Reactions of *N*-Heteroaromatic Bases with Nitrous Acid. Part III.[1] Kinetics of Diazotisation of 2-Aminopyridine

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The kinetics of diazotisation of 2-aminopyridine have been studied in 0·0025—5·0M-perchloric acid. The results suggest that the reaction takes place by one mechanism only. The kinetic form obtained is of the first order in both the amine and nitrous acid. The rate of the reaction shows an exponential catalytic dependence on the concentration of perchloric acid. It also shows a rather small exponential dependence on the concentration of added sodium perchlorate. In perchloric acid solutions the dependence of the rate of the reaction on the H_0 function is only slightly greater than linear, whilst in perchloric acid solutions whose ionic strength is maintained constant by the addition of sodium perchlorate there is an almost linear correlation. The effect of the ionic strength of the medium on the diazotisation of 2-aminopyridine as manifested by the influence of sodium perchlorate is smaller than the effect on the diazotisation of 4-aminopyridine.

DIAZOTISATION of 2-aminopyridine to produce the pyridine-2-diazonium ion has been shown to take place by the action of nitrous acid in dilute mineral acid solutions.[1a] The diazonium ion formed, however, was quite unstable under the conditions of diazotisation and was shown to change almost immediately to 2-hydroxypyridine.[1a] Under similar conditions 4-aminopyridine showed analogous behaviour, but pyridine-4-diazonium ion was more stable than pyridine-2-diazonium ion.[1a] Furthermore, the kinetics of the diazotisation of 4-aminopyridine in perchloric acid (0·0025—5·0M) were similar to those of the nitrosation of aromatic amines in solutions above *ca.* 1M-perchloric acid.[1-3]

This paper presents a study of the kinetics of the diazotisation of 2-aminopyridine in 0·0025—5·0M-perchloric acid. The results show that the reaction is less strongly catalysed by acid when compared with the diazotisation of 4-aminopyridine and nitrosation of aromatic amines in perchloric acid.[1b,2] They also indicate that, under the experimental conditions, the formation of the primary nitrosamine is most probably the rate-determining step.

TABLE 1

Diazotisation of 2-aminopyridine at 2·0°; constancy of $\bar{k}_2$ [equation (1)] at a given acidity

$[HClO_4]$/M	0·25			2·0		2·5			3·5		
10^4[Amine]/M	62·5	125·0	125	0·312	1·0	0·50	0·50	0·75	0·75	0·75	1·25
10^4[Nitrous acid]/M	625	312·5	625	0·624	5·0	2·50	3·25	4·25	2·25	3·75	1·50
$10^2\bar{k}_2$/l mol^{-1} s^{-1}	0·454	0·486	0·456	12·7	13·3	25·7	25·7	26·4	79·7	79·8	79·4

TABLE 2

Diazotisation of 2-aminopyridine at 2·0°; constancy of $\bar{k}_2$ in great excess of nitrous acid

	1·0M-$HClO_4$ + 3·0M-$NaClO_4$			1·0M-$HClO_4$ + 3·5M-$NaClO_4$			0·05M-$HClO_4$ + 2·95M-$NaClO_4$		0·10M-$HClO_4$ + 2·90M-$NaClO_4$	
10^4[Amine]/M	0·60	0·60	0·60	0·50	0·50	0·50	1·0	1·0	1·0	1·0
10^4[Nitrous acid]/M	3·0	6·0	12·0	2·5	5·0	10·0	5·0	10·0	5·0	10·0
$10^2\bar{k}_2$/l mol^{-1} s^{-1}	28·5	30·0	32·2	45·3	46·6	44·2	1·03	0·905	1·41	1·42

RESULTS

As in the case of 4-aminopyridine,[1] the nitrosation of 2-aminopyridine is reversible. However, the reversibility of the reaction becomes more pronounced as the acidity and the ionic strength of the medium increase. Under these conditions, the use of a five- or ten-fold excess in the initial concentration of nitrous acid made it possible to obtain satisfactory stoicheiometric rate-coefficients ($\bar{k}_2$) and, therefore, the reaction could be treated as irreversible. Further, 2-hydroxypyridine does not show any sign of reacting with nitrous acid under the experimental conditions.

In 0·025—5·0M-perchloric acid the rate coefficients calculated from the rate expression (1) were constant

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

over about two half-lives ($t_{\frac{1}{2}}$) and were reproducible when the initial concentrations of the reactants were varied (Table 1). A number of experiments were repeated with a five-, ten-, and twenty-fold excess in the initial concentration of nitrous acid in order to establish the constancy in the values of $\bar{k}_2$ (Table 2).

These results indicate that the reaction is of the first order in each of the reactants and the total order of the reaction is two at all acidities. This was also confirmed by the results obtained for 0·05, 0·25, 0·50, and 3·0M-perchloric acid (Tables 3 and 4).

The results obtained for the various acidities show that $\bar{k}_2$ increases with an increase in the acidity of the medium

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[1] E. Kalatzis, *J. Chem. Soc.* (*B*), (*a*) Part I, 1967, 273; (*b*) Part II, 1967, 277.

[2] (*a*) E. Kalatzis and J. H. Ridd, *J. Chem. Soc.* (*B*), 1966, 529; (*b*) E. C. R. de Fabrizio, E. Kalatzis, and J. H. Ridd, *ibid.*, p. 533; (*c*) B. C. Challis and J. H. Ridd, *J. Chem. Soc.*, 1962, 5208.

[3] E. D. Hughes and J. H. Ridd, *J. Chem. Soc.*, 1958, 58, 65, 82; J. H. Ridd, *Quart. Rev.*, 1961, **4**, 429.

(Table 5), but it remains constant at a given acidity with change in the initial concentration of reactants (Tables 1, 3, and 4). The values of $\bar{k}_2$ determined when the total ionic strength of the perchloric acid solutions was kept constant (3·0 units) by the addition of sodium perchlorate are in Table 6.

TABLE 3

Diazotisation of 2-aminopyridine at 2·0°; variation of reaction rate with initial concentration of reactants

	0·50M-$HClO_4$			
10^4[Amine]/M	62·5	62·5	125·0	125·0
10^4[Nitrous acid]/M	625·0	312·5	312·5	625·0
t/min	10^4[Product]/M *			
11	21·4	11·5	24·0	44·2
26	31·2	18·3	37·2	65·9
42	40·3	23·0	49·8	80·6
52	44·5	27·0	56·0	89·0
62	46·6	30·0	61·0	94·0
72	50·0	32·0	66·9	99·0
114	54·0	39·1	82·7	109·4
210	58·1	50·1	97·4	117·3
$10^2\bar{k}_2$/l mol^{-1} s^{-1}	0·918	0·910	0·900	0·921

* Taken as equivalent to the concentration of the amine reacted

TABLE 4

Diazotisation of 2-aminopyridine in 3·0M-$HClO_4$ at 2·0°; variation of reaction rate with initial concentration of reactants

10^5[Amine]/M	6·0	6·0	12·0	12·0
10^5[Nitrous acid]/M	30·0	60·0	30·0	60·0
t/min	10^5[Product]/M *			
20	0·910	1·87	2·13	3·60
30	1·33	2·46	2·85	4·75
40	1·67	2·96	3·43	5·80
50	1·98	3·43	3·93	6·50
60	2·29	3·78	4·44	7·13
70	2·59	4·10	4·89	7·72
80	2·78	4·31	5·24	8·19
90	3·01	4·60	5·61	8·56
100	3·26	4·78	5·87	8·96
110	3·41	4·95	6·20	9·23
$10^2\bar{k}_2$/l mol^{-1} s^{-1}	44·5	45·5	46·7	43·1

* Taken as equivalent to the concentration of the amine reacted.

TABLE 5

Diazotisation of 2-aminopyridine and 4-aminopyridine at 2·0°; dependence of $\bar{k}_2$ [equation (1)] on the concentration of an excess of perchloric acid

[$HClO_4$]/M	H_0	2-Aminopyridine $10^2\bar{k}_2$/l mol^{-1} s^{-1}	4-Aminopyridine $10^2\bar{k}_2$/l mol^{-1} s^{-1}
0·0025	+1·97 *	0·0274	
0·010	+1·80 *	0·0378	
0·050	+1·29 *	0·114	
0·10	+0·98 *	0·228	
0·25	+0·60	0·449	
0·50	+0·20	0·912	
1·00	−0·22	3·00	
1·50	−0·53	6·32	5·72
2·00	−0·78	13·0	12·4
2·50	−1·01	25·9	26·1
3·00	−1·23	44·9	48·7
3·50	−1·47	79·6	
4·00	−1·72	155·7	
5·00	−2·21	479·8	

* Values determined with pH meter. The other values of H_0 were taken from ref. 4.

The catalytic medium effect of sodium perchlorate on the rate of the reaction was studied by the addition of various concentrations of this salt in 1·0M-perchloric acid (Table 6). The diazotisation of 4-aminopyridine was also examined and the results are in Table 5.

TABLE 6

Diazotisation of 2-aminopyridine at 2·0; dependence of $\bar{k}_2$ on the concentration of perchloric acid and sodium perchlorate

	Perchloric acid and sodium perchlorate to ionic strength of 3·0		Perchloric acid (1·0M) and sodium perchlorate	
[$NaClO_4$]/M	H_0*	$10^2\bar{k}_2$/l mol^{-1} s^{-1}	h_0*	$10^2\bar{k}_2$/l mol^{-1} s^{-1}
3·50			11·5 †	45·4
3·00			9·00	30·2
2·95	+0·66 †	0·967		
2·90	+0·34 †	1·41		
2·75	−0·09 †	3·50		
2·50	−0·40	7·41	7·02	22·5
2·00	−0·71	15·1	5·12	15·1
1·50	−0·90	21·5	4·01	9·09
1·00	−1·04	27·7	3·15	5·58
0·50	−1·17	38·0	2·42	4·36
0·00	−1·23	44·5	1·78	3·00

* These values were taken from ref. 2*c*. † Values obtained by extrapolation of those from ref. 2*c*.

DISCUSSION

The exponential catalytic dependence of the rate of the diazotisation of 2-aminopyridine on H_0 of perchloric acid solutions (Table 5) is smaller than that observed in the diazotisation of 4-aminopyridine[1b] (Table 5) and nitrosation of aromatic amines[2] under the same conditions. This is evident from the slopes of the straight lines obtained when the values of log $\bar{k}_2$ are plotted against H_0. The slopes are 1·07 and 1·33 for 2- and 4-aminopyridine respectively (Figure 1).

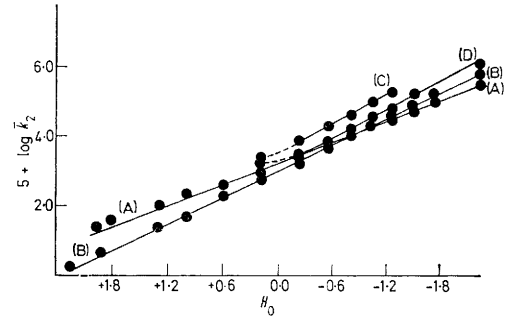

FIGURE 1 Plot of log $\bar{k}_2$ [equation (1)] against $-H_0$ for the diazotisation of 2-aminopyridine (A), 4-aminopyridine[1b] (B), aniline[2c] (C), and nitrosation of *N*-methylaniline[2a] (D) in perchloric acid solutions (see Table 5). The slopes are 1·07 for (A), 1·33 for (B), 1·50 for (C), and 1·45 for (D)

The results of the study of the catalytic effect of perchloric acid on the diazotisation of 2-aminopyridine at constant ionic strength (Table 6) show that there is a linear dependence of the rate of the reaction on the acidity under these conditions, *i.e.* $\bar{k}_2 \propto h_0$, since a plot of log $\bar{k}_2$ against H_0 is a straight line with a slope of

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[4] M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 1.

0·96. This is similar to the diazotisation of 4-aminopyridine [1b] and nitrosation of the aromatic amines [2] (Figure 2).

At low acidities and high concentrations of sodium perchlorate (0·05—0·25M-perchloric acid) the rate expression (1) still holds and the nitrous anhydride mechanism [2] does not seem to contribute to the rate under these conditions (Table 2). Further the rate of the reaction shows an exponential catalytic dependence on the ionic strength of the medium (μ), because a plot of log $\bar{k}_2$ against μ (Table 6) is a straight line with a slope of 0·360, which is reduced to 0·129 when the $\bar{k}_2$ values are corrected to refer to a common value of h_0 corresponding to 1·0M-perchloric acid. This catalytic dependence is less than that observed for the diazotisation of 4-aminopyridine [1b] and nitrosation of aromatic amines [2] (Figure 3).

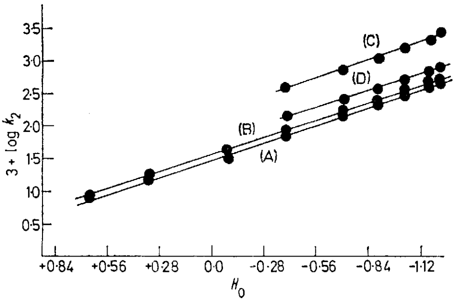


FIGURE 2 Plot of log $\bar{k}_2$ [equation(1)] against $-H_0$ for perchloric acid media containing sufficient sodium perchlorate to bring the ionic strength to 3·0; (A) 2-aminopyridine, (B) 4-aminopyridine,[1b] (C) aniline,[2c] and (D) N-methylaniline.[2a] All four straight lines are drawn with a slope of unity

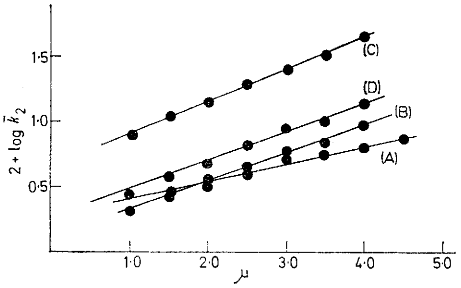
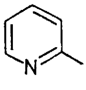
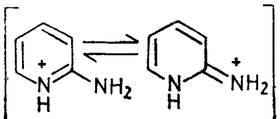


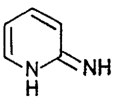
FIGURE 3 Plot of log $\bar{k}_2$ (corrected) against the ionic strength (μ) of the medium, altered by the addition of sodium perchlorate, for the diazotisation of 2-aminopyridine (A), 4-aminopyridine [1b] (B), aniline [2c] (C), and nitrosation of N-methylaniline [2a] (D). The slopes are 0·129 for (A), 0·219 for (B), 0·255 for (C), and 0·232 for (D)

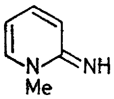
2-Aminopyridine (pK_a 6·82) [5a] is expected to exist as the monocation at all acidities used in the present work and the amino-nitrogen atom of the 2-aminopyridinium ion (pK_a −7·6) [5b] not to be protonated.

The amino-nitrogen atom of the 2-aminopyridinium ion, like that of the 4-aminopyridinium ion,[1,5,6] becomes positively charged due to resonance between species (IIa and b). On the other hand, the non-protonated 2-aminopyridine can be present as the amine (I) or the imine tautomer (III) and both these forms must be in equilibrium with the protonated amine. However, judging from the pK_a value of 1,2-dihydro-2-imino-1-methylpyridine (IV) which is 12·20 [6] and from other work,[7] the concentration of the imine tautomer of 2-aminopyridine must be much less than that of the amine-tautomer.


(I)


(IIa) (IIb)


(III)


(IV)

Equation (1) can be expanded to the rate expressions (2) or (3) since $k_3^0 = k_4^0K$, where K is the dissociation constant of the 2-aminopyridinium ion. The superscript zero refers to media of constant ionic strength.

$$\text{Rate} = k_3^0[\text{HN:C}_5\text{H}_4\text{NH}_2^+][\text{HNO}_2]h_0 \qquad (2)$$

$$\text{Rate} = k_4^0[\text{N:C}_5\text{H}_4\text{NH}_2][\text{HNO}_2]h_0^2 \qquad (3)$$

It can be assumed that the rate-determining stage in the diazotisation of 2-aminopyridine involves the formation of the primary nitrosamine, because the kinetic expressions (2) and (3) are similar to those obtained for the diazotisation of 4-aminopyridine [1b] and nitrosation of aromatic amines.[2]

The rate expression (3) could indicate that the reaction proceeds through a path involving the interaction of non-protonated 2-aminopyridine in the form of the amine or the imine tautomer with the nitrosonium ion, whose concentration is proportional to $[\text{HNO}_2]h_0^2$, and thus increases rapidly with acidity.[1,2,8] However, as in the case of the diazotisation of 4-aminopyridine [1b] and nitrosation of aromatic amines,[2] it is difficult to account for the reaction in this way because the observed rates are too high and the corresponding reactant concentrations low. Further, comparison of the relative rates shown in Table 7 indicates that the diazotisation of 2-aminopyridine is *ca.* 0·7—1·9 times slower than the diazotisation of 4-aminopyridine [1b] in 1·0—5·0M-perchloric acid. This result is contrary to expectation if the reaction is assumed to proceed through the non-protonated form of the amine and the nitrosonium ion, because the concentration of the free 2-aminopyridine is *ca.* 180 times greater than that of free 4-aminopyridine. Moreover, the nitrosation of N-methylaniline is 1·1—4·5 times faster than the diazotisation of 2-aminopyridine for the same acidity range and these values are lower than those expected because the concentration of the non-protonated

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[5] (*a*) A. Albert, R. Goldacre and J. N. Phillips, *J. Chem. Soc.*, 1948, 2240; (*b*) M. L. Bender and Y. J. Chow, *J. Amer. Chem. Soc.*, 1959, **81**, 3929.

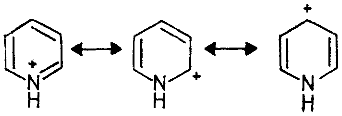
[6] S. J. Angyal and C. L. Angyal, *J. Chem. Soc.*, 1952, 1461.

[7] *Cf.* A. Albert, 'Heterocyclic Chemistry,' Athlone Press, London, 1968, 2nd edn., pp. 83—85.

[8] N. C. Deno, H. E. Berkheimer, W. L. Evans, and H. J. Peterson, *J. Amer. Chem. Soc.*, 1959, **81**, 2344.

N-methylaniline is *ca.* 100 times greater than the concentration of the non-protonated 2-aminopyridine. These arguments are also applicable for the imine tautomer whose concentration is much less than that of the amine tautomer.

The above considerations indicate that equation (2) is perhaps more applicable for the diazotisation of 2-aminopyridine which could be explained by the involvement of the protonated amine and the nitrous acidium ion. A similar explanation was given for the diazotisation of 4-aminopyridine.[1b] The delocalisation of the positive charge in a pyridinium ion into the π system is expected to diminish greatly the electron donor capacity of the heteroaromatic nucleus [resonance species (V)]. The presence of the amino-group in the 2-(or 4-)position would be expected, however, to counterbalance to some extent this diminution in the electron donor capacity of the nucleus through its lone pair of electrons, thus making it possible for an initial association between the positively charged nitrous acidium ion and the *N*-heteroaromatic system to take place, followed by the nitrosation of the amino-nitrogen atom during migration of a proton to the medium. Nonetheless, because of our results the possibility arises that the reaction could be taking place through a mechanism involving other species.



(V)

TABLE 7

Relative rates of the diazotisation of 2-aminopyridine at 2·0°, the diazotisation of 4-aminopyridine at 0°, and the nitrosation of *N*-methylaniline at 0° for various acidities

$[HClO_4]$/M	4-Aminopyridine [1b] / 2-Aminopyridine	*N*-Methylaniline [2a] / 2-Aminopyridine	*N*-Methylaniline [2a] / 4-Aminopyridine [1b]
0·50	0·7	2·0 *	2·9 *
1·00	0·7	1·1	1·6
3·00	1·1	1·7	1·5
5·00	1·9	4·5	2·4

* Nitrosation of *N*-methylaniline [2a] by the nitrous anhydride mechanism contributes significantly to the overall rate of the reaction.

EXPERIMENTAL

Materials.—2- and 4-Aminopyridine and 2- and 4-hydroxypyridine (Fluka; practical grade) were purified by three sublimations. Sodium perchlorate (Fluka; puriss) which gave a negative chloride test, was dried at 140°. Sodium nitrite (AnalaR) was used without further purification after drying under vacuum over phosphoric acid. Perchloric acid (Fluka; puriss) was diluted and molarities of stock solutions were determined by titration against standard alkali solutions. 2-Hydroxypyridine (1 or 2 × 10^{-4}M) was left with 10^{-4}, 10^{-3}, or 10^{-2}M-nitrous acid in 0·0025—5·0M-perchloric acid. Examination of these solutions during 36 h showed no changes in the u.v. spectra. 4-Hydroxypyridine was shown [1b] to be unaffected by nitrous acid under similar conditions.

Kinetic Runs.—These were carried out at 2·0°. 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 (35—75 ml) that after the addition of temperature adjusted aqueous sodium nitrite (5—25 ml) the total volume was 40—100 ml. The reaction mixture was vigorously shaken.

For acidities $\leqslant$0·5M-perchloric acid samples extracted at intervals were diluted 83·3—250 times with 2·0M-hydrochloric acid, which acted as buffer to protonate completely the 2-hydroxypyridine (pK_a 0·75).[9] Under these conditions, the reaction, which is not catalysed by chloride ions,[10] is very slow and the u.v. spectra show no further changes for 3—4 min. Thus, within experimental error (5%), the accuracy of the later measurements was not altered. The u.v. spectra of the diluted solutions were recorded immediately after dilution on a Unicam SP 8000 recording spectrophotometer and the absorption due to 2-aminopyridine was taken at 300 nm (ε 6·57 × 10^3). Pyridine-2-diazonium ion does not interfere with the readings because it is very unstable and is converted into 2-hydroxypyridine almost immediately, which, as the cation, has only a small absorption at 300 nm (ε varies from 6·25 × 10^2 to 2·90 × 10^3 in perchloric acid solutions of H_0 values from $-1·45$ to $+0·66$).

For acidities >1·0M-perchloric acid a portion of the reaction mixture was placed in a pre-cooled Unicam cell (1·0 cm) maintained at 2° and the decrease in the optical density at 300 nm was measured automatically. Temperature equilibrium could be reached in <2 min under these conditions.

In the same way the diazotisation of 4-aminopyridine [1a] was also studied. Absorptions were taken at 262 nm.

Determination of pH.—Because the reactants were added as 2-aminopyridinium perchlorate and free nitrous acid in high concentration in the kinetic solutions containing <0·05M-perchloric acid, it was necessary to determine, by pH meter, the pH of the final solutions. The values were: 1·97, 1·80, and 1·29 for 0·0025, 0·01, and 0·05M excesses of perchloric acid, respectively.

Calculation of Rate Coefficients.—The concentration of the aminopyridine in the reaction mixture was calculated from the expression $[\text{Amine}] = (D - A\varepsilon_2)/(\varepsilon_1 - \varepsilon_2)$ where D is the observed optical density measured at a particular wavelength, A is the initial concentration of the amine,

[9] A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1956, 1294.

[10] E. Kalatzis, unpublished observations.

and ε_1 and ε_2 are the extinction coefficients of the amine and the corresponding hydroxypyridine respectively. The absorption of nitrous acid under the conditions used is negligible.

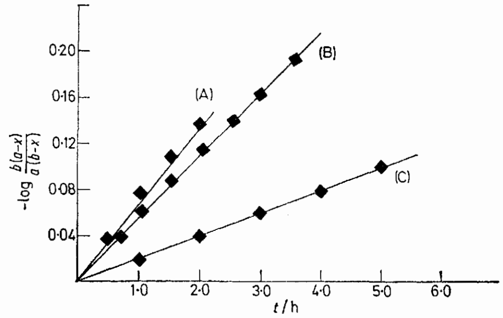


FIGURE 4 Second-order plot of $-\log b(a-x)/a(b-x)$ against time for the diazotisation of 2-aminopyridine at 2·0° in: (A) 1·0M-perchloric acid + 2·5M-sodium perchlorate; (B) 1·0M-perchloric acid + 1·5M-sodium perchlorate, and (C) 0·10M-perchloric acid + 2·90M-sodium perchlorate

The rate coefficients were calculated from the slope of the plots of $\log b(a-x)/a(b-x)$ against time. Typical results are shown in Figure 4. For a number of kinetic experiments the values of $\bar{k}_2$ were also calculated from the usual second-order rate expression by using the individual values of the optical densities. The results were satisfactory and in agreement with second-order kinetics. Typical data are in Table 8.

TABLE 8

Diazotisation of 2-aminopyridine at 2·0°; details of kinetic runs with a five-fold excess of nitrous acid

t/min	10^5[Amine]/M	10^5[Product]/M	$10^2\bar{k}_2$/l mol^{-1} s^{-1}
[HClO$_4$] = 3·0M; [Amine] = 6·0 × 10^{-5}M; [Nitrous acid] = 30·0 × 10^{-5}M			
20	5·09	0·91	46·3
40	4·33	1·67	46·3
60	3·71	2·29	46·3
70	3·41	2·59	47·0
80	3·22	2·78	45·6
100	2·74	3·26	46·4
140	2·20	3·80	43·0
160	1·90	4·10	43·4
[HClO$_4$] = 4·0M; [Amine] = 5·0 × 10^{-5}M; [Nitrous acid] = 25·0 × 10^{-5}M			
15	3·58	1·42	154
18	3·34	1·66	154
21	3·11	1·89	156
24	2·87	2·13	160
30	2·53	2·47	159
36	2·25	2·75	157
42	2·01	2·99	155
48	1·81	3·19	153
54	1·63	3·37	155

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