Reaction of *N*-Heteroaromatic Bases with Nitrous Acid. Part 8.[1] Kinetics of the Diazotisation of 1-Methyl- and 1-Methoxy-4-aminopyridinium Perchlorate in Aqueous Perchloric Acid

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The diazotisation of 1-methyl-4-aminopyridinium perchlorate in 0.25—5.00M-perchloric acid is of first order in both the amine and nitrous acid. The rate coefficients 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 diazotisation of 1-methyl- and 1-methoxy-4-aminopyridinium perchlorate show a rectilinear dependence on the h_0 parameter of the medium. It is suggested that the reaction involves an initial interaction between the nitrosating agent and the heteroaromatic nucleus of the 1-methyl- or the 1-methoxy-4-aminopyridinium ion. pK_a Values are recorded.

Diazotisation of 2- and 4-aminopyridine in aqueous perchloric acid has been postulated to proceed mainly by a reaction of the nitrosating agent with the monoprotonated form of these amines.[2]

This paper presents a study of the kinetics of the diazotisation of 1-methyl- and 1-methoxy-4-aminopyridinium perchlorate in aqueous perchloric acid. The results indicate that the kinetics are similar to those of the diazotisation of the monoprotonated forms of 2- and 4-aminopyridine and their derivatives.[2,3]

Results and Discussion

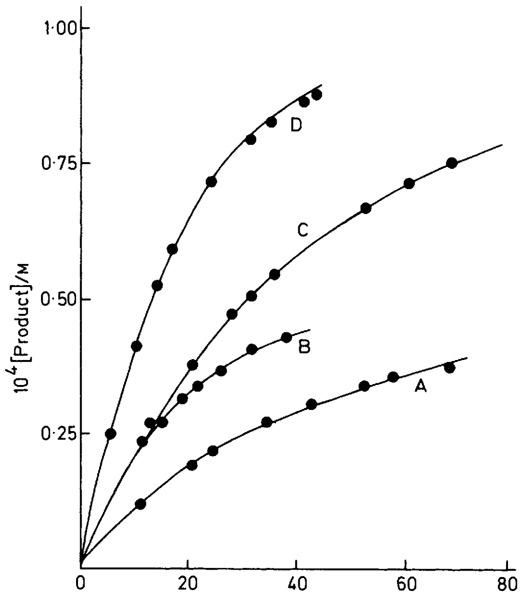
As in the case of 2- and 4-aminopyridine [2] the nitrosation of 1-methyl- and 1-methoxy-4-aminopyridinium perchlorate in aqueous perchloric acid is reversible. However, the use of excess in the initial concentration of nitrous acid made it possible to treat the reaction as practically irreversible. Thus in 0.25—5.00M-perchloric acid the diazotisation of 1-methyl-4-aminopyridinium perchlorate follows rate expression (1).

$$\text{Rate} = \bar{k}_2[\text{1-Substituted 4-aminopyridinium ion}][\text{HNO}_2] \quad (1)$$

Thus at a given acidity 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).

The results obtained for the various acidities show that the values (Table 1) of the stoicheiometric second-order rate coefficients ($\bar{k}_2$) increase with an increase in the acidity of the medium and a plot of log $\bar{k}_2$ against H_0 gave a straight line with a slope of 1.38.

In perchloric acid solutions kept at constant ionic strength of 3.0 by the addition of sodium perchlorate the diazotisation of 1-methyl- and 1-methoxy-4-aminopyridinium perchlorate follows rate expression (1). The values of $\bar{k}_2$ are satisfactorily constant at a given acidity (Table 2) and their dependence on the acidity of the medium kept at constant ionic strength (Table 3) 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 (0.91 and 0.90 for 1-methyl- and 1-methoxy-4-aminopyridinium perchlorate, respectively). These results are similar to those obtained for the diazotisation of the monoprotonated 2- and 4-aminopyridine.[2]



Diazotisation of 1-methyl-4-aminopyridinium perchlorate (amine salt) in 3.50M-perchloric acid and at 2.0°; variation of reaction rate with initial concentration of amine salt and nitrous acid; A, 0.5 × 10^{-4} and 2.0 × 10^{-4}M; B, 0.5 × 10^{-4} and 4.0 × 10^{-4}M; C, 1.0 × 10^{-4} and 2.0 × 10^{-4}M; D, 1.0 × 10^{-4} and 4.0 × 10^{-4}M. Initial rates: A, 1.35 × 10^{-6}; B, 2.55 × 10^{-6}; C, 2.55 × 10^{-6}; D, 5.52 × 10^{-6} mol l^{-1} min^{-1}

The catalytic medium effect of perchloric acid on these reactions was examined by studying the diazotisation of 1-methyl-4-aminopyridinium perchlorate in 1.0M-perchloric acid containing various concentrations of sodium perchlorate (up to 3.5M). The results showed that the values of $\bar{k}_2$ (Table 4) increase with an increase in the ionic strength (μ) of the medium. Thus a plot of log $\bar{k}_2$ against μ gave a straight line with a slope of 0.40, which is reduced to 0.21 when the $\bar{k}_2$ values are corrected to refer to a common value of h_0 corresponding to 1.0M-perchloric acid since the addition of sodium perchlorate increases the acidity of the medium.[2,3] These results are similar to those obtained for the diazotisation of 2- and 4-aminopyridine [2] and they show that the reaction of these amines involves charged species.[4]

The above results indicate that rate expression (1) can be

Table 1. Diazotisation of 1-methyl-4-aminopyridinium perchlorate at 2.0°; dependence of k_2 [equation (1)] on the concentration of an excess of perchloric acid

[$HClO_4$]/M	h_0 *	$10k_2$/l mol^{-1} s^{-1}
0.25	+0.60	0.0276 ± 0.0006
0.50	+0.20	0.284 ± 0.003
1.00	−0.22	0.532 ± 0.021
1.50	−0.53	1.05 ± 0.07
2.00	−0.78	2.69 ± 0.01
2.50	−1.01	6.86 ± 0.84
3.00	−1.23	10.4 ± 0.3
3.50	−1.47	23.4 ± 1.4
4.00	−1.72	56.3 ± 3.5
5.00	−2.21	247 ± 3

* *Cf.* ref. 2*a*.

Table 4. Diazotisation of 1-methyl-4-aminopyridinium perchlorate in 1.0M-perchloric acid at 2.0°; dependence of k_2 [equation (1)] on the concentration of added sodium perchlorate

[$NaClO_4$]/M	h_0 *	$10k_2$/l mol^{-1} s^{-1}
0.00	1.78	0.532 ± 0.021
0.50	2.42	1.11 ± 0.03
1.00	3.15	1.56 ± 0.08
1.50	4.01	2.20 ± 0.09
2.00	5.12	3.90 ± 0.13
2.50	7.02	6.81 ± 0.23
3.00	9.00	10.2 ± 0.4
3.50	11.5	18.8 ± 0.3

* *Cf.* ref. 2*a*.

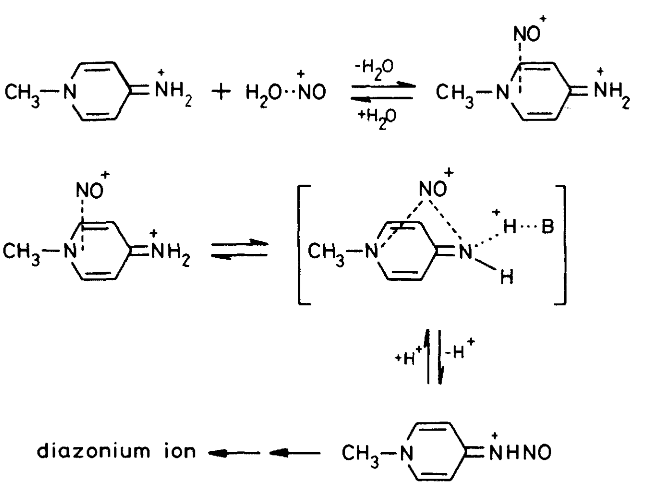
Table 2. Diazotisation of 1-methyl- and 1-methoxy-4-aminopyridinium perchlorate (amine salt) at 2.0°; constancy of k_2 [equation (1)] at a given acidity and at constant ionic strength of 3.0

	1-Methyl-4-aminopyridinium perchlorate						1-Methoxy-4-aminopyridinium perchlorate			
	2.00M-$HClO_4$ + 1.00M-$NaClO_4$			2.50M-$HClO_4$ + 0.50M-$NaClO_4$			1.00M-$HClO_4$ + 2.00M-$NaClO_4$		2.00M-$HClO_4$ + 1.00M-$NaClO_4$	
10^4[Amine salt]$_i$/M	1	1	2	1	2	2	5	5	5	5
10^4[Nitrous acid]$_i$/M	4	8	8	4	4	8	20	40	20	40
k_2/l mol^{-1} s^{-1}	0.810	0.819	0.805	0.983	0.973	1.00	0.069	0.067	0.134	0.136
Mean k_2/l mol^{-1} s^{-1}	0.811 ± 0.007			0.985 ± 0.013			0.068 ± 0.001		0.135 ± 0.001	

Table 3. Diazotisation of 1-methyl- and 1-methoxy-4-aminopyridinium perchlorate at 2.0°; dependence of k_2 [equation (1)] on the concentration of perchloric acid in solutions kept at constant ionic strength of 3.0 by the addition of sodium perchlorate

[$HClO_4$]/M	H_0 *	1-Methyl-4-aminopyridinium perchlorate $10k_2$/l mol^{-1} s^{-1}	1-Methoxy-4-aminopyridinium perchlorate 10^2k_2/l mol^{-1} s^{-1}
0.05	+0.66	0.180 ± 0.005	0.558 ± 0.017
0.10	+0.34	0.510 ± 0.001	1.11 ± 0.06
0.25	−0.09	1.30 ± 0.10	1.73 ± 0.02
0.50	−0.40	1.90 ± 0.04	4.12 ± 0.27
1.00	−0.71	3.90 ± 0.13	6.80 ± 0.14
1.50	−0.90	5.46 ± 0.36	11.2 ± 1.1
2.00	−1.04	8.11 ± 0.07	13.4 ± 0.1
2.50	−1.17	9.85 ± 0.13	16.3 ± 1.3
3.00	−1.23	10.4 ± 0.3	22.0 ± 1.7

* *Cf.* ref. 2*a*.



Scheme

expanded to (2) which is similar to that obtained for the

$$\text{Rate} = k_3[\text{1-Substituted 4-aminopyridinium ion}][HNO_2]h_0 \quad (2)$$

nitrosation and for the diazotisation of the monoprotonated form of 2- or 4-methylaminopyridine [5] and 2- or 4-aminopyridine,[2,3] respectively. It can, therefore, be concluded that nitrosation is the slow step in the diazotisation of the 1-methyl- or 1-methoxy-4-aminopyridinium ion and that the reaction proceeds by an initial association between the nitrosating agent and the *N*-heteroaromatic nucleus of these ions and subsequent nitrosation of the exocyclic amino-group during the loss of one of its protons to the medium as shown in the Scheme. Thus support is provided for an earlier suggestion that the nitrosation of 2- and 4-methylaminopyridine [5] and the diazotisation of 2- and 4-aminopyridine [2,3] in aqueous perchloric acid proceed by an interaction of the monoprotonated form of these amines with the nitrosating agent.

In view of the above results it can be concluded that the presence of the easily removable proton on the ring nitrogen in the case of the monoprotonated 2- and 4-aminopyridine is not a prerequisite for the reaction to take place. It can also be concluded that the replacement of the proton in the 1-position of the protonated heteroaromatic nucleus by the methyl or by the methoxy-group does not alter the mechanism of the reaction. However, such a replacement affects the rate of the reaction. Thus from the values of k_3 (Table 5) it can be seen that relative to the diazotisation of the monoprotonated 4-aminopyridine [2a] the diazotisation of 1-methyl-4-aminopyridinium perchlorate is two times faster whilst that of the 1-methoxy-4-aminopyridinium perchlorate is 2.3 times slower.

These differences in the rates of the reaction must be due

Table 5. Values of k_3 [equation (2)] for diazotisation of 1-methyl- and 1-methoxy-4-aminopyridinium perchlorate (amine salt) in perchloric acid solution kept at constant ionic strength of 3.0 and at 2.0°

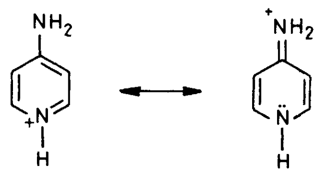
Amine or amine salt	$10^2k_3/$ $l^2\ mol^{-2}\ s^{-1}$
1-Methyl-4-aminopyridinium perchlorate	6.11
4-Aminopyridine [a]	3.03
4-Methylaminopyridine [b]	37.8
1-Methoxy-4-aminopyridinium perchlorate	1.29
4-Aminopyridine 1-oxide [c]	20.6
4-Methylaminopyridine 1-oxide [b]	117

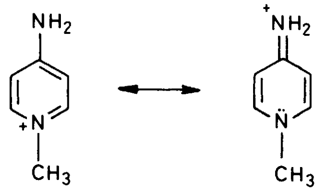
[a] Ref. 2a. [b] Ref. 5. [c] Ref. 3a.

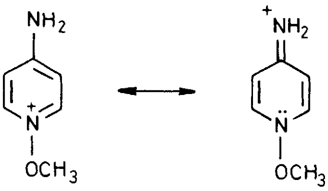
mainly to the $+I$ effect of the 1-methyl group and the $-I$ effect of the 1-methoxy group, respectively. However, they seem to be rather small probably because of steric hindrance associated with the methyl group when attached either to the 1-position of the heteroaromatic nucleus or when attached to the oxygen of the 1-oxide derivative. Thus the diazotisation of 1-methyl-4-aminopyridinium perchlorate is 6.2 times slower than the nitrosation of the mono-protonated 4-methylaminopyridine [5] (Table 5). The effect of the methyl group attached to the ring-nitrogen is expected to have an electronic effect similar to that of the methyl group attached to the exocyclic amino-group for which it has been suggested [5] that it has an enhancing effect on the π-electrons of the *N*-heteroaromatic nucleus thus accelerating the reaction. Therefore the smaller enhancement due to the methyl group observed during the present work is the result of its steric hindrance because of its proximity to the site (most probably the ring-nitrogen) which is involved in the initial interaction of the 1-methyl-4-aminopyridinium ion with the nitrosating agent prior to the formation of the final products. A similar explanation can be given for the observation that the diazotisation of the 1-methoxy-4-aminopyridinium ion is 16 times slower than the diazotisation of the monoprotonated 4-aminopyridine 1-oxide [3a] (Table 5). It has been suggested that in the case of the diazotisation of monoprotonated 4-aminopyridine 1-oxide the oxygen atom of the hydroxy-group enhances the reaction by providing an additional site which is involved in the initial interaction with the nitrosating agent.[3] It is, therefore, very likely that in the case of the 1-methoxy-4-aminopyridinium perchlorate steric hindrance due to the methyl group inhibits the approach of the nitrosating agent to the oxygen atom of the methoxy-group which under these circumstances seems to exhibit mainly its $-I$ effect with the result that the 1-methoxy-4-aminopyridinium ion reacts 2.3 times slower than the monoprotonated 4-aminopyridine [2a] in contrast to monoprotonated 4-aminopyridine 1-oxide [3] which reacts 6.8 times faster than monoprotonated 4-aminopyridine (Table 5).

Support for the above explanations (namely that the methyl group exerts a steric effect) comes from the observation that the pK_a value (-5.89) of the 1-methyl-4-aminopyridinium ion (Table 6) is higher whilst that (-6.66) of the 1-methoxy-4-aminopyridinium ion (Table 6) is lower than the pK_{a_2} value of the 4-aminopyridinium ion (-6.55).[6]

Thus by considering resonance structures (Ib)—(IIIb) it can be seen that because of a steric effect due to the methyl group in the 1-methyl- or 1-methoxy-4-aminopyridinium ion there is less screening in the case of (IIb) and of (IIIb) by the hydrate covering the electron pair of the ring nitrogen (through the protons of the water molecules) than in the case of (Ib). In this way the 1-methyl and 1-methoxy-groups can exert their $+I$ and $-I$ effects, respectively. It is, however, interesting to note that because of the steric effect of the methyl group the observed increasing effect of the NH_3^+ group on the acidity constants of the *m*- and *p*-diammoniobenzenes is far smaller than that of the NMe_3^+ group due to the better screening of the positive charge by the hydrate covering the NH_3^+ group.[7]


(Ia) (Ib)


(IIa) (IIb)


(IIIa) (IIIb)

The pK_a values (Table 6) show also that protonation of the 1-methyl- and 1-methoxy-4-aminopyridinium ions is not significant under the present experimental conditions. Thus, the h_0 parameter in rate equation (2) cannot refer to the protonation of the substrate but it must refer to the protonation of the nitrous acid to form the nitrous acidium ion.

The identity of the nitrosating agent in dilute acid solutions has been discussed recently.[8] So far it has been assumed that kinetic expressions which are similar to expression (2) indicate that the nitrosating agent is the nitrous acidium ion.[1-3,5] It is, however, probable that nitrosation of the *N*-heteroaromatic amines involves the hydrated nitrosonium ion (H_2O^+NO) which loses the water molecule during the process of association with the heteroaromatic nucleus to form the complex shown in the Scheme.

Experimental

Materials.—1-Methyl-4-aminopyridinium perchlorate was prepared by heating 4-aminopyridine (4.7 g; Fluka; puriss) with methyl toluene-*p*-sulphonate (9.3 g; Fluka; pract.) for 20 h at 150 °C. The methylated product was purified by dissolution in ethanol, filtration (charcoal), and then precipitation by adding diethyl ether and then cooling to obtain 1-methyl-4-aminopyridinium toluene-*p*-sulphonate (9.0 g, 64%). This salt (3.8 g) was treated with 70% perchloric acid (2.35 g) overnight and the perchlorate salt precipitated by the addition of a mixture (14 ml) of ethyl acetate and diethyl ether (4 : 10). The precipitate was washed with diethyl ether (50 ml) and then recrystallised (charcoal) from a mixture of ethanol and diethyl ether (3 : 1) to give the *perchlorate salt* (1.0 g, 35%), m.p. 170—172° (Found: C, 34.9; H, 4.33; N, 12.9. $C_6H_9ClO_4N_2$ requires C, 34.5; H, 4.35; N, 13.4%).

Table 6.

	pK_a	Spread (±)	Conc. (10^4M)	A.w.l.[a] (nm)
1-Methyl-4-aminopyridinium perchlorate	−5.89[b]	0.14	0.5	270
1-Methoxy-4-aminopyridinium perchlorate	−6.66[b]	0.10	0.4	273

[a] A.w.l. = analytical wavelength. [b] Refers to the gain of one proton.

1-Methoxy-4-aminopyridinium perchlorate was prepared[9] by heating 4-aminopyridine 1-oxide, prepared as described in ref. 3*a*, with methyl toluene-*p*-sulphonate. The product obtained was treated as described in the previous preparation to obtain 1-methoxy-4-aminopyridinium perchlorate (35%), m.p. 99—101 °C (lit.,[8] 99—101 °C).

Sodium perchlorate (Fluka; puriss), which gave a negative test for chlorides, 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 (Fluka; puriss) was diluted and molarities of stock solutions were determined by titration against standard alkali solutions. Microanalyses were carried out by Dr. Ch. Mantzos.

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 sodium nitrite into nitrous acid), and, when required, sodium perchlorate were mixed to such a volume (35.0, 45.0, or 95.0 ml) that after the addition of temperature-adjusted aqueous sodium nitrite (5.0 ml) the total volume was 40.0, 50.0, or 100.0 ml. The mixture was then vigorously shaken. U.v. spectra of the reaction mixtures were recorded at regular intervals after placing a portion of these mixtures in a precooled Unicam cell (1.0, 5.0, or 10.0 mm) and maintaining the temperature at 2.0 °C. For the diazotisation of 1-methoxy-4-aminopyridinium perchlorate in 0.05M-perchloric acid containing 2.95M-sodium perchlorate samples (2.0 ml) taken at intervals were diluted 100 times with a mixture of perchloric acid and sodium perchlorate to a final strength equal to that of the reaction mixture. For the diazotisation of 1-methyl-4-aminopyridinium perchlorate absorbances were read at 260 nm at which ε of 1-methyl-4-aminopyridinium perchlorate is 15.4×10^3 and ε of 1-methylpyridinium-4-diazonium ion is 2.40×10^3 at all acidities. For the diazotisation of 1-methoxy-4-aminopyridinium perchlorate absorbances were read at 274 nm at which ε for 1-methoxy-4-aminopyridinium perchlorate is 19.8×10^3 and ε for 1-methoxypyridinium-4-diazonium ion is 3.78×10^3 at all acidities. Since 1-methylpyridinium-4-diazonium ion is not very stable under the experimental conditions, the absorbances of the reaction mixtures read at the wavelength (*i.e.* 260 nm) at which spectral examination of the destruction of the diazonium ion gave a good isosbestic point. On the other hand 1-methoxypyridinium-4-diazonium ion is stable for at least 3 h under the present experimental conditions. For all kinetic runs good isosbestic points were obtained.

Table 7. Diazotisation of 1-methyl-4-aminopyridinium perchlorate (amine salt) at 2.0°; constancy of k_2 [equation (1)] during the reaction. [$HClO_4$] 5.00M; [Amine salt]$_i$ 1.25×10^{-5}M; [Nitrous acid]$_i$ 5.00×10^{-5}M

t/min	10^6[Product]/M	k_2/l mol^{-1} s^{-1}
6	4.29	24.5
8	5.32	24.6
10	6.17	24.4
12	7.01	24.8
14	7.59	24.4
17	8.51	24.9
23	9.51	23.6

Determination of pK_a *Values.*—These were measured spectrophotometrically[10] in water and at 2.0 °C (Table 6).

Calculation of Rate Coefficients.—The concentration of 1-methyl- and 1-methoxy-4-aminopyridinium perchlorate in the reaction mixtures was calculated from expression (3)

$$[\text{1-Substituted 4-aminopyridinium perchlorate}] = (D - A\varepsilon_2)/(\varepsilon_1 - \varepsilon_2) \quad (3)$$

where D is the observed optical density measured at a particular wavelength, A is the initial concentration of the 1-substituted 4-aminopyridinium perchlorate, and ε_1 and ε_2 are the extinction coefficients of the 1-substituted 4-aminopyridinium perchlorate and the corresponding diazonium ion. The absorption of nitrous acid under the conditions used is negligible. The rate coefficients were calculated from the usual second-order expression[4b] by using the individual values of absorbances. At a given acidity the rate coefficients are satisfactorily constant for at least 70% reaction in the case of the diazotisation of 1-methyl-4-aminopyridinium perchlorate and 50% reaction in the case of the diazotisation of 1-methoxy-4-aminopyridinium perchlorate. Typical data are in Table 7.

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