Nucleophilic Displacement Reactions in Aromatic Systems. Part XI.[1] Kinetics of the Reactions of 2-Chloro-, of 2-Chloro-3-cyano-, and of 2-Chloro-3-cyano-6-methyl-5-nitropyridine with Aniline and Substituted Anilines in Various Solvents

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Rate coefficients have been measured for the reactions of aniline with 2-chloro-3-cyano-6-methyl- and with 2-chloro-3-cyano-5-nitropyridine in various protic solvents (mainly alkanols) and aprotic solvents at 20°. For selected systems rate coefficients have also been measured at two other temperatures and activation parameters calculated. While dielectric constant as a measure of non-specific solvent effects is probably of some significance, the Lewis acid–base behaviour of the solvent appears to play the dominant role in governing reactivity. This is particularly clear for the series of protic solvents. Values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ vary widely, and for the reactions of 2-chloro-3-cyano-5-nitropyridine various pairs of alcohols show isokinetic temperatures within the range of experiment. Thus the pattern of k values depends critically on temperature. A limited study of the reactions of aniline with 2-chloro-5-nitropyridine in lower alcohols is also presented. Values of the Hammett ρ constant have been measured for the reactions of substituted anilines with 2-chloro-3-cyano-6-methyl-5-nitropyridine in several solvents. The ρ values depend but little on solvent, as suggested in related work.

MOST of the factors which affect the rates of nucleophilic aromatic substitutions have been actively studied in the past twenty years.[2] However, information on the effect of varying the solvent on such reactions is rather limited [3] and generally involves mixed solvents. The use of mixed solvents complicates the interpretation of results because the composition of the solvent near the reactant molecules and activated complexes differs from that in the bulk of the solvent. The main work in which nucleophilic aromatic substitutions have been studied in a range of pure solvents is by Miller and Parker,[4] and by Suhr.[5] Further information on the effect of solvent variation on nucleophilic aromatic substitutions in activated α-chloropyridines is presented in this paper. Very few results are available concerning the variation of the Hammett reaction constant ρ with the nature of the medium, and those that are available mainly involve the dissociation or other reactions of substituted benzoic acids.[6] This paper records a study of the effect of variation of the solvent on ρ for the reactions of *meta*-substituted anilines with 2-chloro-3-cyano-6-methyl-5-nitropyridine.

EXPERIMENTAL

Preparation and Purification of Halogeno-compounds.—3-Cyano-6-methyl-2-pyridone, prepared by Mariella's method,[7] was converted into the 5-nitro-compound and then into the 2-chloro-5-nitro-compound by the method of Perez-Medina *et al.*[8] Four crystallisations from light petroleum (b.p. 60—80°) gave the pure chloro-compound, m.p. 98—99° (lit.,[8] 98—99°). 2-Chloro-3-cyano-5-nitropyridine was prepared by Fanta and Stein's method [9] and had m.p. 122—123° [from light petroleum (b.p. 100—120°)] (lit.,[9] 121—122°) (Found: C, 39·4; H, 1·05; N, 23·0; Cl, 19·5. Calc. for $C_6H_2ClN_3O_2$: C, 39·25; H, 1·1; N, 22·9; Cl, 19·3%).

Purification of Solvents.—Ethanol, ethyl acetate, and toluene were purified as described in Part X.[1] Methanol was purified by Lund and Bjerrum's method.[10] All the other solvents except nitrobenzene were dried over freshly ignited potassium carbonate for several days and then over a molecular sieve (type 4A) for several days. Nitrobenzene was first dried over calcium chloride for three days. Each dry solvent was carefully distilled through a 50 × 1·5 cm Fenske column or a 30 × 5 cm Widmer column, and stored under nitrogen in the dark. The water content of each solvent (Karl Fischer titration [11a]) never exceeded 0·02% w/w and no impurities were detected by g.l.c. For every solvent used the observed b.p. and refractive index agree very closely with recorded values.[11b] All other materials used were purified and manipulated as described in Parts VII [12] or X.[1]

Kinetic Methods.—These were as described in Part X.[1]

DISCUSSION

We assume that the reactions of aniline with α-chloropyridines which are activated by a β-nitro- or a β-cyano-group proceed by the two-stage mechanism of aromatic nucleophilic substitution, with the first stage rate-determining [1] (Scheme). The formation of the activated complex from the reactants involves charge separation and this process would be expected to be facilitated when the ' polarity ' of the solvent is increased.[13] If, as is often done, dielectric constant is taken as a measure of solvent polarity then this prediction is at first sight

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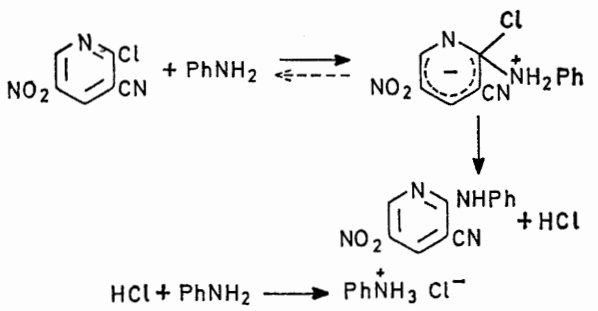
[12] N. B. Chapman, D. K. Chaudhury, and J. Shorter, *J. Chem. Soc.*, 1962, 1975.
[13] C. K. Ingold, ' Structure and Mechanism in Organic Chemistry,' Bell, London, 1969, 2nd edn.

fulfilled by some of the results in Tables 1 and 2. Thus the reaction at 20° of aniline with 2-chloro-3-cyano-6-methyl-5-nitropyridine (Table 1) proceeds much faster



SCHEME

in a range of aliphatic alcohols (10^4k 17·1—27·2, ε 32·6—15·8) or DMF (10^4k 19·4, ε 36·71) than in ethyl acetate (10^4k 0·638, ε 6·02) or toluene (10^4k *ca.* 5×10^{-6}, ε 2·38),

TABLE 1

Reactions of aniline with 2-chloro-3-cyano-6-methyl-5-nitropyridine at 20·0°

Solvent	10^4k (l mol^{-1} s^{-1})	σ*	ε §
MeOH	17·1	0·00	32·6
EtOH	21·5	−0·10	24·3
Pr^{n}OH	25·0	−0·115	20·1
Pr^{i}OH	24·9	−0·19	18·3
Bu^{n}OH	26·7	−0·13	17·1
Bu^{s}OH	27·2	−0·21	15·8
$PhCH_2OH$	2·49	+0·215	13·1
$MeO[CH_2]_2OH$	7·80	+0·19 †	16·0
$Bu^nO[CH_2]_2OH$	8·45	+0·17 †	12·8 ‡
EtOAc	0·638		6·02
$HCO{\cdot}NMe_2$	19·4		36·71
$PhNO_2$	*ca.* 0·05 ‖		34·8
PhMe	*ca.* 5×10^{-6}		2·38

† Values estimated from those of related groups. § Values from ref. 11*b*. ‡ Determined by Mr. C. E. Reed, Department of Physics, University of Hull. Values of σ* from ref. 14 except as indicated. ‖ From activation parameters. Rate coefficients were reproducible to ±2%, except for the reaction in toluene, where reproducibility is only ±5%.

TABLE 2

Reactions of aniline with 2-chloro-3-cyano-5-nitropyridine at 20·0, 30·0, and 40·0°

Solvent	10^4k (l mol^{-1} s^{-1}) 20·0°	(Relative to 6-Me compound, Table 1)	10^4k (l mol^{-1} s^{-1}) 30·0°	40·0°
MeOH	65·3	(3·81)	118	209
EtOH	86·8	(4·03)	151	257
Pr^{n}OH	101	(4·04)	174	288
Pr^{i}OH	101	(4·04)	165	267
Bu^{n}OH	110	(4·12)	188	309
Bu^{s}OH	132	(4·85)	196	283
EtOAc	2·82	(4·41)	5·23	9·21
$HCO{\cdot}NMe_2$	73·1	(3·77)	136	244

Rate coefficients were reproducible to ±2%.

and the situation is similar for 2-chloro-3-cyano-5-nitropyridine at several temperatures (Table 2). However close inspection of Tables 1 and 2 reveals several anomalies. For the alkanols in Tables 1 and 2, 10^4k in fact tends to *increase* as ε *decreases*, but for benzyl alcohol (Table 1), for which ε is 13·1, only slightly below the range for the aliphatic alcohols studied, $10^4k = 2{\cdot}49$, lower than that for Bu^{s}OH (10^4k 27·2) by a factor of 11; and for 2-methoxyethanol, whose value of ε (16·0) is almost the same as that for Bu^{s}OH (15·8), $10^4k = 7{\cdot}8$, *i.e.* lower than that for Bu^{s}OH by a factor of 3·5. Further, the reaction is 400 times slower at 20° in nitrobenzene than in DMF (Table 1), even though their dielectric constants differ but slightly. It is clear that the solvent effect requires a much more detailed analysis than the application of the concept of solvent ' polarity,' as measured by ε.

The results for the protic solvents in Tables 1 and 2 strongly suggest that the dominant influence is the ability of the solvent molecule to act as a proton donor or acceptor in hydrogen bonding with the reactants or activated complex. Thus the reaction appears to be favoured by structural changes in the solvent molecule which increase its Lewis basicity or decrease its Lewis acidity. Increasing the length of an alkyl chain or its extent of branching may be supposed to produce such changes in basicity or acidity corresponding to the more negative values [14] of σ*, and k increases with the increase in the length or branching of the chain. Conversely, the introduction of electron-attracting groups into the alcohol, producing substituted alkyl groups with positive values of σ*, greatly decreases k, *e.g.* the alkoxyethanols and benzyl alcohol (Table 1).

The role of hydrogen bonding in this reaction system may be envisaged in various ways. Obviously hydrogen bonding of alcohol molecules to the nascent $-\overset{+}{N}H_2-$ centre of the activated complex should stabilise it. Hydrogen bonding of an alcohol molecule as proton donor to the diffuse negative region of the activated complex should be much less important. On the other hand hydrogen bonding involving the lone-pair electrons of the reactant aniline might well be a factor stabilising the initial state. The structural changes in the alcohol favouring stabilisation of the activated complex should thus destabilise the initial state. Thus the effects of the two main types of hydrogen bonding, as here envisaged, reinforce each other. Other types of hydrogen bonding might lead to competing effects and this may account for the relatively small structural effect observed for the alkanols. However, the general or non-specific solvent effect [15] as measured by dielectric constant would also be a competing factor since ε tends to decrease as the basicity of the alkanol is increased.

It might be hoped that the solvent effect in this system could be treated in terms of multiple regression of log k on σ* and $(\varepsilon - 1)/(2\varepsilon + 1)$ as for the reaction of diazodiphenylmethane with benzoic acid in alcohols.[16] However, the reactivity range is much smaller than for the latter reaction, and further the *pattern of reactivity as measured by log* k *is not temperature independent.* This

[14] R. W. Taft in ' Steric Effects in Organic Chemistry,' ed. M. S. Newman, Wiley, New York, 1956, ch. 13.
[15] Ref. 6. ch. 5.
[16] N. B. Chapman, M. R. J. Dack, D. J. Newman, J. Shorter, and R. Wilkinson, *J.C.S. Perkin II*, 1974, 962, and earlier papers.

is shown by the results in Tables 2 and 3. The Arrhenius lines for three pairs of alkanol solvents cross in the range 20—40° and there is no doubt that there are other isokinetic temperatures for various solvent pairs above and below this temperature range. Thus at 20 and 30° the order of reactivity is $Bu^nOH < Bu^sOH$, but at 40° the order is $Bu^sOH < Bu^nOH$, with the isokinetic temperature being *ca.* 33°. In these circumstances multiple regression of log k with solvent parameters would be pointless. We have not studied the reactions of 2-chloro-3-cyano-6-methyl-5-nitropyridine in alkanols at more than one temperature (20°), except in one case (Tables 4 and 5), but the same situation seems probable.

TABLE 3

Reactions of aniline with 2-chloro-3-cyano-5-nitropyridine. Activation parameters

Solvent	E (kcal mol^{-1})	log A	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$-\Delta S^{\ddagger}$ (cal mol^{-1} K^{-1})
MeOH	10·65	5·74	10·05	34·3
EtOH	9·9	5·32	9·3	36·2
Pr^nOH	9·6	5·15	9·0	37·0
Pr^iOH	8·85	4·60	8·25	39·5
Bu^nOH	9·4	5·05	8·8	37·5
Bu^sOH	6·95	3·30	6·35	45·5
EtOAc	10·8	4·50	10·2	40·0
$HCO{\cdot}NMe_2$	10·95	6·05	10·35	32·9

Values of E and $\Delta H^{\ddagger}$ are accurate to *ca.* ±0·3 kcal mol^{-1}, values of log A to ±0·2 unit, and values of $\Delta S^{\ddagger}$ to ±1 cal mol^{-1} K^{-1}. Isokinetic temperatures: Pr^n–Pr^iOH 20°, Bu^nOH–Bu^sOH 33°, Pr^nOH–Bu^sOH 38·5°.

TABLE 4

Reactions of aniline with 2-chloro-3-cyano-5-nitro-6-methylpyridine at 20·0, 30·0, 40·0, and 50·0°

	10^4k (l mol^{-1} s^{-1})			
Solvent	20·0°	30·0°	40·0°	50·0°
Bu^sOH	27·2	41·1	59·6	
$Bu^nO[CH_2]_2OH$	8·45	15·4	24·6	
EtOAc	0·638	1·09	1·95	
$PhNO_2$		0·100	0·190	0·385

Rate coefficients were reproducible to ±2%.

For the reactions of both chloro-compounds it is likely that in the temperature range below the lowest of the isokinetic temperatures, the reactivity order would be as follows: MeOH < EtOH < Pr^nOH < Bu^nOH < Pr^iOH < Bu^sOH. This would correspond exactly to the basicity order expected from the σ* values, but at *ca.* 20° the position of Pr^iOH is anomalous (Tables 1 and 2), and at 40° (Table 2) that of Bu^sOH is also anomalous.

TABLE 5

Reactions of aniline with 2-chloro-3-cyano-5-nitro-6-methylpyridine. Activation parameters

Solvent	E (kcal mol^{-1})	log A	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$-\Delta S^{\ddagger}$ (cal mol^{-1} K^{-1})
Bu^sOH	7·2	2·78	6·6	47·8
$Bu^nO[CH_2]_2OH$	9·8	4·21	9·2	41·3
EtOAc	10·2	3·40	9·6	45·0
$PhNO_2$	13·2	4·50	12·6	40·0

Values of E and $\Delta H^{\ddagger}$ are accurate to *ca.* ±0·3 kcal mol^{-1}, values of log A to ±0·2 unit, and values of $\Delta S^{\ddagger}$ to ±1 cal mol^{-1} K^{-1}.

Clearly the activation parameters for the reactions in alkanols are of interest, and for the reactions of 2-chloro-3-cyano-5-nitropyridine these are in Table 3. There are very considerable variations in both E (or $\Delta H^{\ddagger}$) and log A (or $\Delta S^{\ddagger}$), which tend to compensate each other, but the effect of the former is dominant. Utilisation of the greater basicity of the longer chain or more highly branched alkanols in the stabilisation of the activated complex apparently requires a more ordered arrangement of solvent molecules, relative to the initial state, so log A is reduced (or $\Delta S^{\ddagger}$ becomes more negative).

As indicated by the ratio of rate coefficients at 20° the secondary steric effect of the introduction of the 6-methyl group into 2-chloro-3-cyano-5-nitropyridine reduces the reactivity towards aniline by a factor of *ca.* 4.[12] There is little evidence of solvent dependence for this factor except in Bu^sOH, where the ratio appears to be somewhat higher. It may be that the steric effect of the methyl group in twisting the nitro-group is enhanced by the bulky molecules of this solvent. The effect seems to be much the same when DMF or EtOH is the solvent, the ratio then being 3·8 or 4·4 respectively.

A limited study has been carried out on the reactions of aniline with 2-chloro-5-nitropyridine in alkanols (Table 6). This chloro-compound is *ca.* 4000 times less reactive than 2-chloro-3-cyano-5-nitropyridine at 40° and this is due mainly to a considerably higher activation energy (*cf.* Tables 3 and 6), although log A is also reduced. Preliminary measurements gave the unexpected result that between 40 and 70° the rate coefficients for the reaction in methanol and in ethanol are almost the same. More refined studies found rate coefficients for methanol a few percent higher than those for ethanol between 50 and 70° (*cf.* the relationship in Tables 1 and 2). The earlier and the later studies agree in finding the value of E for methanol slightly greater than for ethanol, and the situation appears to be that the range 40—70° lies above the isokinetic temperature for the two solvents. Below 40° the order would be MeOH < EtOH, as with the other chloro-compounds, and presumably essentially, the same solvent factors operate.

TABLE 6

Reactions of aniline with 2-chloro-5-nitropyridine. Rate coefficients at 40·0, 50·0, 60·0, and 70·0° and Arrhenius parameters

	10^6k (l mol^{-1} s^{-1})				E (kcal mol^{-1})	
Solvent	40·0°	50·0°	60·0°	70·0°		log A
MeOH	4·90	9·84	18·6	32·8	13·5	4·11
EtOH (99·8%)	5·07	9·83	18·5	32·3	13·2	3·90
MeOH *		9·02	16·7	29·8	13·15	3·87
EtOH *		8·64	15·8	27·6	12·8	3·60

* Values of k were obtained by extrapolation to $t = 0$.

Rate coefficients were reproducible to ±2%, and values of E are accurate to *ca.* ±0·3 kcal mol^{-1}, and values of log A to ±0·2 unit.

Dipolar Aprotic Solvents.—For DMF the rate coefficient for the reaction of either of the chloro-compounds with aniline is very similar to the corresponding value for methanol or ethanol. This situation contrasts with the reactions of aromatic halogeno-compounds with anionic nucleophiles which are slower in alcohols than in DMF by several powers of 10.[4] This is attributed to the extensive solvation of the anion by hydrogen bonding in the protic solvent. Since aprotic solvents such as DMF are rather poor at solvating anions, anionic nucleophiles are in a fairly exposed and reactive condition therein. Clearly the analogous solvation of uncharged aniline in protic solvents is not nearly such a powerful factor in reducing reactivity relative to the aprotic solvents. However our findings for aniline contrast even with those of Suhr[5] for another uncharged nucleophile, piperidine, which is *ca.* 100 times more reactive towards *p*-fluoronitrobenzene in DMF then in the lower alcohols. Piperidine is a much stronger base than aniline (the pK_a values of the conjugate acids are 11·13 and 4·58 respectively[17]) and presumably the initial state for piperidine is greatly stabilised by hydrogen bonding in protic solvents.

The low reactivity towards aniline of the two chloro-compounds in ethyl acetate is probably due to its low dielectric constant.

The extremely low reactivity of 2-chloro-3-cyano-6-methyl-5-nitropyridine in nitrobenzene is at first sight surprising in view of the high dielectric constant of the solvent and a fair degree of Lewis basicity (the value[18] of $\Delta\nu_D$ is 21). However, charge-transfer complexes are formed when aromatic amines are mixed with aromatic nitro-compounds.[19] When aniline is added to nitrobenzene a deep orange colour is produced, indicating extensive interaction. The low reactivity is therefore probably due to strong complexing of the aniline in the initial state by nitrobenzene.

The activation parameters for the reaction in aprotic solvents (Tables 3 and 5) indicate that changes in reactivity from one solvent to another may involve considerable changes in both enthalpy and entropy of activation.

Hammett Correlations.—Rate coefficients for the reaction of *meta*-substituted anilines with 2-chloro-3-cyano-6-methyl-5-nitropyridine in various protic solvents are in Table 7, together with Hammett ρ values.[20]

Chapman *et al.*[12] recorded ρ values for the reactions with substituted anilines in methanol at 10° of 2-chloro-3-cyano-, 2-chloro-3-cyano-6-methyl-, and 2-chloro-3-cyano-4,6-dimethyl-5-nitropyridine of −3·42, −3·24, and −3·32 respectively. 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. The same authors[12] pointed out that the ρ values for the reactions of anilines with a variety of chloro-compounds in various solvents lay in the range −3·1 to −3·5 at 25°, and thus ρ seemed to be characteristic of the nucleophile aniline, with variations in the chloro-compound and solvent being of secondary importance.

TABLE 7

Reactions of substituted anilines with 2-chloro-3-cyano-5-nitro-6-methylpyridine at 40·0°. Hammett ρ values

	10^5k (l mol^{-1} s^{-1})					
Solvent	*m*-Me	H	*m*-Cl	*m*-NO_2	ρ	*r* *
MeOH		499	38·2	3·31	−3·07	1·000
Bu^tOH	833	596	37·5	2·41	−3·28	0·999
$Bu^nO[CH_2]_2OH$	348	246	11·7	0·943	−3·35	0·999

Rate coefficients were reproducible to ±2%.

* Correlation coefficient.

The value of −3·07 for the reaction at 40° of 2-chloro-3-cyano-6-methyl-5-nitropyridine in methanol obtained in the present work accords fairly well with −3·24 at 10° obtained previously[12] and the relationship $\rho \propto 1/T$.[20] The values of ρ show some indication of becoming more negative as the dielectric constant of the solvent is decreased,[20] but the effect of solvent appears to be small, confirming what was previously suggested (see above[12]). In this respect the reactions of substituted anilines with aromatic chloro-compounds contrast greatly with, for example, the reactions of substituted benzoic acids with diazodiphenylmethane.[16] This difference may reflect a difference in the extent to which polar effects are transmitted through the medium (rather than the molecular cavity) in the two reactions. The diazodiphenylmethane reaction involves rate-limiting proton transfer from the benzoic acid and hence a fairly extended and open activated complex, which may be well surrounded by solvent. On the other hand the reactions of chloropyridines and related compounds with anilines involve a rather crowded activated complex, with the two rings fairly close together. This may result in a high degree of exclusion of solvent from the vicinity of the aniline ring, so that the polar effect of substituents is largely transmitted through the molecular cavity, and hence ρ shows only a slight solvent dependence.

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