Metal-ion Assisted Catalysis of Nucleophilic Attack: Bifunctional Catalysis

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Summary Zinc-ion catalysis of the hydration of acetaldehyde is markedly increased by co-ordination of a ligand bearing a remote general base; this provides positive confirmation of the hypothesis that the hydration, when co-operatively catalysed by zinc and a base, requires independent attack by base and metal ion, *i.e.*, the base must not be co-ordinated to the metal ion.

ZINC ions are known to catalyse the hydration of acetaldehyde.[1] The effectiveness of the zinc ion as a catalyst is increased by bases such as acetate[2] and pyridine,[3] and kinetic analysis indicates that the transition complex for the co-operative reaction contains (in addition to one molecule of acetaldehyde and an unknown number of water molecules) one zinc ion and one free base molecule or ion. The supposition that the active base species is free leads to two predictions: (i) if the carboxylate group and/or pyridine is tightly bound to the zinc ion, no co-operative catalysis should occur, and (ii) if the carboxylate or pyridine group is not co-ordinated but instead held at a fixed, short distance from the zinc ion, intramolecular co-operative catalysis should occur, with a corresponding increase in rate.

Prediction (i) is fulfilled in the case of the chelating picolinate ion (pyridine-2-carboxylate) as previously shown;[3] the oxalate di-anion and bipyridyl ligands are for practical reasons not investigable, but for these the same effect would be expected. To verify (ii) we needed to use a fairly rigid ligand, having a base group which does not co-ordinate to zinc, and which is compatible with the practical requirements of the kinetic experiments. The final choice was the pyridine-2-aldoximate ion, pyox$^-$ (I). The zinc and proton binding constants in this system are already known.[4,5]

TABLE

Catalyst	k_{cat}[a]	Conditions
pyoxH	$<0{\cdot}1$	[b,c]
$(Zn.pyox)^+$	$2{\cdot}7 \pm 0{\cdot}5$	[b,d]
"	$1{\cdot}1 \pm 0{\cdot}2$	[b,e]
"	$1{\cdot}8 \pm 0{\cdot}2$	[b,f]
$(Zn.pyoxMe)^{2+}$ ..	$<0{\cdot}1$	[b,g]
$(Zn(H_2O)_6)^{2+}$	0·018	Ref. 2
$CH_3CO_2^-$	0·031	Ref. 2
$(Zn.picolinate)^4$ ..	0·010	Ref. 3

[a] k_{cat} for a catalyst A is defined as

$$\frac{\delta}{\delta[A]}\left\{\frac{1}{[MeCHO]}\frac{\delta[MeCHO]}{\delta t}\right\}.$$

Units of k_{cat} are $mol^{-1}\ l\ s^{-1}$. [b] Temperature, 0 °C; ionic strength 1·4, adjusted by addition of neutral salt; concentration of acetate buffer, 0·1 mol l^{-1}; maximum total concentration of ligand, 5 mmol l^{-1}. A short light-path was necessitated by the strong absorbance at 300 nm of pyox, and the initial concentration of acetaldehyde was correspondingly high (300 mmol l^{-1}). [c] No zinc present, neutral salt $NaClO_4$, pH 6·0. [d] 0·2 mol l^{-1} $Zn(NO_3)_2$, neutral salt $NaNO_3$, pH 6·0. [e] 0·1 mol l^{-1} $Zn(ClO_4)_2$, neutral salt $NaClO_4$, pH 6·0. [f] 0·1 mol l^{-1} $Zn(ClO_4)_2$, neutral salt $NaClO_4$, pH 6·2. [g] 0·2 moll $^{-1}$ $Zn(NO_3)_2$, neutral salt $NaNO_3$, pH 6·0.

The catalytic activities of species containing pyox are shown in the Table. For comparison, values are also given

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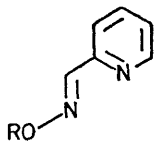
for free zinc ions, the free acetate ion and the zinc–picolinate complex.

In zinc–pyox systems the principal species present at pH 6 are $(Zn.pyox)^+$, $(Zn.pyoxH)^{2+}$ and pyoxH; free $pyox^-$ may be neglected as it has a pK_a *ca.* 10.[4,6] An NaOH titration of pyox in the presence of Zn^{2+} showed that under the conditions of the experiment most, but not all, of the pyox in the system exists as $(Zn.pyox)^+$. The complexity of the equilibria present means that the value of the catalytic constant of the zinc complex cannot be accurately determined (see Table).



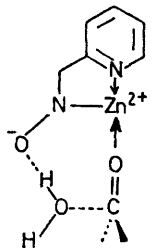
(I); R = negative charge (pyox⁻)
(II); R = H (pyoxH)
(III); R = Me (pyoxMe)

Consistent initial and infinity readings were taken as a sign that the only reaction was the hydration. At higher pyox concentrations a side-reaction set in; kinetic runs in which this occurred were ignored. That the rapid absorbance change observed in the hydration was not in fact due to some reactions of the catalyst was demonstrated by the consistency of the first-order plots in acetaldehyde.

The acceleration of the hydration reaction is not due to the free pyox in solution, as shown by the catalytic constant for pyoxH measured in the absence of zinc ions. A conceivable alternative mechanism for the catalysis is attack at the carbonyl group of acetaldehyde by zinc-bound hydroxide, since the ionisation of zinc-bound water is encouraged by the $pyox^-$ ligand;[4] this hypothesis was tested by blocking the $-O^-$ ion with a methyl group [pyoxMe, (III)]. The zinc–pyoxMe complex was catalytically inactive.

The most plausible mechanism explaining the catalytic activity of the $(Zn.pyox)^+$ complex is shown in the Figure. This invokes general-base-catalysed attack (itself a known feature of acetaldehyde hydration) at a carbonyl group already polarised, and thus activated, by the zinc ion. Kinetically equivalent would be the simultaneous attack of OH^- and H^+ in the complex $(HO.Zn.pyoxH)^+$, but the absence of any co-operative catalysis by general acids and bases in mixed systems (buffers)[2,7] or by the bifunctional picolinic acid zwitterion[3] is against this possibility. Direct nucleophilic attack by the negative oxygen atom is ruled out as the resulting tetrahedral intermediate has no rapid pathway for further reaction.

The mechanism in the Figure differs essentially from the similar phosphate[5] and acetyl group[4] transfer, as in these cases (i) the zinc's role is primarily electrostatic, *viz.*, to attract and bind a negatively-charged substrate, and (ii) the negative oxygen atom acts as a nucleophile, rather than as a general base. The binding constants of zinc to acetaldehyde[2] and to ketones[6] are very low, so positioning of the acetaldehyde cannot here be an important part of the function of the zinc.



FIGURE

The magnitude of the catalysis may be assessed in comparison with the zinc–pyridine co-operative catalysis, as the pyridinium ion and $(Zn.pyoxH)^{2+}$ have similar pK_a values and therefore (if the Brønsted Law approximately holds) comparable catalytic activities. The rate of reaction for the step with the transition complex $[Zn^{2+}.pyridine.MeCHO.(H_2O)_n]$ is 1·3 $mol^{-2}\,l^2\,s^{-1}$ [3] and the effective concentration of base catalyst in $[(Zn.pyox)^+.MeCHO.(H_2O)_n]$ is therefore approximately 2·7/1·3, *ca.* 2 mol l^{-1}. This fairly low value (*cf.* 10—60 for intramolecular carboxylate assistance of ester hydrolysis[8]) may reflect the considerable orientational freedom of the transiently bound acetaldehyde.

The principal conclusion to be drawn is thus that zinc-ion catalysis of the hydration of acetaldehyde is reduced by a bound general base group (*e.g.* picolinate, see Table) and increased by a remote general base—in this instance by a factor of the order of 200.

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