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Inductive and Field Effects in Aromatic Substitution. Part I. Kinetics of Nitration of 4-Phenylpyridine and 4-Benzylpyridine

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The rate profiles for the nitration of 4-phenylpyridine and 4-benzylpyridine in aqueous sulphuric acid indicate that these compounds undergo reaction as the corresponding conjugate acids. Partial rate factors are reported and the rate of *meta*-substitution in the phenyl group is discussed in terms of the field effect of a unit charge placed at the centroid of charge of the pyridyl ring. Comparison with the reactivity of other neutral and positive substrates indicates that the deactivating effect of the protonated pyridyl group accords fairly closely with that expected from this field effect and not at all with that expected from the polarity of the σ -bond to the phenyl ring.

THE recent series of papers entitled 'Substituent Effects of Positive Poles in Aromatic Substitution '1 was largely concerned with the nature of the interaction

by which positive poles of the type $-\dot{X}Me_3$ (X = N, P, As, Sb) deactivate aromatic rings to electrophilic attack. The series now started is intended to deal with a wider range of neutral and charged substituents in order to investigate further the relative importance of inductive and field effects in aromatic substitution. In this paper the substituent studied is the protonated pyridyl group: in the following paper, the substituent is the trichloromethyl group. These studies are needed as part of a general comparison of the groups X and CH₂X in aromatic nitration.

With reactions of substituted pyridines, the interpretation of the substituent effects must be preceded by a mechanistic investigation to determine whether reaction is occurring through the neutral molecules

¹ A. Gastaminza, J. H. Ridd, and F. Roy, J. Chem. Soc. (B), 1969, 684, and references therein.

or through the corresponding conjugate acids. The rate profiles for the nitration of 4-phenylpyridine and 4-benzylpyridine in aqueous sulphuric acid have therefore been determined. While this work was in progress, Katritzky and Kingsland² published a similar kinetic study on the nitration of 2-phenylpyridine; the results of these workers are included in the general discussion.

Products.-The product composition in the nitration of 4-phenylpyridine in concentrated sulphuric acid has been studied previously³ by fractional crystallisation and fractional precipitation of the mononitro-compounds; the yields were ortho, 12.7%, meta, 28.5%, and para, 38.0%. No other products were detected, the missing 20% being presumably lost in handling. We have repeated this product analysis taking advantage of the differences in the u.v. spectra of the mononitro-compounds (see Experimental section). For nitration in

² A. R. Katritzky and M. Kingsland, J. Chem. Soc. (B), 1968, 862.

³ R. Forsyth and F. L. Pyman, J. Chem. Soc., 1926, 2912.

81% sulphuric acid, we find quantitative mononitration with the composition: ortho, 20%; meta, 33%; para, 47%. Essentially the same composition $(\pm 1\%)$ was obtained from nitration in 98% sulphuric acid.

The nitration of 4-benzylpyridine has been reported ⁴ to give 70.2% yield of the para-nitro-compound together with 4.8% of the meta-isomer (isolated after oxidation to *meta*-nitrobenzoylpyridine) and a trace of the ortho-isomer. The three mononitro-compounds have now been prepared (the *meta*-isomer for the first time) and analytical methods developed for determining the composition of the reaction mixture using n.m.r. and g.l.c. The earlier work appears to seriously underestimate the extent of ortho-substitution for we find that nitration in ca. 85% sulphuric acid gives: ortho, 14%; meta, 6%; and para, 80%. The extent of disubstitution is not significant when the concentrations of the reactants are equal.

Kinetics and Mechanism.—The kinetics of nitration of 4-phenylpyridine and 4-benzylpyridine in aqueous sulphuric acid were followed from the u.v. spectra of quenched samples of the reaction mixture.⁵ These reactions have the kinetic form of equation (1), where the concentration terms refer to the stoicheiometric concentrations of the reactants.

Rate =
$$k_2$$
 [aromatic substrate] [nitric acid] (1)

The values of the second-order rate coefficient (k_2) are given in Table 1 and plotted logarithmically in Figure 1 together with the corresponding results for the nitration of benzene⁶ and the benzyltrimethylammonium ion.5

TABLE 1

Second-order rate coefficients (l. $mole^{-1} sec.^{-1}$) for nitration in aqueous sulphuric acid at 24.8°

| | | | | 4-Benzyl-I | l-methyl- |
|------------------|---------------|--------------------------------|---------------|----------------|---------------|
| 4-Phenylpyridine | | 4-Benzylpyridine | | pyridinium ion | |
| H_2SO_4 | | H ₂ SO ₄ | | Ĥ₂SO₄ | |
| (%) | $10^{2}k_{2}$ | (%) | $10^{2}k_{2}$ | (%) | $10^{2}k_{2}$ |
| 75.1 | $0.5\bar{0}$ | 66.4 | $0.2\bar{6}$ | 68.4 | 1.06 |
| 77.1 | $3 \cdot 40$ | 68.3 | 0.98 | 70.2 | 5.10 |
| 78.2 | 8.70 | 70.1 | 4.40 | | |
| 80.0 | $52 \cdot 9$ | 72.8 | 50.7 | | |
| 80.1 | 53.0 | | | | |

The parallelism of the plots at a given acidity implies that the prototropic equilibria possible with the pyridine derivatives are without effect on the rate profile and hence that these compounds are reacting as the conjugate acids. The similarity in the reactivity of 4-benzylpyridine to that of the 4-benzyl-1-methylpyridinium ion (see Table 1) accords with this conclusion. The nitration of 2-phenylpyridine in aqueous sulphuric acid also appears to involve the conjugate acid.²

The parallelism illustrated in Figure 1 also implies that the relative reactivity of these compounds is not a marked function of the acidity and permits the following reactivities to be calculated, relative to that of benzene as unity: 4-phenylpyridinium ion, $2 \cdot 1 \times 10^{-4}$; 4-benzylpyridinium ion, 0.15; 4-benzyl-1-methylpyridinium ion, 0.15. Partial rate factors calculated from these relative rates are collected in Table 2.

TABLE 2

Partial rate factors

| Substrate: | | | | |
|--------------------------|-------------|-----------------------|---------------------------|-------------------------------------|
| | | fo | fm | f_{p} |
| 2-Phenylpyridinium ion * | 1.9 | imes 10 ⁻⁶ | $8.5	imes10^{-6}$ | $2\cdot 2$ $	imes$ 10 ⁻⁵ |
| 4-Phenylpyridinium ion | $1 \cdot 3$ | imes 10 ⁻⁴ | $2{\cdot}1	imes10^{-4}$ | $5.9	imes10^{-4}$ |
| 4-Benzylpyridinium ion | 6·1 | $	imes~10^{-2}$ | $2 \cdot 6 	imes 10^{-2}$ | $7.0 	imes 10^{-1}$ |
| * 10 1 11 11 11 | | 1 | 6 0 C | , |

* Based on the kinetic results in ref. 2 after revision as outlined in the text.

These relative rates and partial rate factors are based on the recent data of Coombes, Moodie, and Schofield⁶ for the nitration of benzene using, where possible, the



FIGURE 1 Rate profiles for nitration in aqueous sulphuric acid: A, benzene (ref. 6); B, 4-benzylpyridine; C, 4-phenylpyridine; D, the benzyltrimethylammonium ion (ref. 5)

acidity range 65-75% sulphuric acid. The values of the second-order rate coefficient obtained by these authors for nitration in 65% sulphuric acid differ by a factor of *ca*. 2 from the values used previously.⁷ Hence, in the comparison of our results with partial rate factors obtained previously, the earlier results have, where appropriate, been revised to accord with these new data.6

DISCUSSION

The partial rate factors in Table 2 show that the rate of substitution at the *para*-position to the $(2-C_5H_5N)$ and $(4-C_5H_5N)$ groups exceeds that at one *meta*-position and that all positions are strongly deactivated with respect to benzene. This pattern is similar to that observed with halogen substituents and can be explained in the same way by assuming that the inductive and field effects of the substituent are partly compensated at the *para*-position by conjugative electron donation 7 N. C. Deno and R. Stein, J. Amer. Chem. Soc., 1956, 78, 578.

⁴ F. Bryans and F. L. Pyman, J. Chem. Soc., 1929, 552.
⁵ T. A. Modro and J. H. Ridd, J. Chem. Soc. (B), 1968, 529.
⁶ R. G. Coombes, R. B. Moodie, and K. Schofield, J. Chem. Soc. (B), 1968, 800.

from the pyridyl ring. The results on the nitration of biphenyl⁸ $(f_m < 1)$ suggest that such conjugative electron donation is not important for meta-substitution so that the *meta*-partial rate factors should provide information on inductive and field effects.

The meta-partial rate factors for the $(4-C_5H_5N)$ and $(2-C_5H_5N)$ groups are less than those of the chlorine substituent⁹ (9×10^{-4}) and the ethoxycarbonyl substituent ¹⁰ (7.9×10^{-3}) : the *meta*-partial rate factor for the $CH_2(4-C_5H_5^{'^{+}})$ group is less than that for the CH_2CN group ¹¹ (0.21) and the CH_2NO_2 group ¹¹ (0.20). It is very difficult to understand this order in terms of the polarisation of σ -bonds of the pyridyl group, for such an interpretation would imply that the carbon atoms of the pyridyl ring were effectively more electronegative than a chlorine atom or the nitrogen atom of a nitro-group. It is therefore useful to see to what extent the strong deactivation produced by a protonated pyridyl group can be understood in terms of the field effect of the positive charge.

In a previous paper,⁵ the substituent effect of the -NMe₃ group at various distances from the aromatic ring was discussed in terms of the quantity $-\log(f_m/f_m^\circ)$ where f_m was defined as a partial rate factor for *meta*nitration in the ion $Ph(CH_2)_n \overset{\neg}{N}Me_3$ and f_m° as that for nitration of the molecule $Ph(CH_2)_nH$. The term $-\log(f_m/f_m^{\circ})$ is then proportional to the increase in the free energy of activation $(\delta \Delta G^{\ddagger})$ for *meta*-nitration when the terminal hydrogen of $Ph(CH_2)_nH$ is replaced by a positive group. Comparison with the effect of charged groups on acid base equilibria then led to the conclusion ⁵ that these values of $\delta \Delta G^{\ddagger}$ derive mainly from the electrostatic interaction between the nitrogen pole and the charge on the ring in the transition state. This charge was taken to be equivalent to a unit charge at the centre of the ring.

The corresponding quantities when the substituent NMe₃ is replaced by the protonated pyridyl group are

TABLE 3

Data for comparing the substituent effects of the pyridinium poles with that of the ammonium poles Substrate:

| | $-\log\left(f_m/f_m^\circ\right)$ | r (Å) |
|------------------------|-----------------------------------|---------------|
| 2-Phenylpyridinium ion | -5.07 | 4.02 |
| 4-Phenylpyridinium ion | -3.68 | 4 ·80 |
| 4-Benzylpyridinium ion | -2.06 | 5·50 * |
| | | |

* Based on a value of 119° for the Ar-C-Ar angle, cf. Chem. Soc. Special Publ. No. 11, 1958, p. 237.

given in Table 3. For the phenylpyridinium ions, $f_m^{\circ} = 1$ by definition: for the benzylpyridinium ion,

⁸ Y. Mizuno and O. Simamura, J. Chem. Soc., 1958, 3875.
 ⁹ J. D. Roberts, J. K. Sanford, F. L. Sixma, H. Cerfontain, and R. Zagt, J. Amer. Chem. Soc., 1954, 76, 4525.
 ¹⁰ C. K. Ingold and M. S. Smith, J. Chem. Soc., 1938, 905.
 ¹¹ J. R. Knowles and R. O. C. Norman, J. Chem. Soc., 1958, 3000

2938.

 f_m° has been taken ⁵ as 3 (the *meta*-partial rate factor for the nitration of toluene). The variation in the term $-\log(f_m/f_m^\circ)$ with the distance between the charge and the centre of the benzene ring is illustrated for the pyridinium ions (triangles) and ammonium ions (open circles) in Figure 2. In defining the distance r, the charge on the protonated pyridyl group has been taken as equivalent to a unit charge at a point 0.54 Å along the line from the centre of the ring to the nitrogen atom. This is the centroid of charge as calculated from the charge distribution given by n.m.r. studies 12 of the pyridinium ion.

The results in Figure 2 (triangles) show that the deactivating effect of the protonated pyridyl ring is



FIGURE 2 Relationship between the deactivating effect of positive groups and the charge separation in the transition state $(r): \bigcirc \cdots \cdot$ points from the *meta*-nitration of the ions $Ph(CH_2)_n NHe_3$; \triangle , \times , \cdots from the pyridinium ions discussed in this paper. For details see text

considerably greater than that expected from this comparison with the ammonium pole. Part of this difference must come from the kind of inductive deactivation of the meta-position found also in biphenyl.8 From the value ¹³ of σ^+_m for the phenyl group (0.109) and the value ¹³ of ρ for nitration (-6.0), the meta partial rate factor for the nitration of biphenyl should be 0.22. The meta partial rate factor of diphenylmethane is not known but that for chlorination is about unity¹⁴ and there is probably no great error in taking this value for nitration also. The results in Figure 2 include values of $-\log(f_m/f_m^\circ)$ where the values of f_m° refer to the corresponding homocyclic compounds (biphenyl and diphenylmethane). These values, shown as crosses are much

¹² T. Schaefer and W. G. Schneider, Canad. J. Chem., 1963, **41**, 966.

¹³ L. M. Stock and H. C. Brown, Adv. Phys. Org. Chem., 1963,

^{1, 35.} ¹⁴ P. B. D. de la Mare, E. A. Johnson, and J. S. Lomas, J. Chem. Soc., 1965, 6893.

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nearer the line drawn through the results for the ammonium poles. Thus to a good approximation, the deactivating effect of a protonated pyridyl group to *meta*-substitution corresponds to the effect of a positive charge at the appropriate position together with the inductive effect as observed in the corresponding homocyclic hydrocarbon.

It would be unwise to extend this approach to a more quantitative comparison of the importance of inductive and electrostatic interaction since the magnitude of the electrostatic interaction should depend not only on the separation of the charges but also on the disposition of the charges in the molecules.¹⁵ The arguments above are merely intended to show that the deactivating effect of a protonated pyridyl group on a nearby phenyl group can be most easily understood as the field effect of a pole. A further justification of this approach will be found in the general comparison of substituent effects in Part III of this series.

EXPERIMENTAL

Materials.--4-Phenylpyridine was a commercial sample and was purified by recrystallisation from water: m.p. 77-78° (lit. 77-78°). The three mononitrophenyl derivatives were prepared and separated as described in the literature: ³ ortho, m.p. 176-177° (lit.³ 178-179°); meta, m.p. 109°-110° (lit.³ 109-110°); para, m.p. 122-123° (lit.³ 123-124°). 4-Benzylpyridine was a commercial sample; it was dried over sodium hydroxide, purified by distillation (b.p. 288°) and shown to be pure by g.l.c. The ortho- and para-nitrobenzyl derivatives were prepared as described in the literature.¹⁶ The ortho-compound was purified by three distillations under reduced pressure (Found: C, 68.0; H, 5.2; N, 13.3. Calc. for C₁₂H₁₀N₂O₂: C, 67.3; H, 4.7; N, 13.1%). The para-nitrobenzyl derivative was purified by recrystallisation from alcohol, m.p. 71-73° (lit., 72-73°). 4-(3-Nitrobenzyl)pyridine was prepared from 4-(4-nitrobenzyl)pyridine by reduction and acetylation to give 4-(4-acetaminobenzyl)pyridine (m.p. 169-172°) followed by nitration to 4-(3-nitro-4-aminobenzyl)pyridine (m.p. 151-153°), diazotisation, and deamination by hypophosphorus acid. The product, 4-(3nitrobenzyl)pyridine, after recrystallisation from water had m.p. 72-73° (Found: C, 66.5; H, 4.9; N, 12.9. $C_{12}H_{10}N_2O_2$ requires C, 67.3; H, 4.7; N, 13.1%). The analysis of the intermediates listed above was also satisfactory. 1-Methyl-4-benzylpyridinium perchlorate was prepared from 4-benzylpyridine by methylation with dimethyl sulphate in dimethoxyethane as solvent. The product was dissolved in ethanol and the perchlorate precipitated by the addition of perchloric acid. The perchlorate had m.p. 101-103° (Found: C, 54.5; H, 5.0; N, 4.7: C₁₃H₁₄ClNO₄ requires C, 55.0; H, 5.0; N, 4.9%). The source and standardisation of the inorganic reagents was as described previously.⁵

Product Analysis.—A solution of 4-phenylpyridine (9.54 $\times 10^{-4}$ M) and nitric acid (3.40 $\times 10^{-3}$ M) in sulphuric acid (100 ml.; 81.1%) was left at 24° until reaction appeared to be complete (*ca.* 1 hr.). A sample (*ca.* 5 ml.) was then taken with a calibrated pipette and diluted to 100 ml. The concentrations of isometic nitro-compounds present were then calculated from the u.v. spectrum using the

following extinction coefficients derived from measurements on solutions of the pure isomers.

| | ortho | meta | para |
|------------------------------|-------|------|-------|
| (250 nm. | 1.25 | 1.63 | 0.523 |
| 10 ⁻⁴ ε < 270 nm. | 0.951 | 2.54 | 1.63 |
| 290 nm. | 0.474 | 1.03 | 2.17 |

This method of analysis was shown to be satisfactory by the use of synthetic mixtures of pure isomers. When applied to reaction mixtures, the sum of the calculated concentrations of mononitro-compounds corresponded closely to the expected value.

Unfortunately, the spectra of the nitrobenzylpyridines are too similar for this method of analysis to be applicable. The nitration of 4-benzylpyridine was therefore carried out under preparative conditions by adding the nitrate, m.p. $108-110^{\circ}$ (lit.¹⁶ 103-106°) to aqueous sulphuric acid (85%).

After neutralisation the reaction mixture was extracted with chloroform and the n.m.r. spectrum taken. The absorption of the methylene bridge in the ortho-nitrocompound is 0.22 p.p.m. to low field of that of the metaand para-nitrocompounds and in this way the mixture was shown to contain 14-16% of the ortho-isomer. The complete analysis was carried out using a Perkin-Elmer 800 g.l.c. instrument with a 4-m. column of XE60 on Aeropack 30. The temperature of the column was programmed to rise from 220 to 240° during the run. Studies with synthetic mixtures showed that complete separation of the three mononitro-compounds, the starting material and the 2,4-dinitro-compound could be obtained in this way. The yield of the dinitro-compound is not significant when concentrations of reactants corresponding to mononitration are used.

Kinetics.—The extent of reaction was determined from the variation in the optical density at 260 nm. in quenched samples of the reaction mixture. The general procedure followed that described previously 5 for the nitration of substituted ammonium ions. In the nitration of 4-phenylpyridine, the initial concentration of the aromatic substrate was varied from 7.57×10^{-4} M to 1.66×10^{-3} M and that of the nitric acid from 1.51×10^{-3} to 3.1×10^{-2} M. The effective extinction coefficient was found to vary from 8.5×10^{-3} to 1.47×10^{-4} during a kinetic run. In the nitration of 4-benzylpyridine, the initial concentration of the aromatic substrate was varied from 1.98×10^{-3} M to 4.40×10^{-3} M and that of the nitric acid from 3.40×10^{-3} M 10^{-3} M to 6.81×10^{-3} M. The effective extinction coefficient was found to vary from 0.45×10^{-4} to 1.1×10^{-4} during a kinetic run. Both substrates gave good second-order kinetics during individual kinetic runs and, for the reaction of 4-phenylpyridine, the second-order rate coefficient at a given acidity was shown to be independent of the initial concentrations of the reactants when varied over the range listed above.

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¹⁵ J. G. Kirkwood and F. H. Westheimer, J. Chem. Phys., 1938, 6, 506, 513.

¹⁶ A. J. Nunn and K. Schofield, J. Chem. Soc., 1952, 583.