85. *Nucleophilic Displacement Reactions in Aromatic Systems. Part I. Kinetics of the Reactions of Chloronitropyridines with Aromatic Amines and with Pyridine.*

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The Arrhenius parameters for the reactions between 2-chloro-5-nitro- and 2-chloro-3-nitro-pyridine and primary aromatic amines have been determined. Also the reactions of the same compounds and those of 4-chloro-3-nitropyridine and of chloro-2 : 4-dinitrobenzene with pyridine have been studied, and Arrhenius parameters evaluated.

The reactions of pyridine, despite its rather greater "nucleophilic power," are significantly slower than those of aniline. This is ascribed to the retarding effect of steric hindrance with pyridine and, more tentatively, to a stabilisation of the transition state by interaction of amino-hydrogen with the oxygen of an *o*-nitro-group, and to increased solvation of the transition state for primary amines.

The observed magnitudes of the Arrhenius parameters for the different reactions are correlated with the structures of the halogeno-compounds, with special reference to steric and polar factors. The influence of nitro-groups and cyclic nitrogen atoms on the mobility of the halogens is elucidated.

During the last fifty years, the kinetics of the nucleophilic displacement of halogen atoms from aromatic carbon atoms in appropriately substituted halogenobenzenes have received considerable attention, and such investigations are in progress at present. When, however, the aromatic carbon atom forms part of a heterocyclic system, our knowledge of the kinetics of these displacement reactions is extremely scanty. The immediate object of the present studies is to remedy this situation, for the subject has considerable intrinsic interest : the ultimate object is to contribute to the theoretical organic chemistry of heterocyclic compounds, particularly of the pyrimidine series, to which many biologically important compounds belong. Lack of quantitative results concerning the reactions of halogen derivatives of even the simplest heterocyclic compounds makes it necessary first to clear the ground by investigations of pyridine derivatives analogous to 2- and 4-halogeno-pyrimidines.

It is commonly asserted (*e.g.*, by Taylor and Baker in Sidgwick's "Organic Chemistry of Nitrogen," Oxford Univ. Press, 1937, p. 523) that in aromatic systems the cyclic nitrogen atom and the substituent nitro-group cause similar disturbances of the aromatic electron cloud. The present communication records kinetic studies which lead to a quantitative

comparison of these effects in terms of the velocity coefficients and Arrhenius parameters of analogous reactions in the pyridine and the benzene series. We are at present also studying the pyrimidine series in similar fashion and filling in certain gaps in our knowledge of the benzene series. This problem has been approached from a different and more fundamental viewpoint by quantum-mechanical methods, mainly the molecular-orbital approximation (Wheland, *J. Amer. Chem. Soc.*, 1942, **64**, 900; Longuet-Higgins and Coulson, *Trans. Faraday Soc.*, 1947, **43**, 87).

Of benzenoid compounds which undergo nucleophilic displacement reactions, chloro-2 : 4-dinitrobenzene has been studied most, and the kinetics of many of its reactions have been examined in detail (Brady and Cropper, *J.*, 1950, 507; Blanksma and Schreinemachers, *Rec. Trav. chim.*, 1933, **52**, 428; van Opstall, *ibid.*, p. 901; Singh and Peacock, *J. Phys. Chem.*, 1936, **40**, 669; *J.*, 1935, 1410). We have therefore chosen analogous pyridine derivatives for our own studies, *viz.*, 2-chloro-5-nitropyridine, which had previously been investigated in a semi-quantitative way by Mangini and Frenguelli (*Gazzetta*, 1943, **73**, 313), and 4-chloro-3-nitropyridine. These compounds also are analogous to 2- and 4-halogenopyrimidines. Halogenonitropyridines are preferable to simple halogenopyridines because they react at speeds conveniently more rapid for kinetic work. Moreover, there is much less information available about the reactions of the benzenoid compounds analogous to halogenopyridines, *viz.*, halogenomononitrobenzenes. We have also included 2-chloro-3-nitropyridine despite the fact that information about the reactions of the analogous but inaccessible chloro-2 : 6-dinitrobenzene is scanty, to complete the series. We chose primary aromatic amines as our nucleophilic reagents in the first place, because they have been widely studied with chloro-2 : 4-dinitrobenzene (Singh and Peacock, *loc. cit.*, van Opstall, *loc. cit.*).

There is some evidence (Banks, *J. Amer. Chem. Soc.*, 1944, **66**, 1127) that reactions of halogenated heterocyclic compounds of the type under review are subject to acid-catalysis under appropriate conditions: we shall present evidence that conditions can be found in which such catalysis is negligible. Also we shall note an example of it. Morley and Simpson (*J.*, 1949, 1014) have provided preparative evidence in support of Banks's views. However, this possibility led us to study one reaction for each halogeno-compound in which no acid is generated during the reaction. Primary amines generate acid (*e.g.*, anilinium ions) during reaction; tertiary amines, however, do not, and we have therefore studied the reactions of pyridine. Whereas the acid-generating reactions should, on Banks's hypothesis, be autocatalytic, those of pyridine and other tertiary amines should be free from this complexity. Very interesting results emerged, so we are at present extending our studies to include other *cyclic* tertiary amines, the reactions of which appear simpler than those of primary amines. We have also examined the reaction of chloro-2 : 4-dinitrobenzene with pyridine for comparison.

4-Chloro-3-nitropyridine presents special difficulties because it is very reactive. It shows a slow but definite reaction with the ethanol used as solvent, and a measurable self-reaction, both of which liberate chloride ion, and its reactions with primary amines appear to be strongly autocatalytic, possibly because of the acid-catalysis discovered by Banks (*loc. cit.*). However, we have been able to study the kinetics of its reactions with pyridine, which are quite regular at low temperatures, and we propose further studies with this compound in other solvents in which it may be possible to eliminate unwanted side reactions.

Previous kinetic studies with the most closely analogous benzenoid compounds, halogeno-2 : 4-dinitrobenzenes, have focused attention on the influence either of the structure of the amine on the reactions (Singh and Peacock, *loc. cit.*) or of variation of the halogen in the halogeno-compound. We shall return to the former problem in the discussion and one of us has discussed the other problem elsewhere (Chapman and Parker, *J.*, 1951, 3301). The influence of a nuclear methyl group in chloro-2 : 4-dinitrobenzene on reactions with aniline has also been investigated incompletely by Lindemann and Pabst (*Annalen*, 1928, **462**, 24). Their views have proved of interest in relation to the discussion which follows, but this is a problem which needs further investigation before much progress can be made, to which subject we hope to give attention in due course.

Experimental

M. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss, Oxford.

Materials.—Chloro-compounds. Chloro-2 : 4-dinitrobenzene was distilled, b. p. 136°/0·2 mm., and the middle fraction was crystallised from ethanol; it had m. p. 51°. 2-Chloro-5-nitropyridine, m. p. 108° (for preparation cf. Caldwell and Kornfeld, *J. Amer. Chem. Soc.*, 1941, **64**, 1696, and Phillips, *J.*, 1941, 12), was crystallised from methanol. 2-Chloro-3-nitropyridine, m. p. 102°, was prepared by the action of phosphorus pentachloride and phosphoryl chloride on 2-hydroxy-3-nitropyridine, and crystallised from methanol with charcoal.

2-Hydroxy-3-nitropyridine was prepared by a method based on that of Binz and Maier-Bode (*Angew. Chem.*, 1936, **49**, 486). The liquor obtained by deamination with nitrous acid of 2-aminopyridine was heated to boiling, then cooled somewhat, and excess of sodium hydroxide pellets added with stirring until sodium sulphate remained undissolved in the hot liquid. After cooling the solid product was filtered off, and boiled with at least two 500-ml. portions of ethanol. After filtration of the hot liquor, it was cooled to 10° and an equal volume of ether added, which completed the separation of the hydrated sodium salt ($C_5H_4N{\cdot}ONa,2H_2O$) of 2-hydroxypyridine, as shining white leaflets, which on being dried at 100° gave the anhydrous salt. The anhydrous sodium salt was nitrated directly with a cold mixture of fuming nitric acid (*d* 1·52) and concentrated sulphuric acid. The product was poured on crushed ice, and the yellow solid which was precipitated was filtered off. A further small amount was obtained by making the filtrate neutral to methyl-orange with concentrated aqueous sodium hydroxide. The combined solids were boiled three times with about 1 l. of methanol. From the resulting solutions, after filtration hot, reasonably pure 2-hydroxy-3-nitropyridine separated, of m. p. 215—217°, and was used for further work. There is no advantage in liberating the pyridone from its salt for nitration.

1-4′-Pyridylpyridinium chloride hydrochloride was prepared by Koenigs and Greiner's method (*Ber.*, 1931, **64**, 1052), using pure dry pyridine and redistilled thionyl chloride. The product, after being washed with ethanol, was a pale yellow powder, m. p. 150—151°, whence 4-hydroxypyridine, isolated as nitrate, m. p. 189—191°, was obtained by heating it with water at 150° for 8 hours in a stainless-steel autoclave (Koenigs and Greiner, *loc. cit.*). The nitrate was converted into 4-hydroxy-3-nitropyridine by nitration with fuming nitric acid (*d* 1·52) in concentrated sulphuric acid (cf. Koenigs and Fulde, *Ber.*, 1927, **60**, 2107, and Crowe, *J.*, 1925, 2028) (Found : N, 20·6. Calc. for $C_5H_4O_3N_2$: N, 20·1%). We find Crowe's method superior, using concentrated and not fuming sulphuric acid as recommended by Koenigs *et al.*; also we find 20 hours' heating on the water-bath sufficient. The method of Koenigs *et al.* gives products difficult to free from dinitro-compounds.

4-Chloro-3-nitropyridine was prepared by a method based on that of Reitmann (*Chemistry and Medicine*, 1934, **2**, 384), who obtained it in a relatively impure state. We find the following procedure, especially the final crystallisation, quite essential to obtaining a pure product. Phosphorus pentachloride (16 g., 0·077 mol.) was covered with phosphoryl chloride and heated to 60°. 4-Hydroxy-3-nitropyridine (10 g., 0·071 mol.) was gradually added, and after the whole had been kept on the warm water-bath for several hours, the phosphoryl chloride was distilled at 15 mm. The residue was treated with ice-water and covered with a layer of ether, and aqueous sodium carbonate added to faint alkalinity to methyl-orange. The ethereal layer was separated, the aqueous layer re-extracted with ether, the ethereal solution dried ($CaCl_2$), the ether removed, and the 4-chloro-3-nitropyridine distilled (b. p. 68—70°/0·5 mm.), forming colourless crystals, m. p. 34°, by crystallisation from sodium-dried ether [Found : C, 37·6; H, 1·6; N, 17·1; Cl (Stepanow), 22·5. Calc. for $C_5H_3O_2N_2Cl$: C, 37·85; H, 1·9; N, 17·65; Cl, 22·4%). The compound must be stored in the cold in a dry atmosphere and liberates chloride ion on brief heating at 100°.

Amines. Aniline, *m*-toluidine, and *p*-phenetidine were purified through their acetyl derivatives, followed by fractionation of the regenerated amine under reduced pressure. *p*-Toluidine (pure commercial) was repeatedly recrystallised from light petroleum (b. p. 40—60°) until it melted sharply at 45°. *p*-Anisidine was treated with charcoal in boiling ethanol, the ethanol removed, and the residue twice recrystallised from light petroleum (b. p. 40—60°)–benzene (4 : 1), and had m. p. 59°. Pyridine (May and Baker, pure) was dried (BaO) and fractionated through a 20-in. Fenske column, a fraction of b. p. 115° being collected; it was also further purified through the pure perchlorate, m. p. 290·5—291°. Small, but definite, differences in reaction rate were observed for the two samples. The results which follow are

for perchlorate-purified pyridine since the reaction liquid darkens considerably with pyridine that has only been redistilled.

Products.—The following products of the reactions studied have not previously been described:

3-*Nitro*-2-p-*toluidinopyridine*, prepared by heating 2-chloro-3-nitropyridine (1 g.) and *p*-toluidine (1 g.) in ethanol (5 c.c.) under reflux for 6 hours, m. p. 73° (red needles) (Found: C, 63·4; H, 4·8; N, 18·2. $C_{12}H_{11}O_2N_3$ requires C, 62·9; H, 4·8; N, 18·3%).

2-*Anilino*-3-*nitropyridine*, m. p. 75° (orange-red needles), similarly prepared (Found: C, 61·6; H, 4·2; N, 19·2. $C_{11}H_9O_2N_3$ requires C, 61·4; H, 4·2; N, 19·5%).

3-*Nitro*-4-p-*toluidinopyridine*, m. p. 123° (bright yellow needles), similarly obtained from 4-chloro-3-nitropyridine (Found: C, 62·5; H, 4·7; N, 18·2. $C_{12}H_{11}O_2N_3$ requires C, 62·9; H, 4·8; N, 18·3%).

The quaternary chlorides obtained from the chloronitropyridines were prepared in the above way, but were difficult to purify and always had low chlorine analyses. They were therefore converted into the corresponding picrates which could be isolated pure:

1-(5-*Nitro*-2-*pyridyl*)*pyridinium picrate*, yellow needles (from methanol), m. p. 181·5° (Found: C, 44·9; H, 2·5; N, 20·2. $C_{16}H_{10}O_9N_6$ requires C, 44·7; H, 2·3; N, 19·5%).

1-(3-*Nitro*-2-*pyridyl*)*pyridinium picrate*, yellow needles (from methanol), m. p. 103° (Found: C, 44·7; H, 2·4; N, 19·4%).

1-(3-*Nitro*-4-*pyridyl*)*pyridinium chloride*, white crystals, m. p. 160—161° (decomp.) (Found: N, 17·3; Cl, 14·6%). $C_{10}H_8O_2N_3Cl$ requires: N, 17·7; Cl, 14·9%).

Solvent.—Commercial absolute ethanol was dried by Lund and Bjerrum's method (*Ber.*, 1931, **64**, 210) and fractionated. Its water content was determined by the Karl Fischer reagent (*Angew. Chem.*, 1935, **48**, 394) and then adjusted to 99·8% (by wt.) by addition of water.

Procedure.—This was similar to that of Singh and Peacock (*J. Phys. Chem.*, 1936, **40**, 669) and of Rheinlander (*J.*, 1923, **123**, 3099). 100 C.c. of a solution, 0·1M. with respect to the chloro-compound and 0·4M. with respect to the amine, were prepared at thermostat temperature. Aliquots were withdrawn at intervals and the solution run into a mixture of 0·05N-silver nitrate and dilute nitric acid, covered with benzene. This process arrests the reaction, fixes the chloride ion formed, and eliminates organic halogen compounds from the aqueous ethanolic layer. The benzene layer was washed twice with water, and the residual silver nitrate determined by the Volhard method; hence the concentration of chloride ion produced could be calculated. In the reaction with *p*-anisidine and *p*-phenetidine the Volhard method could not be used since the ferric iron indicator oxidised the amines giving deeply coloured solutions. In these cases chloride ion was determined gravimetrically. Some of the reactions were also studied by the method of sealed bulbs.

2-Chloro-5-nitro- and 2-chloro-3-nitro-pyridine are quite unaffected by boiling ethanol. 4-Chloro-3-nitropyridine, however, slowly liberates chloride ion in 0·1M-ethanolic solution at 30°, by either solvolysis or self-reaction. This is negligible during the first 200 minutes of the reaction. After 1000 minutes, however, some 45% of the compound has reacted, and the reaction is virtually complete after about 3000 minutes. These results suggest that the reaction is autocatalytic by virtue of the hydrochloric acid liberated by solvolysis. However, in the presence of a three-fold excess of pyridine, no autocatalysis was observed. It appears that under these conditions the predominating reaction is that between the amine and the halogeno-compound. For the reaction of 4-chloro-3-nitropyridine with pyridine at 30°, there is no observable catalysis up to 50% decomposition (cf. p. 441).

Results

Detailed values are given for some of the reactions of each chloro-compound, and all the results are summarised in Table 2. Since the chloro-compounds consume two moles of primary amine per mole,

$$dx/dt = k(a - 2x)(b - x)$$

whence
$$k = \frac{1}{2t(0{\cdot}5a - b)} 2{\cdot}303 \log_{10} \frac{b}{0{\cdot}5a} \cdot \frac{0{\cdot}5a - x}{b - x}$$

For tertiary amines

$$dx/dt = k(a - x)(b - x)$$

whence
$$k = \frac{1}{t(a - b)} 2{\cdot}303 \log_{10} \frac{b}{a} \cdot \frac{a - x}{b - x}$$

Evidence of order of reaction is given in selected cases. The experimentally observed times are recorded in minutes but the velocity coefficients are given in terms of the more usual units, *viz.*, l. mol.$^{-1}$ sec.$^{-1}$. Errors in k given after the $\pm$ sign are mean deviations from the mean. Temperatures are accurate to $\pm 0{\cdot}03°$.

TABLE 1.

Reactions of 2-chloro-5-nitropyridine.

Aniline at 55·0°.

Time (min.)	301	1047	1417	1441	2500	2565
Decompn., %	7·6	24·5	30·3	30·5	46·6	47·7
$k \times 10^6$	11·71	12·08	11·69	11·61	12·10	12·33

Mean $k = 11{\cdot}9 \pm 0{\cdot}2 \times 10^{-6}$.

p-*Toluidine at* 55·0°.

(*a*) Amine 0·400M., chloro-compound 0·100M.

Time (min.)	150	350	500	600	700	800	920	1160
Decompn., %	11·0	23·4	31·4	35·6	40·4	44·1	47·8	55·8
$k \times 10^6$	33·0	34·0	34·3	34·2	34·8	34·7	34·2	35·2

Mean $k = 34{\cdot}3 \pm 0{\cdot}4 \times 10^{-6}$; 50% decompn. at 989 min.

(*b*) Amine 0·200M., chloro-compound 0·0500M.: mean $k = 35{\cdot}9 \pm 0{\cdot}1 \times 10^{-6}$; 50% decompn. at 1883 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 1{\cdot}90$. Ratio of concns. = 2·00.

p-*Anisidine at* 45·0°.

Time (min.)	121·5	250·5	404	470	619
Decompn., %	15·0	28·8	40·7	44·1	58·2
$k \times 10^6$	58·2	60·15	60·1	58·7	59·3

Mean $k = 59{\cdot}3 \pm 0{\cdot}6 \times 10^{-6}$.

Pyridine at 60·0°.

(*a*) Amine 0·4015M., chloro-compound 0·0994M.

Time (min.)	1630	2850	4500	7020	8600	10 400	12 900	16 040
Decompn., %	11·6	17·5	27·2	38·6	45·0	50·6	59·1	66·3
$k \times 10^6$	3·05	(2·60)	2·85	3·02	3·05	3·02	3·13	3·13

Mean $k = 3{\cdot}04 \pm 0{\cdot}06 \times 10^{-6}$; 50% decompn. at 10 180 min.

(*b*) Amine 0·200M., chloro-compound 0·0500M.: mean $k = 2{\cdot}93 \pm 0{\cdot}04 \times 10^{-6}$; 50% decompn. at 21 210 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2{\cdot}08$. Effective ratio of concns. = 2·01.

Reactions of 2-chloro-3-nitropyridine.

p-*Toluidine at* 45·0°.

(*a*) Amine 0·400M., chloro-compound 0·100M.

Time (min.)	245	370	513	651	824	1056	1229	1702
Decompn., %	13·2	18·9	25·5	30·3	36·6	42·9	47·3	57·0
$k \times 10^6$	24·8	24·8	25·5	25·2	25·5	25·2	25·2	24·7

Mean $k = 25{\cdot}1 \pm 0{\cdot}25 \times 10^{-6}$; 50% decompn. at 1352 min.

(*b*) Amine 0·200M., chloro-compound 0·0500M.: mean $k = 24{\cdot}2 \pm 0{\cdot}25 \times 10^{-6}$; 50% decompn. at 2800 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2{\cdot}07$. Ratio of concns. = 2·00.

Pyridine at 60·0°.

(*a*) Amine 0·3996M., chloro-compound 0·0986M.

Time (min.)	2800	5800	8900	12 860	17 230	21 600
Decompn., %	10·9	20·2	28·8	38·6	47·9	56·0
$k \times 10^6$	1·68	1·64	1·64	1·67	1·68	1·69

Mean $k_2 = 1{\cdot}66 \pm 0{\cdot}02 \times 10^{-6}$; 50% decompn. at 18 730 min.

(*b*) Amine 0·200M., chloro-compound 0·0500M.: mean $k = 1{\cdot}61 \pm 0{\cdot}04 \times 10^{-6}$; 50% decompn. at 36 560 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 1{\cdot}95$. Effective ratio of concns. = 1·99.

Reactions of 4-chloro-3-nitropyridine.

Pyridine at 30·0°.

(*a*) Amine 0·400M., chloro-compound 0·100M.

Time (min.)	2320	3800	5600	6800	9860	14 200
Decompn., %	15·9	25·0	34·6	40·2	51·8	65·4
$k \times 10^6$	3·30	3·40	3·47	3·48	3·50	3·67

Mean $k = 3{\cdot}47 \pm 0{\cdot}08 \times 10^{-6}$; 50% decompn. at 8999 min.

(*b*) Amine 0·200M., chloro-compound 0·0500M.: 50% decompn. at 18 530 min. $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2{\cdot}06$. Ratio of concns. = 2·00.

TABLE 1—*continued.*

Reactions of chloro-2 : 4-dinitrobenzene.

Pyridine at 60·0°.

(*a*) Amine 0·3996M., chloro-compound 0·100M.

Time (min.)	311	520	615	750	1010	1075	1317	2570
Decompn., %	11·5	18·6	21·2	25·3	31·2	32·2	37·5	58·6
$k \times 10^6$	15·9	16·6	16·3	16·5	16·1	15·8	15·7	15·3

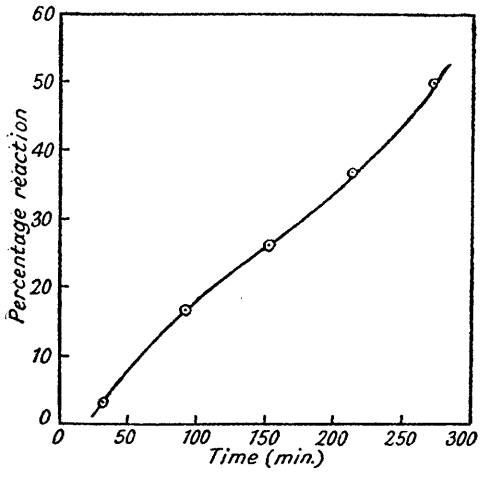
Mean $k = 16·0 \pm 0·4 \times 10^{-6}$; 50% decompn. at 2113 min.

(*b*) Amine 0·200M., chloro-compound 0·0500M.: mean $k = 15·7 \pm 0·2 \times 10^{-6}$; 50% decompn. at 4304 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2·04$. Ratio of concns. = 2·00.

DISCUSSION

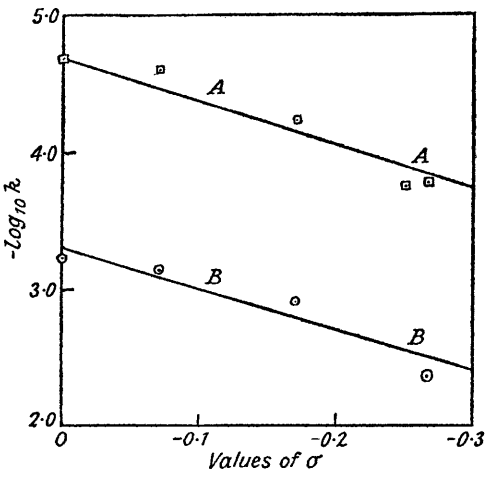
Banks's discovery (*loc. cit.*) of the acid-catalysis of nucleophilic displacement of halogen from halogenonitropyridines implies that the reactions of the primary amines should be autocatalytic, the amine cations formed constituting the acidic species. With the weaker acids—conjugate acids of stronger bases—the acid-catalysis is apparently negligible in the first half of the reactions of 2-chloro-5-nitro- and 2-chloro-3-nitro-pyridines. The

FIG. 1.



Reaction of 4-chloro-3-nitropyridine with aniline in ethanol at 20°.

FIG. 2.



A. Reactions of 2-chloro-5-nitropyridine at 65°.
B. Reactions of chloro-2 : 4-dinitrobenzene at 65°.

autocatalysis is observable, however, even under conditions unfavourable to it, with 4-chloro-3-nitropyridine, as Fig. 1 shows. For the most part the reactions under discussion obey a second-order rate law quite satisfactorily.

The reactions of chloro-2 : 4-dinitrobenzene with primary aromatic amines obey, to a fair degree of approximation, the Hammett ρ–σ relationship (Hammett, "Physical Organic Chemistry," New York, 1942, p. 184). The same relation holds also to much the same degree of accuracy for the reactions of 2-chloro-5-nitropyridine, as Fig. 2 shows. However it has not been possible, because of very unfavourable reaction rates, to cover a sufficiently large range of values of σ to obtain a ρ value of any great accuracy.

Influence of the Structure of the Amine on the Parameters of the Arrhenius Equation.—In its inception, the present work was not primarily concerned with the variations of the structure of the amine. The study of tertiary amines was undertaken in order to eliminate acid-catalysis entirely. Some results of Peacock *et al.* and the authors are collected in Table 3 to illustrate this aspect of the problem. For *primary* aromatic amines the influence of substituents in the base on the energy of activation, E, is in the order expected from their known "nucleophilic powers" as measured by their basic strengths (admittedly

TABLE 2.

Temp.	Amine	2-Chloro-5-nitropyridine (*a*)	2-Chloro-5-nitropyridine (*b*)	2-Chloro-3-nitropyridine (*a*)	2-Chloro-3-nitropyridine (*b*)	4-Chloro-3-nitropyridine (*a*)	4-Chloro-3-nitropyridine (*b*)	1-Chloro-2 : 4-dinitrobenzene (*a*)	1-Chloro-2 : 4-dinitrobenzene (*b*)
45·0°	Aniline	17·4—42·9	6·03—6·27	16·3—49·1	7·88—8·22				
45·0	*p*-Toluidine	9·2—61·8	16·5—17·8	13·2—56·9	24·7—25·5				
45·0	*p*-Anisidine	15·0—58·2	58·2—60·1						
50·0	Pyridine	1·5—29·4	1·25—1·32	12·5—25·2	0·648—0·678	12·4—75·9	1·41—1·52 *	21·7—40·2	7·20—7·62
55·0	Aniline	7·6—47·7	11·61—12·33	27·3—61·0	16·8—17·0				
55·0	*p*-Toluidine	11·0—55·8	33·0—35·2	18·6—48·8	49·3—50·1				
55·0	*p*-Anisidine	23·9—45·7	99·2—101·7						
60·0	Pyridine	11·6—66·3	2·85—3·13	10·9—56·0	1·64—1·69	9·1—60·3	3·53—3·80 *	11·5—58·6	15·3—16·6
65·0	Aniline	8·0—45·6	21·2—22·5	14·0—55·0	30·2—32·3				
65·0	*p*-Toluidine	15·4—53·4	55·8—59·7	16·8—52·2	91·3—94·0				
65·0	*p*-Anisidine	17·4—44·2	166·7—176·7						
70·0	Pyridine	13·5—56·3	6·70—7·03	11·5—60·3	3·53—3·72	21·2—86·8	8·95—9·75 *	15·9—53·5	32·7—33·8
65·0	*m*-Toluidine	32·7—48·3	24·7—26·2						
65·0	*p*-Phenetidine	25·3—52·0	171·7—185·0						

(*a*) Extreme values of percentage reaction. (*b*) Extreme values of $k \times 10^6$.
* Temp. 30° less. (For mean k's at 55° see Table 3.)

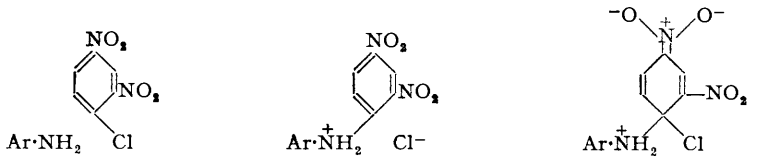
TABLE 3.

Reaction no.	Amine	Chloro-compound	$k^{55} \times 10^6$	E (cals.)	$\log_{10} A$
1	Aniline	Chloro-2 : 4-dinitrobenzene	353	11 200	4·0 [1]
2	*p*-Toluidine	,,	970	10 100	3·6 [1]
3	*p*-Anisidine	,,	2958	9 700	3·9 [1]
4	Pyridine	,,	11·1 ± 0·2	16 700	6·2
5	Aniline	2-Chloro-5-nitropyridine	11·9 ± 0·22	13 100	3·8
6	*p*-Toluidine	,,	34·3 ± 0·4	12 700	3·9
7	*p*-Anisidine	,,	101·2 ± 0·7	11 500	3·5
8	Pyridine	,,	1·97 ± 0·04	18 100	6·3
9	*m*-Toluidine	,,	25·0 ± 0·5 [2]	—	—
10	*p*-Phenetidine	,,	180 ± 5 [2]	—	—
11	Aniline	2-Chloro-3-nitropyridine	16·9 ± 0·1	14 500	5·0
12	*p*-Toluidine	,,	50·0 ± 0·6	13 900	4·9
13	Pyridine	,,	1·03 ± 0·015	18 700	6·3
14	Pyridine	4-Chloro-3-nitropyridine	32·1 ± 0·6	16 900	6·8

Units of A and k are l. mol.$^{-1}$ sec.$^{-1}$. Energies of activation are accurate to ± 300 cals., values of $\log_{10} A$ to ± 0·2 unit.
[1] Singh and Peacock, *loc. cit.* [2] At 65°.

a very rough measure of " nucleophilic power "). With pyridine, however, which may be regarded on the above basis as of greater " nucleophilic power " than aniline, the rate at which chloride ion is displaced from chloro-2 : 4-dinitrobenzene at 55° is *less* than that for aniline by a factor of ~30 because of a marked rise in E partly offset by an increase in the non-exponential term A (Table 3). Similar results are obtained with β- and γ-picolines (Cavell, unpublished). Also for the reactions of 2-chloro-5-nitropyridine and 2-chloro-3-nitropyridine qualitatively similar results are observed.

The transition state for the reaction between chloro-2 : 4-dinitrobenzene and aromatic amines may be represented as a hybrid of the following canonical forms :



The transition state for pyridine is very similar. The nitro-group written as $-NO_2$ has its usual structure. Now in picryl iodide the *o*-nitro-groups are almost perpendicular to the ring (Huse and Powell, *J.*, 1940, 1398) and geometrical considerations make it probable that in chloro-2 : 4-dinitrobenzene the *o*-nitro-group is inclined to the ring and not coplanar with it as is the *p*-nitro group. Experimental evidence is apparently unavailable. To the extent that the *o*-nitro-group is inclined to the ring up to 90°, its conjugation with the ring will be reduced, thus reducing its electromeric effect.

The observed difference in rate between the reactions in question (nos. 1 and 4, Table 3) is partly caused by steric hindrance, as inspection of appropriate models suggests. The probable geometry of the two analogous transition states is indicated in Figs. 3 and 4. Calculation of the steric compressions in each transition state, accepted bond distances and intervalency angles being used, according to the principles set forth by Dostrovsky,

FIG. 3.

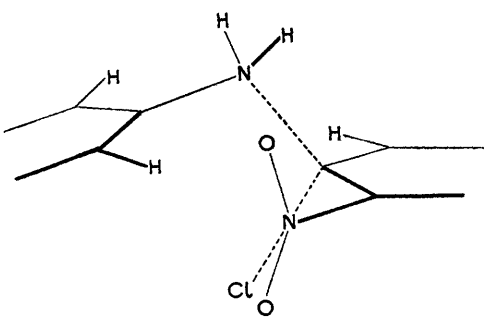
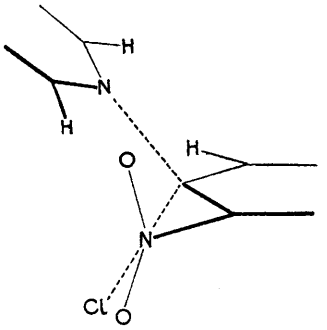
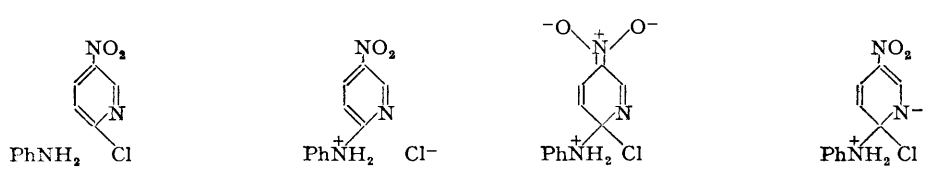


FIG. 4.

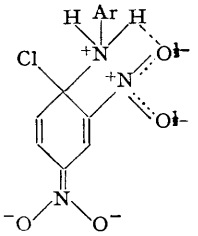
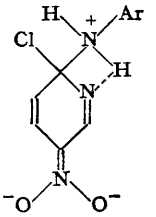


Hughes, and Ingold (*J.*, 1946, 173), confirms the view that the reaction of pyridine is more subject to steric hindrance than is that of aniline. Several assumptions are made in setting up the models of the transition states used, but the same assumptions are made in each case. Thus the *o*-nitro-group has been assumed to adopt the "perpendicular" configuration, for the sake of definiteness, and the C–N partial-bond distance has been set at 10% greater than the length of a single C–N bond (Glasstone, Laidler, and Eyring, "Theory of Rate Processes," New York, 1945, p. 151). The valency angles at the seat of substitution have been taken as tetrahedral. No attempt has been made to assess the compression energies involved, but only to arrive at a qualitative conclusion about the relative importance of steric hindrance in the two cases. Similar conclusions hold good for the reactions of 2-chloro-3-nitropyridine, where the geometrical essentials are virtually the same as with chloro-2 : 4-dinitrobenzene. However, with 2-chloro-5-nitropyridine, similar but smaller differences in rate are observed (Table 3), and in this case it is improbable that steric hindrance is significant, for the calculations suggest very strongly that the *o*-nitro-group is largely responsible for the steric compressions with the other halides. The transition state for the reactions with aniline may be represented thus :



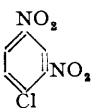
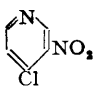
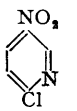
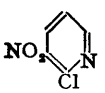
Hence we must seek some other factor to account for the difference of Arrhenius parameters for the reactions of 2-chloro-5-nitropyridine with aniline and pyridine, with the probability that the same factor operates with 2-chloro-3-nitropyridine and chloro-2 : 4-dinitrobenzene. There is a possibility of a variable electrostatic contribution to the different energies of activation, arising from varying interactions between the dipoles of the reagents. For the present, we reserve judgment on this and we neglect it in what follows.

Comparison of reactions 5 and 8 (Table 3) suggests that some factor associated with amino-hydrogen plays an important part in the reaction of aniline. We propose as a tentative hypothesis that there is hydrogen-bond formation in the transition state, with a contribution to the hybrid from the following structures for the different reactions :

A similar idea has been advanced by Lindemann and Pabst (*loc. cit.*) without much evidence in its favour. Although there appears to be no experimental evidence for hydrogen-bond formation in 2-nitrodiphenylamines or 2-anilinopyridines, which might be expected if our hypothesis were true, there is spectroscopic evidence of hydrogen-bond formation in 1-amino-2-nitro- and 2-amino-1-nitro-naphthalene (Hathway and Flett, *Trans. Faraday Soc.*, 1949, **45**, 818), which possess analogous structures. The geometry of the two transition states is compatible with this hypothesis. The energy of formation of the N–H · · · · O bond is ~2000 cal. and of the N–H · · · · N bond ~1930 cal. (Davies, *Ann. Reports*, 1946, **43**, 12), so that this factor alone does not entirely account for the differences in Arrhenius parameters. The formation of the transition states for the reactions of primary amines is probably attended by a greater increase of solvation than with pyridine. Again the essential structural feature appears to be amino-hydrogen. The observed differences therefore probably arise from an interplay of solvation and a " net *ortho* effect," the resultant of steric hindrance, where operative, and hydrogen-bond formation.

Influence of the Structure of the Halogeno-compound on the Parameters of the Arrhenius Equation.—When nucleophilic attack on an aromatic carbon atom occurs, it is probable that the facilitation of the bond-forming process is of major importance. Structural changes reducing electron density at the seat of substitution facilitate these reactions. Consider first the results for the reactions of pyridine assembled in Table 3 and below.

E (cal.)	16 700	16 900	18 100	18 700

Entropies of activation are nearly the same, except for the reaction of 4-chloro-3-nitropyridine, which reacts faster with pyridine than does chloro-2 : 4-dinitrobenzene, by virtue of a somewhat increased value of *A*. Replacement of a *p*-nitro-group by a " *p* "-cyclic nitrogen atom leaves the energy of activation virtually unchanged, but increases *A*, whereas a corresponding change in the *ortho*-position increases *E* by 1400 cal., despite the disappearance of steric hindrance, and leaves *A* unchanged. From the *para*-position the mainly tautomeric effect of a cyclic nitrogen atom is much the same as that of a nitro-group. Considering the *ortho*-position, we ascribe the energy difference (the above figure is the minimum value of the magnitude to be connected with polar effects) to the fact that the *o*-nitro-group operates through a powerful inductive effect and a weakened tautomeric effect, whereas the " *o* "-cyclic nitrogen atom operates through a weak electromeric effect

(*o*-quinonoid contribution to transition state). When, in 2-chloropyridine, a nitro-group is shifted from the position *para* to the chlorine to one *ortho* to it, only a slight increase in energy of activation ensues (reactions 8 and 13, Table 3), despite the intervention of steric hindrance, *i.e.*, the contribution of polar factors to E probably falls, whereas a similar shift of a cyclic nitrogen atom increases the energy of activation by 1800 cal., and lowers A (reactions 14 and 13, Table 2). This is a fundamental difference between nitro-groups and cyclic nitrogen atoms. It renders intelligible the properties, for example, of 2- and 4-chloropyrimidines: 4-chloropyrimidine is very unstable because it readily reacts with itself, whereas 2-chloropyrimidine, having no "*p*"-cyclic nitrogen, reacts with measurable speed with a base as strong as piperidine.

With primary amines as reagents, replacing an *o*-nitro-group by a cyclic nitrogen atom increases the energy of activation by 1800—2600 cal. depending on the amine, A being hardly affected. These reactions are virtually free from steric hindrance, and the differences arise from the structural differences in the halogeno-compounds discussed above and possibly differences in the energy of hydrogen-bond formation in the transition state. The reactions of 2-chloro-3-nitropyridine with primary amines are rather complicated and we defer further discussion of these results until our studies with chloro-2 : 6-dinitrobenzene are complete. It is, however, noteworthy that 2-chloro-3-nitropyridine reacts rather faster with primary amines than does 2-chloro-5-nitropyridine, but the reverse is true for reactions with pyridine.

Finally, we compare the reactions of the chloronitropyridines with those of the chloronitrobenzenes. Direct comparison is impossible because of lack of results with the chloronitrobenzenes. However, the reactions of *o*- and *p*-chloronitrobenzene with aqueous ammonia have energies of activation of 20 500 and 21 400 cal. respectively (Vorozhtov, Jr., and Kobelev, *J. Gen. Chem. U.S.S.R.*, 1939, **9**, 1465) and with piperidine in ethanol the corresponding values are about 18 000 cal. (Chapman, Parker, and Soanes, *Chem. and Ind.*, 1951, 148). The value for aniline will probably exceed 20 000 cal. We may estimate therefore that replacement of cyclic $\geqslant$CH by cyclic nitrogen *para* to chlorine in *o*-chloronitrobenzene will reduce the energy of activation for reaction with aniline by at least 9000 cal., on the assumption that the energies of activation for a hypothetical uncatalysed reaction of aniline with 4-chloro-3-nitropyridine would be approximately the same as for the reaction with chloro-2 : 4-dinitrobenzene, and for the corresponding change in the *ortho* position the reduction will be at least 7000 cal.

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