

Metal-catalysed Hydration of 2-Pyridyloxiran

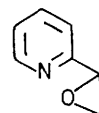
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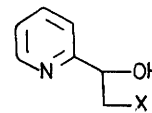
Summary In the presence of Cu^{II} the hydration of 2-pyridyloxiran is accelerated 18,000-fold, and its reaction with Cl^- , Br^- , and MeO^- becomes 100% regiospecific for β -attack.

METAL ions in aqueous solution, particularly Cu^{II} , Ni^{II} , and Zn^{II} , are powerful catalysts for the hydrolysis of co-ordinated esters and amides.¹ We now report that this catalytic ability extends to include epoxide hydration as well and that the reaction of co-ordinated epoxides with nucleophiles can be extremely regiospecific. 2-Pyridyloxiran (**1**) undergoes slow but clean hydration in water and various buffered solutions, the reactions being conveniently monitored by liquid chromatography on a bonded C-18 reverse

phase column. For example, in 0.1M-phosphate buffer at 22°, the half-lives of (**1**) (0.01M) are 158, 285, 250, and 68 h,



(1)



- (2) X = OH
- (3) X = OMe
- (4) X = Cl
- (5) X = Br

at pH 1.9, 5.0, 8.7, and 13.3, respectively. The addition of divalent transition-metal ions (10^{-4}M) greatly increases the

rate of hydration, the magnitude of the catalytic effect decreasing in the order $\text{Cu}^{\text{II}} > \text{Co}^{\text{II}} > \text{Zn}^{\text{II}} \gg \text{Mn}^{\text{II}}$.

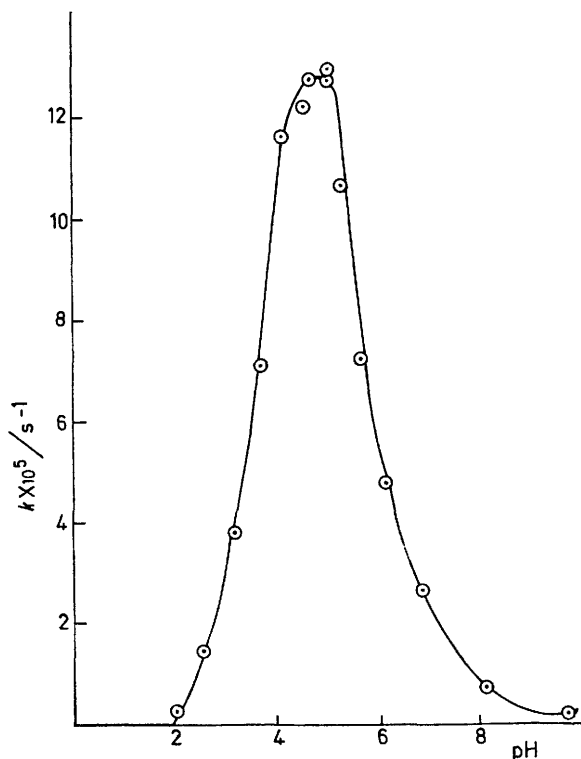


FIGURE. pH Dependence of the rate of copper-catalysed hydration of 2-pyridyloxiran (10^{-2}M) in 0.1M phosphate with 10^{-4}M CuSO_4 at 22° .

The rate of the copper-catalysed hydration is proportional to the copper concentration, and at low pH the reaction obeys pseudo-first-order kinetics. At high pH the rate decreases as the reaction proceeds, probably because the product acts as a tridentate chelating agent and removes the copper in a non-catalytic form. Thus the rate law for the reaction in 0.1M - KH_2PO_4 (pH 5.09) is: $-\text{d}[\text{epoxide}]/\text{d}t = (k_0 + k_m[\text{Cu}^{2+}])[\text{epoxide}]$, where k_0 and k_m , the rate constants for the uncatalysed and catalysed reactions, are $6.75 \times 10^{-7} \text{ s}^{-1}$ and $1.26 \text{ l mol}^{-1} \text{ s}^{-1}$, respectively.

¹ For examples see: D. A. Buckingham, F. R. Keene, and A. M. Sargeson, *J. Amer. Chem. Soc.*, 1974, **96**, 4981; R. P. Houghton and R. R. Puttner, *Chem. Comm.*, 1970, 1270.

² H. Sigel, K. Becker, and D. B. McCormick, *Biochem. Biophys. Acta*, 1967, **148**, 655.

³ A. E. Martell, *Pure Appl. Chem.*, 1968, 129.

The pH-rate profile for the copper-catalysed reaction (Figure) shows a maximum rate occurs at a pH at or near the minimum of the pH-rate profile for the uncatalysed reaction. Thus at pH 5.1 Cu^{2+} causes a rate acceleration of 1.83×10^4 fold. The observed rate decrease as the pH decreases from pH 5.1 is most reasonably attributed to protonation of the pyridine ring preventing copper binding. Correspondingly, the rate profile shows an inflection at pH *ca.* 3.6–3.7, which is approximately the $\text{p}K_a$ of the epoxide as determined by direct titration. This interpretation also agrees with the observed lack of product inhibition at low pH, where the product would be protonated. The hydration rate also decreases as the pH increases from pH 5.1, giving an inflection at pH *ca.* 5.9. This decrease is less easily explained, but may be due to the formation of a catalytically inactive copper species such as the $\text{HPO}_4\text{-Cu}$ complex.² The concentration of monomeric and dimeric hydroxocopper species should be negligible below pH 6.5–7.³

In methanol containing 10^{-4}M Cu^{II} the epoxide (1) (0.01M) reacts rapidly to give exclusively the β -monomethyl ether (3), with no detectable amount of the α -methoxy-isomer. On the other hand in MeOH containing 0.1M NaOMe, the epoxide (1) undergoes both α and β attack in a 1:2 ratio, while in MeOH containing 0.1M toluene-*p*-sulphonic acid the ratio of α to β attack is 85:15. A similar absolute selectivity for β attack was observed in the copper-catalysed formation of the chlorohydrin (4) from (1) in phosphate buffers containing Cl^- . With Tris-HCl buffer and copper, the diol (2) and the chlorohydrin (4) were formed in roughly equal amounts, but the α -chloro-isomer of (4) could not be detected. Parallel results were also obtained using Br as a nucleophile. In this case the bromohydrin (5), an intermediate in the synthesis of the epoxide (1), was the only detectable isomer formed in the presence of copper, although both isomers were formed in aqueous HBr. Thus at least in these three cases, and probably in the case of the hydration as well, the incoming nucleophile attacks exclusively at the β -carbon of the substrate.

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