# 370. *Nucleophilic Displacement Reactions in Aromatic Systems. Part VII.*[1] *Kinetics of the Reactions of Substituted α-Chloropyridines with Aniline and Substituted Anilines in Methanol.*

By N. B. Chapman, D. K. Chaudhury, and J. Shorter.

Second-order rate coefficients have been measured for the reactions, in methanol, of aniline and substituted anilines with substituted α-chloropyridines. In most cases Arrhenius parameters have been evaluated.

The reaction mechanism is discussed with particular reference to the possible role of intermediate complexes. The activating influences of β-nitro- and β-cyano-groups have been elucidated, together with the deactivating influence of methyl groups adjacent to a nitro-group. Arrhenius non-exponential factors are compared with those of analogous reactions.

The Hammett equation is applied to the effect of *meta*- and *para*-substituents in aniline, and the ρ-values calculated are compared with those for reactions of aniline with other chloro-compounds. Nearly all such reactions are characterised by $\rho = -3{\cdot}1$ to $-3{\cdot}5$. The effect of *o*-Me, *o*-F, or *o*-Cl in aniline is discussed in terms of enhanced polar effects and of steric effects; the most important of the latter is inhibition of solvation of the transition state. The effect of substituents in aniline is also discussed with reference to relationships between log $k$ and $pK_a$.

Earlier papers in this series have presented kinetic studies of the nucleophilic displacement of chlorine from aromatic systems under the activating influence of nitro-groups or heterocyclic nitrogen atoms. In particular the reactions of 2-chloro-5-nitropyridine with several nucleophilic reagents have been studied.[2-4] Mariella, Callahan, and Jibril[5] have recently demonstrated the great reactivity of α-chloropyridine derivatives containing a nitro-group in one β-position and a cyano-group in the other β-position. For example, they showed that 2-chloro-3-cyano-4,6-dimethyl-5-nitropyridine reacts rapidly with alcoholic solutions of sodium alkoxide to give the 2-ether. The original intention of the present work was to study the kinetics of the reactions of chlorocyanonitropyridines with alkoxides as nucleophilic reagents, but such reactions were found to be too fast for kinetic investigation by conventional methods. The reactions with aniline (to give the anilinopyridine and aniline hydrochloride) were found more suitable. We have studied the reactions of aniline in methanolic solution with substituted α-chloropyridines chosen to show the activating influence of β-nitro- and β-cyano-groups, and the deactivating influence of methyl groups adjacent to a nitro-group in the pyridine ring. The influence of *meta*- and *para*-substituents in the aniline molecule has been examined, so that Hammett ρ constants[6] can be evaluated for comparison with those for reactions of substituted anilines with other types of chloro-compound. Some *ortho*-substituted anilines have also been studied. The change of solvent from 99·8% ethanol (Parts I—VI) to methanol is part of a programme to study solvent influence on these reactions. The reactions of 2-chloro-5-nitropyridine with aniline now reported provide a link between reactions in ethanol or methanol.

## Experimental

*Preparation and Purification of Chloro-compounds.*—The chloro-compounds were prepared by established methods and were crystallised to constant m. p. from light petroleum, with values agreeing with those in the literature.

[1] Part VI, Capon and Chapman, *J.*, 1957, 600.
[2] Bishop, Cavell, and Chapman, *J.*, 1952, 437.
[3] Cavell and Chapman, *J.*, 1953, 679.
[4] Chapman and Rees, *J.*, 1954, 1190.
[5] Mariella, Callahan, and Jibril, *J. Org. Chem.*, 1955, **20**, 1721.
[6] Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 184.

2-Chloro-3-cyanopyridine was prepared by Taylor and Crovetti's method [7] and had m. p. 107—107·5°.

2-Chloro-5-nitropyridine was prepared as described in Part I [2] and had m. p. 108°.

*2-Chloro-3-cyano-5-nitropyridine.* Mucobromic acid was prepared from technical furfuraldehyde by a modification of Simonis's method.[8] This acid was converted into sodium nitromalondialdehyde by Kuh and Stewart's method.[9] 2-Chloro-3-cyano-5-nitropyridine, m. p. 121—122°, was then made by Fanta and Stein's method.[10]

*2-Chloro-3-cyano-6-methyl-5-nitropyridine.* This was prepared as described by Perez-Medina, Mariella, and McElwain,[11] and had m. p. 98—99°.

*2-Chloro-3-cyano-4,6-dimethyl-5-nitropyridine.* Van Wagtendonk and Wibaut's method was used,[12] except that the nitration and chlorination stages were carried out as recommended by Perez-Medina, Mariella, and McElwain.[11] The product had m. p. 113—114°.

*Purification of Amines.*—In most cases commercial samples of amines were purified by conversion into the pure acetyl derivative (crystallised from 50% aqueous acetic acid). The amine was regenerated by alkaline hydrolysis and isolated by steam-distillation and ether-extraction in the usual way. After the ethereal extract had been dried (KOH) and the ether had been removed, the amine was fractionated under reduced pressure. Commercial samples

TABLE 1.

*2-Chloro-3-cyano-4,6-dimethyl-5-nitropyridine and aniline at* 20·0°. $a$ = 0·1002M, $b$ = 0·02482M.

| Time (hr.) | 24·0 | 48·0 | 72·0 | 96·0 | 120·0 | 144·0 | 168·0 |
|---|---|---|---|---|---|---|---|
| Decompn. (%) | 15·9 | 27·5 | 37·5 | 46·6 | 52·8 | 59·8 | 64·8 |
| $10^5k$ (l. mole$^{-1}$ sec.$^{-1}$) | 2·09 | 2·00 | 2·02 | 2·08 | 2·04 | 2·13 | 2·14 |

Mean $k = 2·07 \pm 0·04 \times 10^{-5}$ l. mole$^{-1}$ sec.$^{-1}$.

*2-Chloro-3-cyano-6-methyl-5-nitropyridine and aniline at* 0·0°. $a$ = 0·1004M, $b$ = 0·02501M.

| Time (min.) | 60·0 | 120·0 | 180·0 | 240·0 | 300·0 | 360·0 | 420·0 |
|---|---|---|---|---|---|---|---|
| Decompn. (%) | 16·1 | 27·0 | 36·3 | 45·2 | 50·0 | 55·6 | 62·0 |
| $10^4k$ (l. mole$^{-1}$ sec.$^{-1}$) | (5·05) | 4·68 | 4·63 | 4·77 | 4·49 | 4·48 | 4·65 |

Mean $k = 4·62 \pm 0·09 \times 10^{-4}$ l. mole$^{-1}$ sec.$^{-1}$.

*2-Chloro-3-cyano-5-nitropyridine and* p-*toluidine at* 10·0°. $a$ = 0·0998M, $b$ = 0·0248M.

| Time (min.) | 3·0 | 4·0 | 6·0 | 8·0 | 10·0 | 12·0 | 14·0 | 16·0 | 18·0 | 20·0 |
|---|---|---|---|---|---|---|---|---|---|---|
| Decompn. (%) | 20·3 | 26·1 | 36·3 | 43·2 | 50·4 | 55·1 | 61·4 | 65·2 | 69·8 | 73·0 |
| $10^2k$ (l. mole$^{-1}$ sec.$^{-1}$) | 1·33 | 1·35 | 1·39 | 1·34 | 1·37 | 1·33 | 1·39 | 1·38 | 1·42 | 1·42 |

Mean $k = 1·37 \pm 0·03 \times 10^{-2}$ l. mole$^{-1}$ sec.$^{-1}$.

*2-Chloro-3-cyano-5-nitropyridine and* m-*nitroaniline at* 0·0°. $a$ = 0·1001M, $b$ = 0·0250M.

| Time (hr.) | 96 | 144 | 192 | 240 | 288 | 336 |
|---|---|---|---|---|---|---|
| Decompn. (%) | 35·5 | 45·8 | 54·1 | 61·2 | 66·3 | 72·6 |
| $10^5k$ (l. mole$^{-1}$ sec.$^{-1}$) | 1·41 | 1·36 | 1·34 | 1·34 | 1·32 | 1·39 |

Mean $k = 1·36 \pm 0·03 \times 10^{-5}$ l. mole$^{-1}$ sec.$^{-1}$.

(Errors in $k$ given after the $\pm$ sign are mean deviations from the mean.)

of some amines were purified by distillation under reduced pressure or by crystallisation. Solid amines had m. p. in accord with recorded values.

*Purification of Solvent.*—Methanol was dried by Lund and Bjerrum's method [13] and fractionated through a 50 × 1·5 cm. Fenske column, the first 10% of the distillate being discarded. The water content, determined by the Karl Fischer method,[14] was invariably between 0·05 and 0·10%.

*Procedure.*—This was a modification of that described in Part I.[2] Aliquot parts of solutions of chloro-compound and of amine in methanol were mixed under nitrogen and at thermostat temperature to give a solution, 0·0250M with respect to chloro-compound and 0·100M with respect

[7] Taylor and Crovetti, *J. Org. Chem.*, 1954, **19**, 1633.
[8] Simonis, *Ber.*, 1899, **32**, 2084.
[9] Kuh and Stewart, U.S.P. 2,606,931/1952; see *Chem. Abs.*, 1953, **47**, 5960f.
[10] Fanta and Stein, *J. Amer. Chem. Soc.*, 1955, **77**, 1045.
[11] Perez-Medina, Mariella, and McElwain, *J. Amer. Chem. Soc.*, 1947, **69**, 2574.
[12] Van Wagtendonk and Wibaut, *Rec. Trav. chim.*, 1942, **61**, 728.
[13] Lund and Bjerrum, *Ber.*, 1931, **64**, 210.
[14] Senman, McComies, and Allen, *Analyt. Chem.*, 1949, **21**, 511.

to amine. At appropriate times the reaction was arrested by adding dilute nitric acid, the excess of reactants and the substituted anilinopyridine product were removed by extraction with ether, and the amine hydrochloride in the aqueous layer was determined by Volhard's method. Experiments of long duration and those at 60° or 70° were carried out by the method of sealed bulbs.

All the chloro-compounds except 2-chloro-3-cyanopyridine reacted slightly but very slowly with the solvent, thus producing a small amount of hydrogen chloride in solution. As a result the effective initial concentration of the chloro-compound in a kinetic experiment was reduced; the effective initial concentration of the amine was also reduced, since a little of the amine was removed instantly as hydrochloride when the reactant solutions were mixed. Further, the chloride ion concentration found at any time during the experiment included that produced by solvolysis before the start of the experiment (the chloride ion concentration produced by solvolysis during the reaction between chloro-compound and amine was never significant). The chloride ion concentration in the stock solution of chloro-compound was always determined just before the start of a kinetic experiment, and the necessary corrections were then applied.

The chloro-compound consumes two moles of amine per mole, so

$$k = \frac{2{\cdot}303}{2t(0{\cdot}5a - b)} \log \frac{b(0{\cdot}5a - x)}{0{\cdot}5a(b - x)},$$

where $a$ is the corrected initial concentration of amine, $b$ is the corrected initial concentration of chloro-compound, $x$ is the concentration of chloride ion at time $t$ (sec.) (corrected for chloride ion present initially), and $k$ is the second-order rate coefficient in l. mole$^{-1}$ sec.$^{-1}$.

TABLE 2.

2-Arylamino-3-cyano-5-nitropyridines.

| 3-Cyano-5-nitropyridine deriv. | M. p. | Found (%) C | H | Formula | Required (%) C | H |
|---|---|---|---|---|---|---|
| 2-Anilino- | 177—178° | 60·3 | 3·6 | $C_{12}H_8N_4O_2$ | 60·0 | 3·4 |
| 2-Anilino-6-methyl- | 174—175 | 61·5 | 4·0 | $C_{13}H_{10}N_4O_2$ | 61·4 | 4·0 |
| 2-Anilino-4,6-dimethyl- | 170—171 | 62·5 | 4·6 | $C_{14}H_{12}N_4O_2$ | 62·7 | 4·5 |
| 2-*p*-Toluidino- | 193—194 | 61·7 | 4·2 | $C_{13}H_{10}N_4O_2$ | 61·4 | 4·0 |
| 2-*m*-Toluidino- | 161—162 | 61·3 | 4·0 | ,, | ,, | ,, |
| 2-*o*-Toluidino- | 152—153 | 61·5 | 3·9 | ,, | ,, | ,, |
| 2-*p*-Chloroanilino- | 229—230 | 52·7 | 2·6 | $C_{12}H_7ClN_4O_2$ | 52·5 | 2·6 |
| 2-*m*-Chloroanilino- | 184—185 | 52·7 | 2·6 | ,, | ,, | ,, |
| 2-*o*-Chloroanilino- | 141—142 | 53·4 | 2·6 | ,, | ,, | ,, |
| 2-*p*-Fluoroanilino- | 217—218 | 55·9 | 2·3 | $C_{12}H_7FN_4O_2$ | 55·8 | 2·7 |
| 2-*m*-Fluoroanilino- | 186—187 | 56·1 | 2·7 | ,, | ,, | ,, |
| 2-*m*-Nitroanilino- | 235—236 | 50·9 | 2·4 | $C_{12}H_7N_5O_4$ | 50·6 | 2·5 |
| 2-*m*-Chloroanilino-6-methyl- | 204—205 | 54·3 | 3·1 | $C_{13}H_9ClN_4O_2$ | 54·1 | 3·1 |
| 2-Methyl-6-*m*-toluidino- | 188—189 | 62·7 | 4·5 | $C_{14}H_{12}N_4O_2$ | 62·7 | 4·5 |

Typical results are shown in Table 1. The mean deviation in $k$ in most experiments was 1—2% over 60—80% of the course of the reaction.

For each of the chloro-compounds except 2-chloro-3-cyano- and 2-chloro-5-nitro-pyridine the concentration of chloride ion liberated at " infinite " time was determined for the reactions with selected amines. In every case 99·5—100·5% of the theoretical value was found, thus indicating irreversibility of the reactions and high purity of reactants.

*Products.*—During the reaction between a chlorocyanonitropyridine and amine, the substituted anilinopyridine formed was precipitated. In a number of cases this product was isolated, purified, and characterised. Table 2 lists the new *compounds* isolated, their m. p., and analyses.

## DISCUSSION

*Formation of Complexes between α-Chloro-nitropyridines and Anilines.*—Methanolic solutions of α-chloronitropyridines give yellow colours instantaneously when mixed with solutions of anilines. A yellow coloration when ethanolic solutions of aniline and 1-chloro-2,4-dinitrobenzene are mixed was observed by Singh and Peacock,[15] and by Ross

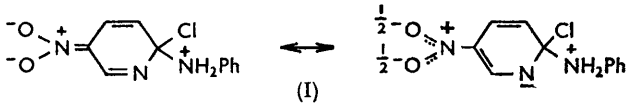
[15] Singh and Peacock, *J. Phys. Chem.*, 1936, **40**, 669.

and Kuntz,[16] who have shown that the yellow colour is due to the formation of a charge-transfer complex between aniline and 1-chloro-2,4-dinitrobenzene. Individual experiments gave consistent second-order rate coefficients, but at rather high initial concentrations of aniline and chlorodinitrobenzene the rate coefficient decreased with increasing aniline concentration. Ross and Kuntz attributed this to reduction, by charge-transfer complex formation, of the effective concentrations of reactants; it was necessary to correct for this in order to obtain true rate coefficients.

It seems likely that the yellow colour observed in the present work is also due to the formation of a charge-transfer complex between the reactants, but we believe that in no case was the concentration of complex other than minute compared with the concentrations of reactants. The rate coefficient in a selected case was unaffected when the concentrations of reactants were one-half of those normally used (Table 3).

*Complex Formation and Reaction Mechanism.*—All the reactions between aniline or substituted anilines as nucleophilic reagents, and the α-chloropyridines studied showed strict second-order kinetics. The reactions thus proceed, in principle, by a bimolecular mechanism. There are two main possibilities for the details of this mechanism: either the reaction proceeds by a synchronous substitution process through the appropriate transition state, or it proceeds through an intermediate complex of some stability, in which case transition states for the formation and for the decomposition of the complex require consideration.[17] The complex might be the yellow charge-transfer complex or it might be a complex of a quinonoid type (I).

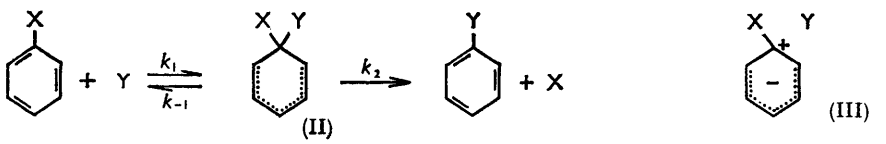
Ross and Kuntz's [16] experiments with aniline and 1-chloro-2,4-dinitrobenzene did not show whether the charge-transfer complex was involved as an intermediate in the nucleophilic substitution or not. Similarly in the present investigation there is no evidence for



(I)

the charge-transfer complex as an intermediate. To postulate such an intermediate would greatly complicate the discussion of structural factors influencing the rate coefficients. Until further information is available on the mechanistic role, if any, of charge-transfer complexes, we prefer for simplicity to disregard them.

There now remains the possibility of an intermediate complex of quinonoid type. Bunnett and Randall [18] have provided convincing evidence that in some cases nucleophilic aromatic substitution involves the formation of such an intermediate complex, thus:



(II) (III)

For the reaction of 1-fluoro-2,4-dinitrobenzene with *N*-methylaniline the observation of general base-catalysis is compelling evidence in favour of this mechanism for this particular case. However, when chlorine or bromine is the expelled ion, no evidence of base-catalysis could be obtained. Bunnett concludes that complex formation is involved in these cases, and very probably in all other cases of aromatic nucleophilic substitution, but that for the expulsion of chlorine from 1-chloro-2,4-dinitrobenzene, the formation of the complex is the rate-determining step, whereas for the fluoro-compound the anionisation of the halogen is rate-determining.

If we accept Bunnett's view, the important transition state for chloro-compounds is

[16] Ross and Kuntz, *J. Amer. Chem. Soc.*, 1954, **76**, 3000.
[17] Bunnett, *Quart. Rev.*, 1958, **12**, 1.
[18] Bunnett and Randall, *J. Amer. Chem. Soc.*, 1958, **80**, 6020.

that involved in complex formation. It may be represented by (III). However, a simple synchronous bimolecular mechanism probably requires that formula (II) shall represent the transition state of the reaction rather than a complex as suggested by Bunnett. In considering the influence of substantial variation of structure on reactivity, the choice between regarding a structure of type (II) as a transition state or a complex seems to us unimportant, if the breakdown of the complex to products is regarded as kinetically unimportant. Moreover, experiments carried out by Mr. A. Buckley have demonstrated that the reaction between 2-chloro-3-cyano-5-nitropyridine and aniline at 10° is not subject to catalysis by acetate ion. In the presence of ~0·09M-sodium acetate the apparent rate-coefficient is raised by about 18%, but about 12% is due to a primary salt effect (as judged by experiments with sodium perchlorate) and the remainder to attack on the chloro-compound by base (acetate or methoxide ion). We therefore treat the reaction between α-chloropyridines and anilines as if it occurs by a one-step mechanism with a structure approximating to (II), or more precisely (I), representing the transition state. It is noteworthy that Bolton, Miller, and Parker,[19] who provided powerful evidence for the intervention of a complex in the reaction of azide ion with *p*-fluoronitrobenzene in *dimethylformamide*, reached the conclusion that " in protic solvents . . . no important concentration of it (the complex) is to be expected."

*Electronic Activation by Nitro- and Cyano-groups in Pyridine* (Table 3).—The cyano-group has a weaker activating effect than the nitro-group. 2-Chloro-3-cyanopyridine did not react with aniline during a week even at 100°; at higher temperatures it gave a complicated reaction. At 100° 2-chloro-3-nitropyridine would react with aniline with a rate coefficient of the order of $10^{-3}$ l. mole$^{-1}$ sec.$^{-1}$ (estimated from Bishop, Cavell, and Chapman's [2] results). Although 2-chloro-3-cyanopyridine is so unreactive, 2-chloro-3-cyano-5-nitropyridine reacts with aniline about 7000 times faster than 2-chloro-5-nitropyridine. At 20° the rate coefficients are $6{\cdot}85 \times 10^{-3}$ and ~$10^{-6}$ l. mole$^{-1}$ sec.$^{-1}$, respectively. (All rate coefficients henceforth mentioned are in l. mole$^{-1}$ sec.$^{-1}$ units.) The activating powers of both the 5-nitro- and the 3-cyano-group may be calculated from these rate coefficients if an estimate can be made for the rate coefficient for the reaction between aniline and 2-chloropyridine in methanol at 20°. This can be done from available results by assuming that $k_a = k_b k_c / k_d$, where $k_a$ refers to the reaction between 2-chloropyridine and aniline in methanol, $k_b$ to that between 2-chloropyridine and piperidine in ethanol,

TABLE 3.

Rate coefficients and Arrhenius parameters for reactions with aniline.

| 2-Chloropyridine | $10^5k$ (l. mole$^{-1}$ sec.$^{-1}$) 20° | 30° | 40° | 50° | $E$ (cal. mole$^{-1}$) | log $A$ | $\Delta H^\ddagger$ (cal. mole$^{-1}$) | $\Delta S^\ddagger$ (cal. mole$^{-1}$ deg.$^{-1}$) |
|---|---|---|---|---|---|---|---|---|
| 5-Nitro- * | 2·10 [a] | 3·69 [b] | 0·490 | 0·930 | 14,900 | 5·06 | 14,300 | −37·2 |
| 3-Cyano-5-nitro | 685 | 1170 [c] | 195 [d] | 385 [e] | 9,800 | 5·18 | 9,200 | −36·7 |
| 3-Cyano-6-methyl-5-nitro- | 168 | 316 | 46·3 [d] | 93·2 [e] | 10,500 | 5·07 | 9,900 | −37·2 |
| 3-Cyano-4,6-dimethyl-5-nitro- | 2·07 | 4·15 | 7·79 | 14·7 | 12,400 | 4·56 | 11,800 | −39·6 |

Values of $k$ are accurate to ±2%, of $E$ and $\Delta H^\ddagger$ to ±300 cal. mole$^{-1}$, of log $A$ to ±0·2 unit, and of $\Delta S^\ddagger$ to ±1 unit.

[a] At 60°. [b] At 70°. [c] When reactant concentrations are one-half of those normally used, $10^5k$ = 1180 l. mole$^{-1}$ sec.$^{-1}$. [d] At 0°. [e] At 10°.

* For reactions in 99·8% ethanol the corresponding values are: $E$ = 13,100 cal. mole$^{-1}$ and log $A$ = 3·8 (cf. ref. 2).

$k_c$ to that between 2-chloro-5-nitropyridine and aniline in methanol, and $k_d$ to that between 2-chloro-5-nitropyridine and piperidine in ethanol. Results for the piperidine reactions are given by Chapman and Rees [4] and by Chapman and Russell-Hill; [20] the values are $4{\cdot}8 \times 10^{-10}$ for 2-chloropyridine and $3{\cdot}5 \times 10^{-3}$ for 2-chloro-5-nitropyridine. The rate coefficient for the reaction between 2-chloropyridine and aniline in methanol at 20° is thus

[19] Bolton, Miller, and Parker, *Chem. and Ind.*, 1960, 1026.
[20] Chapman and Russell-Hill, *J.*, 1956, 1563.

calculated to be $1{\cdot}4 \times 10^{-13}$. The introduction of the 5-nitro-group into 2-chloropyridine thus increases the rate by a factor of about $10^7$ (~7 log units); the further introduction of a 3-cyano-group increases the rate by a factor of about 7000 (~ 4 log units). These values lead to a rate coefficient for 2-chloro-3-cyanopyridine of $\sim 10^{-9}$ at 20° or $\sim 10^{-7}$ at 100°, thus explaining the observations referred to above. The considerably greater activating influence of the nitro-group is thus confirmed. The activating powers are only qualitatively related to the Hammett $\sigma_p$ values of the groups in the benzene system, which are +0·778 for the nitro-group and +0·628 for the cyano-group.[21]

*Deactivating Influence of Methyl Groups in the Pyridine Compounds* (Table 3).—A methyl group between the heterocyclic nitrogen atom and the nitro-group decreases the rate of the reaction with aniline at 20° by a factor of about 4, while methyl groups in both positions adjacent to the nitro-group together decrease the rate by a factor of about 330. This deactivating influence of methyl groups is in the main a secondary steric effect. *ortho*-Substituents may twist the nitro-group out of the plane of the pyridine ring and thus reduce its power of withdrawing electrons by the $-T$ effect. It appears that the secondary steric effect of a first *ortho*-methyl group is small. This is presumably because the nitro-group can bend away and still attain coplanarity with the ring. This is not possible when both *ortho*-positions are occupied by methyl groups.

Our observations and conclusions are similar to those of van Berk, van Langen, Verkade, and Wepster [22] in a semi-quantitative study of methyl-substituted *p*-bromonitrobenzenes. They found that one methyl group adjacent to the nitro-group reduced the rate of the reaction with piperidine by a factor of about 3, while two methyl groups together reduced the rate by a factor of about 250. Capon and Chapman [1] showed that the introduction of a 5-methyl group into 1-chloro-2,4-dinitrobenzene diminished the rate of the reaction with piperidine by a factor of about 4, while Chapman and Rees [4] showed that a 4-methyl group in 2-chloro-5-nitropyridine diminished the rate of the reaction with piperidine by a factor of ~5.

Other factors may contribute to the deactivating influence of methyl groups substituted in 2-chloro-3-cyano-5-nitropyridine. A secondary steric effect involving the cyano-group in 2-chloro-3-cyano-4,6-dimethyl-5-nitropyridine is unlikely. The cyano-group is small and is collinear with the carbon atom of the ring to which it is attached, and an *ortho*-methyl group should therefore not influence the $-T$ effect. Spitzer and Wheland [23] showed that such a secondary steric effect did not occur in the reaction of 5-bromo-2-cyano-*m*-xylene with piperidine.

There remains the possible influence of the $+I$ effect of the methyl group. The methyl groups in the pyridine compounds are in *meta*-positions to the seat of substitution. For various systems undergoing nucleophilic substitution Chapman and his colleagues [1,4] and Brieux and Deulofeu [24] have shown that the polar deactivating effect of *meta*-methyl groups is small. It is not, however, always negligible and it seems possible that an appreciable part of the deactivating influence of the methyl group in the reaction of 2-chloro-3-cyano-6-methyl-5-nitropyridine with aniline is due to the $+I$ effect. Significant polar effects of *meta*-methyl groups were observed by Chapman and Rees [4] in the reactions of substituted 2-chloropyrimidines with piperidine.

*Arrhenius Parameters for the Reactions of α-Chloropyridines with Aniline.*—These are shown in Table 3. In the main, changes in reactivity are governed in this series by changes in $E$ (or $\Delta H^{\ddagger}$). Log $A$ (or $\Delta S^{\ddagger}$) is constant within experimental error except for reactions of 2-chloro-3-cyano-4,6-dimethyl-5-nitropyridine, where log $A$ is slightly lower and $\Delta S^{\ddagger}$ is slightly more negative than for the other reactions. The introduction of methyl groups into the positions *ortho* to the nitro-group would not be expected to change log $A$ greatly,

[21] Jaffé, *Chem. Rev.*, 1953, **53**, 191.
[22] van Berk, van Langen, Verkade, and Wepster, *Rec. Trav. chim.*, 1956, **75**, 1137.
[23] Spitzer and Wheland, *J. Amer. Chem. Soc.*, 1940, **62**, 2995.
[24] Brieux and Deulofeu, *J.*, 1954, 2519.

TABLE 4.

Rate coefficients and Arrhenius parameters for the reactions of 2-chloro-3-cyano-5-nitropyridine with substituted anilines.

| Amine | $10^5k$ (l. mole$^{-1}$ sec.$^{-1}$) 0° | 10° | 20° | 30° | 40° | $E$ (cal. mole$^{-1}$) | log $A$ |
|---|---|---|---|---|---|---|---|
| Aniline | 195 | 385 | 685 | 1170 | — | 9,800 | 5·18 |
| *o*-Toluidine | — | 27·2 | 58·3 | 127 | 252 | 13,300 | 6·70 |
| *m*-Toluidine | — | 568 | — | — | — | — | — |
| *p*-Toluidine | — | 1370 | — | — | — | — | — |
| *o*-Fluoroaniline | 2·55 | 5·58 | — | 23·1 | — | 12,150 | 5·13 |
| *m*-Fluoroaniline | — | 20·6 | — | — | — | — | — |
| *p*-Fluoroaniline | — | 324 | — | — | — | — | — |
| *o*-Chloroaniline | — | 0·299 | — | 1·55 | 3·25 | 13,900 | 5·23 |
| *m*-Chloroaniline | — | 18·0 | 38·7 | 76·3 | — | 12,100 | 5·60 |
| *p*-Chloroaniline | — | 65·6 | 130 | 241 | — | 10,900 | 5·22 |
| *m*-Nitroaniline | — | 1·36 | 3·06 | — | — | — | — |

Values of $k$ are accurate to ±2%, of $E$ to ±300 cal. mole$^{-1}$, and of log $A$ to ±0·2 unit.

since these positions are remote from the reaction centre. The approximate constancy of $\Delta S^{\ddagger}$ over three of the four reactions implies that potential energy factors dominate the changes in $\Delta H^{\ddagger}$. The size and orientation of the cyano-group are such that no primary steric effect is involved. The difference in log $A$ terms between reactions of 2-chloro-3-cyano-4,6-dimethyl-5-nitropyridine and those of the other compounds seems just significant and is unexpected. This compound differs from the others in that the nitro-group is twisted out of the plane of the ring, but there is no obvious way of relating this to the effect on log $A$.

We may compare the log $A$ values found in the present work with those for the reactions of other types of chloro-compound with aniline and substituted anilines. Table 4 records Arrhenius parameters for the reactions of 2-chloro-3-cyano-5-nitropyridine with a number of substituted anilines. (These are discussed in detail below.) With the exception of the reaction with *o*-toluidine all the reactions studied in the present work have log $A$ values lying in the range 4·6—5·6. For the reactions of anilines with 2-chloro-3(or 5)-nitropyridine in ethanol, Bishop, Cavell, and Chapman [2] found log $A$ in the range 3·5—5·0. The values calculated by Chapman, Parker, and Soanes [25] from the results of Singh and Peacock [15] for the reaction of 1-chloro-2,4-dinitrobenzene with anilines in ethanol lie between 3·5 and 5·5. Similar values were obtained for aniline and methyl-substituted 1-chloro-2,4-dinitrobenzenes by Capon and Chapman.[1] Log $A$ values for the reactions between substituted benzoyl chlorides and anilines in various solvents mainly lie in the range 3·5—5·0.[26-28] In terms of the collision theory, in all the above reactions the probability factor $P$ ($A = PZ$) is about $10^{-7}$. The magnitude of $P$ is apparently governed by the underlying similarity of the reactions, *i.e.*, they all involve nucleophilic displacement of chlorine on carbon by aniline. Variations in the structure of the chloro-compound and amine, and in solvent effects, are of secondary importance.

For the reaction of aniline with 2-chloro-5-nitropyridine a change of solvent from 99·8% ethanol to " dry " methanol results in an increase in $E$ of some 1000 cal. mole$^{-1}$ and in log $A$ of about 1·2 units. We defer discussion of these observations until more results are available.

*Application of the Hammett* $\rho\sigma$ *Equation.*—Numerous substituent ($\sigma$) and reaction constants ($\rho$) have been calculated by Hammett [6] and by Jaffé,[21] and the Hammett equation has been shown to relate structure to reactivity with fair precision in many cases. For *para*-substituents involved in strong mesomeric interaction with the benzene ring, two different $\sigma$-values seemed to be required for each substituent. van Bekkum, Verkade, and Wepster [29]

[25] Chapman, Parker, and Soanes, *J.*, 1954, 5033.
[26] Mather and Shorter, *J.*, 1961, 4744.
[27] Stubbs and Hinshelwood, *J.*, 1949, S71.
[28] Bose and Hinshelwood, *J.*, 1958, 4085.
[29] van Bekkum, Verkade, and Wepster, *Rec. Trav. chim.*, 1959, **78**, 815.

have recently criticised this concept of the " duality of σ-constants." They have suggested that each substituent apparently showing this behaviour in fact possesses a wide *range* of σ-values corresponding to variable mesomeric interactions with the ring, and that it is incorrect to assign to such substituents just two values of σ. It follows that *para*-substituents should normally not be used to evaluate ρ-constants. Wepster holds that most groups with powerful mesomeric effects should not be used in determining ρ-values even as *meta*-substituents, although the *m*-nitro-group is regarded as reliable. Wepster has recalculated many ρ-values on this basis and he uses these to calculate σ-constants appropriate to various reactions for substituents showing mesomeric interactions.

The reactions of chlorocyanonitropyridines with substituted anilines obey the Hammett relation with considerable precision. If the σ-values given by Jaffé [21] are applied for all substituents available, $\rho = -3{\cdot}47$ and $\log k_0 = -2{\cdot}42$ (correlation coefficient, $r = 0{\cdot}997$; standard deviation, $s = 0{\cdot}08$). When Wepster's method is applied, $\rho = -3{\cdot}42$ and $\log k_0 = -2{\cdot}47$ ($r = 0{\cdot}998$; $s = 0{\cdot}07$).

The ρ-value for the reaction between 2-chloro-3-cyano-6-methyl-5-nitropyridine and anilines (aniline, *m*-chloroaniline, and *m*-toluidine) at 10° is −3·24, while for the reaction of 2-chloro-3-cyano-4,6-dimethyl-5-nitropyridine with anilines (aniline, *m*- and *p*-toluidine) at 10°, $\rho = -3{\cdot}32$. (Values of *k* are in Table 5.) In these instances good linear relations are also obtained, although the number of substituents and the range of σ-values are limited. The use of the *p*-methyl group is, of course, not strictly in accord with Wepster's views, but its mesomeric effect is not very powerful. Even though the reactivity of the chlorocyanonitropyridines varied some three-hundred-fold the variation in ρ value was not more than ±3% from the mean value of −3·33, when the value of −3·42 was used for 2-chloro-3-cyano-5-nitropyridine. For the reaction at 20° of 2-chloro-3-cyano-5-nitropyridine with anilines (aniline, *m*- or *p*-chloroaniline, *m*-nitroaniline) $\rho = -3{\cdot}39$, slightly less than the value for 10°, however calculated. The point for *p*-Cl fits well with the others. Values of ρ usually decrease with increase in temperature. A change of 10° is too small to give any precise information about the effect of temperature on ρ, but the observed effect is in the right direction.

*The ρ-Values for the Reactions of Anilines with Other Chloro-compounds.*—Data are available for the reactions of anilines with a number of other chloro-compounds, and variations in ρ with the nature of the chloro-compounds and solvent are next examined. Table 6 contains ρ-values calculated by Jaffé.[21]

TABLE 5.

Rate coefficients for the reactions of 2-chloro-3-cyano-4,6-dimethyl-5-nitropyridine (A) and of 2-chloro-3-cyano-6-methyl-5-nitropyridine (B) with substituted anilines at 10°.

| | $10^5k$ (l. mole$^{-1}$ sec.$^{-1}$) for reaction with | | | |
|---|---|---|---|---|
| Chloro-compound | aniline | *m*-toluidine | *p*-toluidine | *m*-chloroaniline |
| A | 1·0 * | 1·60 | 3·62 | — |
| B | 93·2 | 153 | — | 5·61 |

* From Arrhenius parameters.

TABLE 6.

ρ-Values for reactions of amines with various chloro-compounds.

| Reaction | Solvent | Temp. | ρ |
|---|---|---|---|
| Subst. aniline + benzoyl chloride | Benzene | 25° | −2·78 |
| Subst. *o*-toluidine + benzoyl chloride | Benzene | 25 | −2·73 |
| Subst. *o*-anisidine + benzoyl chloride | Benzene | 25 | −2·61 |
| Subst. aniline + 1-chloro-2,4-dinitrobenzene | Ethanol | 25 | −3·98 |
| | | 35 | −3·20 |
| | | 45 | −3·06 |
| | | 100 | −2·42 |
| Subst. aniline + 1-chloro-2,4-dinitronaphthalene | Ethanol | 25 | −3·73 |
| Subst. aniline + 2-chloro-5-nitropyridine | Ethanol | 65 | −3·69 |

Discussion of Table 6 is complicated by the use of different temperatures. Although cursory examination suggests that the ρ-values vary with the chloro-compounds and solvents, this conclusion is not valid. According to Wepster,[29] Jaffé's ρ-values are sometimes in error because he frequently utilised substituents of powerful mesomeric effect including methoxy- and ethoxy-groups. Considering only suitable substituents, Wepster has recalculated ρ for the reaction between anilines and benzoyl chloride [29] at 25° and found it to be −3·21. With substituted *o*-toluidines and *o*-anisidines the values were −3·12 and −3·40, respectively. The ρ-values for the reaction between anilines and 1-chloro-2,4-nitrobenzene (Singh and Peacock [15]) were recalculated as −2·92 and −3·08 for 45° and 35°, respectively. If we assume [21] that $\rho \propto 1/T$, for 25° the ρ-value for this reaction should be about −3·2. Wepster found the ρ-value for the same reaction at 100° (van Opstall's results [30]) to be −2·70, *i.e.*, about −3·5 for 25°. The ρ-value of −3·976 for 25° for this reaction evaluated by Jaffé from van Opstall's results and also the ρ-value of −3·73 for the reaction between 1-chloro-2,4-dinitronaphthalene and anilines are greatly exalted by the inclusion of *p*-methoxy- and *p*-ethoxy-groups. Much lower values would be obtained if more suitable groups were used. The ρ-value for the reaction between anilines and 2-chloro-5-nitropyridine at 65° calculated by Jaffé corresponds to a value of about −4 at 25°. This is much too high because of the inclusion of methoxy- and ethoxy-groups. (Existing data are too sparse for recalculation of ρ in the last three reactions mentioned.)

The mean ρ-value of −3·33 for 10° for the reactions of anilines with chlorocyanonitropyridines corresponds to a value of about −3·2 for 25°. Thus, as far as can be seen, for all the reactions in Table 6, as well as those studied in the present work, ρ lies in the range −3·1 to −3·5 for 25°. It thus seems probable that ρ is characteristic of the nucleophile (aniline) and that variations in the chloro-compound and the solvent are of secondary importance. Litvinenko *et al.*[31] have, however, found ρ = −4·79 for the reaction of picryl chloride with substituted anilines in benzene at 25°; a very good linear relation was obtained, even though *p*-methoxy-, *p*-methyl-, and *p*-chloro-groups were utilised. Because of the presence of three nitro-groups it may well be that this reaction proceeds by a mechanism involving an intermediate complex of quinonoid type, similar to those known to be formed, for example, by 2,4,6-trinitroanisole and alkoxide ions; [32] this reaction may therefore not be strictly comparable with those previously discussed.

*Arrhenius Parameters for the Reactions of Substituted Anilines with 2-Chloro-3-cyano-5-nitropyridine.—The* " ortho-*effect.*" Arrhenius parameters and rate coefficients are given in Table 4. In discussing these it is necessary to consider the arrangement of the reactant molecules in the transition state. There is fair freedom of rotation about the C–N partial bond between the two reacting molecules, and the system may take up any configuration between two extremes, as in the transition state for the reaction between benzoyl chloride and aniline discussed by Mather and Shorter.[26] For the latter reaction it was argued that an " extended configuration " was more likely than a " compact " one. The same arguments apply to the present case, and we suggest that the transition state will be arranged as shown in Fig. 1.

*The chloroanilines.* Log *A* for reactions of the three chloroanilines has a mean value of 5·35 ± 0·17, compared with 5·18 for that of aniline. There is no specific effect of *o*-Cl. Inspection of a model of the transition state shows that *o*-Cl restricts slightly the rotation of the aniline ring about the ring–N bond, although such movement is already greatly restricted by the proximity of the aniline ring and the chlorine atom being displaced. In view of later discussion it seems likely that the absence of any effect of *o*-Cl on log *A* is due to compensation of two opposing factors: a steric effect as just discussed tending to decrease log *A*, and steric inhibition of solvation of the transition state tending to raise log *A*.

[30] van Opstall, *Rec. Trav. chim.*, 1933, **52**, 901.
[31] Litvinenko, Syrovatka, Skoropisova, and Ostrovskaya, *Ukrain. khim. Zhur.*, 1959, **25**, 189.
[32] Meisenheimer, *Annalen*, 1902, **323**, 205.

The activation energies for reactions of *m*- and *p*-chloroaniline are in accord with the operation of the $+T$ and $-I$ effects of *m*-Cl and *p*-Cl. The high value of $E$ for the reaction of *o*-chloroaniline is probably due to a powerful $-I$ effect and possibly also to a reduction in the $+T$ effect as compared with *p*-chloroaniline, since it involves an *ortho*-quinonoid structure. Steric inhibition of solvation may also contribute to the high value of $E$.

*The fluoroanilines.* Log $A$ for the reaction of *o*-fluoroaniline is very close to log $A$ for that of aniline. The model shows that *o*-F does not restrict the rotation of the aniline ring about the ring–N bond any more than a hydrogen atom does. The low reactivity

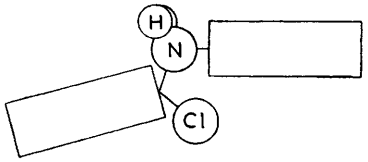



FIG. 1.

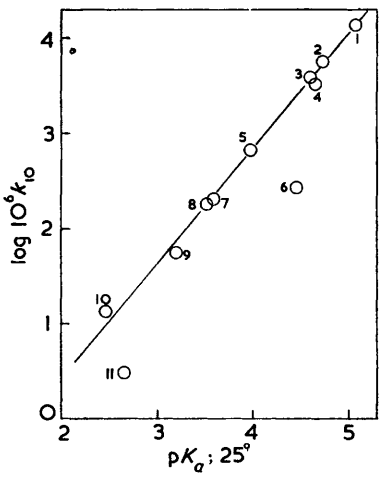



FIG. 2. Plot of log $10^6k_{10}$ for the reaction of 2-chloro-3-cyano-5-nitropyridine with substituted anilines in methanol (ordinate) against $pK_a$ for substituted anilinium ions in water at 25°. (Values of $pK_a$ from Biggs and Robinson, *J.*, 1961, 388.)

1, *p*-Me. 2, *m*-Me. 3, H. 4, *p*-F. 5, *p*-Cl. 6, *o*-Me. 7, *m*-F. 8, *m*-Cl. 9, *o*-F. 10, *m*-$NO_2$. 11, *o*-Cl.

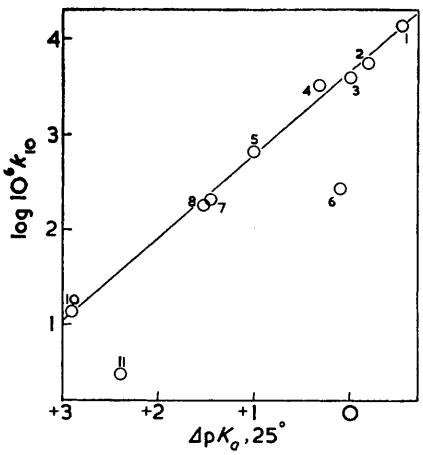



FIG. 3. As for Fig. 2; values of $\Delta pK_a$ are relative to aniline for methanol at 25°. (Values of $\Delta pK_a$ from Kilpatrick and Arenberg, *J. Amer. Chem. Soc.*, 1953, **75**, 3812.) Key as Fig. 2.

of *o*-fluoroaniline compared with *p*-fluoroaniline is thus presumably due to an enhanced $-I$ effect and a reduced $+T$ effect rather than to primary steric effects. Log $k/k_0$ ($k$ refers to *o*-fluoroaniline and $k_0$ to aniline) may thus be taken as a measure of the polar effect of *o*-F. At 10° the value is −1·84; the corresponding value for *p*-fluoroaniline is −0·08. The ratio of these is 23. By studying acidic and basic ester hydrolysis Taft [33] has derived values of $\sigma^*$, a measure of the polar effects of *ortho*-substituents on the same scale as Hammett's $\sigma$ for *meta*- and *para*-substituents.[6] For *o*-F $\sigma^* = 0{\cdot}24$; for *p*-F $\sigma_p = +0{\cdot}06$, so the ratio $\sigma^*/\sigma_p$ is ~4.

The relative polar effect of *o*-F and *p*-F in aniline assessed above is thus much larger than $\sigma^*/\sigma_p$. On a Hammett plot the point for *p*-F lies somewhat above the line. This

[33] Taft, in Newman's "Steric Effects in Organic Chemistry," Wiley, New York, 1956, Chapter 13.

may be due to a powerful operation of the $+E$ effect of which the $\sigma_p$-value takes no account. If it be assumed that in the absence of this effect *p*-fluoroaniline would lie on the Hammett line, log $k/k_0$ for *p*-F would be −0·21. The relative polar effect of *o*-F and *p*-F in aniline would then be about 8·8, *i.e.*, much nearer to $\sigma^*/\sigma_p$.

o-*Toluidine.* log $A$ is about 1·5 units higher than for the reaction of aniline; $E$ is about 3500 cal. mole$^{-1}$ higher. Steric inhibition of solvation of the transition state is probably responsible. The magnitude of the effect seems at first sight to be rather large, considering that the van der Waals radii of chlorine and methyl differ by only 0·2 Å. Inspection of a model of the transition state reveals that this increase of 0·2 Å might be

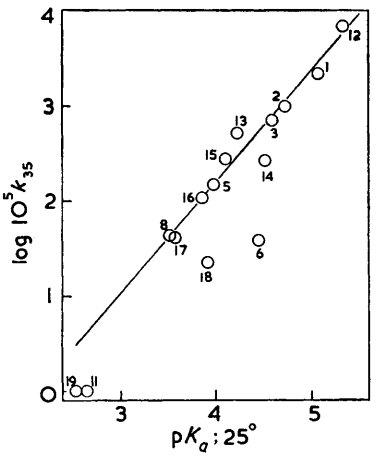



FIG. 4. Plot of log $10^5k_{35}$ for the reactions of 1-chloro-2,4-dinitrobenzene with substituted anilines in ethanol (ordinate) against p$K_a$ for substituted anilinium ions in water at 25°. [Values of $k$ from Singh and Peacock, *J. Phys. Chem.*, 1936, **40**, 669; and of p$K_a$ from Biggs and Robinson, *J.*, 1961, 388, except for 1- and 2-naphthylamine (from Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469).] Key as for Fig. 2; also: 12, *p*-MeO. 13, *m*-MeO. 14, *o*-MeO. 15, 2-$C_{10}H_7$. 16, *p*-Br. 17, *m*-Br. 18, 1-$C_{10}H_7$. 19, *o*-Br.

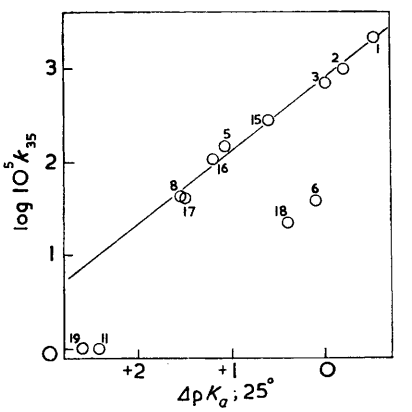



FIG. 5. As for Fig. 4; values of $\Delta$p$K_a$ are relative to aniline for ethanol at 25°. (Values of $\Delta$p$K_a$ from Kilpatrick and Arenberg, *J. Amer. Chem. Soc.*, 1953, **75**, 3812, or Goodhue and Hixon, *ibid.*, 1934, **56**, 1329; the value for 1-naphthylamine is corrected for a misprint in Goodhue and Hixon's paper.) Key as Fig. 4.

critical; the hydrogen atoms of the amino-group and of the methyl group are in steric interaction with each other. This may have a considerable effect on the increase in solvation which generally occurs in going from the initial to the transition state.

In this connexion it is of interest that in the reaction of benzoyl chloride and aniline in benzene the introduction of a methyl group or other *ortho*-substituent into aniline has no effect on log $A$.[27] On the other hand in nitrobenzene solution *ortho*-substituents raise log $A$ by up to 1 unit.[28] These observations are readily explained by supposing that steric inhibition of solvation of the transition state by *ortho*-substituents is of considerable importance in the polar solvent.

*Relationship between log* k *for Reaction of Substituted Anilines with 2-Chloro-3-cyano-5-nitropyridine and* p$K_a$ *Values of the Anilinium Ions.*—The relationship between log $k$ values for *meta*- and *para*-substituted anilines and Hammett $\sigma$-values has been discussed above. A more direct correlation would be with the p$K_a$ values for the substituted anilinium ions. This correlation might even be useful for *ortho*-substituted compounds to which the

Hammett equation is not applicable. Such a correlation was examined by Stubbs and Hinshelwood [27] for the reaction of benzoyl chloride and substituted anilines in benzene. They found a linear relationship which applied to *ortho*-, *meta*-, and *para*-substituted anilines.

In Fig. 2 values for log $k$ for the reactions of 2-chloro-3-cyano-5-nitropyridine with substituted anilines at 10° are plotted against p$K_a$ at 25° for water; in Fig. 3, $\Delta$p$K_a$ values for methanol are used. For *meta*- and *para*-compounds a good linear relationship is found. Log $k$ and p$K_a$ are both dependent on the availability of the lone-pair of electrons at the amino-group. In Fig. 2 the point for *o*-fluoroaniline lies on the line, but those for *o*-toluidine and *o*-chloroaniline lie well below the line. We have already suggested that fluorine in the *ortho*-position influences reactivity by virtue of a large polar effect, steric effects being small, while the *o*-methyl group exerts considerable steric inhibition of solvation. It is presumably this difference between fluorine and methyl which is reflected in the log $k$–p$K_a$ graph. That points for chlorine and methyl are similarly placed in these graphs suggests that with chlorine too there is steric inhibition of solvation of the transition state, even though this is not apparent in log $A$ (see p. 1983).

Similar graphs for the reactions between 1-chloro-2,4-dinitrobenzene and substituted anilines in ethanol [15] are shown in Figs. 4 and 5, where p$K_a$ values for water and $\Delta$p$K_a$ values for ethanol, respectively, are used. The points for *o*-Me, *o*-Cl, and *o*-Br are well below the line, while that for *o*-OMe is not far from the line. β-Naphthylamine fits with the *meta*- and *para*-substituted compounds, whereas the point for α-naphthylamine is well below the line. α-Naphthylamine is effectively an *ortho*-substituted compound by virtue of steric interactions involving the 8-hydrogen atom.

Bose and Hinshelwood [28] plotted log $k$ at 25° for the benzoyl chloride and aniline reaction in several polar solvents against p$K_a$ in water at 25°. A straight line could be drawn through the points for each solvent and these lines were parallel to each other and to the line for benzene as solvent.[27] Examination of their results shows that with polar solvents the points for *ortho*-groups lie well below the corresponding lines, whereas with benzene the points for *ortho*-groups lie near the line. This confirms the view that the behaviour of *ortho*-groups in the benzoyl chloride and aniline reaction in polar solvents is probably connected with the steric inhibition of solvation of the transition state.

One of us (D. K. C.) is indebted to the University of Hull for a Research Studentship. We also thank the Distillers Co. Ltd. (Chemical Division) for financial support.

THE UNIVERSITY, HULL. [*Received, November 6th*, 1961.]