Base-catalysed Deprotonation in Pyridine *N*-Oxides and Pyridinium Salts

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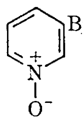
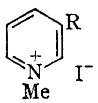
THE acidity of ring protons in heterocyclic aromatic systems has stimulated considerable discussion recently. Proton exchange in five-membered rings has been studied in detail,[1] and an investigation of H–D exchange in some halogenopyridines has been reported.[2] With 3-chloropyridine in strong base deprotonation occurs readily at C-4 but not at C-2.[2] This accounted for the observation[3] that 3,4-, but not 2,3-pyridynes, are produced from 4-unsubstituted 3-halogenopyridines; no explanation was presented for the lack of reactivity of C-2–H, which went contrary to the order of ground state $(\pi + \sigma)$ electron densities[4] and to the calculated relative stabilities of 2,3- and 3,4-pyridynes.[5] Base-catalysed deprotonations of some pyridine *N*-oxides and pyridinium salts are now described. The results shed light on some unexpected orientations observed in a number of nucleophilic substitution and addition reactions[6] undergone by these chemically and biochemically interesting species.

H–D exchange in 3-bromopyridine 1-oxide (I) with $0{\cdot}1$N-NaOD in D_2O was followed by n.m.r.

spectroscopy. The spectrum of (I) in H_2O was as expected:[7] 1H singlet at τ 1·87 (H-2), 1H quartet at τ 2·04 (H-6), 1H quartet at τ 2·65 (H-4), and 1H quartet at τ 2·89 (H-5). At 5°, only C-2–H exchanged readily in the presence of 0·1N-NaOD, whereas at 50°, exchange at C-2 was too rapid to measure but exchanges at C-6 and C-4 could be followed. The *pseudo*-first-order rate constants were obtained (no correction for dilution of D_2O applied): $k^{5^\circ}_{\text{H-2}} = 1\cdot7 \times 10^{-4}$ sec.$^{-1}$; $k^{50^\circ}_{\text{H-6}} = 3\cdot9 \times 10^{-5}$ sec.$^{-1}$; $k^{50^\circ}_{\text{H-4}} = 4\cdot6 \times 10^{-6}$ sec.$^{-1}$ ($k^{50^\circ}_{\text{H-6}}/k^{50^\circ}_{\text{H-4}} = 8\cdot4$). No exchange at C-5 was observed.[8] The retention time of the deuterated product on g.l.c. was the same as that of (I). It is tempting to predict that in a non-protic solvent 2,3-pyridyne 1-oxide would be formed from 3-bromopyridine 1-oxide more readily than would 3,4-pyridyne 1-oxide provided the rate-determining step is the proton abstraction. The order of reactivities observed here (2- > 6- > 4- ≫ 5-) is different from that in 3-chloropyridine (4 ≫ 2,6).[2] A possible explanation for the lack of reactivity of the α-protons in 3-chloropyridine (and hence of the fact that 2,3-pyridynes are not formed from such a compound) is that the transition state for the base-catalysed deprotonation has appreciable carbanion character. This could lead to a kinetically important repulsion of the developing carbanion by the adjacent lone-pair of electrons on nitrogen during proton abstraction from the α-position, which would greatly destabilise this transition state as compared to that for C-4 attack. This situation would not obtain in the *N*-oxides and the order of reactivities is that expected on the basis of the net ($\pi + \sigma$) electron densities at the various nuclear positions. Pyridine *N*-oxide itself did not undergo H–D exchange with 0·2N-NaOD in D_2O at 50°, but did do so at the α-positions at 90°.


(I)


(II: R = Me)
(III: R = CN)
(IV: R = CO_2Me)

3-Methylpyridine methiodide (II) did not exchange with 0·1N-NaOD in D_2O at 5°.* At 26° exchange did take place at C-2 and C-6 but even at 60° and with 20% NaOD solution no exchange occurred at C-4. Rate determinations for the deprotonation of (II)—(IV) were subject to a larger experimental error than those for (I), but the relative rates for pairs of positions within the same molecule were as reliable. In 0·1N-NaOD in D_2O at 26° $k^{26^\circ}_{\text{H-2}} = 9\cdot1 \times 10^{-4}$ sec.$^{-1}$ and $k^{26^\circ}_{\text{H-6}} = 7\cdot45 \times 10^{-4}$ sec.$^{-1}$ ($k^{26^\circ}_{\text{H-2}}/k^{26^\circ}_{\text{H-6}} = 1\cdot2$). 3-Cyanopyridine methiodide (III) underwent exchange at C-2 at 5° in 0·01N-NaOD in D_2O; at 26° exchange at C-2 was too fast to measure but took place at convenient rates at C-6 and C-4. The order of reactivity was 2- ≫ 6- > 4- ≫ 5- ($k^{5^\circ}_{\text{H-2}} = 1\cdot1 \times 10^{-3}$ sec.$^{-1}$; $k^{26^\circ}_{\text{H-6}} = 2\cdot9 \times 10^{-4}$ sec.$^{-1}$; $k^{26^\circ}_{\text{H-4}} = 1\cdot8 \times 10^{-4}$ sec.$^{-1}$). At room temperature and with 0·1N-NaOD *all the ring protons underwent exchange*,† and some hydrolysis of the cyano-group became apparent.[9] No evidence for the formation of a *pseudo*-base was obtained from the n.m.r. spectra of the pyridinium salts. Methyl nicotinate methiodide (IV) does not undergo exchange at 5° with 0·01N-NaOD (pD ≃ 11); at 60°, hydrolysis of the ester group is apparent. At 26°, C-2–H exchanges to the extent of 0·2 atoms % after 15 min. Hydrolysis of the ester group (indicated by the appearance of CH_3OD) occurs slowly, precluding the determination of rate constants.

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* The n.m.r. assignments for the 2- and 6-protons were made on the basis of the spectra of 3-methyl-[2- and 6-^{2}H]-pyridine methiodide. No loss of deuterium was observed when solutions of these compounds in aqueous KOH were kept at 0°. Exchange occurred readily at 26°.

† The n.m.r. spectrum in D_2O, including the lines for C-5–H, disappears. That this is not due to the formation of a free radical species was shown by observing the n.m.r. spectrum in aqueous NaOH under the same conditions.

[1] R. A. Olofson and J. M. Landesberg, *J. Amer. Chem. Soc.*, 1966, **88**, 4263; R. A. Olofson, J. M. Landesberg, K. N. Houk, and J. S. Michelman, *ibid*, p. 4265.

[2] J. A. Zoltewicz and C. L. Smith, *J. Amer. Chem. Soc.*, 1966, **88**, 4766.

[3] H. J. den Hertog and H. C. van der Plas, *Adv. Heterocyclic. Chem.*, 1965, **4**, 121.

[4] W. Adam and A. Grimison, *Tetrahedron*, 1965, **21**, 3417.

[5] H. L. Jones and D. L. Beveridge, *Tetrahedron Letters*, 1964, 1577.

[6] (a) R. A. Abramovitch and J. G. Saha, *Adv. Heterocyclic Chem.*, 1966, **6**, 229. (b) R.E. Lyle and P. S. Anderson, *ibid.*, p. 45.

[7] R. A. Abramovitch and J. B. Davis, *J. Chem. Soc.*, in the press. Only the low-resolution spectra are given here. The high resolution spectra and coupling constants will be discussed in the full paper. Sodium 3-(trimethylsilyl)-propanesulphonate was used as the internal standard. There was a slight shift of the lines to higher field when the base was added to the solution.

[8] A qualitatively similar order of reactivities (2- > 6- > 4- > 5-) has been found for the related exchange in 3-chloropyridine 1-oxide. (J. A. Zoltewicz and G. M. Kauffman, *Tetrahedron Letters*, in the press. We thank Dr. Zoltewicz for communicating this result to us prior to its publication.)

[9] E. M. Kosower and J. W. Patton, *Tetrahedron*, 1966, **22**, 2081.

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