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Kinetics, Stoichiometry and Mechanism in the Bromination of Aromatic Heterocycles. IV* Aqueous Bromination of Imidazo[1,2-*a*]pyridine

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Abstract

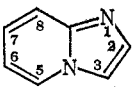
The reaction of imidazo[1,2-*a*]pyridine with bromine has been studied in dilute acidic aqueous solution at 25°C. The bimolecular rate coefficient for attack by Br_2 on the molecular substrate at the 3-position is found to be

$$k_{b1}^{0} = 1{\cdot}30(\pm 0{\cdot}05) \times 10^{9}\ \mathrm{dm^3\ mol^{-1}\ s^{-1}}$$

We find pK_a(imidazo[1,2-*a*]pyridine–H^+, aq., 25°C) = 6·65 and pK_a(3-bromoimidazo[1,2-*a*]pyridine–H^+, aq., 25°C) = 4·95. The latter compound reacts with bromine in aqueous acetate buffer at pH 4.

Introduction

Imidazo[1,2-*a*]pyridine (1) shows selective electrophilic substitution at the 3-position, in reaction with Br_2 (aq.),[1] *N*-bromosuccinimide (CCl_4),[1] *N*-chlorosuccinimide[2] and with HNO_3 (H_2SO_4).[2] The production of 5-bromo-3-methylimidazo[1,2-*a*]pyridine using *N*-bromosuccinimide ($CHCl_3$) at room temperature[2] suggests the 5-position as the second most reactive site.



(1)

Paudler and Blewitt[1] have correlated the preference for substitution at the 3-position with a high frontier electron density. Total π-electron densities did not discriminate clearly between various sites of attack. Such comparisons are more soundly based when the species involved in the pathway to reaction products are established by kinetic methods. We have therefore determined the rate law for the reaction of bromine with (1) in aqueous solution and established the corresponding mechanism.

Experimental

Imidazo[1,2-*a*]pyridine was prepared by the method of Roe.[3] The crude perchlorate was precipitated from ethanol and twice recrystallized to m.p. 242°C (lit.[3] 243°C).

3-Bromoimidazo[1,2-*a*]pyridine was obtained by treating aqueous imidazo[1,2-*a*]pyridinium perchlorate (1·0 g, 5 mmol, in 50 cm^3 of HBr 0·1 mol dm^{-3}, KBr 1 mol dm^{-3}) with bromine (960 mg, 6 mmol in 50 cm^3 of KBr 1 mol dm^{-3}). Excess aqueous NaOH was added before extraction with

* Part III, *Aust. J. Chem.*, 1974, **27**, 2343.

[1] Paudler, W. W., and Blewitt, H. L., *J. Org. Chem.*, 1965, **30**, 4081.
[2] Paolini, J. P., and Robins, R. K., *J. Org. Chem.*, 1965, **30**, 4085.
[3] Roe, A. M., *J. Chem. Soc.*, 1963, 2195.

chloroform. Evaporation of the extract gave white solid, m.p. 95°C from cyclohexane (lit.[2] 93°C) (Found: Br, 40·9. Calc. for $C_7H_5BrN_2$: Br, 40·5%).

Dissociation Constant of Imidazo[1,2-a]pyridinium Cation (aq., 25°C)

A Radiometer PHM 26 pH-meter was used for potentiometric titrations of 25 cm^3 of 0·005 mol dm^{-3} aqueous solutions of imidazo[1,2-*a*]pyridinium perchlorate in water at 25°C, using NaOH (0·025 mol dm^{-3}). 3-Bromoimidazo[1,2-*a*]pyridine (aq., 0·005 mol dm^{-3}) was titrated with HBr (aq., 0·020 mol dm^{-3}). Values of pK_a, averaged over the range 30–70% neutralization, are found to be:

$$pK_a \text{ (imidazo[1,2-}a\text{]pyridinium cation, aq., 25°C)} = 6{\cdot}65$$

$$pK_a \text{ (3-bromoimidazo[1,2-}a\text{]pyridinium cation, aq., 25°C)} = 4{\cdot}95$$

The former has been reported to be 6·79 in aqueous solution at 20°C[4] and 5·06 in 90% EtOH,H_2O.[5]

Kinetics and Stoichiometry of Bromination

The coulo-chrono-potentiometric method described in Part I[6] was used to study the kinetics and stoichiometry of reaction between bromine and imidazo[1,2-*a*]pyridine in the presence of excess H^+ and Br^-.

Results and Discussion

Reactivity profiles obtained for the bromination of imidazo[1,2-*a*]pyridine, in moderately acidic solutions, were refreshingly uncomplicated compared with our recent experience. Reactivity, *in situ*, decreased linearly toward zero at unit stoichiometry (1·00 ± 0·01) in the same manner as found for pyrazole.[6] Product analysis confirmed the selective production of the 3-bromo derivative under these conditions and independent tests showed no perceptible reactivity of this product.

Observed second-order rate coefficients, k_2, were calculated according to the definition

$$-dC(Br_2)/dt \equiv k_1 C(Br_2) \equiv k_2 C(Br_2) C(I)$$

where $C(Br_2)$ and $C(I)$ refer to analytical concentrations of bromine and substrate, respectively.

Values of $k_{2,obs}$ were found to be independent of $C(Br_2)$ and $C(I)$, but decreasing with increases of $[Br^-]$ and $[H^+]$. Assuming that reaction occurs by attack of molecular bromine on unprotonated imidazo[1,2-*a*]pyridine, bimolecular rate coefficients were estimated in 17 runs with various $[H^+]$, $[Br^-]$ and C(HBr), in the range 0·1–0·9 mol dm^{-3}. Deviations from constancy were within the range to be accepted as effects of specific ion concentrations. It is notable that these effects were rather smaller than those found with other azoles. Extrapolation to zero C(HBr) gives the bimolecular rate constant for the reaction

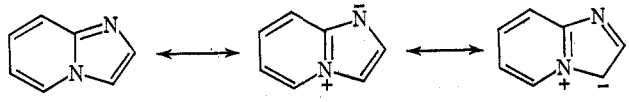
$$\text{imidazo[1,2-}a\text{]pyridine} + Br_2 \rightarrow \text{3-bromoimidazo[1,2-}a\text{]pyridine} \quad \text{(aq., 25°)}$$

as $k_{bi}^{\circ} = 1{\cdot}30 \pm 0{\cdot}05 \times 10^9$ dm^3 mol^{-1} s^{-1}.

The bimolecular rate constant for attack by molecular bromine on the 3-position in imidazo[1,2-*a*]pyridine is about one order of magnitude less than would be expected for reaction occurring at every encounter between pairs of molecules. The 3-carbon

[4] Armarego, W. L. F., *J. Chem. Soc.*, 1964, 4226.
[5] Paudler, W. W., and Blewitt, H. L., *J. Org. Chem.*, 1966, **31**, 1295.
[6] Boulton, B. E., and Coller, B. A. W., *Aust. J. Chem.*, 1971, **24**, 1413.

atom, in this case, is 2000 times more reactive than the analogous 5-position in imidazole, while the 2-position in the 3-bromo derivative is no more reactive than the corresponding position (4-) in imidazole.[7] It may be argued that a degree of aromaticity in the pyridine ring is recovered by release of electron density from the bridgehead nitrogen into the imidazole ring, shown as in the tautomers (2), (3) and (4). The elevated reactivity and selectivity for reaction at the 3-position may then be interpreted in terms of the localization of negative charge at the 3-position.



(2) (3) (4)

Further Reaction at Higher pH

Under the weakly acidic conditions existing in aqueous acetate buffer at *c.* pH 4 the reaction of imidazo[1,2-*a*]pyridine with bromine continued to a stoichiometry of 3. Under the same conditions the 3-bromo derivative was reactive toward bromine. In both cases a yellow-green colour appeared, similar to that of 2-aminopyridine. Further work is necessary to establish whether a second stage of electrophilic substitution is competitive with an oxidative cleavage of the 5-membered ring.

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[7] Boulton, B. E., and Coller, B. A. W., *Aust. J. Chem.*, 1974, **27**, 2343.