Reactions of *N*-Heteroaromatic Bases with Nitrous Acid. Part 6.[1] Kinetics of the Nitrosation of 2- and 4-Methylaminopyridine and their 1-Oxide Derivatives

By **Evangelos Kalatzis** * and **Panayiotis Papadopoulos**, The National Hellenic Research Foundation, 48 Vassileos Konstantinou, Athens, Greece

The nitrosation of 2- and 4-methylaminopyridine and their 1-oxide derivatives in 0.002—5.00M-perchloric acid is of first order in both the amine and nitrous acid. The respective nitrosamines formed are easily denitrosated under the experimental conditions. The rate coefficients of the nitrosation increase with an increase in the concentration of perchloric acid and sodium perchlorate. In perchloric acid solutions whose ionic strength is maintained constant by the addition of sodium perchlorate the rate coefficients of the nitrosation of 2- and 4-methylaminopyridine only show a rectilinear dependence on the h_0 parameter of the medium. The nitrosation of 2- and 4-methylaminopyridine proceeds mainly by the interaction of the nitrous acidium ion with the protonated form of these amines whilst the nitrosation of 2- and 4-methylaminopyridine 1-oxide proceeds by the simultaneous interaction of the nitrous acidium ion with the protonated and the free form of both amines. The nitrous acidium ion seems to show a distinct discrimination in its reaction with the free form of the amines as evidenced by a rectilinear relationship between the rate coefficients of their notrosation and their K_a values. The protonated amine 1-oxides react faster than the protonated amines when the hydroxy-group is in the *para*-position with respect to the amino-group and therefore not involved in hydrogen bonding with it. The nitrosation of the free and the protonated amines involves an initial interaction between the nitrosating agent and the heteroaromatic nucleus. The present results show that the formation of the respective *N*-nitroso-derivative is the rate-determining stage of the diazotisation of the *N*-heteroaromatic amines over the whole of the acid range examined. pK_a Values are recorded.

NITROSATION of secondary α- and γ-*N*-heteroaromatic amines is easily effected in dilute acid solutions but the nitsosamines formed are easily denitrosated under these conditions.[2a]

This paper presents a study of the kinetics of the nitrosation of 2- and 4-methylaminopyridine and their 1-oxide derivatives in 0.002—5.00M-perchloric acid and the results confirm an earlier assumption [1,2b,3] that the rate-determining stage in the diazotisation of α- and γ-aminopyridines is the formation of the respective nitrosamines. The results provide more information about the mechanism of this reaction which is thought to involve an initial interaction between the nitrosating agent and the heteroaromatic ring system of both the free and the protonated form of the amines. It is noteworthy, however, that the nitrosation of the aromatic amines was assumed to involve an initial interaction between the nitrosating agent and the aromatic nucleus only in the case of the protonated form of these amines.[4,5]

RESULTS AND DISCUSSION

In contrast to the nitrosation of the secondary aromatic amines [4] the nitrosation of 2- and 4-methylaminopyridine and their 1-oxide derivatives in 0.002—5.00M-perchloric acid solutions is reversible because of the ease of denitrosation of the respective nitrosamines formed during the reaction. The reversibility of the reaction was more pronounced at higher acidities especially in the case of 2-methylaminopyridine 1-oxide whose nitrosation was therefore studied only in ≤0.10M-perchloric acid. Under the present experimental conditions the denitrosation obeys [6] rate expression (1) in which $\bar{k}_1$ is the stoicheiometric first-order rate coefficient. It is noteworthy that rate expression (1) is also similar to that observed in the denitrosation of the aliphatic [7] and aromatic [8] nitrosamines in dilute acid solutions.

The stoicheiometric second-order rate coefficients

$$\text{Rate} = \bar{k}_1\,[\text{Nitrosamine}] \qquad (1)$$

($\bar{k}_2$) of the nitrosation of 2- and 4-methylaminopyridine and their 1-oxide derivative in 0.002—5.00M-perchloric acid solutions obtained by using rate expression (2) and various initial concentrations of reactants were

$$\text{Rate} = \bar{k}_2[\text{Amine}][\text{Nitrous acid}] - \bar{k}_1\,[\text{Nitrosamine}] \qquad (2)$$

satisfactorily constant at a given acidity (Table 1) for more than 70% reaction (Table 2). Rate expression (2) was reduced to rate expression (3) when only the initial

$$\text{Rate} = \bar{k}_2[\text{Amine}][\text{Nitrous acid}] \qquad (3)$$

stages of the reaction were considered. Thus a two-fold increase in the concentration of either reactant caused a two-fold increase in the initial rate of the reaction, whilst a two-fold increase in the concentration of both reactants caused a four-fold increase (Figure 1).

The values of $\bar{k}_2$ increase with an increase in the acidity of the medium (Tables 1 and 3) and the plots of the values of log $\bar{k}_2$ against the values of H_0 of the acid solutions (Table 3) are straight lines only for the nitrosation of 2- and 4-methylaminopyridine with slopes of 1.18 and 1.37, respectively, whilst for the nitrosation of 2- and 4-methylaminopyridine 1-oxide the plots are curves with rising slopes.

The catalytic medium effect of perchloric acid on the nitrosation of 2- and 4-methylaminopyridine and 4-methylaminopyridine 1-oxide was studied in 1.00M-perchloric acid containing various concentrations of

sodium perchlorate (up to 3.50M). The results showed that the values of $\bar{k}_2$ (Table 4) increase with an increase in the ionic strength of the medium (μ) and the plots of log $\bar{k}_2$ against μ are straight lines with slopes of 0.47, 0.46, and 0.41, respectively. The nitrosation of 2-methylaminopyridine 1-oxide however was studied in 0.01M-perchloric acid containing various concentrations of sodium perchlorate (up to 0.14M) and a plot of log $\bar{k}_2$ against $\sqrt{\mu}$ is a straight line with a slope of 0.23. (It is useful to note that in this case a plot of log $\bar{k}_2$ against μ approximates to a straight line with a slope of 0.48 probably because the values of $\bar{k}_2$ do not vary greatly with μ.) These results, which are similar to those of the diazotisation of the primary heteroaromatic amines,[2b,3] suggest that the nitrosation of the respective secondary amines involves charged species.

TABLE 1

Nitrosation at 2.0°; constancy of $\bar{k}_2$ [equation (2)] at a given acidity

	2-Methylaminopyridine						4-Methylaminopyridine							
$[HClO_4]$/M	0.10			1.50			1.00				4.00			
10^4[Amine]$_i$/M	6.0	12.0	12.0	1.0	1.0	2.0	1.2	1.2	2.4	2.4	0.3	0.3	0.6	0.6
10^4[Nitrous acid]$_i$/M	72.0	36.0	72.0	6.0	12.0	12.0	6.0	12.0	6.0	12.0	0.9	1.8	0.9	1.8
$10^2\bar{k}_2$/l mol^{-1} s^{-1}	0.677	0.658	0.669	34.4	35.9	34.4	22.8	22.6	21.2	22.4	2 890	2 920	2 910	3 050
Mean $10^2\bar{k}_2$/l mol^{-1} s^{-1}	0.668 ± 0.010			34.9 ± 0.9			22.2 ± 0.7				2 942 ± 73			

	2-Methylaminopyridine 1-oxide						4-Methylaminopyridine 1-oxide					
$[HClO_4]$/M	0.05			0.10			0.01			5.00		
10^4[Amine]$_i$/M	10.0	20.0	20.0	10.0	20.0	20.0	4.5	9.0	9.0	0.08	0.16	0.16
10^4[Nitrous acid]$_i$/M	100	100	200	100	100	200	22.5	22.5	45.0	0.16	0.16	0.36
$10\bar{k}_2$/l mol^{-1} s^{-1}	7.20	7.56	7.51	8.18	8.71	8.28	0.303	0.317	0.323	4 430	4 410	4 220
Mean $10\bar{k}_2$/l mol^{-1} s^{-1}	7.42 ± 0.20			8.39 ± 0.28			0.314 ± 0.010			4 354 ± 116		

TABLE 2

Nitrosation at 2.0°; constancy of $\bar{k}_2$ [equation (2)] during the reaction and in large excess of sodium perchlorate and nitrous acid

2-Methylaminopyridine

$[HClO_4]$ 0.10M + $[NaClO_4]$ 2.90M
$[Amine]_i$ 2.0×10^{-4}M
$[Nitrous\ acid]_i$ 16×10^{-4}M

t/min	10^4[Product]/M	$10\bar{k}_2$/l mol^{-1} s^{-1}
16	0.405	1.53
26	0.597	1.51
41	0.839	1.52
61	1.06	1.48
86	1.26	1.49
116	1.41	1.45
136	1.48	1.46
156	1.53	1.45

4-Methylaminopyridine 1-oxide

$[HClO_4]$ 1.50M
$[Amine]_i$ 7.2×10^{-5}M
$[Nitrous\ acid]_i$ 35.8×10^{-5}M

t/min	10^5[Product]/M	$10\bar{k}_2$/l mol^{-1} s^{-1}
3.5	1.16	2.41
8.0	2.38	2.50
12.0	3.18	2.49
20.0	4.31	2.50
30.0	5.14	2.49
36.0	5.47	2.51
46.0	5.81	2.51
56.0	6.02	2.53

It must be noted that the second-order rate expression (3) without changing to a third-order rate expression, *i.e.* second order with respect to nitrous acid and first order with respect to the amine, was obeyed throughout the acid range studied especially in ≤0.50M-perchloric acid in the presence of excess of nitrous acid and excess of sodium perchlorate (Tables 1, 2, and 5). Thus any contribution to the overall rate of the nitrosation of 2- and 4-methylaminopyridine and their 1-oxide derivatives from the nitrous anhydride mechanism, which follows third-order kinetics and is greatly enchanced under the above conditions,[4a,5,9] can be excluded (Table 5). This result although similar to that observed in the diazotisation of 2- and 4-aminopyridine and their 1-oxide derivatives,[2b,3] is contrary to that observed in the nitrosation of the secondary and in the diazotisation of the primary aromatic amines more basic than *p*-nitroaniline at acidities ≤0.50M-perchloric acid because these

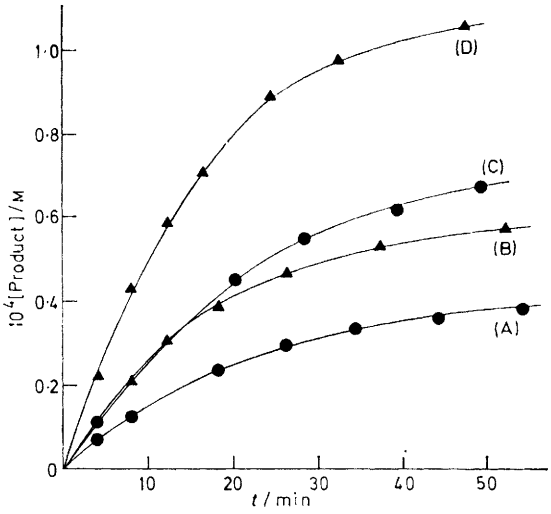


FIGURE 1 Nitrosation of 2-methylaminopyridine in 2.00M-perchloric acid and at 2.0°; variation of reaction rate with initial concentration of amine and nitrous acid: (A) 1.0×10^{-4} and 4.0×10^{-4}M; (B) 1.0×10^{-4} and 8×10^{-4}M; (C) 2.0×10^{-4} and 4.0×10^{-4}M; (D) 2.0×10^{-4} and 8×10^{-4}M. Initial rates (A) 1.67×10^{-6}; (B) 3.17×10^{-6}; (C) 3.17×10^{-6}; (D) 6.17×10^{-6} mol l^{-1} min^{-1}

reactions follow third-order kinetics and are known to proceed by the nitrous anhydride mechanism.[4a,5]

The acid catalysis of perchloric acid on the nitrosation of 2- and 4-methylaminopyridine and 4-methylaminopyridine 1-oxide was determined in solutions kept at constant ionic strength of 3.00 whilst the acid catalysis on the nitrosation of 2-methylaminopyridine 1-oxide was determined in solutions kept at constant ionic strength of 0.122 by the addition of sodium perchlorate (Table 6). The results showed that the dependence of the values of $\bar{k}_2$ of the nitrosation of 2- and 4-methylaminopyridine on the acidity of the medium at constant ionic strength is rectilinear, *i.e.* $\bar{k}_2 \propto h_0$, since in both cases a plot of log $\bar{k}_2$ against $-H_0$ is a straight line with a slope of almost unity (0.90 and 0.93, respectively). However, the dependence of the values of $\bar{k}_2$ of the nitrosation of 2- and 4-methylaminopyridine 1-oxide on the acidity of the medium also at constant ionic strength is not rectilinear because the respective plots of log $\bar{k}_2$ against $-$pH and $-H_0$ (Table 6) are curves with rising slopes.

Rate expression (3), which was also observed in the case of the diazotisation of 2- and 4-aminopyridine and their 1-oxide derivatives [2b,3] can be expanded to rate expressions (4) or (5) for the nitrosation of 2- and 4-methylaminopyridine because these amines must be present almost entirely as the monocations (pK_a 7.13 and 9.65,[10] respectively) at all acidities examined in the present work and for their case $k_2 \propto h_0$ and equation (6), in which K_a is the thermodynamic dissociation constant of the conjugate acid of the amine, is applicable.

$$\text{Rate} = \bar{k}_3[\text{Protonated amine}][HNO_2]h_0 \quad (4)$$

$$\text{Rate} = \bar{k}_4[\text{Free amine}][HNO_2]h_0^2 \quad (5)$$

$$[\text{Free amine}]h_0 = [\text{Protonated amine}]K_a \quad (6)$$

The catalytic effect of perchloric acid on the nitrosation of 2- and 4-methylaminopyridine is similar to that observed in the case of the diazotisation of 2- and 4-aminopyridine (see for example Figure 2) for which the same rate expressions (4) and (5) were established.[2b,3a] Therefore for reasons similar to those already presented [2b,3a] rate expression (4) is considered to be more applicable than (5) for the case of the nitrosation of 2-

TABLE 3

Nitrosation at 2.0°; dependence of $\bar{k}_2$ [equation (2)] on the concentration of an excess of perchloric acid

$[HClO_4]$/M	H_0	2-Methylaminopyridine $10^2\bar{k}_2$/l mol^{-1} s^{-1}	4-Methylaminopyridine $10^2\bar{k}_2$/l mol^{-1} s^{-1}	2-Methylaminopyridine 1-oxide $10^2\bar{k}_2$/l mol^{-1} s^{-1}	4-Methylaminopyridine 1-oxide $\bar{k}_2$/l mol^{-1} s^{-1}
0.0020	+2.46 *			4.55 ± 0.17	
0.0025	+2.32 *			4.91 ± 0.20	
0.010	+2.05 *	0.0803 ± 0.0018	0.0585 ± 0.0002	6.18 ± 0.10	0.0314 ± 0.0010
0.025	+1.61 *			7.00 ± 0.25	
0.050	+1.30 *	0.281 ± 0.018	0.300 ± 0.008	7.42 ± 0.20	
0.070	+1.16 *			7.70 ± 0.27	
0.100	+1.00 *	0.668 ± 0.010	0.474 ± 0.014	8.39 ± 0.28	0.0948 ± 0.0058
0.250	+0.60	2.04 ± 0.06	1.66 ± 0.08		0.190 ± 0.004
0.500	+0.20	4.23 ± 0.06	5.73 ± 0.14		0.374 ± 0.001
1.00	−0.22	11.6 ± 0.3	22.4 ± 0.7		1.01 ± 0.04
1.50	−0.53	34.9 ± 0.9	59.5 ± 1.2		2.43 ± 0.09
2.00	−0.78	76.3 ± 3.6	143 ± 2		5.30 ± 0.04
2.50	−1.01	178 ± 9	312 ± 16		10.9 ± 0.3
3.00	−1.23	361 ± 16	662 ± 6		21.7 ± 0.4
3.50	−1.47	746 ± 18	1 383 ± 50		43.6 ± 0.7
4.00	−1.72	1 501 ± 85	2 940 ± 73		85.3 ± 3.4
5.00	−2.23	5 283 ± 200			435 ± 12

* Values determined with pH meter. The other values of H_0 taken from M. A. Paul and D. A. Long, *Chem. Rev.*, 1957, **57**, 1.

TABLE 4

Nitrosation of 2- and 4-methylaminopyridine and their 1-oxide derivatives at 2.0°; dependence of $\bar{k}_2$ [equation (2)] on the concentration of sodium perchlorate

		1.00M-$HClO_4$			0.01M-$HClO_4$		
		2-Methylaminopyridine	4-Methylaminopyridine	4-Methylaminopyridine 1-oxide	2-Methylaminopyridine 1-oxide		
$[NaClO_4]$/M	h_0 *	$\bar{k}_2$/l mol^{-1} s^{-1}			$10[NaClO_4]$/M	pH	$10^2\bar{k}_2$/l mol^{-1} s^{-1}
0.00	1.78	0.116 ± 0.003	0.224 ± 0.007	1.01 ± 0.04	0.00	2.05	6.18 ± 0.10
0.50	2.42	0.227 ± 0.002	0.414 ± 0.001	1.67 ± 0.04	0.10	2.05	6.33 ± 0.16
1.00	3.25	0.407 ± 0.004	0.720 ± 0.022	2.83 ± 0.04	0.25	2.05	6.49 ± 0.16
1.50	4.01	0.680 ± 0.030	1.22 ± 0.04	4.67 ± 0.07	0.50	2.05	6.94 ± 0.18
2.00	5.12	1.11 ± 0.07	2.24 ± 0.04	7.08 ± 0.16	0.75	2.05	6.67 ± 0.20
2.50	7.02	1.91 ± 0.04	3.76 ± 0.05	11.3 ± 0.2	1.00	2.05	7.08 ± 0.12
3.00	9.00	3.43 ± 0.08	5.93 ± 0.08	18.2 ± 0.5	1.40	2.05	7.20 ± 0.14
3.50	11.5	5.18 ± 0.01	9.81 ± 0.06	28.4 ± 0.8			

* *Cf.* ref. 3*a*.

and 4-methylaminopyridine and it is interpreted as describing a reaction between the protonated amine and the nitrous acidium ion. Additional support for rate expression (4) comes from the observation that the values of $\bar{k}_2$ of the nitrosation of 2- and 4-methylaminopyridine are respectively 4.7 and 8.6 times greater than the nitrosation of *N*-methylaniline [4a] in 3.0M-perchloric acid. These results are contrary to those which would have been expected if rate expression (5) were valid (*i.e.* if the reaction involved the free amine and the nitrosonium ion [2b,3a]) because the concentration of the non-protonated *N*-methylaniline is 190 and 63 100 times greater than the concentration of the non-protonated 2- and 4-methylaminopyridine, respectively. Moreover, 2-methylaminopyridine is 330 times greater than that of 4-methylaminopyridine.

The acid catalysed mechanism described by rate expression (4), however, cannot alone explain the results of the nitrosation of 2- and 4-methylaminopyridine 1-oxide because, as in the case of the diazotisation of 2- and 4-aminopyridine 1-oxide,[3b] the dependence of the values of $\bar{k}_2$ (Table 6) on the acidity of the medium is not rectilinear. The free forms of 2- and 4-methylaminopyridine 1-oxide (pK_a 2.81 and 3.85,[11] respectively) must be present in significant amounts under the present experimental conditions and therefore nitrosation by the interaction of the free amines with the nitrous acidium ion must contribute significantly to the observed rate of the reaction, as in the case of the diazotisation of 2- and 4-aminopyridine 1-oxide.[3b] Such a reaction path which was also observed to contribute significantly to the rate of the nitrosation of *m*- and *p*-chloro-*N*-methylaniline [4b] and to be the main reaction path for the diazotisation of 2-amino-5-chloropyridine 1-oxide,[1] obeys rate expression (7) at constant ionic strength.

TABLE 5

Nitrosation of 4-methylaminopyridine and 2-methylaminopyridine 1-oxide at 2.0°; constancy of $\bar{k}_2$ [equation (2)] in a large excess of sodium perchlorate and nitrous acid

4-Methylaminopyridine

	0.05M-$HClO_4$ + 2.95M-$NaClO_4$				0.10M-$HClO_4$ + 2.90M-$NaClO_4$				0.25M-$HClO_4$ + 2.75M-$NaClO_4$				0.50M-$HClO_4$ + 2.50M-$NaClO_4$			
10^4[Amine]$_i$/M	1.2	1.2	2.4	2.4	1.2	1.2	2.4	2.4	1.2	1.2	2.4	2.4	0.6	0.6	1.2	1.2
10^4[Nitrous acid]$_i$/M	12.0	24.0	12.0	24.0	12.0	24.0	12.0	24.0	6.0	12.0	6.0	12.0	3.0	3.0	3.0	6.0
$\bar{k}_2$/l mol^{-1} s^{-1}	0.116	0.114	0.112	0.110	0.233	0.236	0.222	0.222	0.571	0.568	0.555	0.572	1.28	1.22	1.13	1.13
Mean $\bar{k}_2$/l mol^{-1} s^{-1}	0.113 ± 0.003				0.228 ± 0.007				0.566 ± 0.009				1.19 ± 0.07			

2-Methylaminopyridine 1-oxide

	0.010M-$HClO_4$ + 0.112M-$NaClO_4$			0.025M-$HClO_4$ + 0.097M-$NaClO_4$			0.050M-$HClO_4$ 0.072M-$NaClO_4$			0.100M-$HClO_4$ + 0.022M-$NaClO_4$		
10^3[Amine]$_i$/M	1.0	2.0	2.0	1.0	2.0	2.0	1.0	2.0	2.0	1.0	2.0	2.0
10^3[Nitrous acid]$_i$/M	10.0	10.0	20.0	10.0	10.0	20.0	10.0	10.0	20.0	10.0	10.0	20.0
$10^2\bar{k}_2$/l mol^{-1} s^{-1}	6.52	6.60	6.49	7.36	7.54	7.21	7.73	7.50	7.58	8.18	8.70	8.28
Mean $10^2\bar{k}_2$/l mol^{-1} s^{-1}	6.54 ± 0.06			7.37 ± 0.16			7.60 ± 0.12			8.39 ± 0.28		

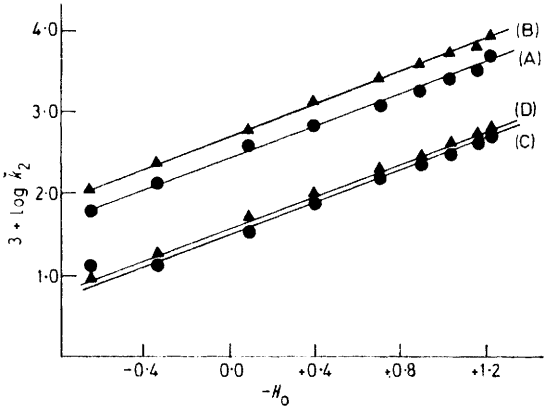


FIGURE 2 Plot of log $\bar{k}_2$ [equation (2)] against $-H_0$ for perchloric acid solutions kept at constant ionic strength of 3.0 by the addition of sodium perchlorate: (A) 2-methylaminopyridine; (B) 4-methylaminopyridine; (C) 2-aminopyridine; [3a] and (D) 4-aminopyridine.[2b] All four straight lines are drawn with a slope of almost unity

$$\text{Rate} = k_3' \text{ [Free amine][HNO}_2\text{]}h_0 \qquad (7)$$

The contribution of the two reaction paths to the nitrosation of 4-methylaminopyridine 1-oxide, which is present almost completely as the conjugate acid under the present experimental conditions, can be evaluated from rate expressions (3), (4), and (7) since at a given acidity the order of the reaction with respect to the amine and the nitrous acid remains the same in these expressions. Thus equation (8) is derived from (4), (6), and (7) and equation (9) from (3) and (8).

$$\text{Rate} = (k'_3K_a + k_3h_0) \text{ [Protonated amine][HNO}_2\text{]} \qquad (8)$$

$$\bar{k}_2 = k'_3K_a + k_3h_0 \qquad (9)$$

Equation (9) is similar to that observed in the diazotisation of α- and γ-aminopyridines [1-3] and therefore from a plot of $\bar{k}_2$ against h_0, which is a straight line with a slope of k_3 and an intercept of $k_3'K_a$, the values of k_3 and k_3'

the values of $\bar{k}_2$ of the nitrosation of 4-methylaminopyridine are almost twice as great as those of the nitrosation of 2-methylaminopyridine in perchloric acid solutions of constant ionic strength of 3.00 (Table 6). This result provides further support for rate expression (4) because the concentration of the non-protonated

have been evaluated not only for the nitrosation of 4-methylaminopyridine 1-oxide but also for the nitrosation of 2- and 4-methylaminopyridine (Table 7) since in this case equation (9) is also applicable.

Equation (9), however, is not applicable for the case of the nitrosation of 2-methylaminopyridine 1-oxide because the concentration of the free form of this amine (pK_a 2.81) is considerable and cannot be neglected under the present experimental conditions. The concentration of the protonated form of this amine is therefore calculated by using equation (10) and the result of a combination of equations (8), (10), and then (3) is equation (11) in which h_0 is replaced by $[H^+]$ for acidities $\leqslant$0.10M-perchloric acid. Thus from a plot of $\bar{k}_2/h_0$ against $1/(h_0 + K_a)$ which is a straight line with a slope of

$$[\text{Protonated amine}] = \frac{h_0}{h_0 + K_a}[\text{Amine}] \qquad (10)$$

$$\frac{\bar{k}_2}{h_0} = k_3 + (k_3' - k_3)\,K_a \frac{1}{h_0 + K_a} \qquad (11)$$

$(k_3' - k_3)K_a$ and an intercept of k_3, values of k_3 and k_3' for the nitrosation of 2-methylaminopyridine 1-oxide have been calculated (Table 7) for solutions of perchloric acid of constant ionic strength of 0.122. Furthermore the nitrosation of 4-methylaminopyridine 1-oxide has also been studied in solutions of perchloric acid of

TABLE 6

Nitrosation of 2- and 4-methylaminopyridine and their 1-oxide derivatives at 2.0°; dependence of $\bar{k}_2$ [equation (2)] on the concentration of perchloric acid in solutions kept at constant ionic strength (μ) by the addition of sodium perchlorate

		μ 3.00		
		2-Methylamino-pyridine	4-Methylamino-pyridine	4-Methylaminopyridine 1-oxide
		$\bar{k}_2$/l mol^{-1} s^{-1}		
$[HClO_4]$/M	H_0 *			
0.05	+0.66	0.0649 ± 0.0011	0.113 ± 0.003	0.939 ± 0.048
0.10	+0.34	0.142 ± 0.006	0.228 ± 0.007	1.28 ± 0.06
0.25	−0.09	0.344 ± 0.008	0.566 ± 0.009	2.33 ± 0.08
0.50	−0.40	0.610 ± 0.041	1.19 ± 0.07	4.10 ± 0.20
1.00	−0.71	1.11 ± 0.07	2.24 ± 0.04	7.08 ± 0.16
1.50	−0.90	1.64 ± 0.09	3.26 ± 0.13	10.2 ± 0.2
2.00	−1.04	2.25 ± 0.15	4.30 ± 0.14	13.0 ± 0.3
2.50	−1.17	2.85 ± 0.09	5.53 ± 0.30	17.4 ± 0.9
3.00	−1.23	3.61 ± 0.16	6.62 ± 0.06	21.7 ± 0.4

	μ 0.122			
	2-Methylaminopyridine 1-oxide		4-Methylaminopyridine 1-oxide	
$10^2[HClO_4]$/M	pH	$10^2\bar{k}_2$/l mol^{-1} s^{-1}	pH	$10^2\bar{k}_2$/l mol^{-1} s^{-1}
0.25	2.40	5.34 ± 0.23		
1.00	2.05	6.54 ± 0.06	1.98	3.81 ± 0.11
2.50	1.61	7.37 ± 0.16	1.55	5.18 ± 0.09
5.00	1.30	7.60 ± 0.12	1.28	7.60 ± 0.01
7.00	1.16	7.64 ± 0.18	1.10	9.24 ± 0.35
10.0	1.00	8.39 ± 0.28	0.98	11.1 ± 0.8

* *Cf.* ref. 3*a*.

TABLE 7

Values of k_3' and k_3 [equations (9) and (11)] for the nitrosation of 2- and 4-methylaminopyridine and their 1-oxide derivatives in perchloric acid solutions kept at constant ionic strength (μ) and at 2.0°

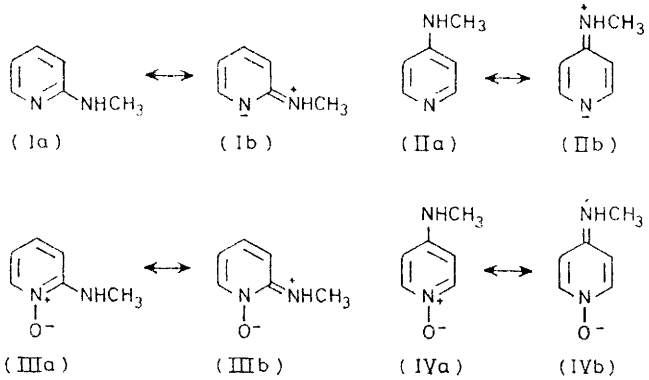
		μ 3.00			μ 0.122		
Amine	pK_a	$10^2k_3'/K_a$	$10^{-3}k_3'$/ l^2 mol^{-2} s^{-1}	10^2k_3/ l^2 mol^{-2} s^{-1}	$10^2(k_3' - k_3)K_a$	$10^{-2}k_3'$/ l^2 mol^{-2} s^{-1}	10^2k_3/ l^2 mol^{-2} s^{-1}
4-Methylaminopyridine	9.65[c]	14.3	639 000	37.8			
4-Aminopyridine [a]	9.11[f]	0.794	10 230	3.03			
2-Methylaminopyridine	7.13	6.30	850	20.0			
2-Aminopyridine [b]	6.82[f]	0.717	47.4	2.54			
N-Methylaniline [c]	4.85[g]	1.41	1.00	4.44			
Aniline [c]	4.60[h]	2.51	1.00	16.1			
4-Methylaminopyridine 1-oxide	3.85[i]	81.9	5.78	117	2.95	2.10	81.8
4-Aminopyridine 1-oxide [d]	3.69[i]	19.5	0.955	20.6			
2-Methylaminopyridine 1-oxide	2.81		1.31[j]	18.2[j]	7.35	0.476	12.7
2-Aminopyridine 1-oxide [d]	2.67[i]	7.82	0.0366	0.161			

[a] Ref. 2*b*. [b] Ref 3*a*. [c] Ref 4*b*. [d] Ref 3*b*. [e] Ref 10. [f] Ref. 12*b*. [g] A. L. Bacarella, E. Grunwald, H. P. Marshall, and E. I. Purlee, *J. Org. Chem.*, 1955, **20**, 747. [h] A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 1961, 388. [i] Ref. 11. [j] Values estimated from those determined at constant ionic strength of 0.122.

constant ionic strength of 0.122 and values of k_3 and k_3' (Table 6) were then calculated graphically from equation (11). From the ratios of the values of k_3 and k_3' for the nitrosation of 4-methylaminopyridine at constant ionic strengths of 3.00 and 0.122 [*i.e.* $(k_3')_{3.00} : (k_3')_{0.122}$ 27.5 and $(k_3)_{3.00} : (k_3)_{0.122}$ 1.43] which were assumed to be equal to the respective ratios of the nitrosation of 2-methylaminopyridine 1-oxide, values of k_3 and k_3' for the nitrosation of the latter amine at constant ionic strength of 3.00 were therefore estimated (Table 7) for comparison purposes.

From the values of k_3' and k_3 (Table 7), which were determined by the method of least squares, it is seen that the free forms of 2- and 4-methylaminopyridine and their 1-oxide derivatives are more reactive towards the nitrous acidium ion than the protonated forms and that the nitrous acidium ion seems to show a distinct discrimination towards the free form of these amines as is evident from a plot of log $(k_3'/{}_0k_3')$ against log $(K_a/{}_0K_a)$ (${}_0k_3'$ and ${}_0K_a$ for 2-methylaminopyridine are taken as reference values) which is rectilinear with a slope of −0.81. These results are similar to those of the diazotisation of α- and γ-aminopyridines [1-3] but they contrast with those of the nitrosation and diazotisation of the aromatic amines [4b] for which the values of k_3' appear to approach a limiting value of *ca.* 1 000 l^2 mol^{-2} s^{-1} under the same experimental conditions.[4b,5]

The methylamino-group attached to the 2- or the 4-position of the pyridine ring must be poorer in electrons than the heteroaromatic nucleus as a result of structures (Ib)—(IVb) which contribute significantly to the hybrid



structure of the molecules and are responsible for the enhancement of the basicity of the ring nitrogen.[12] The results of the nitrosation of the free 2- and 4-methylaminopyridine and their 1-oxide derivative can, therefore, be explained by assuming that the reaction involves an initial interaction between the nitrous acidium ion and the heteroaromatic nucleus (perhaps more particularly the ring nitrogen) followed, as a result of electronic rearrangement in the molecule, by the migration of the nitrosating agent towards the amino-group which is thus nitrosated.

Although there is some uncertainty in the values of k_3' due to the fact that the intercepts of the plots of k_2 against h_0 are small, especially in the case of the more basic amines, it is in interesting to note that a comparison of the rectilinear relationship between log $(k_3'/{}_0k_3')$ and log $(K_a/{}_0K_a)$ for the nitrosation of the secondary amines with that for the diazotisation of the primary *N*-heteroaromatic amines (Figure 3) reveals

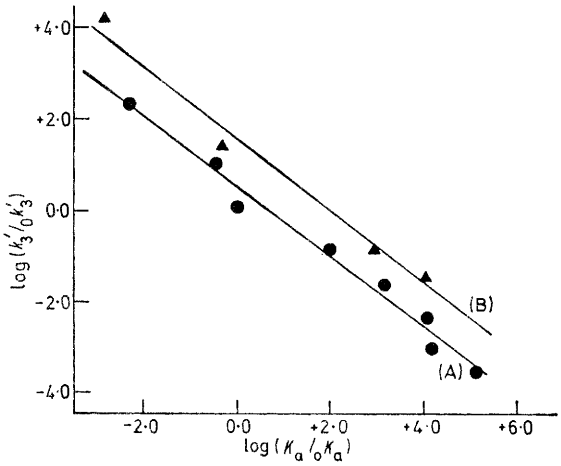


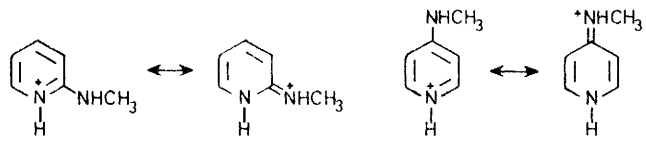
FIGURE 3 Plot of log $(k_3'/{}_0k_3')$ against log $(K_a/{}_0K_a)$ for the diazotisation of α- and γ-aminopyridines (A) and for the nitrosation of α- and γ-methylaminopyridines (B). Values of ${}_0k_3'$ and ${}_0K_a$ of 2-aminopyridine are taken as reference values

that the values of k_3' of the nitrosation are greater than would be expected if only the increase in the basicity due to the methyl-group were considered. These results are again in contrast to those of the nitrosation and diazotisation of the aromatic amines for which, as was mentioned earlier, the values of k_3' appear to approach the same limiting value.[4b,5]

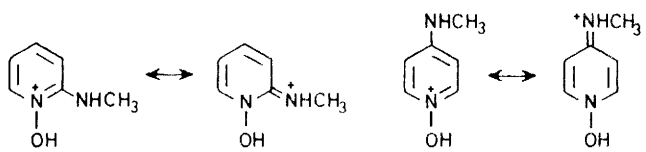
The results of the nitsosation of protonated 2- and 4-methylaminopyridine (values of k_3 in Table 7) can be explained by proposing a mechanism simliar to that proposed for the diazotisation of protonated primary *N*-heteroaromatic amines,[1,2b,3a] namely that the reaction proceeds by initial association between the positively charged nitrous acidium ion and the protonated *N*-heteroaromatic nucleus followed by the nitrosation of the amino-nitrogen during migration of a proton to the medium as shown in the Scheme. This is because the amino-nitrogen becomes strongly positively charged due to structures (Vb)—(VIIIb) which contribute significantly to the resonance hybrid of the molecules thus making difficult direct interaction of the amino-group with the positively charged acidium ion.

It is noteworthy that the nitrosation of the protonated 2- and 4-methylaminopyridine and their 1-oxide derivatives is faster than the diazotisation of the corresponding α- and γ-aminopyridines [1-3] (Table 7). This must be due to the greater electronic contribution of the methylamino-group to the *N*-heteroaromatic nucleus compared with that of the primary amino-group through resonance structures (Vb)—(VIIIb) which would enhance the initial association of the nitrous acidium ion with the *N*-heteroaromatic nucleus of the secondary amines. In

contrast to the above results the nitrosation of the protonated secondary aromatic amines is slower than the diazotisation of the corresponding primary aromatic amines because electron donation of the methyl group to the amino-nitrogen has mainly a retarding effect on the proton loss to the medium and little effect on the π-electrons of the aromatic ring [4b] (Table 7). Although the electron donation of the methyl group to the amino-nitrogen in the *N*-heteroaromatic series must also have a retarding effect on the proton loss to the medium, this effect is presumably less significant than the enhancing



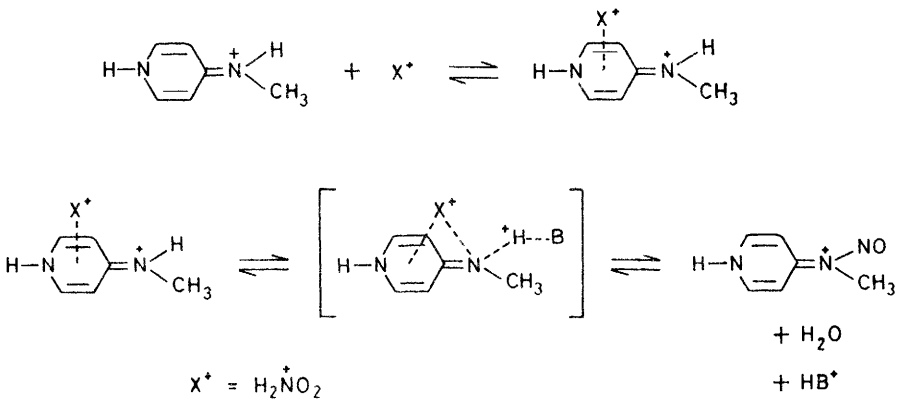
(Va) (Vb) (VIa) (VIb)



(VIIa) (VIIb) (VIIIa) (VIIIb)

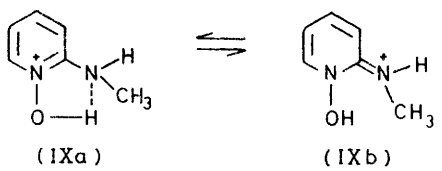
effect it has on the π-electrons of the *N*-heteroaromatic nucleus thus accelerating the reaction (Table 7).

The results of Table 7 also indicate that although protonated 2-methylaminopyridine 1-oxide is 1.1 times less reactive than protonated 2-methylaminopyridine, protonated 4-methylaminopyridine 1-oxide is 3.1 times more reactive than protonated 4-methylaminopyridine. This result is similar to that of the diazotisation of the corresponding primary amines [1] (Table 7) and therefore can be explained by assuming that the oxygen atom of the hydroxy-group enhances the nitrosation of the protonated 4-methylaminopyridine 1-oxide because it provides an additional site (extension of the heteroaromatic nucleus) which is involved in the initial interaction of the heteroaromatic nucleus with the nitrous acidium ion. On the other hand the slightly lower reactivity of protonated 2-methylaminopyridine 1-oxide compared with that of protonated 2-methylaminopyridine is attributed to hydrogen bond formation between the methylamino- and the hydroxy-group which would be responsible for structure (IXa) becoming more stable than structure (IXb). This result is similar to that of the diazotisation of the protonated 2-amino-

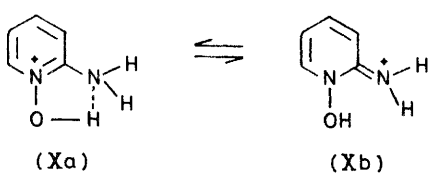


SCHEME

pyridine 1-oxide.[1] It is, however, noteworthy that 2-methylaminopyridine 1-oxide is 113 times more reactive than 2-aminopyridine 1-oxide whilst 4-methylaminopyridine 1-oxide is only 5.7 times more reactive than 4-aminopyridine 1-oxide (Table 7). This difference in the ratios of the reactivities between the 2- and 4-isomers cannot be due only to an increase in the electron donation of the heteroaromatic nucleus in the case of 2-methylaminopyridine 1-oxide due to the presence of the methyl group, because this increase should be at the most equal, if not less, than that in the case of 4-methylaminopyridine 1-oxide. Rather this difference is due to the fact that the intramolecular hydrogen bonding between the methylamino- and the hydroxy-group [structure (IXa)] in 2-methylaminopyridine 1-oxide takes place to a lesser extent than between the



(IXa) (IXb)



(Xa) (Xb)

amino- and the hydroxy-group of 2-aminopyridine 1-oxide [structure (Xa)] presumably because of steric hindrance due to the methyl group. Thus the electron-donor capacity of the heteroaromatic nucleus of proton-

ated 2-methylaminopyridine 1-oxide is greatly enhanced.

It is interesting to note that free and protonated γ-aminopyridines and their 1-oxide derivatives are more reactive than the respective free and protonated α-aminopyridines and their 1-oxide derivatives because the heteroaromatic nucleus of the γ-aminopyridines is richer in electrons than that of the α-aminopyridines. In the case of the free amines this must be due to the same factors which are also responsible for the greater basic strength of the γ-isomers compared with that of the α-isomers [12] and in the case of the protonated amines this must be due to the greater stability [12b] of the *para*-quinonoid structures (VIb) and (VIIIb) compared with the *ortho*-quinonoid structures (Vb) and (VIIb).

It is noteworthy that a methyl group when attached to the amino-group of 4-aminopyridine increases the value of k_3 12.5 times whilst when attached to the amino-group of 2-aminopyridine it increases the value of k_3 7.8 times (Table 7). This also may be due to the greater stability of the *para*-quinonoid structure (VIb) compared to that of the *ortho*-quinonoid structure (Vb) thus making electron donation of the methyl group to the heteroaromatic nucleus more effective in the case of the γ-isomer. This effect is not seen in the case of the 1-oxide derivatives because of hydrogen bond formation between the hydroxy- and the amino-group as discussed above [structures (IXa) and (Xa)]. Thus the methyl group when attached to the amino-group of 4-aminopyridine 1-oxide increases the value of k_3 only 5.7 times whilst when it is attached to that of 2-aminopyridine 1-oxide increases the value of k_3 113 times (Table 7).

EXPERIMENTAL

Materials.—2-Methylaminopyridine was prepared [13] by reacting 2-aminopyridine (Fluka; purum) with sodamide (Fluka; pract.) and then dimethyl sulphate (Merck; 98%) in dry ether. The product finally extracted was distilled at 60 °C and 0.2 mmHg (lit.,[13] 90 °C and 9 mmHg) in 60% yield.

4-Methylaminopyridine was prepared [14] by reacting 4-chloropyridine (Fluka; purum) with 40% aqueous methylamine (Fluka; purum) at 130—135 °C for 4.5 h and then 150—155 °C for another 7 h in the presence of copper sulphate. The product obtained after extraction with ether was sublimed three times at 100 °C and 0.1 mmHg, yield 70%, m.p. 125—127 °C (lit.,[14] 124—125 °C).

2-Methylaminopyridine 1-oxide was prepared [15] by the oxidation of 2-chloropyridine (Fluka; purum) with 30% hydrogen peroxide (Merck; pro analysi) to 2-chloropyridine 1-oxide which was then reacted with 25% aqueous methylamine (Fluka; purum) at 140 °C for 12 h. The product obtained was recrystallized from ethyl acetate and then sublimed twice at 80 °C and 0.4 mmHg, yield 60%, m.p. 103—105 °C (lit.,[15] 103—105 °C).

4-Methylaminopyridine 1-oxide was prepared [11] by reacting 4-chloropyridine 1-oxide (Fluka; purum) with 25% aqueous methylamine (Fluka; purum) at 140 °C for 20 h. The product obtained after extraction of the solid residue with ethanol was recrystallized from dioxan and sublimed twice at 165 °C and 0.2 mmHg, yield 65%, m.p. 199—120 °C (hygroscopic) (lit.,[11] 192—194 °C).

2-Nitrosomethylaminopyridine was prepared [2a] by reacting sodium nitrite (AnalaR) with 2-methylaminopyridine in hydrochloric acid (Merck; purum) solution. The product obtained was distilled at 53—55 °C and 0.4 mmHg (lit.,[2a] 53—55 °C and 0.4 mmHg) in 80% yield.

4-Nitrosomethylaminopyridine was prepared [2a] by reacting sodium nitrite (AnalaR) with 4-methylaminopyridine in hydrochloric acid (Merck; purum) solution. The product obtained was sublimed twice at 60 °C and 0.1 mmHg, yield 85%, m.p. 82—84 °C (lit.,[2a] 84 °C).

2-Nitrosomethylaminopyridine 1-oxide was prepared by reacting 2-methylaminopyridine 1-oxide (2.3 g) dissolved in 25% hydrochloric acid (43 ml; Merck; purum) and water (5 ml) with sodium nitrite (19.3 g; AnalaR) dissolved in water (35 ml) at 0 °C for 45 min. The mixture was treated with solid sodium carbonate until alkaline and then extracted with ether. The solid obtained after evaporation of the ether extracts was sublimed twice at 90 °C and 0.4 mmHg to give *2-nitrosomethylaminopyridine 1-oxide* (1.6 g, 70%), m.p. 126—128 °C (Found: C, 46.8; H, 4.65; N, 27.8. Calc. for $C_6H_7N_3O_2$: C, 47.05; H, 4.6; N, 27.45%).

4-Nitrosomethylaminopyridine 1-oxide was prepared by reacting 4-methylaminopyridine 1-oxide (0.5 g) dissolved in 25% hydrochloric acid (15 ml; Merck; purum) and water (5 ml) with sodium nitrite (1.5 g) dissolved in water (10 ml) at 0 °C for 20 min. The mixture was treated with solid sodium carbonate until alkaline and then extracted with ether. The solid obtained after evaporation of the ether extracts was sublimed twice at 110 °C and 0.2 mmHg to give *4-nitrosomethylaminopyridine 1-oxide* (0.4 g, 80%), m.p. 141—143 °C (hygroscopic). (Found: C, 47.35; H, 4.3; N, 27.8. Calc. for $C_6H_7N_3O_2$: C, 47.05; H, 4.6; N, 27.45%).

Sodium perchlorate (Merck; pro analysi) which gave a negative chloride test, was dried at 140 °C for 4 h. Sodium nitrite (AnalaR) was used without further purification after being dried under vacuum over phosphorus pentaoxide. Perchloric acid (Merck; pro analysi) was diluted and molarities of stock solutions were determined by titration against standard alkali solutions. Microanalyses were carried out by Dr. Ch. Mantzos. All purified products had satisfactory elemental analysis.

Kinetics.—Runs were carried out at 2.0 °C. Temperature-adjusted aqueous solutions of calculated concentrations of amine, perchloric acid (concentration adjusted to allow for the conversion of the amine into the perchlorate salt and sodium nitrite into nitrous acid), and, when required, sodium perchlorate were mixed to such a volume (45.0 or 95.0 ml) that after the addition of temperature-adjusted aqueous sodium nitrite (5.0 ml) the total volume was 50.0 or 100.0 ml. The mixture was then vigorously shaken.

For the nitrosation of 2- and 4-methylaminopyridine in 0.01—0.25M-perchloric acid samples (1.0—5.0 ml) taken at intervals were diluted 10—50 times with either sodium hydroxide or perchloric acid solution to a final strength of 0.01M or 0.10M, respectively. Under these conditions, the reaction either stopped (in 0.01M-NaOH) or was very slow (0.1M-$HClO_4$) as shown by the u.v. spectra which showed no further changes for *ca.* 5 min (experimental error 5%). U.v. spectra were recorded immediately after dilution on a Unicam SP 1800 or 8000 recording spectrophotometer. In 0.25—5.00M-perchloric acid the u.v. spectra of the mixtures were recorded at regular intervals after having placed a portion of these mixtures in a precooled Unicam cell (1.0 cm) and maintaining the temperature at 2.0 °C. For the

nitrosation of 2-methylaminopyridine in 0.01—5.00M-perchloric acid absorbances were read at 308 nm at which ε of 2-methylaminopyridine is 5.58×10^3 for all acidities and ε of 2-nitrosomethylaminopyridine is 9.56×10^3, 9.69×10^3, 10.1×10^3, and 10.2×10^3 for $H_0 + 0.60$, $+0.20$, -0.23, and $\leqslant -0.78$ respectively, whilst in 0.01M-sodium hydroxide absorbances were read at 282 nm at which ε is 2.08×10^3 and 9.55×10^3 for 2-methylamino- and 2-nitrosomethylamino-pyridine, respectively. For the nitrosation of 4-methylaminopyridine in 0.01—0.50M-perchloric acid absorbances were read at 292 nm at which ε is 4.41×10^3 and 14.7×10^3 for 4-methylamino- and 4-nitrosomethylamino-pyridine, respectively, for all acidities.

For the nitrosation of 2-methylaminopyridine 1-oxide in 0.002 5—0.10M-perchloric acid samples (3.0—5.0 ml) taken at intervals were diluted to 50.0 ml with excess sodium hydroxide to a final strength of 0.01M solution in which the reaction stopped. The u.v. spectra of the diluted solutions were recorded immediately after dilution. Absorbances were then read at 326 nm at which ε of 2-methylaminopyridine 1-oxide is 4.87×10^3 and of 2-nitrosomethylaminopyridine 1-oxide is 2.56×10^2. For the nitrosation of 4-methylaminopyridine 1-oxide in 0.01—5.00M-perchloric acid the u.v. spectra of the reaction mixtures were recorded at regular intervals after having placed a portion of these mixtures in a precooled Unicam cell (1.0 cm) and maintaining the temperature at 2.0 °C. Absorbances were read at 300 nm at which ε of 4-methylaminopyridine 1-oxide is 6.29×10^3 and ε of 4-nitrosomethylaminopyridine 1-oxide is 14.5×10^3. In all kinetic runs satisfactory isosbestic points were obtained.

Determination of pH.—Because the reactants were present as 2- and 4-methylaminopyridinium perchlorate and 2- and 4-methylaminopyridinium 1-oxide perchlorate and as free nitrous acid in high concentrations in the kinetic solutions containing <0.10M-perchloric acid, it was necessary to determine, by pH meter (Philips 9414), the pH of the final solutions. The values obtained are in Tables 3—5.

Determination of pK_a *Values.*—These were measured spectrophotometrically in water [16] (Table 8).

TABLE 8

	pK_a	Spread (±)	Concentration (10^5M)	A.w.l.[a] (nm)
2-Methylaminopyridine [b]	7.13 [c]	0.04	11.1	328
2-Methylaminopyridine 1-oxide [d]	2.81 [c]	0.03	10.0	252

[a] A.w.l. = analytical wavelength. [b] At 20°. [c] Refers to the gain of one proton. Buffers used had ionic strength 0.01 (except *d*). [d] At 2°.

Calculation of Rate Coefficients.—The concentration of the amines in the reaction mixtures was calculated from the expression $[\text{Amine}] = (D - A\varepsilon_2)/(\varepsilon_1 - \varepsilon_2)$ where D is the observed absorbance measured at a particular wavelength, A is the initial concentration of the amine, and ε_1 and ε_2 are the extinction coefficients of the amine and the corresponding nitrosamine, respectively. The absorption of nitrous acid under the conditions used is negligible. The

$$k_2 = \ln\left[\frac{(K^{-1} + a + b + m - 2x)(K^{-1} + a + b - m)}{(K^{-1} + a + b - m - 2x)(K^{-1} + a + b + m)}\right]\frac{1}{m}\frac{1}{t} \quad (12)$$

rate coefficients were calculated from equation (12) which was derived from the usual rate expression for a second-order reversible reaction [17] and in which a and b are the initial concentrations of the reactants, x is the concentration of the product at time t, $m = \sqrt{(K^{-1} + a + b)^2 - 4ab}$, and K is the equilibrium constant of the reaction under a particular set of conditions. The value of K was calculated from equation (13) in which x_e is the concentration of the nitrosamine at equilibrium which is taken as equal to the

$$K = \frac{x_e}{(a - x_e)(b - x_e)} \quad (13)$$

concentration of the nitrosamine formed when the absorbance of the reaction mixture does not change for at least three concecutive readings. Typical kinetic data are in Table 2.

[0/202 *Received, 4th February,* 1980]

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