Reactions of *N*-Heteroaromatic Bases with Nitrous Acid. Part 7.[1] Kinetics of the Nitrosation of Secondary and of the Diazotisation of Primary β-Aminopyridines

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

The nitrosation of 3-methylaminopyridine and 3-methylaminopyridine 1-oxide and the diazotisation of 3-amino-, 3-amino-2-chloro-, and 3-amino-6-methoxy-pyridine in 0.002—0.50M-perchloric acid are first-order in both the amine and nitrous acid. The rate coefficients of these reactions increase with an increase in the concentration of perchloric acid and of 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 3-methylaminopyridine and of the diazotisation of 3-aminopyridine show only a rectilinear dependence on the $[H^+]$ of the medium. The nitrosation of 3-methylaminopyridine and the diazotisation of 3-amino- and 3-amino-6-methoxy-pyridine proceed mainly by the interaction of the nitrous acidium ion with the monoprotonated form of these amines whilst the nitrosation of 3-methylaminopyridine 1-oxide and the diazotisation of 3-amino-2-chloropyridine proceed by the simultaneous interaction of the nitrous acidium ion with the protonated and the free form of both amines. The nitrosation and diazotisation of the free β-aminopyridines involve an initial interaction between the nitrous acidium ion and the heteroaromatic nucleus whilst the nitrosation and diazotisation of the monoprotonated β-aminopyridines proceed by direct interaction between the nitrous acidium ion and the amino-group. These results are contrary to those of the nitrosation and diazotisation of the free and the protonated aromatic amines. Furthermore the nitrous acidium ion seems to show a distinct discrimination in its reaction with the free β-aminopyridines as is evident from a rectilinear relationship between the rate coefficients of their nitrosation and diazotisation and their K_{a_1} values. The similarity between the nitrosation and the diazotisation results shows that the formation of the nitrosamine is the rate-determining stage of the diazotisation of the β-aminopyridines in the acid range examined. pK_a Values are recorded.

DIAZOTISATION of β-aminopyridines is considered to be similar to that of the aromatic amines because of the formation of rather stable diazonium ions.[2] However, no detailed studies on the mechanism of the nitrosation and the diazotisation of β-aminopyridines have been reported.

This paper presents a study of the kinetics of the nitrosation of 3-methylaminopyridine and 3-methylaminopyridine 1-oxide and of the diazotisation of 3-amino-, 3-amino-2-chloro-, and 3-amino-6-methoxy-pyridine in 0.002—0.50M-perchloric acid. The results indicate that formation of the nitrosamine is the rate-determining step in both reactions and that contrary to the results of the nitrosation and diazotisation of the aromatic amines [3,4] the reactions take place either by an initial interaction of the nitrous acidium ion with the heteroaromatic nucleus of the free β-aminopyridines or by a direct attack of the nitrous acidium ion on the amino-group of their monoprotonated form.

RESULTS AND DISCUSSION

In 0.002—0.50M-perchloric acid solutions the nitrosation of 3-methylaminopyridine and 3-methylaminopyridine 1-oxide and the diazotisation of 3-amino-, 3-amino-2-chloro-, and 3-amino-6-methoxy-pyridine follow rate expression (1). Thus the stoicheiometric

$$\text{Rate} = \bar{k}_2[\text{Amine}][\text{Nitrous acid}] \quad (1)$$

second-order rate coefficients ($\bar{k}_2$) obtained by using rate expression (1) and various initial concentrations

TABLE 1

Nitrosation of 3-methylaminopyridine and diazotisation of 3-amino-, 3-amino-2-chloro-, and 3-amino-6-methoxy-pyridine at 2.0°; constancy of $\bar{k}_2$ [equation (1)] at a given acidity

	3-Methylaminopyridine						3-Aminopyridine					
$[HClO_4]$/M	0.01			0.50			0.05			0.20		
$10^4[\text{Amine}]_i$/M	1.4	2.8	2.8	0.1	0.1	0.2	1.0	2.0	2.0	0.2	0.4	0.4
$10^4[\text{Nitrous acid}]_i$/M	2.8	1.4	2.8	0.1	0.2	0.1	2.0	1.0	2.0	0.4	0.2	0.4
$\bar{k}_2$/l mol^{-1} s^{-1}	0.597	0.582	0.579	108	117	105	4.55	4.54	4.38	35.9	33.8	34.1
Mean $\bar{k}_2$/l mol^{-1} s^{-1}	0.586 ± 0.010			110 ± 6			4.49 ± 0.10			34.6 ± 1.1		
	3-Amino-2-chloropyridine						3-Amino-6-methoxypyridine					
$[HClO_4]$/M	0.025			0.100			0.05			0.25		
$10^4[\text{Amine}]_i$/M	1.5	1.5	3.0	1.0	1.0	2.0	0.5	0.5	1.0	0.25	0.25	0.50
$10^4[\text{Nitrous acid}]_i$/M	1.5	3.0	3.0	1.0	2.0	2.0	1.0	1.0	1.0	0.50	1.0	0.50
$\bar{k}_2$/l mol^{-1} s^{-1}	2.59	2.79	2.54	8.93	9.46	9.36	1.50	1.54	1.44	11.4	11.4	10.3
Mean $\bar{k}_2$/l mol^{-1} s^{-1}	2.64 ± 0.13			9.25 ± 0.28			1.49 ± 0.05			11.0 ± 0.6		

of the reactants remained constant (Table 1) for more than 70% reaction (Table 2). Moreover, the validity of rate expression (1) was confirmed by the observation

TABLE 2

Nitrosation of 3-methylaminopyridine and diazotisation of 3-amino-2-chloropyridine at 2.0°; constancy of $\bar{k}_2$ [equation (1)] during the reaction

3-Methylaminopyridine

$[HClO_4]$	0.14M
$[NaClO_4]$	0.36M
$[Amine]_i$	5.0×10^{-5}M
$[Nitrous\ acid]_i$	2.5×10^{-5}M

t/min	10^5[Product]/M	$10\bar{k}_2$/l mol^{-1} s^{-1}
3	0.550	29.3
4	0.714	30.4
5	0.843	30.2
7	1.08	30.6
10	1.35	30.6
13	1.56	30.9
17	1.78	31.1
22	1.96	31.1

3-Amino-2-chloropyridine

$[HClO_4]$	0.10M
$[Amine]_i$	1.0×10^{-4}M
$[Nitrous\ acid]_i$	2.0×10^{-4}M

t/min	10^5[Product]/M	$\bar{k}_2$/l mol^{-1} s^{-1}
2	1.94	9.48
4	3.50	9.93
6	4.59	9.82
8	5.36	9.52
10	6.08	9.57
13	6.83	9.37
19	7.95	9.45
25	8.70	9.78

that for a number of acidities 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.

The values of $\bar{k}_2$ (Table 3) increase with an increase in the acidity of the medium and a plot of log $\bar{k}_2$ against $-$pH is a straight line for the nitrosation of 3-methylaminopyridine and the diazotisation of 3-aminopyridine with slopes of 1.24 and 1.25, respectively. However, similar plots for the diazotisation of 3-amino-2-chloro- and 3-amino-6-methoxy-pyridine are curves with rising slopes.

The values of $\bar{k}_2$ (Table 4) of the nitrosation of 3-methylaminopyridine and the diazotisation of 3-aminopyridine in 0.01M-perchloric acid solutions containing various concentrations of sodium perchlorate increase with an increase in the ionic strength of the medium (μ) because a plot of log $\bar{k}_2$ against $\sqrt{\mu}$ (Table 4) gave straight lines with slopes of 1.06 and 0.91, respectively. These results, which show the similarity that exists between the nitrosation and the diazotisation of the β-aminopyridines, suggest that these reactions involve charged species.[5a]

In solutions of perchloric acid kept at constant ionic strength of 0.50 by the addition of sodium perchlorate the values of $\bar{k}_2$ (Table 5) increase with an increase in the acidity of the medium. Thus a plot of log $\bar{k}_2$ against $-$pH is a straight line for the nitrosation of 3-methylaminopyridine and 3-methylaminopyridine 1-oxide with slopes of 1.00 and 0.93, respectively, and also for the diazotisation of 3-amino- and 3-amino-2-chloro-pyridine with slopes of 1.02 and 0.91, respectively. However, a similar plot for the diazotisation of 3-amino-6-methoxy-pyridine is a straight line only for low acidities whilst for higher acidities it becomes a curve with a decreasing slope (Figure).

It is noteworthy that the second-order rate expression (1) was obeyed throughout the acid range studied in the present work without changing to a third-order rate expression. Thus it can be concluded that the nitrous anhydride mechanism, which follows third-order kinetics [3,4] (first-order with respect to the amine and second-order with respect to nitrous acid) does not contribute to the nitrosation of 3-methylaminopyridine and 3-methylaminopyridine 1-oxide and to the diazotisation of 3-amino-, 3-amino-2-chloro-, and 3-amino-6-methoxy-pyridine even when these reactions are carried

TABLE 3

Nitrosation of 3-methylaminopyridine and diazotisation of 3-amino-, 3-amino-2-chloro-, and 3-amino-6-methoxy-pyridine at 2.0°; dependence of $\bar{k}_2$ [equation (1)] on the concentration of an excess of perchloric acid

	3-Methylamino-pyridine		3-Aminopyridine		3-Amino-2-chloro-pyridine		3-Amino-6-methoxy-pyridine	
$[HClO_4]$/M	pH *	$\bar{k}_2$/l mol^{-1} s^{-1}	pH *	$\bar{k}_2$/l mol^{-1} s^{-1}	pH *	$\bar{k}_2$/l mol^{-1} s^{-1}	pH *	$\bar{k}_2$/l mol^{-1} s^{-1}
0.0025	2.53	0.124 ± 0.005						
0.002			2.69	0.100 ± 0.003				
0.010	2.12	0.589 ± 0.011	2.02	0.649 ± 0.014			2.13	0.521 ± 0.027
0.020	1.75	1.42 ± 0.02						
0.025					1.70	2.82 ± 0.23	1.67	0.691 ± 0.050
0.032					1.60	4.04 ± 0.09		
0.050	1.34	4.79 ± 0.18	1.40	4.46 ± 0.10	1.33	5.23 ± 0.35	1.31	1.50 ± 0.05
0.075					1.17	6.76 ± 0.30	1.06	2.49 ± 0.11
0.100	1.00	12.5 ± 0.2	1.00	10.6 ± 0.5	0.97	9.30 ± 0.28	0.96	3.57 ± 0.12
0.140					0.82	12.5 ± 0.6	0.81	5.32 ± 0.19
0.200	0.70	32.8 ± 0.7	0.70	34.0 ± 1.1				
0.250					0.60	26.5 ± 1.2	0.60	11.1 ± 0.6
0.355					0.40	47.9 ± 3.7		
0.500	0.20	108 ± 6	0.20	116 ± 1	0.20	92.5 ± 0.9	0.20	23.4 ± 0.5

* Values determined by pH meter.

out in the presence of excess of sodium perchlorate, which is known to catalyse the formation of nitrous anhydride [6] (Table 6). These results are contrary to those of the nitrosation of *N*-methylaniline [3] and the diazotisation of aniline [4] in ≤0.5M-perchloric acid solutions because under these conditions the more basic aromatic amines are known to react mainly with nitrous anhydride.[4]

It follows from the present results that the nitrosation of 3-methylaminopyridine and 3-methylaminopyridine 1-oxide and the diazotisation of 3-amino-, 3-amino-2-chloro-, and 3-amino-6-methoxy-pyridine can be examined together because these reactions show similar kinetic behaviour.

Rate expression (1) can therefore be expanded to (2) for the nitrosation of 3-methylaminopyridine (pK_{a_1} 6.41 at 20° and pK_{a_2} −2.17 at 20°) and the diazotisation

TABLE 4

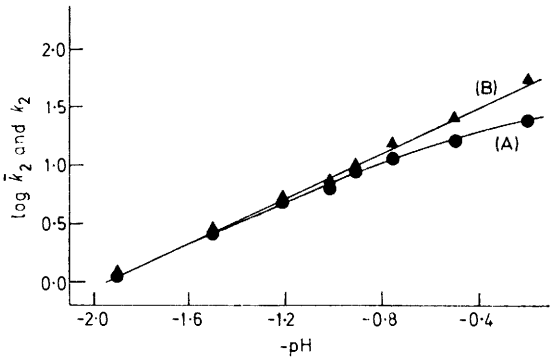
Nitrosation of 3-methylaminopyridine and diazotisation of 3-aminopyridine in 0.01M-perchloric acid and at 2.0°; dependence of $\bar{k}_2$ [equation (1)] on the concentration of sodium perchlorate

	3-Methylaminopyridine	3-Aminopyridine
$[NaClO_4]$/M	$\bar{k}_2$/l mol^{-1} s^{-1}	$\bar{k}_2$/l mol^{-1} s^{-1}
0.00	0.589 ± 0.011	0.649 ± 0.014
0.01	0.721 ± 0.019	0.734 ± 0.018
0.02	0.776 ± 0.023	0.768 ± 0.012
0.05	0.923 ± 0.020	0.919 ± 0.020
0.07	1.02 ± 0.03	0.954 ± 0.020
0.10	1.12 ± 0.03	1.11 ± 0.04
0.15	1.38 ± 0.04	1.24 ± 0.03
0.20	1.55 ± 0.04	1.40 ± 0.04

of 3-aminopyridine (pK_{a_1} 6.03 [7] at 20° and pK_{a_2} −1.38 at 20°) because these amines must be present almost

$$\text{Rate} = k_3[\text{Monoprotonated amine}][HNO_2][H^+] \quad (2)$$

entirely as the monocations under the present experimental conditions and in this case $\bar{k}_2 \propto [H^+]$. However, diazotisation of the α- and γ-aminopyridines,[1,8] the contribution to the overall rate of the reaction from a reaction path described by rate expression (3) cannot be neglected. Thus it is useful to determine separately



Plot of log $\bar{k}_2$ (A) and log k_2 (B) against −pH for the diazotisation of 3-amino-6-methoxypyridine in perchloric acid solutions kept at a constant ionic strength of 0.50 by the addition of sodium perchlorate

the contribution of the two reaction paths described by rate expressions (2) and (3).

$$\text{Rate} = k_3'[\text{Free amine}][HNO_2][H^+] \quad (3)$$

Equation (4) is, therefore, the result of a combination of equations (2) and (3) because [Free amine][H$^+$] = [Monoprotonated amine]K_{a_1}, where K_{a_1} is the thermodynamic dissociation constant of the conjugate monoacid

$$\text{Rate} = (k_3'K_{a_1} + k_3[H^+])\text{-}[\text{Monoprotonated amine}][HNO_2] \quad (4)$$

$$\bar{k}_2 = k_3'K_{a_1} + k_3[H^+] \quad (5)$$

of the amine. Equation (5) can be derived from equations (1) and (4) for the nitrosation of 3-methylaminopyridine and for the diazotisation of 3-aminopyridine at constant ionic strength because these amines are present

TABLE 5

Nitrosation of 3-methylaminopyridine and 3-methylaminopyridine 1-oxide and diazotisation of 3-amino-, 3-amino-2-chloro-, and 3-amino-6-methoxy-pyridine at 2.0°; dependence of $\bar{k}_2$ [equation (1)] on the concentration of perchloric acid in solutions kept at a constant ionic strength of 0.50 by the addition of sodium perchlorate

		3-Methylamino-pyridine	3-Methylaminopyridine 1-oxide	3-Aminopyridine	3-Amino-2-chloro-pyridine	3-Amino-6-methoxy-pyridine
$[HClO_4]$/M	pH	$\bar{k}_2$/l mol^{-1} s^{-1}	$\bar{k}_2$/l mol^{-1} s^{-1}	$\bar{k}_2$/l mol^{-1} s^{-1}	$\bar{k}_2$/l mol^{-1} s^{-1}	$\bar{k}_2$/l mol^{-1} s^{-1}
0.010	1.90	2.19 ± 0.08	2.61 ± 0.12	2.34 ± 0.04		1.19 ± 0.08
0.025	1.50	5.71 ± 0.12	6.01 ± 0.34	6.35 ± 0.12	6.14 ± 0.16	2.62 ± 0.05
0.050	1.21	10.4 ± 0.1	11.2 ± 0.5	12.5 ± 0.5	11.1 ± 0.2	4.74 ± 0.05
0.075	1.02	16.1 ± 0.9	16.0 ± 0.9	17.5 ± 0.1	14.5 ± 0.6	6.42 ± 0.28
0.100	0.91	23.3 ± 0.6	21.3 ± 0.5	24.8 ± 0.9	21.5 ± 1.2	8.71 ± 0.42
0.140	0.76	30.8 ± 0.4	29.4 ± 0.8		23.8 ± 0.5	11.2 ± 0.3
0.250	0.50	54.6 ± 1.9	53.5 ± 2.5	68.4 ± 0.8	51.9 ± 1.2	15.7 ± 0.2
0.500	0.20	108 ± 6	98.4 ± 3.5	116 ± 1	92.5 ± 0.8	23.4 ± 0.5

the concentration of the free form of 3-methylaminopyridine 1-oxide (pK_{a_1} 1.67 at 2° and pK_{a_2} −2.42 at 25°) or of 3-amino-2-chloropyridine (pK_{a_1} 1.96 at 2° and pK_{a_2} −3.64 at 25°) is comparable to that of the monoprotonated form and therefore the overall rate of the nitrosation of the former or of the diazotisation of the latter amine cannot be described by rate expression (2) only, because, as in the case of the nitrosation or the almost entirely as the conjugate monoacids under the present experimental conditions. However, for the case of the nitrosation of 3-methylaminopyridine 1-oxide and the diazotisation of 3-amino-2-chloropyridine equation (6) can be derived from equations (1) and (4) because under the present experimental conditions the concentration of the free form of these amines is comparable to that of the monoprotonated form which is

given by equation (7). Values of k_3' and k_3 (Table 7) were, therefore, evaluated by plotting either $\bar{k}_2$ against $[H^+]$ or $\bar{k}_2/[H^+]$ against $1/[H^+] + K_{a_1}$ [equations (5) and (6), respectively] and then calculating the slopes and intercepts of the straight lines obtained.

$$\frac{\bar{k}_2}{[H^+]} = k_3 + (k_3' - k_3)K_{a_1}\frac{1}{[H^+] \times K_{a_1}} \quad (6)$$

$$[\text{Monoprotonated amine}] = \frac{[H^+]}{[H^+] + K_{a_1}}[\text{Stoicheiometric amine}] \quad (7)$$

write rate expression (1) as rate expression (8) in which the value of k_2 is given by equation (9) because the concentration of the monoprotonated amine can be obtained from equation (10). When the values of log k_2 were,

$$\text{Rate} = k_2[\text{Monoprotonated amine}][HNO_2] \quad (8)$$

$$k_2 = \bar{k}_2(1 + [H^+]/K_{a_2}) \quad (9)$$

$$[\text{Monoprotonated amine}] = \frac{[\text{Amine}]}{(1 + [H^+]/K_{a_2})} \quad (10)$$

therefore, plotted against −pH a straight line was obtained with a slope of 0.95 (Figure) thus showing that

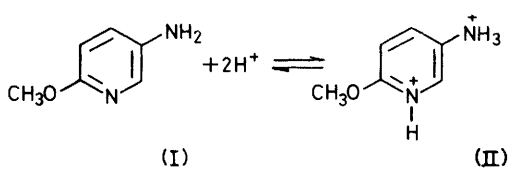
TABLE 6

Nitrosation of 3-methylaminopyridine and 3-methylaminopyridine 1-oxide and diazotisation of 3-amino-, 3-amino-2-chloro-, and 3-amino-6-methoxy-pyridine at 2.0°; constancy of $\bar{k}_2$ [equation (1)] in the presence of sodium perchlorate

	3-Methylaminopyridine						3-Methylaminopyridine 1-oxide					
	0.075M-$HClO_4$ + 0.425M-$NaClO_4$			0.250M-$HClO_4$ + 0.250M-$NaClO_4$			0.010M-$HClO_4$ + 0.490M-$NaClO_4$			0.050M-$HClO_4$ + 0.450M-$NaClO_4$		
10^4[Amine]$_i$/M	0.7	0.7	1.4	0.1	0.1	0.2	1.6	1.6	3.2	1.6	3.2	3.2
10^4[Nitrous acid]$_i$/M	0.7	1.4	0.7	0.1	0.2	0.2	1.6	3.2	3.2	3.2	1.6	3.2
$\bar{k}_2$/l mol^{-1} s^{-1}	15.7	17.1	15.4	52.8	56.2	53.2	2.55	2.54	2.76	11.0	11.4	11.7
Mean $\bar{k}_2$/l mol^{-1} s^{-1}	16.1 ± 0.9			54.1 ± 1.9			2.62 ± 0.12			11.4 ± 0.4		

	3-Aminopyridine 0.01M-$HClO_4$ + 0.490M-$NaClO_4$			3-Amino-2-chloropyridine 0.100M-$HClO_4$ + 0.400M-$NaClO_4$			3-Amino-6-methoxypyridine					
							0.025M-$HClO_4$ + 0.475M-$NaClO_4$			0.075M-$HClO_4$ + 0.425M-$NaClO_4$		
10^4[Amine]$_i$/M	1.4	1.4	2.8	1.0	2.0	2.0	0.5	0.5	1.0	0.5	0.5	1.0
10^4[Nitrous acid]$_i$/M	1.4	2.8	1.4	2.0	1.0	2.0	1.0	2.0	1.0	1.0	2.0	1.0
$\bar{k}_2$/l mol^{-1} s^{-1}	2.39	2.31	2.32	21.1	22.8	20.5	2.56	2.64	2.64	6.29	6.24	6.74
Mean $\bar{k}_2$/l mol^{-1} s^{-1}	2.34 ± 0.04			21.5 ± 1.1			2.61 ± 0.05			6.42 ± 0.28		

From the plot of log $\bar{k}_2$ against −pH for the diazotisation of 3-amino-6-methoxypyridine (Figure) it can be seen that the rectilinear relationship predicted from equation (5) holds for acidities up to 0.1M-perchloric acid and that above this acidity the plot is a curve with decreasing slope. This deviation from a rectilinear relationship is presumably due to the formation of the dication (II) of the amine (pK_{a_1} 4.62 at 2° and pK_{a_2} 0.25 at 2°) in considerable amounts under the present experimental conditions. Since it is unlikely that the dication would participate in the reaction it is convenient to rewrite rate expression (1) as rate expression (2) in which the value of k_2 is given by equation (3) because the concentration of the monoprotonated amine can be obtained from equation (4). When the values of log k_2 were, therefore, plotted against −pH a straight line was obtained with a slope of 0.95 (Figure) thus showing that the diazotisation of 3-amino-6-methoxypyridine obeys rate expression (2) at constant ionic strength. Thus values of k_3' and k_3 (Table 7) for this reaction were calculated from equation (5) in which $\bar{k}_2$ was substituted by k_2.



(I) (II)

Rate expressions (2) and (3) are similar to those obtained in the nitrosation [1] and diazotisation [8,9] of α- and γ-aminopyridines and therefore they are taken to indicate that the nitrosation of 3-methylaminopyridine and 3-methylaminopyridine 1-oxide and the diazotisation of 3-amino-, 3-amino-2-chloro-, and 3-amino-6-methoxy-pyridine involve the interaction of the nitrous acidium ion with the protonated [rate expression (2)] and the free form [rate expression (3)] of these amines. The alternative possibility for rate expression (2) is (11) and this would indicate that in this case the reactions involve the free form of the amines and the nitrosonium ion. However, this alternative possibility is excluded

TABLE 7

Values of k_3' and k_3 [equations (5) and (6)] in perchloric acid solutions kept at constant ionic strength of 0.50 and at 2.0°

Amine	pK_{a_1}	pK_{a_2}	$10k_3'K_{a_1}$	$(k_3' - k_3)K_{a_1}$	$10^{-2}k_3'$/ l^2 mol^{-2} s^{-1}	k_3/ l^2 mol^{-2} s^{-1}
3-Methylaminopyridine	6.41 [a]	−2.17 [a]	5.13		13 190	171
3-Aminopyridine	6.03 [a,b]	−1.25 [c]	9.98		10 690	194
3-Amino-6-methoxypyridine	4.62 [c]	+0.25 [c]	4.44		185	78
3-Amino-2-chloropyridine	1.96 [c]	−3.64 [d]		2.07	3.33	144
3-Methylaminopyridine 1-oxide	1.67 [c]	−2.42 [d]		1.43	2.27	160

[a] At 20°. [b] Ref. 6. [c] At 2°. [d] At 25°.

(as in the case of the nitrosation and diazotisation of the α- and γ-aminopyridines [1,8,9]) because the concentration of the free amines and of the nitrosonium ion is

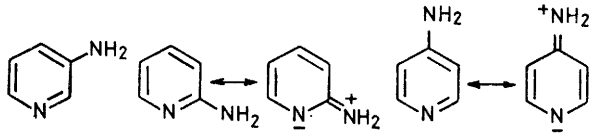
$$\text{Rate} = k_4\,[\text{Free amine}][HNO_2]\,h_0^2 \qquad (11)$$

too low to account for the observed rates of the above reactions even if these reactions were assumed to take place on encounter.[5b] This argument is supported by the observation that in 0.50M-perchloric acid 3-aminopyridine and 3-methylaminopyridine are 1.3 and 1.1 times more reactive than 3-amino-2-chloro-pyridine and 3-methylaminopyridine 1-oxide, respectively, in spite of the fact that the concentration of the free form of the former amines is respectively 17 400 and *ca.* 60 000 times smaller than that of the latter amines (Table 5).

The values of k_3' and k_3 (Table 7), which were determined by the method of least squares, show that the free form (k_3') of the β-aminopyridines is more reactive than the protonated form (k_3) towards the nitrous acidium ion. Moreover, in contrast to the nitrosation and the diazotisation of the aromatic amines more basic than *p*-nitroaniline for which the values of k_3' appear to approach a limiting value,[3,4] the nitrous acidium ion shows a distinct discrimination in its reaction with the free β-aminopyridines examined in this work and does not seem to approach a limiting value. Indeed a plot of log ($k_3'/{}_0k_3'$) against log ($K_{a_1}/{}_0K_{a_1}$) is a straight line with a slope of −0.81 ($_0k_3'$ and $_0K_{a_1}$ refer to 3-aminopyridine). These results are similar to those of the nitrosation and the diazotisation of the α- and γ-aminopyridines [1,8b] and they suggest that the nitrosating agent associates with the heteroaromatic nucleus first (most probably the basic centre) and then, as a result of electronic rearrangement, it migrates to 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 interesting to note that the free β-aminopyridines are more reactive than the free α- and γ-aminopyridines [1,8,9] of comparable basicity. Thus the values of k_3' of the nitrosation of 3-methylaminopyridine and of the diazotisation of 3-aminopyridine at a constant ionic strength of 0.50 are 1.6 and 22.6 times greater than those of the nitrosation of 2-methylaminopyridine [1] and of the diazotisation of 2-aminopyridine,[9b] respectively, at a constant ionic strength of 3.0 in spite of the fact that the latter amines are, respectively, 5.3 and 6.2 times more basic than the former amines and that the ionic strength of their reaction solutions is 6 times greater. This is most probably due to the greater electron-donor capacity of the amino-group in the 3-position of the pyridine ring compared with that in the 2- or the 4-position. This is because the amino-group in the 3-position is subject mainly to an inductive effect [structure (III)] whilst the amino-group in the 2- or the 4-position is subject mainly to a resonance effect [structures (IVb) and (Vb)] which is more effective in depleting the amino-group of its electron pair.

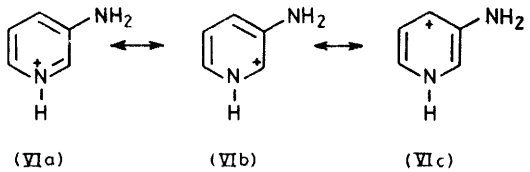
It is evident from the values of k_3 (Table 7) that protonated β-aminopyridines are more reactive than protonated α- or γ-aminopyridines.[1,8,9] Thus protonated 3-methylaminopyridine is 855 or 452 times more reactive than the protonated 2- or 4-methylaminopyridine,[1] respectively. Also protonated 3-methylaminopyridine 1-oxide is 880 or 137 times more reactive than protonated 2- or 4-methylaminopyridine 1-oxide,[1] respectively. These differences are difficult to explain by assuming that



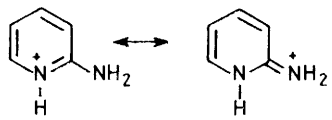
(iii) (IVa) (IVb) (Va) (Vb)

nitrosation or diazotisation of the protonated β-aminopyridines involves attack of the nitrous acidium ion on the heteroaromatic nucleus as for nitrosation or diazotisation of the protonated α- and γ-aminopyridines.[1,8,9] This is because the differences in the reactivities indicated above are too large to be attributed to a greater electron-donor capacity of the heteroaromatic nucleus of the β-aminopyridines compared with that of the α- and γ-aminopyridines. Indeed these differences should have been in the opposite direction if the reactions involved an attack of the nitrous acidium ion on the heteroaromatic nucleus, because the electron donor capacity of the heteroaromatic nucleus of the protonated β-aminopyridines must be much smaller than that of the α- and γ-aminopyridines. This is so because, in the case of the protonated β-aminopyridines, the positive charge of the ring nitrogen is delocalised only into the π-system of the heteroaromatic nucleus [structures (VIb and c)], whilst in the case of the protonated α- and γ-aminopyridines the delocalisation of the positive charge into the π-system of the ring is greatly diminished by resonance between the positively charged ring nitrogen and the exocyclic amino-group [structures (VIIb) and (VIIIb)].

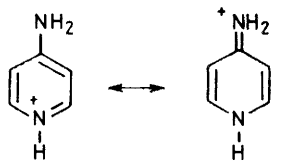
It is therefore more likely that nitrosation and diazotisation of the protonated γ-aminopyridines proceed by a reaction path which involves direct attack of the nitrous acidium ion on the exocyclic amino-nitrogen and then migration of an amino-proton to the medium as shown in the Scheme. This reaction path resembles that of nitrosation and diazotisation of the free form of the aromatic amines by the nitrous acidium ion,[3b,4] in that the nitrosating agent directly attacks the amino-group and does not interact with the aromatic ring and that the values of k_3 (Table 7) show only a very small increase with an increase in the basic strength of the amines. Thus in the case of the protonated β-aminopyridines a plot of log ($k_3/{}_0k_3$) against log ($K_{a_2}/{}_0K_{a_2}$) gives a straight line with a slope of only −0.06 ($_0k_3$ and $_0K_{a_2}$ refer to 3-aminopyridine). However, 2-amino-6-methoxypyridine is much less reactive than expected from the above plot although it has a high pK_{a_2} value



(VIa) (VIb) (VIc)



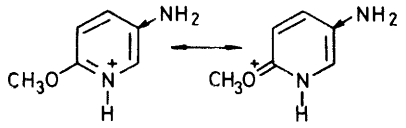
(VIIa) (VIIb)



(VIIIa) (VIIIb)

(Table 7). This is most probably due to a decrease in the acidity of the amino-protons because structure (IXb) would be expected to contribute significantly to the resonance hybrid of the molecule thus greatly decreasing the attraction exerted by the protonated heteroaromatic nucleus on the amino-group. Thus the retarding effect on the migration of an amino-proton to the medium seems in this case to be more important than the increase in the availability of the electron pair of the amino-group.

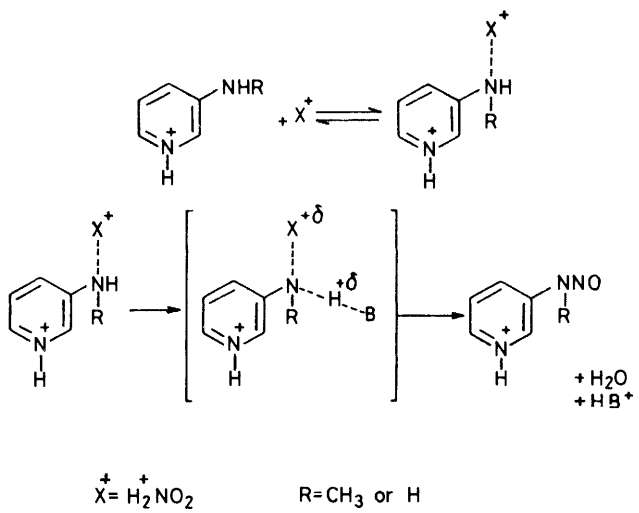
It is noteworthy that the values of k_3 (Table 7) do not vary greatly from one another and that they tend to approach a limiting value of *ca.* 200 l^2 mol^{-2} s^{-1} at constant ionic strength of 0.50. These results are similar to those of nitrosation and diazotisation of the free aromatic amines more basic than *p*-nitroaniline,[3b,4] for which the values of k_3 do not differ greatly from one another but they approach a limiting value of *ca.* 180 l^2 mol^{-2} s^{-1} at low ionic strengths. It is difficult to explain these results by assuming that the nitrous acidium ion acting, as a strong nitrosating agent, cannot discriminate between the protonated amine molecules because such limitation was not evident in the case of the free 3-aminopyridines and in the free 2- and 4-aminopyridines.[8b] It is, however, more likely that the above results are due to the opposite directions in which the polarisability and the polarisation of the amino-group act in the transition state. Thus during the approach of the nitrosating agent the polarisability of



(IXa) (IXb)

the amino-group becomes more important than its polarisation, which exerts only a small decreasing effect on the k_3 values. This explanation may also be applicable for the case of nitrosation and diazotisation of free aromatic amines.

It seems therefore reasonable that the values of k_3 should tend towards an upper limit corresponding to the complete availability of the lone pair of electrons of the amino-nitrogen, which for the free aromatic amines and the monoprotonated β-aminopyridines seems to be about the same. Since the differences in the values of k_3 are relatively small it appears that only great changes in the polarisation of the amino-group would have a substantial effect on the values of k_3. Thus the value of k_3 of the diazotisation of *p*-nitroaniline [4a] is 161 l^2 mol^{-2} s^{-1} but that of 2,4-dinitroaniline [4a] is only 3.7 l^2 mol^{-2} s^{-1}.



X= $H_2NO_2^+$ R=CH_3 or H

SCHEME

EXPERIMENTAL

Materials.—3 Methylaminopyridine was prepared [10] by treating 3-aminopyridine (Fluka; purum) with toluene-*p*-sulphonate (Fluka; pract.), methylating the toluene-*p*-sulphonamide formed with dimethyl sulphate (Merck; 98%). and then hydrolysing the methyl derivative with 80% sulphuric acid. The product obtained after extraction with ether was distilled twice at 110 °C and 7 mmHg (lit.,[10] 110 °C and 7 mmHg), yield 65%. 3-Methylaminopyridine 1-oxide was prepared [11] by treating 3-methylaminopyridine with acetic anhydride (Fluka; purum) and then oxidising the *N*-acetyl derivative dissolved in acetic acid (Fluka; purum) with 35% hydrogen peroxide (Merck; pro analysi). The product obtained after hydrolysis with hydrochloric acid, neutralisation with solid sodium hydroxide, and then extraction with chloroform (solution saturated with sodium chloride) was recrystallized from ethyl acetate and then sublimed twice at 95 °C and 0.1 mmHg, yield 50%, m.p. 110—112 °C. 3-Aminopyridine (Fluka; purum) was sublimed twice at 35 °C and 0.2 mmHg. 3-Amino-2-chloropyridine (Fluka; purum) was sublimed twice at 60 °C and 0.05 mmHg. 3-Amino-6-methoxypyridine

(Aldrich; 95%) was twice distilled over potassium hydroxide at 120 °C and 15 mmHg. 3-Hydroxypyridine (Fluka; purum) was sublimed twice at 65 °C and 0.2 mmHg. 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. All purified products had satisfactory elemental analysis. Microanalyses were carried out by Dr. Ch. Mantzos.

3-Nitrosomethylaminopyridine was prepared by treating sodium nitrite (4 g) in water (15 ml) with 3-methylaminopyridine (1.5 g) in a solution of concentrated hydrochloric acid (15 ml) and water (30 ml) at 0 °C. After 20 min standing the reaction solution was treated with solid sodium carbonate until alkaline and then extracted with ether. The liquid obtained was distilled twice at 114 °C and 4 mmHg to give *3-nitrosomethylaminopyridine* (1.2 g, 80%) (Found: C, 52.8; H, 5.35; N, 30.3. $C_6H_7N_3O$ requires C, 52.55; H, 5.1; N, 30.6%). 3-Nitrosomethylaminopyridine 1-oxide was prepared by reacting sodium nitrite (0.5 g) in water (10 ml) with 3-methylaminopyridine 1-oxide (0.3 g) in 2.5M-hydrochloric acid (20 ml) at 2 °C. After 15 min the solution was treated with solid sodium carbonate until alkaline and then evaporated to dryness under vacuum (Büchi apparatus). The residue was extracted with chloroform (Sohxlet apparatus) and then the solid obtained after evaporation of the chloroform extract was sublimed twice at 105 °C and 0.2 mmHg to give *3-nitrosomethylaminopyridine 1-oxide* (0.24 g, 80%), m.p. 147—149 °C (Found: C, 47.35; H, 4.65; N, 27.2. $C_6H_7N_3O_2$ requires C, 47.05; H, 4.6; N, 27.45%).

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 mixtures were then vigorously shaken and their u.v. spectra were recorded at regular intervals, after having placed a portion of these mixtures in a pre-cooled Unicam cell (1.0 cm) and maintaining the temperature at 2.0 °C.

For the nitrosation of 3-methylaminopyridine and 3-methylaminopyridine 1-oxide absorbances in both cases were read at 340 nm at which ε of 3-methylaminopyridine, 3-nitrosomethylaminopyridine, and 3-nitrosomethylaminopyridine 1-oxide are 3.03×10^3, 2.74×10^2 and 3.92×10^2, respectively, for all acidities examined. Values of ε of 3-methylaminopyridine 1-oxide at various acidities are in Table 8.

TABLE 8

Extinction coefficients of 3-methylaminopyridine 1-oxide and 3 amino-2-chloropyridine at various pH values and at 2.0 °C

pH	3-Methylaminopyridine 1-oxide $10^{-3}\varepsilon$ at 340 nm	3-Amino-2-chloropyridine $10^{-3}\varepsilon$ at 330
0.20	3.13	5.39
0.50	3.09	5.29
0.60		5.17
0.76	3.05	4.85
0.82		4.78
0.91	2.98	4.40
1.02	2.92	4.30
1.17		4.00
1.21	2.81	3.97
1.33		3.66
1.50	2.71	3.40
1.60		3.22
1.70		2.89
1.90	2.57	

For the diazotisation of 3-amino-, 3-amino-6-methoxy-, and 3-amino-2-chloro-pyridine, absorbances were read at 315, 303, and 330 nm, respectively. At all acidities values of ε at 315 nm are 3.36×10^3 for 3-aminopyridine, 0 for 3-hydroxypyridine, 4.24×10^2 for pyridine-3-diazonium ion; at 303 nm 6.55×10^2 for 3-amino-6-methoxypyridine, 16.4×10^3 for 6-methoxypyridine-3-diazonium ion; at 330 nm 1.11×10^3 for 2-chloropyridine-3-diazonium ion. Values of ε of 3-amino-2-chloropyridine at various acidities are in Table 8.

Under the present experimental conditions the diazonium ions of 3-amino-6-methoxy- and 3-amino-2-chloro-pyridine are stable for at least 24 and 3 h, respectively, whilst that of 3-aminopyridine is the least stable and its decomposition to 3-hydroxypyridine is *ca.* 7% after 1 h. Good isosbestic

TABLE 9

	Temp. (°C)	pK_{a_1} [a]	Spread (±)	Concentration (10^5M)	A.w.l. [b] (nm)	Temp. (°C)	pK_{a_2} [c]	Spread (±)	Concentration (10^5M)	A.w.l [b] (nm)
3-Aminopyridine						2	−1.25	0.05	16.8	315
						20	−1.38	0.02	11.3	315
3-Methylaminopyridine	20	6.41 [d]	0.03	5.22	267	20	−2.17	0.02	4.35	267
3-Nitrosomethylaminopyridine	20	3.20 [d]	0.04	7.37	300					
3-Dimethylaminopyridine	20	6.67 [d]	0.03	21.6	300	20	−1.91	0.01	21.6	340
3-Methylaminopyridine 1-oxide	2	1.67	0.03	20.0	360	25	−2.42	0.03	12.0	340
3-Amino-2-chloropyridine	2	1.96	0.05	10.0	326					
	25	1.79	0.01	10.0	326	25	−3.64	0.07	10.0	324
3-Amino-6-methoxypyridine	2	4.62 [d]	0.04	20.6	305	2	0.25	0.06	10.3	285
	25	4.24 [d]	0.02	20.0	305	25	0.21	0.06	10.0	285
4-Nitroaniline	2	1.16	0.04	5.0	380					

[a] Values refer to the gain of one proton. [b] A.w.l. = analytical wavelength. [c] Values refer to the gain of a second proton. [d] Buffers used had ionic strength 0.01.

points were therefore obtained for *ca.* 100% reaction during the kinetic runs for the diazotisation of 3-amino-6-methoxy- and 3-amino-2-chloro-pyridine and for 70% reaction during the kinetic runs for the diazotisation of 3-aminopyridine.

Determination of pH.—Because the reactants were present as the perchlorate salts of the amines and as free nitrous acid in high concentrations in some cases, especially in the very dilute perchloric acid solutions ($\leqslant 0.10$M), it was necessary to determine, by pH meter, the pH of the final solutions at 2°. The values obtained are in Tables 3, 5, and 8.

Determination of pK_a *Values.*—These were measured spectrophotometrically [12] in water at 2, 20, and 25 °C (Table 9).

Calculation of Rate Coefficients.—The concentration of the amine in the reaction mixtures was calculated from the expression [Amine] = $(D - A\varepsilon_2)/(\varepsilon_1 - \varepsilon_2)$ where D is the observed optical density 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 or diazonium ion, respectively. The absorption of nitrous acid under the conditions used is negligible. The rate coefficients were calculated from the usual second-order expression [5c] by using the individual values of absorbances. Typical data are in Table 3. Values of K_a determined at 2° (Table 9) were used when calculating values of k_3' and k_3.

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