the conditions of pH adjustment (see Experimental section). The discrepancy is 0.014 l mol^{-1} s^{-1}. If the hydroxide-dependent part of k_{Zn} is given by 7×10^5 l^2 mol^{-2} s^{-1} $[OH^-]$,[1] the pH difference of 0.27 units results in an expected discrepancy in rate at *ca.* pH 6 of $(7 \times 10^5) \times 10^{-8} \times 10^{0.27}$ l mol^{-1} s^{-1}, *i.e.* 0.013 l mol^{-1} s^{-1}. The acetate and py values of k_{Zn} are therefore mutually consistent.

In both systems the ratio $k_{ZnA} : k_{Zn}$ (or $k_{2A} : k_2$) is of interest as it represents the ability of a bound base to block the approach of a substrate to the metal ion. Its value in the case of acetate is 0.57 : 1, much as expected if the bidentate acetate simply renders about one third of the metal's solid angle of approach inaccessible to substrates. In the case of py the corresponding value of 0.56 : 1 is less exact as, apart from the crude estimate of K_{L_2}, contributions to the rate of terms containing k_{ZnA_2} and k_{2A_2} were assumed to be *ca.* 0. To check this, one may set an upper limit on them by applying the same steric argument to the second ligand base as to the first so that $k_{Zn} - k_{ZnA} \lesssim k_{ZnA} - k_{ZnA_2}$ and $k_2 - k_{2A} \lesssim k_{2A} - k_{2A_2}$. The upper limits thus calculated are 0.01 l mol^{-1} s^{-1} for k_{ZnA_2} and 0.4 l^2 mol^{-2} s^{-1} for k_{2A_2}. The greatest possible contribution to $k_{obs.}$ of the k_{ZnA_2} term is 0.0003 s^{-1}, which may be neglected, and that from the k_{2A_2} term is 0.002 s^{-1} for the most concentrated buffers, much less for the others; this would not be negligible but would appear as a sharp positive deviation to high [A] in Figure 7. As this was not observed, the actual value of k_{2A_2} must be smaller and terms containing it can be neglected.

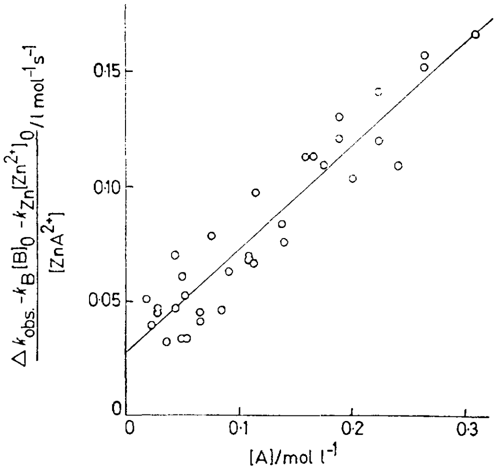

FIGURE 7 Analysis of rate equation in py [see equation (8) and text]

It should be stressed that the analysis in this section does not exclude all other kinetic interpretations; it is simply intended to demonstrate that the observed co-operativity can be explained quantitatively by a simple and plausible picture. The most serious assumption has been to ignore the possible appearance of catalytically active hydrolysed species, *i.e.* to ignore the potentially composite nature of the rate constants. Experimental investigation of this would introduce far too many kinetic parameters, and work to be published deals with the hydroxide dependence of a kinetically much simpler system.

SUMMARY

The principles of the rate laws observed may be summarised as a co-operative effect in the catalysis of

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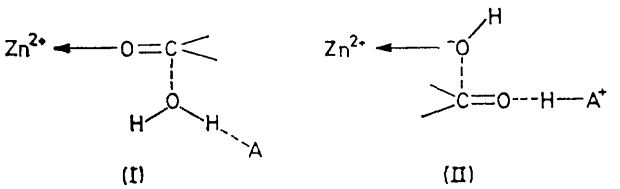
[14] D. W. Archer and C. B. Monk, *J. Chem. Soc.*, 1964, 3117.
[15] R. S. Kolat and J. E. Powell, *Inorg. Chem.*, 1962, **1**, 293.

acetaldehyde hydration between the zinc ion and a free base, together with a blocking (or antico-operative) effect between zinc ion and bound ligand. The closeness of the plots in Figures 1 and 2 to linearity must be regarded as coincidental (contrast *e.g.* Figure 4 of ref. 1).

So far no conclusions have been drawn as to the detailed mechanism of the attack. Since neither zinc nor base forms a long-lived complex with an aldehyde, a termolecular collision must be involved, and the most plausible mechanism for the co-operative path, shown in (I), utilises concerted Lewis-acid and general-base catalysis. This, however, cannot be distinguished kinetically from the mechanism in (II), involving concerted hydroxide-donor and general-acid catalysis. The rate constants are of the right magnitude for either: considering (I), py would be expected to be a better co-catalyst than acetate, as indeed it is. From the Brønsted law, $1 \leqslant k_2(\text{py}) : k_2(\text{acetate}) \leqslant K_b(\text{py}) : K_b(\text{acetate})$, where K_b is the base's protonation constant. In fact the k_2 and K_b ratios are roughly 4 and 10 : 1 respectively, which serves to vindicate the meaningfulness of the rate constants. The rates are, however, equally compatible with mechanism (II), as can easily be shown.



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Termolecular collisions are relatively infrequent, and the rate could therefore in principle be increased by reducing the molecularity. There is preliminary evidence [16] that this is indeed so, and experiments are in progress to investigate this both for weak bases and for hydroxide ion, another base capable of acting co-operatively with zinc ions, which has not been discussed in this paper.

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