The nmr spectrum indicated it to be a 1:2 mixture of 2-dimethylamino-2-oxazolinium hydrochloride and the desired product: nmr ($CDCl_3$) −2.95 (s, 6), −3.62 (m, 4), −3.29 (s, 3), −4.08 (m, 1), −4.91 (m, 1). Since the materials are isomeric and both require 1 mol of base to generate 2-dimethylamino-2-oxazoline, the mixture was used without further purification in the next step.

2-Dimethylamino-2-oxazoline.—To 24.15 g (0.16 mol) of N,N-dimethyl-N′-(2-chloroethyl)urea dissolved in 50 ml of methanol was added, all at once, 160 ml of 1.000 *N* potassium methoxide in methanol. An immediate precipitate of potassium chloride was noted and the mixture was heated under reflux with magnetic stirring for 1.5 hr. The precipitated potassium chloride was removed by suction filtration. The methanol was removed from the filtrate at reduced pressure and 50 ml of CH_2Cl_2 was added to precipitate the remaining KCl, which was filtered off (total weight of KCl, 11.90 g; 99.8%). The CH_2Cl_2 solution was dried over $CaSO_4$ for 3 hr and filtered and the CH_2Cl_2 was removed at reduced pressure to give 18.13 g (99.4%) of crude product. Distillation at reduced pressure gave 10.42 g of colorless, mobile liquid, bp 96–98.5° (80 mm). The nmr spectrum contained a sharp singlet at −2.965 (6 H) and an A_2B_2 multiplet at −3.79 (2 H) and −4.315 ppm (2 H), in accord with the proposed structure. The ir spectrum (CCl_4, CS_2) showed 1670 (N=CO) and 936 cm^{-1}, characteristic of the oxazoline ring.

2-Dimethylamino-2-oxazolinium Tetrafluoroborate.—In a nitrogen-filled drybox 1.48 g (0.01 mol) of trimethyloxonium tetrafluoroborate was slurried in 20 ml of dry CH_2Cl_2. To this stirred slurry was added dropwise 1.14 g (0.01 mol) of 2-dimethylamino-2-oxazoline in 10 ml of dry CH_2Cl_2. The reaction mixture was stirred at room temperature for 1 hr. The CH_2Cl_2 solution was concentrated at reduced pressure to a small volume causing the formation of a white precipitate, which was collected by suction filtration to give 1.66 g (77%) of small white crystals: mp 168.5–169.5° dec; nmr (CD_3CN) −3.14 (s, 6), −3.25 (s, 3), −3.93 (m, 2), −4.63 (m, 2); ir (Nujol mull) 1700 (broad, NC^+O) and 1170 cm^{-1} (very broad, BF_4^-).

Registry No.—**4,** 19587-77-0; **5,** 7259-82-7; **6,** 19587-79-2; **8,** 19587-80-5; **9,** 19598-91-5; **10,** 12344-31-9; **17,** 19587-81-6; **18,** 19587-82-7; **19,** 19587-83-8; **23,** 6299-37-2; 1,3-bis(2-bromoethyl)imidazolidine-2,4,5-dione, 19587-84-9; N-acetyl-1,3-bis(2-chloroethyl)urea, 19587-85-0; 2,4-bis(2-chloroethyl)benzo-2,4-diazepine-1,3,5-trione, 19587-86-1; 2-dimethylamino-2-oxazoline, 19587-87-2; 2-dimethylamino-2-oxazolinium tetrafluoroborate, 19598-92-6.

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Base-Catalyzed Hydrogen–Deuterium Exchange in Some Pyridine N-Oxides. Chloro and N-Oxide Rate Factors and Mechanism[1,2]

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Rates of deuterium–hydrogen exchange for deuterated pyridine N-oxide (I) and 3-chloro- (II) and 3,5-dichloropyridine N-oxide (III) in CH_3ONa–CH_3OH were obtained by nmr methods. At 138° relative rates for I-4, I-3,5, and I-2,6 are 1.0, 10, and 1500, respectively. At 50° relative rates for II-4, I-2,6, II-6, III-4, II-2, and III-2,6 are 0.37, 1.0, 12.2, 1370, 1840, and 11800. Log rate factors (relative to benzene) at 50° for Cl and N-oxide groups are *o*-Cl = 3.27 ± 0.24; *p*-Cl = 0.95 ± 0.14; *o*-NO = 9.58, and *p*-NO = 5.88. The N-oxide group is one of the most strongly activating groups for carbanion formation yet reported; its effect appears to be largely inductive. Exchange proceeds by direct deprotonation to give carbanions.

Base-catalyzed hydrogen exchange reactions in aromatic carbocyclic systems have been studied in considerable detail[4] and continue to draw interest as the fine points of the reaction mechanism become clearer.[5,6] Considerable attention has recently been directed to exchange in heteroaromatic ring systems, particularly five-membered-ring systems forming ylidic intermediates.[7] Information relating to exchange at annular positions in the six-membered heterocycles is more sparse.[2,8,9]

An intriguing problem is posed by the mechanism of base-catalyzed hydrogen–deuterium exchange on six-membered heteroaromatic substrates since they readily add nucleophiles.[10] For such compounds hydrogen exchange could take place on the adduct which results from the addition of base to the ring (addition–deprotonation pathway) or it could result from attack of base directly on a ring hydrogen.

This paper is one of several reporting a systematic study of hydrogen–deuterium exchange in heteroaromatic systems. This study is an attempt to elucidate the effects of heteroatoms on the position and rate of exchange and on the mechanism. We report a kinetic study of sodium methoxide catalyzed H–D exchange of deuterated forms of pyridine N-oxide (I) and of 3-chloro-(II) and 3,5-dichloropyridine N-oxide (III) in methanol. Chlorine substituents were chosen since they activate aromatic rings for hydrogen exchange. Moreover, methoxide ion catalyzed hydrogen exchange

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[1] This work was presented in part at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967.

[2] A preliminary account of this work has appeared: J. A. Zoltewicz and G. M. Kauffman, *Tetrahedron Lett.*, 337 (1967).

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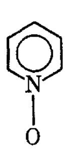

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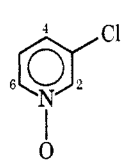
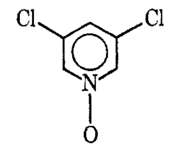


II



III

data are available for 1,3-dichlorobenzene-2-*d* (IV) in methanol;[11] this compound provides a convenient reference substrate for comparisons between the benzene and pyridine N-oxide ring systems.

Experimental Section

Pyridine-d_5 N-Oxide.—Pyridine N-oxide (15.4 g, 0.19 mol) was dissolved in 27 g (1.35 mol) of deuterium oxide and 3 g of sodium deuteroxide. The solution was heated in a Monel bomb at 180–210° for 3 hr. After extraction the product was dried by azeotropic distillation in benzene and crystallized from that solvent. The product is very hygroscopic and material used in the kinetic study was doubly sublimed and dried under vacuum over phosphorus pentoxide. The white crystals melted at 65–67° (lit.[12] mp 66–68°). Mass spectral analysis indicated an over-all deuterium content of 76%. The nmr spectrum of the product showed an area ratio of the 3,5 and 4 protons to the 2,6 protons of 1.59 (1.50 for equilibrium distribution).

3,5-Dichloropyridine N-Oxide.—A mixture of 13.2 g of 3,5-dichloropyridine and 13 ml of 40% peroxyacetic acid was allowed to stand at room temperature for 3 days. The solution then was heated at 70–80° for 3 hr with 10 ml of 30% hydrogen peroxide. Volatile materials were removed under reduced pressure and the solid residue was dissolved in 50 ml of chloroform. After drying overnight (K_2CO_3) and treatment with charcoal, the chloroform was removed to give 12.5 g (84.5% yield) of the white crystalline N-oxide, mp 109–111.5°. The analytical sample, mp 110–111.5°, was prepared by recrystallization from ether.

Anal. Calcd for $C_5H_3Cl_2NO$: C, 36.59; H, 1.83; N, 8.54. Found: C, 36.80; H, 1.91; N, 8.75.

3,5-Dichloropyridine-d_3 N-Oxide.—Deuteration of 3,5-dichloropyridine N-oxide was accomplished according to reported conditions.[2] The product contained 97% D at each position as indicated by mass spectrometry and by nmr analysis employing *t*-butyl alcohol standard. By combustion analysis the value is 95 ± 2% deuterium. Exchange rates at positions 2,6 and 4 were obtained using this substrate.

3-Chloropyridine-4-*d* N-Oxide.—3-Chloropyridine-4-*d*[9a] was oxidized with peroxyacetic acid according to the method in the literature.[13] Analysis of the N-oxide by nmr employing *t*-butyl alcohol as an internal reference standard indicated >95% deuteration. This substrate was employed to determine exchange rates at the 4 position of II.

3-Chloropyridine-2,6-d_2 N-oxide was prepared by deuteration of 3-chloropyridine N-oxide.[2] Analysis by nmr indicated 94% 2-D and 81% 6-D. Mass spectrometry indicated an average of 88% D for the two positions. This substrate was used in the determination of exchange rates at the 2 and 6 positions of II.

Rate Expression.—The exchange reaction may be symbolized

$$\mathrm{ArD}_n + n\mathrm{ROH} \underset{k_{-2}(\mathrm{RO}^-)}{\overset{k_2(\mathrm{RO}^-)}{\rightleftarrows}} \mathrm{ArH}_n + n\mathrm{ROD}$$

where *n* is the number (1 or 2) of chemically equivalent exchanging positions. Experimentally, because the concentration of RO^- catalyst remains constant, the rate is pseudo first order within a given run. Since there is no important equilibrium isotope effect, it may be assumed that $k_2 = k_{-2}$, $a = (\text{substrate})_0$, $b = (\mathrm{ROH})_0$, x = mole fraction of D in substrate, $(\mathrm{ROD}) = (x_0 - x)an$, $(\mathrm{ROH}) = b - (x_0 - x)an$. The rate of disappearance of deuterated substrate is

$$-\frac{\mathrm{d}x}{\mathrm{d}t} = \frac{k_2(\mathrm{RO}^-)}{b}\{x[b - (x_0 - x)an] - (1 - x)(x_0 - x)an\} \quad (1)$$

At equilibrium, $x_e = anx_0/(an + b)$. Substituting and integrating gives

$$k_{\mathrm{exp}}t = k_2(\mathrm{RO}^-)t\left(\frac{an + b}{b}\right) = 2.303 \log\left(\frac{x_0 - x_e}{x - x_e}\right) \quad (2)$$

where

$$k_2 = \frac{k_{\mathrm{exp}}}{(\mathrm{RO}^-)}\left(\frac{b}{an + b}\right) \quad (3)$$

In our studies the fraction $b/(an + b)$ generally exceeded 0.9, even in cases where several centers in substrate were involved in exchange. Consequently this fraction was assumed to equal one.

In using nmr spectra to follow exchange, the ratio of the area of the nmr signal of the proton of interest, A, to the area of reference standard proton, A_{std}, was determined. The actual

$$k_{\mathrm{exp}}t = 2.303 \log \frac{(A/A_{\mathrm{std}})_e - (A/A_{\mathrm{std}})_0}{(A/A_{\mathrm{std}})_e - (A/A_{\mathrm{std}})} \quad (4)$$

equation employed to obtain rate constants was eq 4. Note that the nmr ratios are directly proportional to the mole fraction of hydrogen at each reactive position. Hence, rate constants for substrates having two chemically equivalent positions, the 2,6 positions of I, for example, represent values for exchange at just a single position.

Reagents.—*t*-Butyl alcohol was distilled from potassium *t*-butoxide and stored under dry nitrogen. Methanol was dried by distillation from magnesium methoxide. Sodium methoxide stock solutions were prepared by dissolving freshly cut sodium in dry methanol in a dry nitrogen atmosphere. The solutions were standardized by adding an aliquot to excess standard hydrochloric acid and titrating potentiometrically with standard sodium hydroxide. Stock solutions of deuterated pyridine N-oxides were prepared by weighing a sample of the N-oxide and an equivalent amount of a proton reference compound, *t*-butyl alcohol or *p*-xylene, into a volumetric flask and filling to the mark with dry methanol. All transfers of the N-oxide were done in a dry nitrogen atmosphere. The solutions were protected from the air by serum stoppers and all transfers were made by syringe.

Kinetic Procedure. Pyridine-d_5 N-Oxide.—The reaction solution for a typical run was prepared by syringing aliquots of sodium methoxide and the N-oxide stock solution containing the reference compound into a 1-ml volumetric flask and filling with dry methanol. N-Oxide concentration was generally 0.5–0.8 *M* after mixing. One aliquot of this solution was placed in a nitrogen-filled nmr tube which was then sealed. Another aliquot of the reaction solution was titrated. The reaction was initiated by immersing the nmr tube in a constant-temperature bath and the nmr spectrum of the quenched mixture was obtained on a Varian A-60A spectrometer and integrated. At the conclusion of exchange at the 2,6 positions the nmr tube was placed in a higher temperature bath and exchange at the 3,5 and 4 positions followed.

The ratio of the areas of the nmr peaks of the reacting site and of the reference compound provides a measure of the extent of reaction. The ratios used were based on the average of five or more integration sweeps, caution being taken to avoid saturation effects. The butyl protons of *t*-butyl alcohol or the ring protons of *p*-xylene were used as references for exchange at the 2,6 position. The 2,6-H signal was used as the reference signal for exchange at the 3,5 and 4 positions.

Kinetic plots were constructed by plotting the log term in eq 4 against time. Pseudo-first-order rate constants, k_{exp}, were obtained from the slope of the best visual line through the points. This procedure is preferred to use of a least-squares treatment since scatter in the data is not completely random. The more or less constant integration error in the areas of the peaks becomes a large relative error late in the reaction. Good straight lines were generally obtained through two to three half-lives with some scatter toward the end of the reaction. The base concentrations shown are corrected for solution expansion by multiplying concentrations at room temperature by the ratio of the density of methanol[14] at the reaction temperature to that at room temperature. Results are given in Table I. The base concentration in runs 1–3, Table I, is varied by a factor of 10 and the rate constants show some variation as the concentration increases. It is not clear whether this is due to experimental error or whether this may be due to a salt effect.

We find no evidence for an equilibrium isotope effect. The

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TABLE I

RATES OF DEDEUTERATION OF PYRIDINE-d_5 N-OXIDE IN METHANOLIC SODIUM METHOXIDE

Run no.	Position of exchange	Temp,[a] °C	(CH_3ONa)[b]	10^4k_{exp}, sec^{-1}	10^4k_2, M^{-1} sec^{-1}
1	2,6	75	0.46	4.33 ± 0.05	(9.50 ± 0.21)
2	2,6	75	0.046	0.195 ± 0.010	4.23 ± 0.25
3	2,6	75	0.094	0.500 ± 0.023	5.32 ± 0.27
4	2,6	100	0.045	3.77 ± 0.13	38.9 ± 5.0
5	2,6	100	0.045	3.57 ± 0.08	79.5 ± 5.3
6	2,6	117.2	0.021	6.48 ± 0.37	306 ± 24
7	2,6	117.2	0.021	6.48 ± 0.27	306 ± 21
8[c]	2,6	117.2	0.021	5.93 ± 0.25	280 ± 20
9[d]	2,6	117.2	0.021	5.57 ± 0.22	263 ± 18
10	3,5	110.5	0.43	0.432 ± 0.012	1.00 ± 0.05
11[e]	3,5	110.7	0.41	0.452 ± 0.007	1.11 ± 0.06
12	3,5	138	0.085	1.20 ± 0.02	14.2 ± 0.7
13	3,5	138	0.041	0.473 ± 0.013	11.5 ± 0.6
14	4	110.5	0.43	0.0400 ± 0.0017	0.095 ± 0.006
15[e]	4	110.7	0.41	0.0540 ± 0.0012	0.133 ± 0.008
16	4	138	0.085	0.120 ± 0.003	1.42 ± 0.07
17	4	138	0.041	0.0470 ± 0.0037	1.14 ± 0.11

[a] ±0.2°. [b] Corrected for solution expansion. [c] Contains added water: $(H_2O)/(\text{N-oxide}) = 0.6$. [d] Contains added water: $(H_2O)/\text{N-oxide} = 1.2$. [e] Acid quench method.

equlibrium distribution of deuterium in these reactions is, within experimental error, about ±5%, equal to the mole fraction of deuterium in the system. That this is also true in D_2O is indicated by the preparative deuteration of pyridine N-oxide.

In basic methanol solution the nmr signals of the 3,5 and 4 protons overlap but the exchange rates of the 3,5 and 4 protons differ by about a factor of 10 and it is possible to separate the rates of the two positions by a consideration of the exchange in the combined peak area. Kinetically the situation can be treated as parallel reactions producing a common product.[15]

A typical plot of one of the runs (run 12–16, Table I) is shown in Figure 1. The curved pseudo-first-order plot of the combined signal, $\log\ [(A_{3,5+4}/A_{std})_e - (A_{3,5+4}/A_{std})]$, becomes linear after the more acidic 3,5 position has essentially completely reacted. The line for the slower 4 position can be drawn from the linear portion of the curve. This line is a plot of $\log\ [(A_4/A_{std})_e - (A_4/A_{std})]$. Values of $(A_4/A_{std})_e - (A_4/A_{std})$ were then calculated for the first part of the reaction and were subtracted from the measured values of the composite function to give values of $(A_{3,5}/A_{std})_e - (A_{3,5}/A_{std})$. Logarithms of these values were then plotted to give the curve for 3,5 exchange shown in Figure 2.

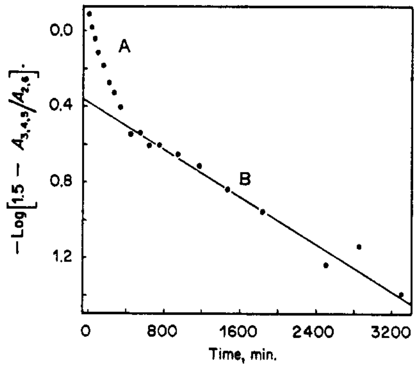

Figure 1—Typical kinetic run (run 12–16 in Table I) for hydrogen exchange at the 3,5 and 4 positions of pyridine-3,4,5-d_3 N-oxide with CH_3ONa in CH_3OH. Region A refers to dedeuteration at positions 3,5 and 4 while region B corresponds to dedeuteratation at position 4.

The reference area used for these positions was the signal area of the 2,6 protons. This position is in isotopic equilibrium with the solvent under the conditions for exchange of the 3,5 and 4 positions. As a result, the area of the 2,6 protons is not precisely constant but decreases slightly due to back deuteration. The small change in the area of the 2,6-H signal, however, has only a small effect on the slope of the line, at most, 2 or 3% and no attempt was made to correct for this small error.

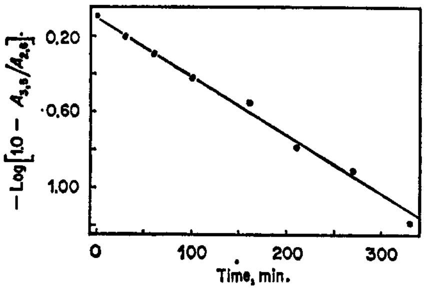

Figure 2.—A plot of dedeuteration at positions 3,5 of pyridine-3,4,5-d_3 N-oxide after correcting for exchange at position 4. Data are taken from region A in the kinetic plot in Figure 1.

As a check on this analysis of the kinetics of 3,5 and 4 exchange, a run (run 11–15, Table I) was made in which the two positions could be analyzed separately. Aliquots of the reaction solution were sealed in glass tubes and heated at the reaction temperature. Periodically, a tube was removed and quenched by cooling and the contents were acidified with perchloric acid. In acid solution the 3,5-H and 4-H signals in the nmr are resolved, so the areas of the peaks may be determined separately. (In acid solution the 4-H signal is at lower field than the 3,5-H signal.[16]) Acidification thus allowed separate determination of the rates at the two positions. Rate constants determined in this manner were in good agreement for the 3,5-H reaction and somewhat poorer agreement for the 4-H position.

Kinetic Procedure. Chloropyridine N-Oxides.—Kinetic runs were conducted using an nmr spectrometer equipped with a Varian V-6057 variable-temperature accessory. In most of the runs the probe itself was used as a constant-temperature device. The temperature scale of the probe was calibrated in the usual manner using the chemical shift of ethylene glycol as a function of temperature.[17]

In a typical run a dry nmr tube was filled with nitrogen and immersed in a Dry Ice–acetone bath. An aliquot of the N-oxide solution was syringed into the tube followed by an aliquot of sodium methoxide solution. N-Oxide concentration was 0.3–0.8 *M* after mixing. Just prior to insertion of the sealed tube into the probe the tube was warmed and the reactants were mixed. The tube was allowed to equilibrate 7–10 min in the probe after which the spectrum was obtained and integrated. Areas of the nmr signals employed in construction of the rate plots represent the average of several integration sweeps through the peaks. The time at the midpoint of the scanning interval was recorded

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(16) R. A. Abramovitch and J. B. Davis, *J. Chem. Soc., B*, 1137 (1966).

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Table II

Rates of Dedeuteration of 3-Chloropyridine-d_x N-Oxide in Methanolic Sodium Methoxide

Run no.	Position of exchange	Temp, °C	$(CH_3ONa)^a$	10^4k_{exp}, sec^{-1}	10^5k_2, M^{-1} sec^{-1}
1	2	22	0.0427	1.33 ± 0.01	3.11 ± 0.15
2	2	22	0.111	3.48 ± 0.03	3.13 ± 0.16
3	2	22	0.111	4.22 ± 0.05	3.80 ± 0.20
4	2	35	0.0619	8.67 ± 0.11	14.0 ± 0.7
5	2	35	0.0810	12.7 ± 0.2	14.1 ± 0.7
6[b]	2	52.8	0.00959	4.38 ± 0.13	45.7 ± 2.7
7[b]	2	52.8	0.00959	5.45 ± 0.16	56.8 ± 3.3
8[c]	4	60	0.595	0.202 ± 0.018	0.0338 ± 0.0035
9[c]	4	60	0.441	0.135 ± 0.006	0.0307 ± 0.0021
10	4	70	0.839	0.697 ± 0.020	0.0830 ± 0.0048
11	4	70	0.839	0.705 ± 0.037	0.0840 ± 0.0060
12	4	80	0.620	1.92 ± 0.08	0.310 ± 0.020
13	4	80	0.620	1.83 ± 0.12	0.295 ± 0.024
14[c]	6	50	0.0747	0.183 ± 0.005	0.245 ± 0.014
15[c]	6	50	0.194	0.587 ± 0.042	0.302 ± 0.026
16	6	60	0.106	0.982 ± 0.029	0.927 ± 0.054
17	6	60	0.106	1.13 ± 0.04	1.06 ± 0.07
18	6	75	0.0598	2.35 ± 0.03	3.92 ± 0.20
19	6	75	0.0782	2.93 ± 0.10	3.75 ± 0.23

[a] Corrected for solution expansion. [b] Acid quench method. [c] External bath, thermal quench method.

as the time of reaction. Equilibrium values for the area ratios are experimental values except for those involving the 4 position of II. In these runs, since it was not practical to determine them experimentally, they were calculated assuming the absence of an equilibrium isotope effect. Runs in which equilibrium was attained showed, within experimental error (±5%), a statistical distribution of isotope between solvent and substrate.

After completing the reaction of the 2 position of II or the 2,6 position of III the same reaction solutions were used to study the 6 position of II and the 4 position of III, respectively. The 4,5-H signal of II was used as the reference standard for runs involving exchange at the 2 and 6 positions of this same molecule. For runs involving the 4 position of II, the combined areas of the 2 and 6 positions served as the standard. In the case of III added *t*-butyl alcohol served as the standard for exchange at all positions.

Pseudo-first-order rate constants were determined from the best visual line drawn through the data plotted according to eq 4. The data gave good straight lines for two to three half-lives in most cases. A typical plot is given in Figure 3. An exception was exchange of the 4 position in II where methoxydechlorination was a competing reaction. Rate constants for exchange at this position are based on only the first half-life of the reaction. The reactions are first order in base as can be seen from runs 1–5 of Table II and runs 3, 5, and 6 of Table III. Rate constants were generally repeatable within about 10%. Temperatures in the nmr probe are resettable to ±2° and are constant only to ±1° under typical conditions.[17] This, no doubt, is responsible for much of the scatter in the rate constants and the uncertainties in the activation parameters.

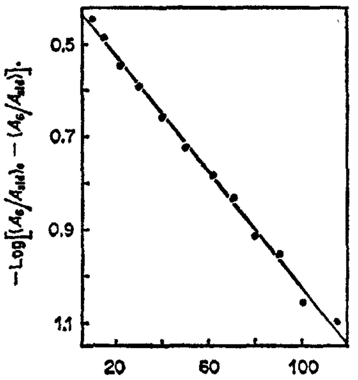

Figure 3.—A typical kinetic run (run 18 in Table II) for the dedeuteration of 3-chloropyridine-6-*d* N-oxide with CH_3ONa in CH_3OH. The variable-temperature nmr probe was employed to maintain a controlled temperature.

Several runs were made in an external bath using either the thermal or acid quench techniques described for I. These are so indicated in the tables.

Errors.—The estimated errors in the rate constants were determined by standard methods.[18] Errors in k_{exp} estimated from the standard deviations of the nmr measurements were 2–3%. These are shown in Table I for exchange at the 2,6 position of I. Uncertainties estimated from the point scatter in the kinetic plots were in the range 2–5%. Since these are of the same order of magnitude the latter estimate is shown in the tables for all other runs.

Titration of the reaction mixtures after reaction sometimes showed base concentrations to be low by several per cent. The titrations are in themselves uncertain, however, owing to the small volumes of solution available and the low concentration of base. Only a single titration for each run was possible. There seemed to be no systematic loss of base. Some uncertainty in this quantity must also result from the approximate correction applied to the concentration for the expansion of the solution at the reaction temperatures. We estimate the over-all uncertainty in the base concentrations reported may be as much as 5%. Thus the second-order rate constants are probably uncertain in the range of 5–10%. Repeatability of the rate constants was generally within 10%.

Results

The N-oxide group strongly activates the aromatic ring hydrogen atoms for hydrogen–deuterium exchange. The reactivity order for dedeuteration in pyridine N-oxide is 2,6 ≫ 3,5 > 4; kinetic data are given in Table I. The 2,6 positions exchange readily at temperatures as low as 75°, while convenient dedeuteration rates for the 3,5 and 4 positions require temperatures well above 100°.

Evidence for the order in which the hydrogen or deuterium atoms at the several positions of II and III undergo exchange has been presented.[2] The order of decreasing ease of exchange is 2 > 6 > 4 > 5. Exchange at position 5 was not observed owing to the incursion of methoxydechlorination at higher reaction temperatures. The same reactivity order has been reported for exchange in 3-bromopyridine N-oxide in

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[18] W. N. Bond, "Probability and Random Errors," E. Arnold and Co., London, 1935, p 91.

TABLE III

RATES OF DEDEUTERATION OF 3,5-DICHLOROPYRIDINE-d_3 N-OXIDE IN METHANOLIC SODIUM METHOXIDE

Run no.	Position of exchange	Temp, °C	$(CH_3ONa)^a$	10^4k_{exp}, sec^{-1}	10^3k_2, M^{-1} sec^{-1}
1	2,6	0	0.114	2.80 ± 0.13	2.45 ± 0.17
2	2,6	0	0.114	3.13 ± 0.03	2.75 ± 0.14
3	2,6	10	0.0221	1.52 ± 0.04	6.87 ± 0.39
4	2,6	10	0.113	5.12 ± 0.13	(4.52 ± 0.25)
5	2,6	10	0.0433	2.82 ± 0.07	6.50 ± 0.36
6	2,6	10	0.0637	4.30 ± 0.38	6.74 ± 0.68
7	2,6	22	0.0110	2.87 ± 0.08	26.0 ± 1.5
8[b]	2,6	30	0.0099	4.95 ± 0.22	50.0 ± 3.4
9[b]	2,6	30	0.0099	5.27 ± 0.17	53.1 ± 3.2
10	4	22	0.111	1.98 ± 0.07	1.79 ± 0.11
11	4	22	0.111	2.45 ± 0.12	2.21 ± 0.15
12	4	35	0.0421	3.60 ± 0.10	8.56 ± 0.50
13	4	35	0.0619	4.37 ± 0.15	7.05 ± 0.48
14	4	50	0.0106	3.48 ± 0.15	32.9 ± 0.22

[a] Corrected for solution expansion. [b] Acid quench method.

TABLE IV

RELATIVE RATES AND ACTIVATION PARAMETERS FOR DEUTERIUM–HYDROGEN EXCHANGE OF SOME PYRIDINE N-OXIDES IN METHANOLIC SODIUM METHOXIDE AT 50° [a]

Compd	Position of exchange	Relative rate	ΔH,* kcal/mol	ΔS*, eu
I	2,6	1.0	26.4 ± 1.1	+1.7 ± 2.6
I	3,5	(0.0067)[b]	(27.1 ± 1.3)[b]	(−6.7 ± 3.2)[b,c]
I	4	(0.00067)[b]	(26.1 ± 1.7)[b]	(−13.9 ± 4.5)[b,c]
II	2	1840	16.4 ± 1.4	−14.4 ± 2.8
II	4	0.37	25.5 ± 2.6	−2.9 ± 3.5
II	6	12.2	22.9 ± 2.0	−4.1 ± 3.1
III	2,6	11800	16.0 ± 0.7	−11.7 ± 1.3
III	4	1370	18.4 ± 1.8	−8.8 ± 2.4

[a] Parameters were determined by a least-squares treatment in which individual second-order rate constant were given equal weight. Rate constants in parentheses in Tables I and III were not included. H. D. Young, "Statistical Treatment of Experimental Data," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 115–123. [b] Approximate value, based upon only two temperatures. [c] At 110°.

$NaOD-D_2O$.[19] The order of exchange for III is 2,6 > 4.[20] The rate data for these compounds are presented in Tables II and III.

Rate constants for exchange at position 4 of II are approximate values because methoxydechlorination of II occurs under conditions required for exchange. Nucleophilic substitution of chloride by methoxide ion in II has been studied.[13] At 50° it is estimated that exchange occurs *ca.* seven to eight times faster than substitution (both rates extrapolated). The presence of chloride ion was easily detected in the reaction mixture by precipitation with silver ion. Titration of reaction mixtures indicated that about 9–12% loss of base and substrate had occurred at the end of one half-life of the exchange reaction. Exchange rate plots were linear over one half-life but showed curvature over longer periods. The reported pseudo-first-order rate constants are based on the initial, linear portion of the curve. The second-order rate constants were calculated using the initial base concentrations.

Substitution was not a serious side reaction for exchange at the 2 or 6 positions of II because of the generally lower temperatures and/or base concentrations. Only traces of chloride ion were detectable after exchange of III.

The effect of water on the exchange rates for pyridine-d_5 N-oxide was determined. Addition of 0.6 and 1.2 mol of water/mol of N-oxide (runs 8 and 9, Table I) reduced the reaction rate only slightly. The presence of trace amounts of water in other runs probably has no significant effect on the rate constants.

Rate constants were extrapolated to 50° using the Arrhenius equation. Relative rates using the exchange rate for the 2,6 positions of I as a standard as well as activation parameters are given in Table IV. It is evident that both ΔH^* and ΔS^* influence relative positional reactivities.

Rate Factors.—A quantitative measure of the ability of a Cl atom or an N–O group to activate the aromatic nucleus for base-catalyzed hydrogen exchange is obtained from a comparison of second-order rate constants according to the partial rate factor method. The following treatment assumes that the effect of Cl and N–O substituents on the energy of activation for hydrogen exchange are additive.[21] Using logarithmic symbolism the values in Table V may be written. *ortho* and *para* rate factors are symbolized by o_f and p_f, respectively; k_0 is the second-order rate constant for dedeuteration of benzene, the reference substrate. Included in this set is the rate constant (extrapolated) for methoxide ion catalyzed exchange of 1,3-dichlorobenzene-2-d[11] (IV). Inclusion of this value allows an estimate of the rate factor for the N–O group

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[19] R. A. Abramovitch, G. M. Singer, and A. R. Vinutha, *Chem. Commun.*, 55 (1967).

[20] Although the order of decreasing ease of exchange in both II and III corresponds to decreasing chemical shift in the nmr spectra, relative chemical shifts are not good criteria for the relative rates of deprotonation. Thus for 3-chloropyridine the order of the chemical shift (increasing field) is 2-H, 6-H, 4-H, and 5-H, but it is 4-H which undergoes the most rapid base-catalyzed exchange.[9a]

[21] Pyridine N-oxide is considered to be a derivative of benzene in which an annular C–H is replaced by an annular N–O. The position of an N-oxide group relative to a C–D reaction center is indicated by *ortho*, *meta*, or *para* nomenclature.

TABLE V

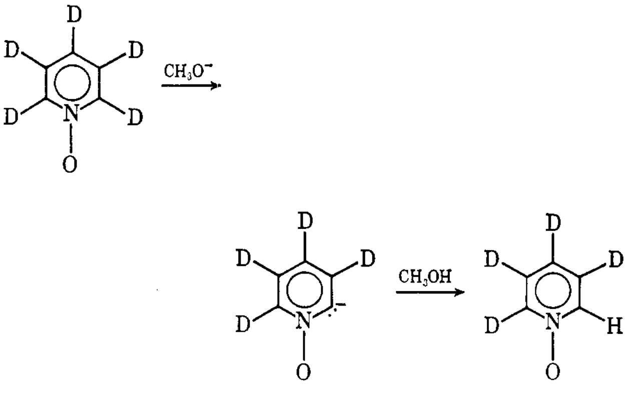
	Log k_2 (50° extrapolated)
$\log k_{2(\text{I-2,6})} = \log k_0 + o_f^{\text{NO}}$	−4.625
$\log k_{2(\text{II-2})} = \log k_0 + o_f^{\text{NO}} + o_f^{\text{Cl}}$	−1.355
$\log k_{2(\text{II-6})} = \log k_0 + o_f^{\text{NO}} + p_f^{\text{Cl}}$	−3.534
$\log k_{2(\text{II-4})} = \log k_0 + p_f^{\text{NO}} + o_f^{\text{Cl}}$	−5.052
$\log k_{2(\text{III-2,6})} = \log k_0 + o_f^{\text{NO}} + o_f^{\text{Cl}} + p^{\text{Cl}}$	−0.550
$\log k_{2(\text{III-4})} = \log k_0 + p_f^{\text{NO}} + 2o_f^{\text{Cl}}$	−1.483
$\log k_{2(\text{IV-2})} = \log k_0 + 2o_f^{\text{Cl}}$	−7.360

to be made. From these equations three independent values of the o_f^{Cl} [22] and two values of the p_f^{Cl} [23] may be obtained. The average log chloro factors with their standard deviations are $o_f^{\text{Cl}} = 3.27 \pm 0.24$; $p_f^{\text{Cl}} = 0.95 \pm 0.14$. The logarithmic value of the *para* N–O factor,[24] p_f^{NO}, is 5.88 and the *ortho* factor,[25] o_f^{NO}, is 9.58. The uncertainty in the N–O factors is almost certainly larger than that of the Cl factors, owing to the extensive extrapolations. The log k_0 value of −14.2 is in approximate agreement with an earlier derived value of −16.8 (40°).[6]

Discussion

Mechanism.—Several types of deprotonation mechanisms need to be considered to account for hydrogen exchange in pyridine N-oxides. The first type has been found to be the effective mechanism in the vast majority of base-catalyzed exchange reactions in carbocyclic aromatic systems.[4] This pathway involves proton abstraction by base to give an intermediate carbanion. Scheme I illustrates this mechanism for pyridine-d_5 N-oxide.

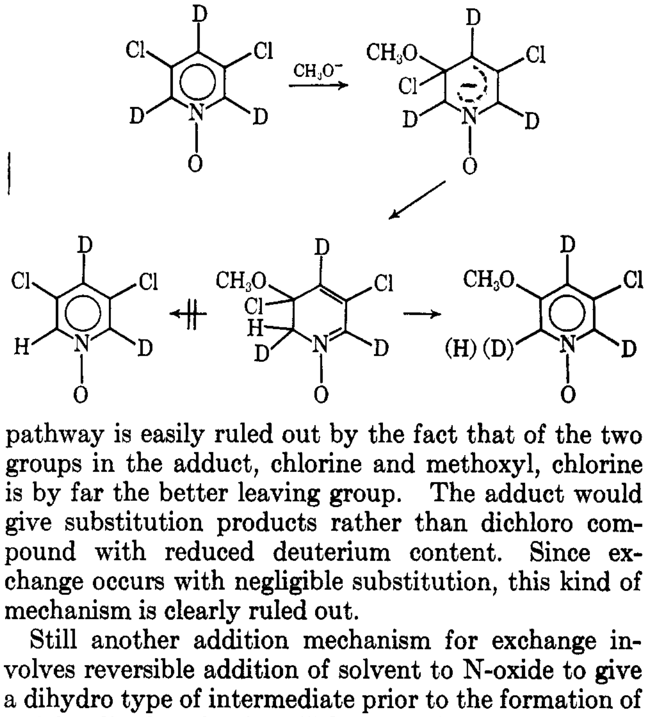
SCHEME I



The positional order of exchange and the relative rates give strong indication that the exchange observed for N-oxides does involve proton abstraction by methoxide ion to give an intermediate carbanion. The N-oxide reactivity pattern resembles closely those found in many carbocyclic systems for base-catalyzed hydrogen exchange.[4] More importantly, the relative rates of dedeuteration of I parallel those for the decarboxylation of the isomeric N-methylpyridinium carboxylate betaines.[26,27] Relative rates of decarboxylation of these betaines at 196° at positions 2, 3, and 4 are 1600, 2.8, and 1, respectively. These decarboxylation reactions presumably involve the intermediate formation of carbanions. Relative rates for the dedeuteration of I at 138° are 2:3:4 = 1500:10:1. While the close numerical correspondence of the positional reactivities of this reaction with our data is probably coincidental, the formation of similar intermediates would be expected to take place with similar reactivity patterns.

It is necessary to consider a second type of mechanism for exchange. Since pyridine N-oxides readily add nucleophiles, hydrogen exchange could take place on the anionic adduct formed by the addition of methoxide ion to carbon. This mechanism is indicated for 3,5-dichloropyridine-d_3 N-oxide in Scheme II. This

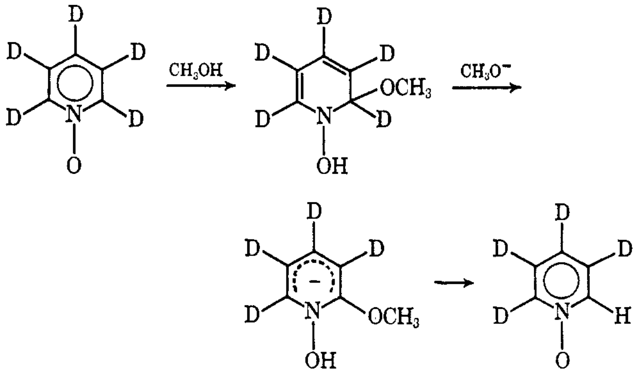
SCHEME II



pathway is easily ruled out by the fact that of the two groups in the adduct, chlorine and methoxyl, chlorine is by far the better leaving group. The adduct would give substitution products rather than dichloro compound with reduced deuterium content. Since exchange occurs with negligible substitution, this kind of mechanism is clearly ruled out.

Still another addition mechanism for exchange involves reversible addition of solvent to N-oxide to give a dihydro type of intermediate prior to the formation of a delocalized carbanion (Scheme III). Precedent for

SCHEME III



this type of pathway is found in the reaction of the 4-cyano adduct of the nicotinamide group of nicotinamide–adenine dinucleotide. Base-catalyzed exchange of this dihydropyridine derivative takes place only at

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(22) III-4 *vs.* II-4, III-2,6 *vs.* II-6, and II-2 *vs.* I-2,6.

(23) III-2,6 *vs.* II-2 and II-6 *vs.* I-2,6.

(24) III-4 *vs.* IV-2.

(25) Obtained from the *para* N–O factor and the log *ortho/para* ratio of 3.70 (II-2 *vs.* II-4). This value of the log *ortho/para* ratio may be compared with that (3.19) obtained at 138° by direct comparison of the I-2,6 and I-4 rates. The later value at the higher temperature is smaller as expected.

(26) P. Haake and J. Mantecon, *J. Amer. Chem. Soc.*, **86**, 5230 (1964).

(27) J. A. Zoltewicz, G. M. Kauffman, and C. L. Smith, *ibid.*, **90**, 5939 (1968).

the 4 position.[28] Little is known about the characteristics of such a mechanism. It would be highly coincidental that such a pathway would give rise to a positional reactivity pattern which is an imitation of that for direct deprotonation.

In light of the proposed mechanism involving carbanion formation by direct deprotonation the positional reactivity pattern indicates that the primary mode of activation by the N-oxide group is inductive. Typically, inductive effects fall off rapidly as the distance between the activating group and the reaction site is increased.

Dipole moment,[29] infrared,[30] and nmr[16] studies indicate the presence of a resonance effect in the ground states of N-oxides. However, the donation of electrons into the ring by the oxygen of the N-oxide group must have only a minor influence on exchange reactivities. The relative rates of exchange of I and of decarboxylation of N-methylpyridinium carboxylates are proportional on a logarithmic scale. These carboxylates do not contain oxygen capable of donating electrons into the ring. The minor importance of electron donation by oxygen in the exchange reactions is understandable. The orbitals of the generated carbanions are orthogonal to the orbitals of the π system and interaction between them is at a minimum.

Rate Factors.—Our determination of partial rate factors for substituents assumes that the same reaction mechanism is followed by all the reactions considered here and that the effects of the several substituents on the reaction site are additive. The general agreement of the rate factors determined from different compounds having a rate spread of about 10^4 (50°) supports these assumptions.

The magnitudes of the *ortho* and *para* N-oxide log rate factors, 9.58 and 5.88, respectively, are to be compared with those for fluorine, 5.25 and 1.13,[6] respectively. Fluorine is known to exert one of the most powerful acidifying effects on aryl hydrogens.[4] Clearly the effect of the highly polar N-oxide group is considerably greater.

The mechanism for the hydrogen exchange reactions may be written so the rate of collapse to starting materials of the hydrogen-bonded anion, A, may successfully compete with the rate of replacement of one hydrogen bond for another to give B. When this occurs the observed rates include contributions from these steps in addition to the initial step giving A. We expect this mechanism, internal return, to be important in the exchange reactions reported here. Delocalized anions are not formed and the acidity of the annular positions is considerably less than that of the solvent.[31] The observed ΔS^* values are in keeping with this suggestion. According to the internal return mechanism ΔS^* is a composite of the entropy changes of the several steps and the observed values may be less negative than those for normal second-order reactions.[6] Our ΔS^* values, Table IV, include positive and negative values and range over 16 eu.

$$\mathrm{C{-}D} + \mathrm{CH_3O^-} \rightleftarrows \underset{\mathrm{A}}{\mathrm{C^- \cdots DOCH_3}} \xrightarrow{\mathrm{HOCH_3}} \underset{\mathrm{B}}{\mathrm{C^- \cdots HOCH_3}} \longrightarrow \text{exchange}$$

In summary, pyridine N-oxides undergo hydrogen exchange by simple deprotonation reactions. Positional reactivity is determined primarily by the activating effect of the N-oxide group and secondarily by chlorine substituents. Entropies of activation suggest that a more detailed description of the exchange mechanism must include internal return.

Registry No.—I-d_5, 19639-76-0; II-4-d, 19639-77-1; II-2,6-d_2, 19639-78-2; III, 15177-57-8; III-d_3, 19639-80-6.

Acknowledgment.—We are pleased to acknowledge helpful discussions with Professor Gardiner Myers.

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(28) A. San Pietro, *J. Biol. Chem.*, **217**, 579 (1955).

(29) A. R. Katritzky, E. W. Randall, and L. E. Sutton, *J. Chem. Soc.*, 1769 (1957).

(30) A. R. Katritzky, A. M. Monro, J. A. T. Beard, D. P. Dearnaley, and N. J. Earl, *ibid.*, 2182 (1958).

(31) M. Eigen, *Angew. Chem. Intern. Ed. Engl.*, **3**, 1 (1964).

Cyanation and Hydrocyanation of Unsaturated Hydrocarbons. II. Oxidation and Reduction of the Intermediate[1,2]

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The cyanation of the heavily arylated hydrocarbon 4a-methyl-1,3,9-triphenyl-4aH-fluorene (Ia) proceeds almost quantitatively when solutions prepared from the hydrocarbon and sodium cyanide in aprotic solvents are treated with certain oxidizing agents. Of a number of oxidants studied, chromium trioxide, lead dioxide, and sodium 9,10-anthraquinone-1-sulfonate are most effective, and the last is the most conveniently used. Certain dibenzofulvenes, namely 9-benzylidenefluorene (IIa), 9-(*p*-bromobenzylidene)fluorene (IIc), and 9-ethylidenefluorene (IIe), are cyanated when treated with the same combinations of reagents, and the yields, especially from the arylidene compounds, are high. The roles in the cyanation process of the carbanions formed by addition of cyanide ion to the unsaturated systems, of radicals formed from such carbanions by electron exchange, and of hydrocyanation products formed by protonation of the carbanions are discussed.

The facile reaction of cyanide ion with 4a-methyl-1,3,9-triphenyl-4aH-fluorene (Ia) is attributed to the presence in this hydrocarbon of an extended, conjugated π-bond system, which stabilizes the incipient carbanion through resonance.[2a] This structural feature, as well

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(2) For previous related papers, see (a) B. E. Galbraith and H. R. Snyder, *J. Org. Chem.*, **32**, 380 (1967), and (b) R. G. Landolt and H. R. Snyder, *ibid.*, **33**, 403 (1968).