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HYDROGEN-DEUTERIUM EXCHANGE IN SOME HALOPYRIDINE N-OXIDES: RELATIVE POSITIONAL REACTIVITIES

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Base-catayzed hydrogen exchange in carboyclic aromatic systems is understood in great detail (1). Proton exchange in five-membered heterocyclic rings, particularly those forming ylidic intermediates, is of considerable current interest (2). Deprotonation of six-membered heterocyclic ring systems such as pyridines, by contrast, presently is characterized by a paucity of data and a multiplicity of proposed mechanisms (3).

We wish to report conditions to induce base-catalyzed H-D exchange at several positions in 3,5-dichloropyridine N-oxide (I) and in 3-chloropyridine N-oxide (II) and to give relative rates of deprotonation for positions within each of these substrates. This work represents the most extensive study to date of proton exchange in a pyridine N-oxide.

Treatment of I with a 0.1 N solution of NaOD in D_2O at 74° for 1 1/2 hours followed by isolation gave a product (70%) which possessed an n.m.r. spectrum essentially identical with that of I. Pyridine I exhibits an A_2B spectrum with a doublet at 1.53τ and a triplet at 2.21τ in methanol (4) (area ratio is 2:1). That this product indeed contained deuterium followed from a quantitative comparison of integrated areas of a known mixture of product and

$\underline{t}$-C_4H_9OH reference standard in methanol. Exchange occurred at three positions of I; > 97 atom % deuterium was introduced. To differentiate between the reactivity of 2, 6-H and 4-H of I, a solution of 3, 5-dichloropyridine N-oxide-$\underline{d}_3$ (from the previous experiment) in 0. 01 $\underline{N}$ CH_3ONa in CH_3OH at 22° was examined after two hours. The increase in the 2, 6-H/4-H area ratio to 13/1 indicated exchange had occured more rapidly at the 2, 6-positions. The relative order of deprotonation of I is established and is summarized in Fig. I.

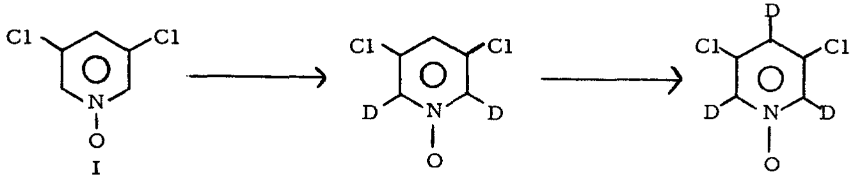
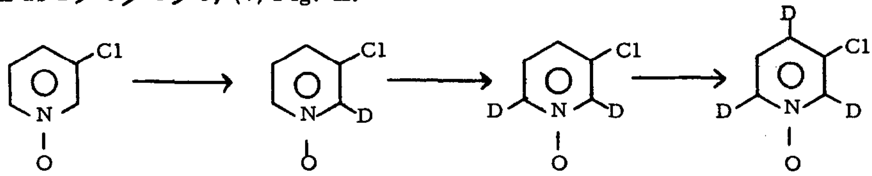


FIG. I

Similar experiments were performed with II and again the site of hydrogen exchange was ascertained by n. m. r. (5). After II was heated in 0. 1 $\underline{N}$ NaOD in D_2O at 74° for two hours there was isolated a product (60%) having a spectrum (aqueous solution) consisting of a pair of AB doublets at 2. 21 and 2. 36τ (J=8. 8 cps; area ratio is 1:1) and very weak signals at lower field. These doublets are characteristic of 4-H and 5-H of II and this substance may be formulated as 3-chloropyridine N-oxide-2, 6-$\underline{d}_2$ (>95 atom % deuterium). A solution of this dideuterated material in 0. 04 $\underline{N}$ CH_3ONa in CH_3OH at 22° was examined periodically over three hours; the signal at lowest field (2-H) increased in intensity as dideuterated II was converted into 3-chloropyridine N-oxide-6-$\underline{d}$. Exchange, therefore, is more rapid at 2-H than at 6-H. In another experiment II was heated in 0. 04 $\underline{N}$ KOD in D_2O containing a known quantity of $\underline{t}$-C_4H_9OD at 74°. Periodic examination of the reaction mixture provided spectra having as essential features a pair of doublets at 2. 21 (4-H) and 2.36τ (5-H) with a singlet superimposed at 2.36τ. This singlet continued to increase in intensity with time. Comparison of these signals to that for *t*-C_4H_9OD standard indicated there was no detectable exchange at 5-H but that deuterium was being introduced at position-4. This series of observations establishes the order of decreasing ease of hydrogen exchange in II as $2 > 6 > 4 > 5$, (7) Fig. II.



II

FIG. II

Approximate relative rates of H-D exchange for pairs of positions within I and within II were obtained by kinetic studies in CH_3OD or D_2O. Substrate in reaction mixtures was analyzed for hydrogen content by n.m.r. and the exchange reaction was found to obey first order kinetics when log (R_o/R) vs time was plotted. In this term R_o is the initial value for the ratio of the area of the signal of the reacting hydrogen to the area of standard; R is this value at some intermediate time. Either a non-reacting center of substrate itself or added *t*-C_4H_9OH served as an internal reference standard. Half-lives were estimated and relative rates were approximated by calculating the inverse of the ratio of the half-lives for exchange at the two positions studied (8). Examination of reaction mixtures for chloride ion indicated little or no dechlorination took place (9).

The data in Table I indicate the deprotonation rate for I at the 2,6-position is about 10-fold greater than at the 4-postion. In II exchange at 2-H is approximately 100-times faster than at 6-H and deprotonation at 6-H is, in turn, about 100-times faster than at 4-H. Although there was no detectable exchange at 5-H, a conservative estimate of the rate spread between the most reactive and least reactive sites of II is a factor of 10^5-10^6. Exchange at equivalent positions, moreover, appears to be faster in I than in II. It may be concluded tenatively that an N-O grouping is more effective than a Cl-atom in activating equivalent positions of an aromatic ring for hydrogen exchange.

TABLE I.
Approximate Relative Rates of H-D Exchange

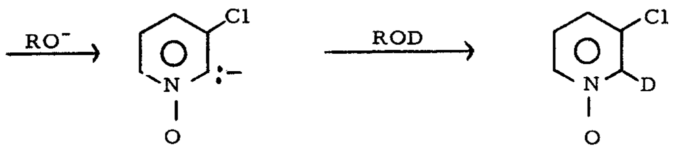
Pyridine N-Oxide	Base/Solvent	Estimated Half-Life	Estimated Rate Ratio
3,5-Dichloro[c] I	0.06 $\underline{N}$ CH_3ONa/CH_3OD[a]	2,6-H, 10 min.	2,6-H/4-H, 10
		4-H, 3 Hrs.	
3-Chloro II	0.06 $\underline{N}$ CH_3ONa/CH_3OD[a]	2-H, 30 Min.	2-H/6-H, 10^2
		6-H, 6 days	
	0.045 $\underline{N}$ $NaOD/D_2O$[b]	6-H, 40 min.	6-H/4-H, 10^2
		4-H, 2 days	

[a] At room temperature. [b] At 74 . [c] Satisfactory elemental analyses were obtained for this compound. m.p. 110-111.5°.

Two possible mechanisms to explain exchange are as follows. In Scheme I base (lyate ion) attacks hydrogen to give a localized anion which then captures deuterium from solvent to form labelled substrate. This sequence is like that

SCHEME I

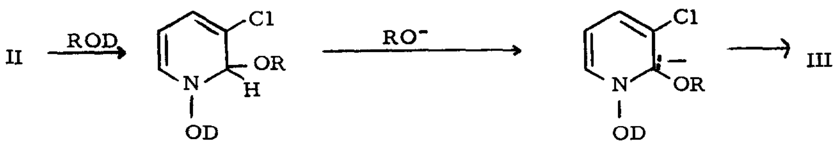
II



III

proposed for exchange in carbocyclic and five-membered heterocyclic systems. In the addition-elimination sequence of Scheme II, solvent adds to substrate prior to deprotonation to form a delocalized anion.

SCHEME II



This second possibility may be characteristic of those substrates which readily add nucleophiles. Studies in progress are designed to distinguish among these and other possibilities.

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4. All n. m. r. spectra were obtained on a Varian A-60A spectrometer. Chemical shifts were measured relative to t-C_4H_9OH (8.78τ) internal standard and are not extrapolated to infinite dilution. Shifts refer to the center of multiplets.

5. The signal order for the ABCD spectrum of II in water is 2-H (1.65τ), 6-H (1.73τ), 4-H (2.21τ) and 5-H (2.36τ). Our assignment of coupling constants in II ($J_{4,5}$ = 8.8 cps; $J_{5,6}$ = 6.0 cps; $J_{4,6}$ = 1.6 cps; $J_{2,4}$ =

$J_{2,6}$ = 1.5 cps) is similar to that in 3-chloropyridine (6) ($J_{4,5}$=8.2 cps; $J_{5,6}$=4.5 cps; $J_{4,6}$=1.7 cps; $J_{2,4}$=2.4 cps; $J_{2,6}$= 0.3 cps; $J_{2,5}$= 0.8 cps).

6. For a thorough analysis of the n.m.r. spectra of 3-substituted pyridines see (a) V.J. Kowaleski and D. G. de Kowaleski, *J. Chem. Phys.*, **36**, 266 (1962); (b) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N.J., 1965, p. 112.

7. The exchange order in N-oxides I and II is distinctly different from that in their respective free bases. In CH_3OD it is 4-H in 3,5-dichloropyridine which exchanges most rapidly and the most reactive site in 3-chloropyridine is position-4. See J. A. Zoltewicz and C. L. Smith, *J. Am. Chem. Soc.*, **88**, 4766 (1966).

8. This kinetic approach does not consider a reverse D-H exchange between reaction products to regenerate the original reactants. Half-lives would change by a few percent with the application of a correction for approach to equilibrium. Little change in the rate ratio would result.

9. Dechlorination prevented observation of exchange at 5-H of II. The rate constant (extrapolated) for methoxydechlorination of II at 74° is 1.66×10^{-5} $M^{-1}Sec^{-1}$. See M. Liveris and J. Miller, *J. Chem. Soc.*, 3486 (1963).

10. Member (1966) of the NSF Summer Research Participation Program for College Teachers.