Electrophilic Aromatic Substitution. Part 18.[1] Nitration of Acetanilide and Some Analogues: a Reconsideration

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The kinetics of nitration and the proportions of products formed, in sulphuric acid of a range of concentrations, have been measured for 3,4-dihydroquinolin-2(1*H*)-one, indolin-2-one *N*-*o*-tolylacetamide, methyl *N*-phenylcarbamate, methyl *N*-phenylacetimidate, and *p*-methoxyacetanilide. Comparison with the behaviour of acetanilide and anisole leads to the conclusion that acetanilide is nitrated as the free base and not as the cation, in contradiction of earlier arguments. The marked increase in *o* : *p* ratio observed in the nitration of acetanilide and its homologues as the acidity of the reaction medium is lowered is attributed to decreasing hydrogen bonding. The behaviour of 3,4-dihydroquinolin-2(1*H*)-one and methyl *N*-phenylcarbamate removes the possibility of an earlier favoured special mechanism for the *ortho*-substitution, involving initial attack by the electrophile at carbonyl oxygen.

The utility of rate *vs.* acidity plots as criteria in deciding whether a base reacts as such or as the corresponding cation is discussed. For weak bases, especially those containing oxygen functions, the occurrence of hydrogen bonding can render the criterion ambiguous or anomalous, and the dichotomy of free base and cation is too simple. In such cases, structure permitting, the kinetic ambiguity or anomaly can be accompanied by marked acidity dependence of product ratios.

THE $\frac{1}{2}o : p$ ratio for the nitration of acetanilide with reagents prepared from nitric acid and acetic anhydride is greater than the statistical value. For reaction at 25 °C it was found [2] to be 1.7 : 1, and higher values have been reported.[3] The contrast between these results and those for nitration in sulphuric acid (Table 1) led to the proposal that in acetic anhydride operation of a new electrophile capable of effecting *ortho*-substitution by the mechanism shown in the Scheme, led to augmentation of the $\frac{1}{2}o : p$ ratio above the value for reaction in sulphuric acid characteristic of nitration by nitronium ion.[3,4] Whilst the need to involve a special electrophile has been questioned [5] (nitronium tetrafluoroborate in acetonitrile gave $\frac{1}{2}o : p$ ratio = 1.7 : 1 at −10 °C [3]), and previous [2] and present results indicate that nitronium ion can produce high $\frac{1}{2}o : p$ ratios, the nature of the electrophile operating in nitric acid–acetic anhydride remains uncertain.[6] However, the idea that initial reaction of the electrophile at the nucleophilic carbonyl oxygen atoms provided a route to *ortho*-substitution was argued to be supported by the following evidence.[2]

Whilst nitration of acetanilide and α-chloroacetanilide in acetic anhydride gave high $\frac{1}{2}o : p$ ratios, those for ααα-trifluoroacetanilide and *N*-methylsulphonylaniline (a compound of reactivity very similar to that of acetanilide) were less than the statistical value (Table 1), evidently because of the feeble nucleophilic characters of the oxygen atoms in these last two compounds. The comparison in the case of acetanilide between nitration in acetic anhydride and in sulphuric acid was held to be invalid because the slope of the rate profile for nitration in sulphuric acid appeared to indicate that the cation of acetanilide was reacting. In contrast, α-chloroacetanilide reacted as the free base. The substantial changes

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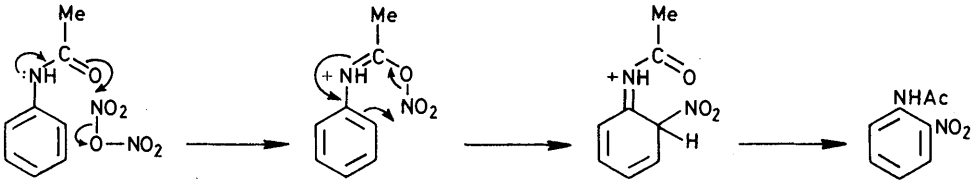
[3] B. M. Lynch, C. M. Chen, and Y.-Y. Wigfield, *Canad. J. Chem.*, 1969, **46**, 1141.
[4] R. O. C. Norman and G. K. Radda, *J. Chem. Soc.*, 1961, 3030; J. R. Knowles and R. O. C. Norman, *ibid.*, p. 3888.
[5] J. H. Ridd, 'Studies on Chemical Structure and Reactivity,' Methuen, London, 1966.
[6] N. C. Marziano, J. H. Rees, and J. H. Ridd, *J.C.S. Perkin II*, 1974, 600.

in the values of the $\frac{1}{2}o : p$ ratios observed for nitrations of these compounds in a range of sulphuric acid concentrations (Table 1) were attributed for acetanilide to changing solvation (hydrogen bonding) of the cation, and for α-chloroacetanilide to changing solvation of the free base (with protonation being possible at the highest acidities).

The purpose of this paper is to refute the conclusions that a special mechanism for *ortho*-nitration of the form shown (Scheme) exists, and that in sulphuric acid acetanilide reacts as its cation. We also comment more generally on the use of the slopes of rate profiles as mechanistic criteria.



SCHEME

TABLE 1

$\frac{1}{2}o : p$ Ratios for the nitration of acetanilide and some analogues [a]

Compound	$\frac{1}{2}o : p$ Ratio (%H_2SO_4)					
Acetanilide	0.03 (98.0)	0.10 (80.9)	0.24 (72.9)	0.35 (67.7)	0.40 (65.8)	1.7 [b]
α-Chloroacetanilide	0.08 (98.0)	0.28 (85.0)	0.59 (68.6)			2.0 [b]
ααα-Trifluoroacetanilide	0.13 (98.0)	0.18 (85.3)	0.22 (80.2)			0.26 [b]
N-Methylsulphonylaniline	0.22 (98.0)	0.41 (85.3)	0.5 (80.2)			0.75 [b]

[a] Ref. 2, which contains fuller results. [b] Nitration in HNO_3–Ac_2O.

EXPERIMENTAL

Materials.—Sulphuric acid, acetic anhydride, acetic acid, urea, and sulphamic acid were AnalaR reagents. Concentrations of diluted acids were determined by density measurements to an accuracy of ±0.1%. Nitric acid was purified by distillation from sulphuric acid.

Indolin-2-one [m.p. 127 °C (from water)], *N*-*o*-tolyacetamide [m.p. 110—111 °C (from water)], *o*-nitroaniline {m.p. 70.5 °C [from light petroleum (b.p. 60—80 °C)]}, *m*-nitroaniline [m.p. 114 °C (from benzene)], *p*-nitroaniline [m.p. 147—148 °C (from benzene)], and 4-methoxy-3-nitroaniline [m.p. 129 °C (from ethanol)] were purified by recrystallisation.

The following compounds were prepared by acetylation of the corresponding amines; 2′-methyl-3′-nitroacetanilide [m.p. 157—158 °C (from water)], 2′-methyl-4′-nitroacetanilide [m.p. 199 °C (from aq. ethanol)], 2′-methyl-5′-nitroacetanilide [m.p. 152 °C (from aq. ethanol)], 2′-methyl-6′-nitroacetanilide [m.p. 158 °C (from aq. ethanol)], 4′-methoxyacetanilide [m.p. 131 °C (from water with decolourising charcoal)], 4′-methoxy-3′-nitroacetanilide [m.p. 118 °C (from aq. ethanol)].

3,4-Dihydroquinolin-2(1*H*)-one [m.p. 163 °C (from aq. ethanol)] was prepared from indan-1-one.[7] Methyl *N*-phenylcarbamate {m.p. 46 °C [from light petroleum (b.p. 40—60 °C)]} was prepared by the standard method.[8]

In preparing methyl *N*-phenylacetimidate [9] freshly distilled dimethyl sulphate was used, since the presence of acidic impurities gave *NN*-dimethylaniline as the major product. The product was purified by distillation (b.p. 78—80 °C at 12 mmHg) and the purity was checked by ^{1}H n.m.r. [τ ($CDCl_3$) 6.21 (3 H, s, OMe) and 8.21 (3 H, s, Me)]. At no time was any *N*-methylacetanilide identified as an impurity. The product was unstable, being easily hydrolysed to acetanilide.

Methyl *N*-*p*-methoxyphenylacetimidate was prepared in the same way. An earlier report [10] stated that it had been purified by distillation (b.p. 115—116 °C at 10 mmHg). The compound started to decompose at this temperature and purification, mainly separation of ester from dimethyl sulphate, was carried out by column chromatography [neutral alumina; light petroleum (b.p. 60—80 °C)]. Purity was checked by ^{1}H n.m.r. [τ ($CDCl_3$) 6.30 (6 H, s, OMe) and 8.21 (3 H, s, Me)]; $\nu_{max.}$ (C=N) 1 665 cm^{-1}.

3,4-Dihydro-6- and -8-nitroquinolin-2(1*H*)-one were prepared by nitration in sulphuric acid at room temperature. Nitric acid (*d* 1.5; 0.14 cm^3) in 78% sulphuric acid (20 cm^3) was added to a solution of 3,4-dihydroquinolin-2(1*H*)-one (0.50 g) in 78% sulphuric acid (100 cm^3). After 10—15 min the solution was quenched in ice-cold water. This solution was extracted with dichloromethane (3 × 30 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to yield a pale green solid (0.63 g). This on t.l.c. (chloroform as solvent), showed two spots (R_F 0.4 and 0.2), the slower moving being the more intense. The mixture was separated by column chromatography [silica gel; 1 : 3 chloroform–light petroleum (b.p. 60—80 °C)]. After elution of the first product the solvent was changed to a 3 : 1 ratio to elute the second product. The first component (0.08 g) was the 8-*nitro-derivative*, m.p. 149 °C (from methanol) (Found: C, 56.6; H, 4.6. $C_9H_8N_2O_3$ requires C, 56.2; H, 4.2%); τ [$(CD_3)_2SO$] 0.1br (1 H, s, NH), and 1.94 (1 H, d), 2.30 (1 H, d), and 2.81 (1 H, t), (aromatic protons). The other product (0.58 g) was the 6-nitro-derivative, m.p. 205 °C (from acetone) (lit.,[11] 204 °C); τ [$(CD_3)_2SO$] 0.1br (1 H, s, NH), and 1.83 (s, overlaying one peak of d centred at 1.87; 2 H in all) and 2.95 (1 H, d, *J* 2.0 Hz) (aromatic protons). The yield of 8-nitro-derivative was improved by carrying out the reaction in 56% sulphuric acid.

3,4-Dihydro-5- and -7-nitroquinolin-2(1*H*)-ones were prepared from nitroindan-1-ones by the Schmidt reaction.

[7] L. H. Briggs and G. C. De Ath, *J. Chem. Soc.*, 1937, 456.
[8] W. Hertschel, *Ber.*, 1885, **18**, 978.
[9] A. Bühner, *Annalen*, 1904, **333**, 293.
[10] A. Pilotti, A. Reuterhäll, and K. Torsell, *Acta Chem. Scand.*, 1969, 818.
[11] H. Ueda, *Proc. Japan Acad.*, 1939, **15**, 148.

Indan-1-one was nitrated by the literature method,[12] the product being a mixture of two mononitro-isomers (46% yield). Attempts to separate these isomers by column chromatography were unsuccessful; the products slowly decomposed on the neutral alumina. The Schmidt reaction was then carried out on the mixture, in the way described [7] for the formation of dihydroquinolone. The product (73% yield) was purified by column chromatography [silica gel; 1 : 1 chloroform–light petroleum (b.p. 60—80 °C)]. The 7-nitro-compound was eluted first; m.p. 244 °C (from ethanol) (lit.,[13] 242—243 °C); τ [$(CD_3)_2SO$] −0.45br (1 H, s, NH) and 2.30 (1 H, d), 2.37 (1 H, s), and 2.62 (1 H, d) (aromatic protons). This was followed by a mixture of 7- and 5-nitro-compounds. Some minor products, identified by n.m.r. as nitrodihydroisoquinolones, were also collected when the polarity of the solvent was increased. The separation of 5-nitrodihydroquinolone from the 7-nitro-isomer was not attempted. A ^{1}H n.m.r. spectrum of the mixture showed τ −0.5vbr (NH), and 2.12 (d), 2.30 (m), 2.40 (d), 2.52 (m), and 2.80 (t) (aromatic protons).

The 5- and 7-nitroindolin-2-ones were prepared by nitration of indolin-2-one in mixed acid by the method used with dihydroquinolone, again giving an almost quantitative yield of mononitro-products. The mixture was separated by column chromatography [silica gel; 1 : 3 chloroform–light petroleum (b.p. 60—80 °C)], giving the 7-nitro-isomer, m.p. 254—255 °C (decomp.) (from acetone) (lit.,[14] 256 °C) (8%) and the 5-nitro-isomer, m.p. 243 °C (from methanol) (lit.,[15] 240—241 °C) (80%). The ^{1}H n.m.r. spectra were almost identical with those of the dihydroquinolones.

Methyl *N*-nitrophenylcarbamates were prepared from the corresponding nitroanilines and methyl chloroformate by the literature method.[8] The reactions of the nitroanilines were slower than that of aniline. The reaction with *o*-nitroaniline was the slowest, producing only 25% of nitro-product after 24 h at room temperature. The *m*- and *p*-isomers were purified by recrystallisation: *m*-isomer, m.p. 149—150 °C (from benzene) (lit.,[16] 147—149 °C); *p*-isomer, m.p. 179 °C (from ether) (lit.,[16] 179.5 °C). The *o*-isomer was separated from starting material by column chromatography [neutral alumina; light petroleum (b.p. 60—80 °C)], and recrystallised {m.p. 52 °C [from light petroleum (b.p. 60—80 °C)] (lit.,[16] 53 °C)}.

4′-Methoxy-2′-nitroacetanilide. Nitric acid (*d* 1.5; 0.21 cm³) in 75% sulphuric acid (40 cm³) was added to a solution of *p*-methoxyacetanilide (0.35 g) in 75% sulphuric acid (40 cm³). After 6 min the solution was quenched in ice-cold water (400 cm³) and the resulting solution was extracted with dichloromethane (3 × 30 cm³). The combined extracts were dried ($MgSO_4$) and evaporated to yield a yellow solid (0.46 g). This was recrystallised (ethanol and charcoal); m.p. 153 °C (lit.,[17] 153 °C).

The homogeneity of all aromatic compounds used was verified by g.l.c.

Kinetic Measurements.—The conventional method was used.[18] Kinetic runs were usually followed, by using Pye-Unicam SP 800 and 1800 instruments, for about 10 half-lives. Rate constants were then calculated from 'infinity' absorbances. Guggenheim's method was used for very slow reactions, when readings after 10 half-lives might have been affected by decomposition of the solution.

Product Studies.—Two methods were used: (*a*) when analysis was to be carried out by n.m.r. spectroscopy; (*b*) when analysis was to be carried out by g.l.c.

(*a*) A solution of the aromatic substrate was prepared in sulphuric acid (50 cm³) of the required concentration. The strength of this solution was calculated to be such that the final concentration of substrate in the nitration run would be *ca.* 6×10^{-3} mol dm^{-3}. A sample (usually 20 cm³) of this solution was added to more sulphuric acid (25 cm³) containing urea ([urea] = 0.03M) and nitric acid (at least a ten-fold excess over substrate) at 25 °C. The mixture was shaken vigorously during the 10 half-lives allowed for reaction, and then quenched in ice-cold water (500 cm³). The resulting solution was extracted with ethyl acetate (10 × 10 cm³) (dichloromethane was used with product runs from methyl *N*-phenylcarbamate). After drying ($MgSO_4$ and Na_2CO_3) the combined extracts were evaporated to give the solid, and this was dried (70 °C) for at least 1 h, and then weighed.

For reactions in which the high concentration of nitric acid would give a half-life of < 10 s, equimolar quantities of substrate and nitric acid were employed, the mixture being stirred vigorously in a pleated flask.

(*b*) Analysis by g.l.c. requires a much lower substrate concentration. A stock solution of substrate in acetic acid was prepared. A sample (typically 0.1 cm³ of a solution containing 1—2 mg of aromatic) was added to sulphuric acid (50 cm³) of the required concentration, containing urea ([urea] = 0.03M) and nitric acid at 25 °C. The reaction was carried out as described for method (*a*). After quenching in ice-cold water (500 cm³), a known amount of reference standard was added and the mixture was extracted with dichloromethane (10 × 10 cm³). After drying ($MgSO_4$) the combined extracts were concentrated (2–3 cm³).

In the nitration of methyl *N*-phenylacetimidate, because the products would be unstable in dilute acid they were hydrolysed to nitroanilines. Solutions of methyl *N*-phenylacetimidate and nitric acid were prepared as described for method (*a*) except that the overall volume of sulphuric acid was reduced to 25 cm³. After the reaction was complete the solution was quenched in ice-cold water (200 cm³) containing 1M-sodium acetate solution (100 cm³). The resulting solution was adjusted to pH = 4 by addition of 5M-sodium hydroxide and left for 30 min to allow complete hydrolysis. A known amount of reference standard was added and the mixture was extracted 5 times with ethyl acetate. After drying ($MgSO_4$ and Na_2CO_3) the combined extracts were freed from solvent by fractional distillation (6 in glass column packed with glass helices). The column was rinsed into the distillation flask with a small volume of ethyl acetate, giving a concentrated solution (2—3 cm³) of the nitration products.

The various extraction methods mentioned above were tested on synthetic mixtures of the nitro-products concerned and in all cases were found to give quantitative yields.

Reaction mixtures from the following were analysed by

[12] C. K. Ingold and T. Piggott, *J. Chem. Soc.*, 1923, 1469.
[13] Z.-H. Yang, *J. Taiwan Pharm. Assoc.*, 1952, **4**, 18.
[14] R. T. Coutts, K. W. Hindmarsh, and E. Mah, *Canad. J. Chem.*, 1970, **48**, 3747.
[15] W. C. Sumpter, M. Miller, and M. E. Magan, *J. Amer. Chem. Soc.*, 1945, **67**, 499.
[16] I. Heilbron and H. M. Bunbury, 'Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1946.
[17] F. Reverdin and A. Bucky, *Ber.*, 1906, **39**, 2689.
[18] R. G. Coombes, R. B. Moodie, and K. Schofield, *J. Chem. Soc.* (*B*), 1968, 800.

n.m.r. (100 MHz): nitrodihydroquinolones, nitroindolinones, 2′-methylnitroacetanilides, and methyl *N*-nitrophenylcarbamates. Attempts to carry out the analysis by g.l.c. failed because of decomposition of compound on the various columns used. No reproducibility was achieved even with successive injections of the same solution.

Dihydroquinolone and Indolinone.—Nitration mixtures from each of these compounds gave ^{1}H n.m.r. spectra [solvent $(CD_3)_2SO$] with similar splitting patterns for the aromatic protons. In the case of dihydroquinolone comparison of the spectrum of the nitration mixture with those for 6-, 8-, 7-, and (7 + 5)-nitrodihydroquinolone showed the 5- and 7-nitro-isomers to be absent.

The ratios of isomers present in the nitration product were calculated from the integration curve. From the curve areas in the regions τ 1.8—2.2 (x) and 2.2—2.5 (y), the ratio of 8- to 6-nitrodihydroquinolone $[2y/(x - y)]$ is obtained. The same relation holds for the ratio of 7- to 5-nitroindolinone.

N-o-*Tolylacetamide.*—The peaks due to the acetyl protons gave the following τ values in $(CD_3)_2SO$: 2′-methyl-3′-nitro- (7.91), 2′-methyl-4′-nitro- (7.84), 2′-methyl-5′-nitro- (7.86), 2′-methyl-6′-nitro-acetanilide (7.96). The ratios of isomers were calculated from the peak areas on the expanded trace, or from the integration curve. The former method was the more accurate (tested with synthetic mixtures).

Methyl N-*Phenylcarbamate.*—The *o*-, *m*-, and *p*-nitro-derivatives gave methoxy-signals [solvent $(CD_3)_2CO$] with τ 6.20, 6.23, and 6.23, respectively. The spectrum of the nitration mixture did not show the presence of the *m*-isomer (characteristic ' aromatic ' peaks were absent), and g.l.c. showed it to be absent (3% SE 30 column at 167 °C; flow rate of nitrogen 40 cm^3 min^{-1}; retention times: *o*-isomer 220 s, *m*-isomer 505 s, *p*-isomer 630 s). The *o* : *p* ratio was calculated from the peak areas of the methoxy-signal.

p-*Methoxyacetanilide and Methyl* N-*Phenylacetimidate.*—Reaction mixtures were analysed on a Pye 104 gas chromatograph (flame ionisation detector). Areas under peaks were determined using either a disc integrator or a Pye ' minigrator '. The response of the detector to the products and to the reference standard was determined by calibration. The following example, involving calibration for nitroanilines, is typical.

Mixtures of *o*-, *m*-, and *p*-nitroanilines and 4-methoxy-3-nitroaniline (the reference standard) were prepared with dichloromethane as solvent Three samples from each solution were analysed and the average area ratio (nitroaniline to ref. standard) was calculated for each solution. A calibration graph was then plotted of this area ratio against the molar ratio (nitroaniline to ref. standard) and the slope was evaluated. By using the value obtained, area ratios from chromatograms of reaction mixtures could be converted into molar ratios and yields.

Conditions of analysis are given in Table 2.

Protonation of Dihydroquinolone, Indolinone, and Methyl N-*Phenylcarbamate.*—The spectrophotometric method [19] was used. Absorbances were measured with an SP 1800 spectrophotometer (1 cm path length). The difference in extinction coefficients at two wavelengths, chosen to be those of maximum absorption of the free base and conjugate acid, were plotted against H_A. The upper and lower arms of the sigmoid curve so generated were approximately straight lines, and usually inclined at a slight angle to the H_A axis. These lines were extrapolated to provide values of the difference in extinction coefficients at intermediate acidities.[20]

TABLE 2

G.l.c. conditions

Product	Standard	Column [a] (T/°C)
4′-Methoxy-2′-nitroacetanilide 4′-Methoxy-3′-nitroacetanilide	2′-Methyl-4′-nitroacetanilide	3% SE silicone (213)
o-Nitroaniline [b] *m*-Nitroaniline [b] *p*-Nitroaniline [b]	4′-Methoxy-2′-nitroaniline	0.75% Polyethylene glycol (200)

[a] All on Chromosorb W (6 ft); nitrogen carrier at 40 cm^3 min^{-1}. [b] From hydrolysis of the nitration products of methyl *N*-phenylacetimidate.

RESULTS

Kinetics.—Second-order rate constants for nitrations at 25 °C are given in Table 3. Rate profiles are shown in Figures 1 and 2. In 63% sulphuric acid the rate of nitration of *p*-methoxyacetanilide was higher when urea was added than when sulphamic acid was added to the reaction mixture, presumably because *p*-methoxyacetanilide is easily nitrosated and sulphamic acid is a better ' nitrous trap ' than urea.[21] In 66% sulphuric acid use of urea or sulphamic acid gave identical results.

Yields of Mononitro-compounds.—The yields from the nitrations of those compounds whose product mixtures were analysed by n.m.r. were calculated from the weights of the final products. It was assumed that the final product was wholly a mixture of mononitro-compounds unless the n.m.r. spectrum showed otherwise. The error in this method is much greater than that involved when analysis is carried out by g.l.c., and it has been assumed that a yield >90% is quantitative. The results are in Table 4.

The total yield of mononitro-products from dihydroquinolone in sulphuric acid was always low (88—92%). The extraction procedure used was shown to be quantitative, as are the yields of mononitro-products from nitration in acetic anhydride.

The yield of mononitroindolinones dropped at low acidities (>64% sulphuric acid) and the reaction mixtures were dark coloured. The coloured products were not extracted into ethyl acetate. Nitration of indolinone in acetic anhydride gave a very poor yield

[19] D. W. Farlow and R. B. Moodie, *J. Chem. Soc.* (*B*), 1970, 334.

[20] C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, N. Shakir, and A. M. White, *Tetrahedron*, 1965, **21**, 1055.

[21] D. L. H. Williams, *J.C.S. Perkin II*, 1975, 655.

(*ca.* 25%) and the n.m.r. spectrum showed that small amounts of mononitroindolinones were formed.

Nitration of *N*-*o*-tolylacetamide in sulphuric acid gave quantitative yields, with all four of the possible isomers being formed. The variation of isomer proportions with acidity is shown in Figure 3. Nitration in acetic anhydride gave only two isomers; the yield was never greater than 80%.

Nitration of methyl *N*-phenylcarbamate was straightforward, yields being quantitative in all experiments. Only the *o*- and *p*-nitro-isomers were identified in the product.

The products of nitration of *p*-methoxyacetanilide, analysed by g.l.c., are shown in Table 5. As mentioned, this substrate was very susceptible to nitration *via* nitrosation, which probably explains the large changes in isomer proportions over the acidity range studied. Addition of the aromatic substrate by pipetting a small volume from a stock solution in acetic acid into a solution of nitric acid in sulphuric acid gave an immediate colouration of the acetic acid layer before the layers could be mixed. The method in which a solution of substrate in sulphuric acid was prepared prior to the reaction and the reaction was initiated by mixing this solution with that of nitric acid in sulphuric acid resulted in slightly different isomer ratios. At lower acidities the amount of the 2-nitro-isomer was further reduced by adding sulphamic acid instead of urea as a nitrosation inhibitor. All that could be concluded was that nitrosation does affect the isomer distribution but most probably not to the extent that this ratio changes with acidity. It seems that the product ratio depends significantly on acidity.

The results for nitration of methyl *N*-phenylacetimidate are shown in Table 6. Yields were inexplicably

TABLE 3

Second-order rate coefficients for nitration in sulphuric acid at 25.0 ± 0.1 °C [a]

H_2SO_4/% [b]	$[HNO_3]$/mol dm^{-3}	k_2/dm^3 mol^{-1} s^{-1}
	Dihydroquinolone [c]	
65.8	1.03×10^{-1}	1.06×10^{-3}
68.5	1.01×10^{-1}	3.81×10^{-3}
69.3	9.96×10^{-2}	7.31×10^{-3}
72.4	8.37×10^{-2}	5.86×10^{-2}
74.0	3.01×10^{-2}	1.92×10^{-1}
76.8	5.99×10^{-2}	1.79
79.4	4.88×10^{-4}	1.39×10
	Indolinone [d]	
62.6	1.47×10^{-1}	1.57×10^{-3}
65.8	1.07×10^{-1}	4.71×10^{-3}
68.5	1.10×10^{-1}	1.45×10^{-2}
70.6	3.34×10^{-2}	5.71×10^{-2}
72.4	2.60×10^{-2}	2.05×10^{-1}
74.0	1.53×10^{-2}	4.99×10^{-1}
76.8	8.50×10^{-3}	3.67
79.4	2.74×10^{-4}	2.34×10
	N-*o*-Tolylacetamide [e]	
68.1	8.72×10^{-2}	1.25×10^{-3}
69.2	2.08×10^{-1}	2.33×10^{-3}
73.3	2.53×10^{-3}	4.72×10^{-2}
76.3	8.58×10^{-3}	5.66×10^{-1}
78.4	2.39×10^{-3}	3.63
78.9	2.55×10^{-3}	4.39
	Methyl *N*-phenylcarbamate [e]	
58.9	2.07×10^{-1}	6.53×10^{-4}
59.9	1.86×10^{-1}	1.26×10^{-3}
63.3	2.04×10^{-1}	8.86×10^{-3}
63.8	1.98×10^{-1}	1.07×10^{-2}
64.1	2.04×10^{-1}	1.12×10^{-2}
66.1	1.60×10^{-1}	5.00×10^{-2}
68.7	2.74×10^{-3}	3.05×10^{-1}
70.3	2.08×10^{-3}	8.79×10^{-1}
73.2	5.28×10^{-4}	6.14
74.3	5.32×10^{-4}	1.16×10
	Methyl *N*-phenylacetimidate [e]	
75.8	2.06×10^{-1}	9.58×10^{-4}
78.9	1.18×10^{-2}	1.60×10^{-2}
80.2	1.00×10^{-2}	4.53×10^{-2}
83.7	5.45×10^{-3}	1.11
85.6	1.11×10^{-3}	8.01
	p-Methoxyacetanilide [f]	
63.2 [g]	1.91×10^{-1}	2.38×10^{-3}
66.1	1.57×10^{-1}	1.33×10^{-2}
68.7	7.41×10^{-2}	6.81×10^{-2}
70.3	1.12×10^{-2}	2.06×10^{-1}
73.4	2.27×10^{-3}	1.51
76.7	5.69×10^{-4}	2.11×10
	Methyl *N*-*p*-methoxyphenylacetimidate [e]	
65.9	2.02×10^{-1}	9.47×10^{-4}
69.6	1.00×10^{-1}	1.78×10^{-2}
72.9	7.36×10^{-2}	1.56×10^{-1}
75.7	8.28×10^{-2}	1.81

[a] [Urea] *ca.* 3×10^{-2} mol dm^{-3}; [AR] *ca.* 10^{-4} mol dm^{-3}. [b] ±0.1%. [c] Measurements at 310 nm. [d] Measurements at 315 nm. [e] Measurements at 325 nm. [f] Measurements at 330 nm. [g] Sulphamic acid present.

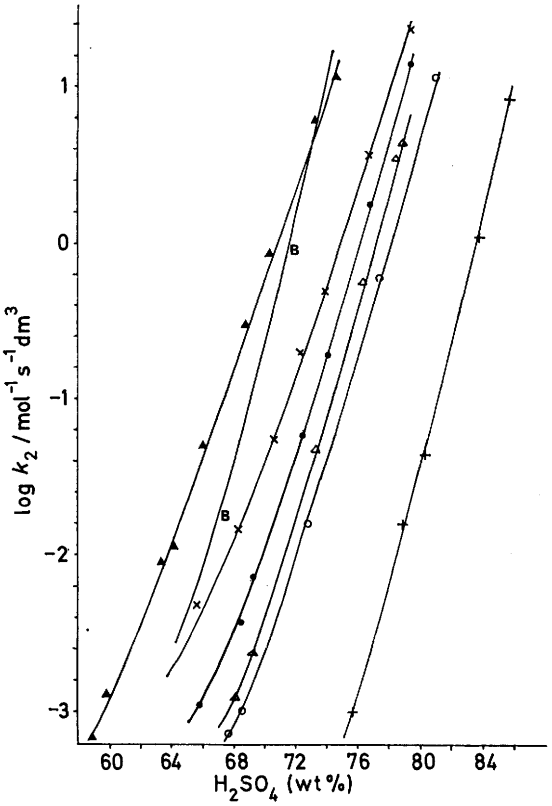


FIGURE 1 Rate profiles for nitration in sulphuric acid; ▲, methyl *N*-phenylcarbamate; ×, indolinone; ●, dihydroquinolone; △ *N*-*o*-tolylacetamide; ○, acetanilide; +, methyl *N*-phenylacetimidate; B, benzene

TABLE 4

Products of nitration of dihydroquinolone, indolinone, *N*-*o*-tolylacetamide, and methyl *N*-phenylcarbamate at 25 °C

Compound	Reagent	Isomers (%) [a]				Total yield (%)	$\frac{1}{2}o : p$ ratio [c]
Dihydroquinolone		*x*-Nitroquinolone					
		$x = 8$			$x = 6$		
	78.8% H_2SO_4	16.7			83.3	92.1	0.20
	75.8% H_2SO_4	18.0			82.0	89.7	0.22
	73.2% H_2SO_4	21.9			78.1	88.6	0.28
	68.5% H_2SO_4	27.5			72.5	90.1	0.38
	64.0% H_2SO_4	31.7			68.3	90.0	0.46
	58.9% H_2SO_4	37.5			62.5	89.2	0.6
	54.7% H_2SO_4	43.4			56.6	88.3	0.77
	Ac_2O–HNO_3	49.2			50.8	103	0.97
	Ac_2O–HNO_3	49.5			50.5	96	0.98
Indolinone		*x*-Nitroindolinone					
		$x = 7$			$x = 5$		
	78.8% H_2SO_4	11.1			88.9	90.2	0.12
	75.8% H_2SO_4	14.5			85.5	96.3	0.17
	72.6% H_2SO_4	17.7			82.3	99.8	0.21
	68.5% H_2SO_4	18.7			81.3	97.7	0.23
	64.1% H_2SO_4	23.1			76.9	87.2 [b]	0.30
N-*o*-Tolylacetamide		2-Methyl-*x*-nitroacetanilide					
		$x = 3$	$x = 4$	$x = 5$	$x = 6$		
	83.7% H_2SO_4	10.7	32.2	52.7	4.4	92.8	0.14
	80.2% H_2SO_4	12.8	27.4	47.4	12.4	98.4	0.45
	78.8% H_2SO_4	10.8	28.2	46.7	14.3	89.7	0.51
	73.2% H_2SO_4	9.4	30.7	35.2	24.7	98.3	0.80
	68.5% H_2SO_4	8.8	28.1	30.0	33.1	97.1	1.18
	64.0% H_2SO_4	8.1	23.4	22.2	46.3	90.4 [b]	1.98
	Ac_2O–HNO_3		43.0		57.0	79.0	1.33
	Ac_2O–HNO_3		43.9		56.1	67.0	1.28
Methyl *N*-phenylcarbamate		Methyl *N*-*x*-nitrophenylcarbamate					
		$x = 2$			$x = 4$		
	73.2% H_2SO_4	57.5			42.5	92.8	0.67
	69.9% H_2SO_4	61.3			38.7	97.5	0.79
	65.9% H_2SO_4	62.5			37.5	96.4	0.83
	63.8% H_2SO_4	63.2			36.8	103.5	0.86
	58.9% H_2SO_4	67.6			32.4	99.7	1.04
	56.6% H_2SO_4	70.2			29.8	97.3	1.18
	Ac_2O–HNO_3	79.1			20.9	96.1	1.89

[a] ±5%. [b] Reaction mixtures were dark in colour; n.m.r. spectrum showed impurities. [c] Or other appropriate quantity, depending on the substrate.

low; the starting material was pure and the extraction procedure was shown to give a quantitative extraction of nitro-anilines from a solution of pH 4. G.l.c. showed no other major peaks which could explain the loss in mass balance. T.l.c. of the nitration product after hydrolysis again showed only the nitroanilines to be present. The isomer ratio remains constant over the acidity range studied, but no conclusions can be reached because of the poor yields.

TABLE 5

Products of nitration of *p*-methoxyacetanilide in aqueous sulphuric acid at 25 °C

H_2SO_4 (%)	Method *	Nitrosation trap	4-Methoxy-*x*-nitroacetanilide (%) †		Yield (%)
			$x = 2$	$x = 3$	
79.6	(*a*)	Urea	4.8	95.2	96.4
76.8	(*a*)	Urea	6.3	93.7	96.9
70.3	(*a*)	Urea	25.1	74.9	100.8
69.9	(*b*)	Urea	28.9	71.1	90.6
69.9	(*b*)	Sulphamic acid	25.9	74.1	92.3
68.7	(*a*)	Urea	39.9	60.1	99.4
66.1	(*a*)	Urea	58.6	41.4	98.5
66.1	(*b*)	Urea	50.2	49.8	98.7
66.1	(*b*)	Sulphamic acid	37.5	62.5	90.3
65.9	(*b*)	Sulphamic acid	37.7	62.3	88.5
63.8	(*a*)	Urea	66.6	33.4	98.5
63.8	(*a*)	Sulphamic acid	66.5	33.5	100.0
63.2	(*b*)	Sulphamic acid	58.0	42.0	97.4

* (*a*) Addition of substrate by pipetting stock solution directly into nitric acid solution; (*b*) preparation of aromatic solution in sulphuric acid, and mixture with nitric acid solution using Y-tube. † ±2%.

TABLE 6

Products of nitration of methyl *N*-phenylacetimidate in aqueous sulphuric acid at 25 °C

H_2SO_4 (%)	Methyl *N*-*x*-nitrophenylacetimidate (%) [a]			Yield (%)
	$x = 2$	$x = 3$	$x = 4$	
85.6	9.4		90.6	30.4
79.3	9.5		90.5	35.9
79.3	9.6		90.4	44.1
75.7	10.9	1.2	91.9	46.0

[a] ±2%.

Protonation of Dihydroquinolone, Indolinone, and Methyl N-*Phenylcarbamate in Sulphuric Acid.*—Results are summarised in terms of the equation $\log I = m(-H_A) - pK_a$ as follows (compound, m, pK_a): dihydroquinolone, 1.03, −2.05; indolinone, 1.03, −2.73; methyl *N*-phenylcarbamate, 1.21, −4.86. For acetani-

lide reported values are $m = 1.0$, $pK_a = -1.32$,[22] and $m = 1.1$, $pK_a = -1.74$.[23] The absorption of solutions

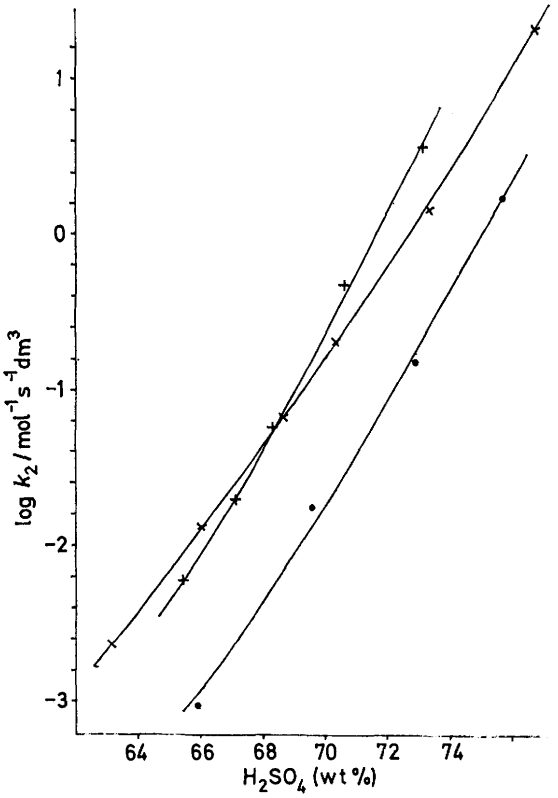


FIGURE 2 Rate profiles for nitration in sulphuric acid; +, benzene; ×, *p*-methoxyacetanilide; ●, methyl *N*-*p*-methoxyphenylacetimidate

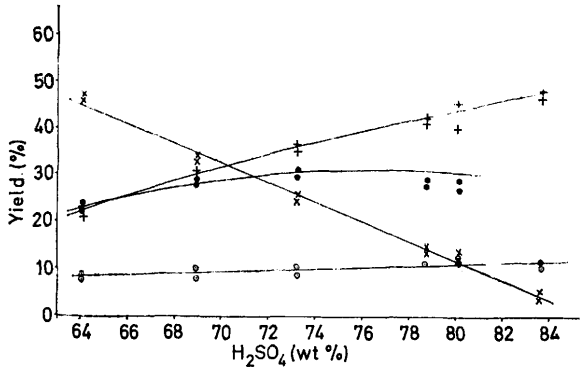


FIGURE 3 Nitration of *N*-*o*-tolylacetamide; yields of isomers: +, 2′-methyl-5′-nitroacetanilide; ×, 2′-methyl-6′-nitroacetanilide; ●, 2′-methyl-4′-nitroacetanilide; ○, 2′-methyl-3′-nitroacetanilide

of methyl *N*-phenylcarbamate in >92% sulphuric acid increased with time, probably because of sulphonation. At these acidities absorbances were extrapolated to zero time.

Rate profiles for nitration, corrected to represent reaction of the free bases, are given in Figure 4, that for acetanilide being obtained by using $m = 1.1$ and $pK_a = -1.74$.

[22] J. W. Barnett and C. J. O'Connor, *J.C.S. Perkin II*, 1973, 220.

DISCUSSION

The Reacting Species in the Nitration in Sulphuric Acid of Acetanilide and its Analogues.—Methyl *N*-phenylacetimidate gave good first-order kinetics [despite the poor yields obtained from this substrate, the rate constants for nitration and the absence of *m*-nitroaniline from the hydrolysed product exclude the possibility that hydrolysis preceded nitration and that the results relate to nitration of $PhNH_3^+$.[24] Absence of nitroacetanilides excludes the alternative mode of hydrolysis.

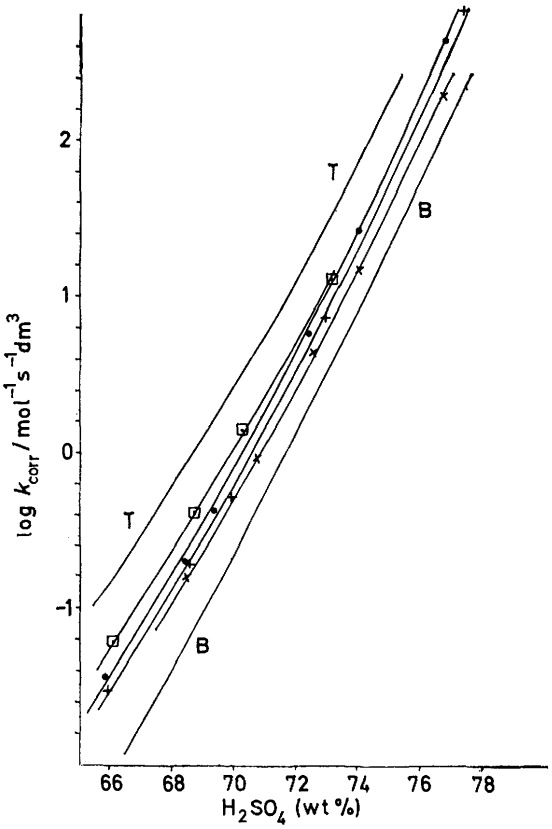


FIGURE 4 Corrected rate profiles for nitration of free bases in sulphuric acid: T, toluene; □, methyl *N*-phenylcarbamate; ●, dihydroquinolone; +, acetanilide; ●, indolinone; B, benzene

In fact the solutions of the acetimidate in the acids used were stable, changes in their spectra being slow as compared with the rates of nitration. In 82% sulphuric acid the solutions were stable during 6 h, but, of course, in dilute acid (2M) change was rapid]. It seems safe to assume that this base (pK_a *ca.* 4.6) reacts as its cation $Ph^+NH{:}C(OMe)Me$, and since the rate constants are about 200 times smaller than those for acetanilide, that it is improbable that the latter is nitrated as the cation $Ph^+NH{:}C(OH)Me$.

Further evidence for nitration *via* the free base comes from the nitration of methyl *N*-phenylcarbamate. This

[23] S. Rysman de Lockerente, P. van Brandt, and A. Bruylants, *Bull. Cl. Sci. Acad. Roy. Belg.*, 1972, **58**, 23.

[24] S. R. Hartshorn and J. H. Ridd, *J. Chem. Soc.* (*B*), 1968, 1063.

compound is half-protonated in 72% sulphuric acid, and nitration is bound to involve the more reactive free base. The structure ($PhNH{\cdot}CO_2Me$) is similar to that of acetanilide, and when the rate profiles for the two compounds, corrected for the degree of protonation so as to give rate constants appropriate to the free bases, are compared (Figure 4), the two compounds are seen to be closely similar in their reactivities.

Thus, the comparison with model compounds indicates that, in contradiction of the earlier conclusion,[2] acetanilide is nitrated as the free base, despite the small proportion of substrate which is present in this form. The similarity of the slopes of observed rate profiles (Figure 1) and the magnitudes of corrected rate constants (Figure 4) suggest that dihydroquinolone, indolinone, and *N*-*o*-tolylacetamide also react as the free bases.

The corrected rate constants for acetanilide, appropriate to the free base, are well below the limiting values set by diffusion control (Figure 4). In fact, in sulphuric acid acetanilide is less reactive than toluene. This is noteworthy since acetanilide reacts at the limiting rate when nitrated in acetic anhydride.[25] In such a typical electrophilic substitution as chlorination in acetic acid, acetanilide is about 5 000 times more reactive than toluene [26] (results for other electrophiles seem not to be available). The point is discussed below.

The earlier conclusion,[2] that in sulphuric acid acetanilide is nitrated as its cation, was based on the slope of the observed rate profile, which appeared to be appropriate to reaction *via* a dominant species.[27] Slopes of rate profiles are reviewed below. We note here that the slight curvature shown by the rate profiles of anilides at low acidities does not signal any gross change of mechanism; the phenomenon was previously attributed to activity coefficient effects.[2,27]

Figure 2 shows the rate profiles for nitration of *p*-methoxyacetanilide and methyl *N*-*p*-methoxyphenylacetimidate. It has been noted previously that at lower acidities, *p*-methoxyacetanilide may be undergoing some nitration *via* nitrosation, and this may explain the shallower slope of the rate profile as compared with that of the imidate, which provides a model for the cation. In 76% sulphuric acid *p*-methoxyacetanilide is only about 5 times more reactive than its ' fixed cation.' This small difference suggests that *p*-methoxyacetanilide is reacting as the conjugate acid.

Comparison of the observed rate of nitration with the calculated encounter rate supports this conclusion. Using a pK_a value of -1.2 and the fact that the protonation follows the H_A acidity function,[28] the rate constant for the nitration *via* the free base can be calculated; for 73% sulphuric acid it is 82.1 $dm^3\ mol^{-1}\ s^{-1}$. The rate constant for the nitration of mesitylene in 70.3% sulphuric acid, that is the encounter rate constant at that acidity, is 9.3 $mol^{-1}\ s^{-1}\ dm^3$. Extrapolations using acidity functions introduce errors of uncertain magnitude, but it appears unlikely that the nitration of *p*-methoxyacetanilide involves the free base.

Variation of Isomer Proportions with Nitrating Conditions.—The variation in $\frac{1}{2}o : p$ ratios (or corresponding quantities for bicyclic compounds) of nitration products with acidity (Table 4) is shown in Figure 5. As well as those for compounds studied in this work, previously published [2] results for other substrates are included. Remarkable similarities amongst the behaviours of these various compounds over the acidity range studied are seen. Especially noteworthy is the similarity between the behaviour of anisole and that of the various anilides. No reason why straight, almost parallel lines should be

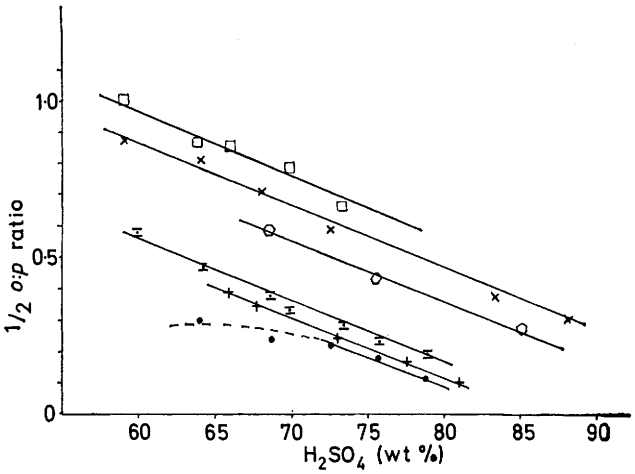


FIGURE 5 Variation of $\frac{1}{2}o : p$ ratio (or its equivalent) for nitration in sulphuric acid: □, methyl *N*-phenylcarbamate; ×, anisole; ○, α-chloroacetanilide; dihydroquinolone; +, acetanilide; ●, indolinone

formed is known. What is shown is that all the compounds are similarly affected by changes in the medium in which nitration is carried out. The gradual change in $\frac{1}{2}o : p$ ratio with acidity corresponds to the variation in the activity coefficient with acidity in the case of anisole, where the activity coefficient of the substrate can be measured.[29] The change is a measure of the substrate–solvent interaction, or hydrogen bonding of the compound in the acidic medium.

From the similarities of the dependences of $\frac{1}{2}o : p$ ratios on the medium, the variations in isomer ratios in the anilides studied can be attributed to the involvement of hydrogen-bonded species in the nitration reaction. This is an argument similar to that recently postulated [29] to explain the results for anisole, except that in the case of the anilides there is a complex equilibrium relationship amongst free base, hydrogen-bonded free base, and conjugate acid species. That the rate constants for nitration calculated for the free base of acetanilide are less than the encounter rate constants

[25] S. R. Hartshorn, R. B. Moodie, and K. Schofield, *J. Chem. Soc.* (*B*), 1971, 2454.
[26] P. B. D. de la Mare and M. Hassan, *J. Chem. Soc.*, 1958, 1519.
[27] J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, ' Nitration and Aromatic Reactivity,' Cambridge University Press, 1971, ch. 8.
[28] C. J. Giffney and C. J. O'Connor, *J.C.S. Perkin II*, 1975, 706.
[29] J. W. Barnett, R. G. Coombes, J. G. Golding, R. B. Moodie, K. Schofield, G. D. Tobin, and J. B. Weston, *J.C.S. Perkin II*, 1977, 248.

(see above), although acetanilide reacts at the limiting rate in acetic anhydride, supports the view that hydrogen bonding is important in sulphuric acid solutions. Anisole also reacts at a rate slightly below the encounter value in sulphuric acid and this has been explained by the fact that involvement of the hydrogen-bonded species would reduce the rate of encounter for electrostatic reasons and possibly also reduce the intrinsic reactivity.[29]

The change in $\frac{1}{2}o : p$ ratio with acidity is even more pronounced in the results obtained from *N*-*o*-tolylacetamide (Figure 3), but there are complications here with all four possible isomers being formed. Again, the changes in isomer ratios are at present assumed to be due to medium effects, as there is no evidence of *ipso*-attack [30] at the methyl group. No adduct formation was observed by n.m.r. spectroscopy during nitration in acetic anhydride, or loss in yield at low acidities due to nucleophilic capture of the *ipso*-Wheland intermediate. The most pronounced effect is the change in proportions of the 5- and 6-nitro-isomers with acidity. This type of dependence on acidity limits the utility or partial rate factors.

The results obtained from the nitration of methyl *N*-phenylacetamidate seem to show that the isomer proportions do not vary with acidity. This would fit the theory mentioned above as the substrate is protonated, so that the reacting species does not vary much with the acidity of the medium. However, as the yield of nitroproducts was low no definite conclusions can be reached.

Variation in $\frac{1}{2}o : p$ *Ratio with Nitrating Conditions.*— The increase in $\frac{1}{2}o : p$ ratio for a number of compounds, on changing from nitration in sulphuric acid to nitration in acetic anhydride, is shown in Table 7. The main purpose of this work was to test the view that there exists a special mechanism for *o*-nitration in acetic anhydride which operates by means of attack at the carbonyl group of the anilide, as described above. This special mechanism ought to operate with *N*-*o*-tolylacetamide, the oxygen atom of the acetamido-group presumably being sufficiently nucleophilic to allow attack of the nitrating species,[2] but would be impossible for dihydroquinolone (1) because of the geometry of the amide grouping.

TABLE 7

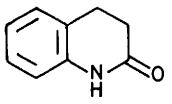
Variation in $\frac{1}{2}o : p$ ratio with nitrating conditions

Compound	77% H_2SO_4	66% H_2SO_4	Ac_2O–HNO_3
Acetanilide [2]	0.15	0.40	1.7
α-Chloroacetanilide [2]	0.38	0.62	2.0
Dihydroquinolone [a]	0.24	0.45	0.96
Methyl *N*-phenylcarbamate [a]		0.82	1.89
N-*o*-Tolylacetamide [a]			1.03
Methyl phenethyl ether [2,4]	0.30	0.41	0.92
Benzyl methyl ether [2,4]		0.24	0.61
Anisole [29]		0.75	1.40
ααα-Trifluoroacetanilide [2]	0.2		0.3
N-Methylsulphonylaniline [2]	0.2		0.75

[a] This work.

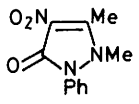
For all the anilides in Table 7 except ααα-trifluoroacetanilide (and *N*-methylsulphonylaniline) there is a qualitatively similar change from low to high values of the $\frac{1}{2}o : p$ ratio as the acidity of the nitrating medium is lowered. This suggests that the kind of change being observed does not depend upon the acylamino-group being able to adopt a particular orientation. Again, the special mechanism for *ortho*-nitration involving coordination of the electrophile with the carbonyl oxygen atom would require nucleophilic character in that oxygen atom, and in this respect the case of methyl *N*-phenylcarbamate is especially striking. In this compound the carbonyl oxygen atom is only weakly nucleophilic, and yet the change in $\frac{1}{2}o : p$ ratio is marked.

It is not possible to see any evidence for the occurrence of the special mechanism of *ortho*-substitution in the form discussed. Whether the results for the anilides, and also for some ethers (Table 7), require further special consideration is still a question. What is observed is a rise in the $\frac{1}{2}o : p$ ratio as the hydrogen bonding between substrate and medium decreases, and this leads in several cases to values of the ratio greater than the statistical, for reaction in acetic anhydride (Tables 1 and 4), and less commonly in dilute sulphuric acid (Table 4). The high $o : p$ ratios are difficult to account for if acylamino-groups are supposed to be acting as conventional conjugative substituents; substituents which would be expected to exert the opposite effect in this way, such as nitro, produce very high $o : p$ ratios,[31] and in molecular chlorination the $f_o : f_p$ ratio for acetanilide is about 0.24 : 1.[26]

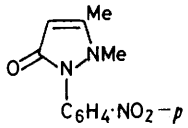


(1)

(2)



(3)



(4)

Two other possible causes of the high $o : p$ ratio found with the anilides should be mentioned. First, there might be a special mechanism involving attack by the nitrating agent at the acylated nitrogen atom, followed by a rearrangement of the nitramine type. Attempts to prepare *N*-nitroacetanilide have failed, and the relevance of the quantitative *para*-nitration of *N*-methylacetanilide [2] is not clear. However, the variations of the $o : p$ ratios with solvent viscosity in the nitramine rearrangement are opposite to that found in the rearrangement of *N*-methyl-*N*-nitroaniline.[32] Secondly, there is the possibility that *ipso*-nitration followed by *ortho*-migration

[30] R. B. Moodie and K. Schofield, *Accounts Chem. Res.*, 1976, **9**, 287.

[31] P. B. D. de la Mare and J. H. Ridd, 'Aromatic Substitution: Nitration and Halogenation,' Butterworths, London, 1959, p. 81.

[32] W. N. White, H. S. White, and A. Fentiman, *J. Org. Chem.*, 1976, **41**, 3166.

occurs; the results provide no evidence on this point, and indeed the change of $o:p$ ratio with acidity again appears to be in the wrong direction for such an explanation.[30]

Use of Slopes of Rate Profiles in Determining the Reacting Species in the Nitration of Bases in Sulphuric Acid.—The slopes have been widely used in elucidating the mechanisms of the nitration of bases, and this criterion led to the mistaken conclusion that acetanilide is nitrated in sulphuric acid as its cation [2] (see above). The basis of the method has been discussed.[27] In using it the values of log k_2(obs.) are plotted against some measure of acidity such as weight percentage of sulphuric acid or an acidity function; such plots are linear over short ranges of acidity.

The slope for the nitration of benzene was thought to be odd [18] as the value of d(log k_2)/d[$-(H_R + \log a_{H_2O})$] increases from 1.0 in the range 63—68% sulphuric acid to 1.2 at higher acidities. It has since been found that for other deactivated compounds, *e.g.* *p*-dichlorobenzene, the slope is parallel to that of benzene.[33] The possibility [34] that the non-linearity for benzene may be due to closeness to the encounter rate can be discounted; calculation [35] shows that even in 80% sulphuric acid the rate of nitration of benzene is only affected to a small extent by diffusion control. The change in slope at high acidities noted with benzene may be due to the failure of the acidity function ($H_R + \log_{10} a_{H_2O}$) correctly to represent the ionisation of nitric acid at higher acidities.

In reconsidering the slopes of rate profiles we have compared the behaviour of a range of substrates with that of benzene. For the scheme:

$$HNO_3 + H^+ \underset{}{\overset{K}{\rightleftharpoons}} NO_2^+ + H_2O$$

$$AR + NO_2^+ \xrightarrow{k^{AR}} \text{products}$$

the Brönsted rate equation gives equation (i). If

$$k_2^{AR}(\text{obs.}) = k^{AR}K y_{AR} y_{HNO_2} a_{H^+}/a_{H_2O} y_{\neq} \quad \text{(i)}$$

symbols with superscript bz relate to benzene, we then have equation (ii). If the ratio of activity coefficients

$$\log k_2^{AR}(\text{obs.}) = \log k_2^{bz}(\text{obs}). + \log(k^{AR}/k^{bz}) + \log(y_{AR} y_{\neq}^{bz}/y_{\neq}^{AR} y_{bz}) \quad \text{(ii)}$$

were unity the plot of log k_2^{AR}(obs.) *vs.* log k_2^{bz}(obs.) would be rectilinear with unit slope. We have evaluated these slopes for a range of compounds which react below the diffusion rate and for which results at 25 °C have been reported (Table 9), and to assist this evaluation have made additional measurements on benzene at >76% sulphuric acid (Table 8). Where possible in the cases of compounds nitrated *via* the minority species the slope obtained by using the observed rate constant and that obtained by using the corrected rate constant are given.

There is quite a large scatter in the values of the slopes (Table 9), although the scatter is no greater than found for plots of log k_2^{AR}(obs.) *vs.* [$-(H_R + \log a_{H_2O})$]. The rate profiles for the majority of the neutral compounds,

TABLE 8

Second-order rate coefficients for nitration of benzene in sulphuric acid at 25.0 ± 0.1 °C [a]

H_2SO_4 (%) [b]	[HNO_3]/ mol dm^{-3}	[AR]/ mol dm^{-3}	k_2/ dm^3 mol^{-1} s^{-1} [c]
76.8	5.68×10^{-3}	8.1×10^{-5}	6.94×10
79.4	4.12×10^{-4}	4.0×10^{-5}	1.03×10^3
82.0	4.18×10^{-4}	4.0×10^{-5}	2.62×10^4

[a] Made with a Nortec Industries (Canterbury) stopped-flow spectrometer (XF–3A). [b] ±0.1%. [c] ±10%; values for k_2 are averaged from at least four separate kinetic runs at each acidity; measurements were made at 300 nm.

many extending over a large acidity range, are almost parallel to that for benzene with d[log k_2^{AR}(obs.)]/d[log k_2^{bz}(obs.)] > 0.95.

For some nitro-compounds slopes are considerably lower than this, as they are also for some heterocyclic compounds such as 2-methoxyisoquinolinium and 2-hydroxyisoquinolinium. The nitro-compounds are certainly influenced by hydrogen bonding [36] and the same is probably true of the heterocyclic compounds.

It has been suggested that values of d[log k_2^{AR}(obs)]/d($-H_0$) greater than 1.7 are characteristic of majority species reactions.[34] 1-Phenylpyrazolium (2) was anomalous and the same is true in terms of the present criterion (Table 9).

Consideration of Table 9 suggests that values of d[log k_2^{AR}(obs.)]/d[log k_2^{bz}(obs.)] > 0.85 are characteristic of the reactions of majority species. Of the compounds which are nitrated *via* the majority species, 57% have a slope in the range 0.9—1.1 and a further 20% can be included if the range is extended to 0.85—1.15. That certain compounds give a lower slope, for example benzenesulphonic acid, may be due to the inadequacy of results available for them, causing large errors in the evaluation of the slope. Other exceptions include those compounds mentioned above, certain heterocyclic compounds containing a carbonyl group (see below), and *p*-methoxyacetanilide. With the last compound nitration *via* nitrosation might have affected the kinetic results.

If the value 0.85 is taken as the rough dividing line between slopes for majority and minority species the cases of compounds giving slopes close to this value are clearly ambiguous in terms of this criterion; such is the case of acetanilide. In such cases the slope of the rate profile is not on its own a reliable criterion of mechanism. The ambiguity is not removed in the case of a base by correction ' of the rate constants using the ionisation ratio, for such ' correction ' will *always* increase the slope even in cases where it is illegitimate.

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TABLE 9

Plot of $\log^{10}k_2^{AR}$(obs.) *vs.* $\log^{10}k_2^{bz}$(obs.) for nitrations in aqueous sulphuric acid at 25 °C *

Neutral compounds	% H_2SO_4	$\frac{d[\log k_2^{AR}(obs.)]}{d[\log k_2^{bz}(obs.)]}$	Intercept	Correl. coefft.
Benzylidyne trifluoride [a]	75.4—80.9	1.050 9	−4.727 2	0.999 9
Bromobenzene [33]	67.5—74.7	1.047 2	−1.202 2	0.999 6
p-Bromochlorobenzene [b]	74.0—81.7	0.949 0	−3.072 5	0.998 0
2-Bromo-1,3-xylene [b]	62.8—74.7	0.996 6	0.627 4	0.999 2
Chlorobenzene [33]	67.5—77.4	1.033 2	−1.196 1	0.999 4
o-Chloronitrobenzene [36]	79.9—81.4	9.916 0	−5.107 7	0.999 3
p-Chloronitrobenzene †,[36]	79.9—81.6	0.764 3	−6.005 5	0.999 8
p-Chlorotoluene [b]	63.0—74.5	0.939 6	0.083 7	0.998 0
o-Dibromobenzene [b]	72.4—79.4	1.046 4	−3.042 9	0.999 8
p-Dibromobenzene [b]	67.1—81.7	0.949 0	−2.941 8	0.997 9
2,5-Dibromotoluene [b]	69.6—79.1	1.008 3	−1.596 3	0.997 7
o-Dichlorobenzene †,[33]	77.5—80.9	0.986 1	−2.797 6	1.000 0
m-Dichlorobenzene †,[33]	75.4—79.2	1.177 1	−2.775 2	1.000 0
p-Dichlorobenzene [33]	73.2—80.9	0.996 7	−3.179 4	0.999 1
Fluorobenzene [33]	67.5—77.0	1.000 3	−0.889 7	0.999 6
Iodobenzene [33]	67.5—74.9	0.957 1	−0.731 9	0.999 7
m-Nitrotoluene [c]	72.3—81.6	0.906 8	−4.840 7	0.999 8
p-Nitrotoluene [36]	70.8—82.1	0.949 7	−3.082 0	0.996 4
1,2,4-Trimethyl-3-nitrobenzene †,[d]	69.2—74.1	0.937 3	−0.794 8	1.000 0
1,2,4-Trimethyl-6-nitrobenzene †,[d]	69.2—74.1	0.968 1	−1.112 3	1.000 0
1,2,4-Trimethyl-5-nitrobenzene †,[d]	69.2—74.1	0.885 8	−1.760 6	0.999 9
Anions				
Benzenesulphonic acid †,[e]	76.9—81.4	0.772 4	−4.587 4	1.000 0
Mesitylenesulphonic acid [e]	64.8—71.9	0.856 3	−0.298 8	0.999 7
2-Phenylethanesulphonic acid [e]	63.4—76.0	0.973 5	0.039 5	0.997 3
Phenylmethanesulphonic acid [e]	68.7—80.0	0.854 4	−1.175 9	0.988 1
3-Phenylpropane-1-sulphonic acid [e]	63.4—71.9	0.937 4	0.450 2	0.999 6
Cations				
Benzylammonium †,[f]	78.7—80.1	0.640 0	−1.580 0	0.999 9
Benzyltrimethylammonium [f]	74.5—81.6	0.885 8	−4.187 6	0.999 8
$Ph[CH_2]_2N^+Me_3$ (25.1 °C) [g]	63.4—76.5	1.041 6	−0.751 9	0.999 8
$Ph[CH_2]_3N^+Me_3$ (25.1 °C) [g]	63.4—68.3	1.050 0	0.370 0	1.000 0
Trimethyl-*p*-tolylammonium [h]	75.8—81.7	0.925 9	−4.816 0	0.997 7
Phenyltrimethylstibonium [i]	76.0—82.2	0.876 1	−4.364 3	0.998 2
$1\text{-}PhC_6H_{10}N^+H_3$ [j]	68.3—75.5	0.684 4	−2.413 6	0.991 8
$1\text{-}PhC_6H_{10}N^+Me_3$ [j]	75.0—79.9	0.969 4	−3.967 3	0.997 3
trans-$2\text{-}PhC_6H_{10}N^+H_3$ [j]	67.0—72.7	0.967 4	−1.142 6	0.997 4
trans-$2\text{-}PhC_6H_{10}N^+Me_3$ [j]	66.0—72.9	1.059 3	−1.217 5	0.998 9
cis-$2\text{-}PhC_6H_{10}N^+H_3$ [j]	67.0—72.9	0.969 2	−1.077 4	0.999 6
cis-$2\text{-}PhC_6H_{10}N^+Me_3$ [j]	67.9—73.0	0.961 7	−1.497 9	0.999 5
$p\text{-}R_3N^+\cdot[CH_2]_n\cdot C_6H_4\cdot[CH_2]_n\cdot N^+R_3$				
$n = 3$, R = H [k]	65.8—69.6	0.839 2	0.112 2	0.998 3
$n = 3$, R = Me [k]	66.5—69.8	0.942 1	0.113 3	0.994 0
$n = 2$, R = H [k]	68.7—75.0	0.772 8	−1.640 8	0.995 2
$n = 1$, R = H †,[k]	76.8—80.3	0.803 3	−5.688 2	1.000 1
$R_2N^+\text{–}[CH_2]_m\text{–}R_2N^+$ $p\text{-}[CH_2]_n\text{–}C_6H_4\text{–}[CH_2]_n$				
$n = 3$, $m = 2$, R = Me [k]	72.5—78.7	0.841 1	−3.297 7	1.002 5
$n = 2$, $m = 2$, R = H [k]	73.7—80.6	0.924 0	−3.820 6	0.998 2
$n = 2$, $m = 2$, R = Me [k]	74.3—80.3	0.877 7	−3.876 9	0.999 2
Substituted benzene perchlorate salts				
$1\text{-}CH_2\cdot N^+H_3$,4-Me [l]	63.6—71.4	0.982 3	−0.518 3	0.988 0
$1\text{-}[CH_2]_2\cdot N^+H_3$,4-Me [l]	64.5—70.2	0.703 4	−0.048 0	0.999 0
$1\text{-}[CH_2]_2\cdot S^+Me_2$,4-$[CH_2]_2\cdot S^+Me_2$	70.9—76.7	0.922 0	−2.241 9	0.995 7
Heterocyclic compounds				
4-Benzyl-1-methylpyridinium †,[m]	68.4—70.2	1.048 0	−0.673 3	1.000 1
4-Benzylpyridine (24.8 °C) [m]	66.4—72.8	0.982 9	−0.726 3	0.999 6
2-Chlorothiophen [n]	66.5—72.9	0.891 1	0.545 6	0.998 0
1,2,Dihydro-1,5-dimethyl-4-nitro-2-phenylpyrazol-3-one [37]	75.4—80.8	0.318 3	−3.738 6	0.999 8
free base [37]	75.4—80.8	0.563 8	−1.846 0	0.999 4
1,2-Dihydro-1,5-dimethyl-2-*p*-nitrophenylpyrazol-3-one [37]	76.7—81.6	0.367 6	−4.633 0	0.983 3
free base [37]	76.7—81.6	0.544 7	−1.019 6	0.990 5
1-(2,6-Dimethylphenyl)pyrazole [o]	74.9—79.2	0.955 7	−2.781 2	0.999 9
3,4-Dimethylthiazol-2(3*H*)-one [38]	75.8—82.2	0.399 5	−0.273 1	0.997 6
free base [38]	75.8—82.2	0.602 4	1.270 7	0.999 3
2-Hydroxyisoquinolinium [p]	76.4—81.2	0.773 9	−6.357 6	0.998 4
4-Hydroxyquinoline †,[q]	80.7—81.4	0.752 4	−4.952 5	0.999 9
Isoquinolinium [r]	71.3—81.3	0.828 9	−6.016 6	0.999 0

TABLE 9 (*Continued*)

Plot of $\log^{10}k_2^{Ar}$(obs.) *vs.* $\log^{10}k_2^{bz}$(obs.) for nitrations in aqueous sulphuric acid at 25 °C *

Neutral compounds	% H_2SO_4	$\frac{d[\log k_2^{AB}(obs.)]}{d[\log k_2^{bz}(obs.)]}$	Intercept	Correl. coeffit.
2,6-Lutidine 1-oxide †,‡,[p]	78.2—81.4	0.522 9	−8.965 5	1.000 1
2-Methoxyisoquinolinium [p]	76.4—81.6	0.789 5	−6.925 5	0.998 7
2-Methoxy-4-methylthiazole [38]	65.8—80.9	1.021 9	0.471 4	0.999 3
2-Methylisoquinolinium [r]	71.3—81.3	0.842 4	−6.035 8	0.996 3
1-Methyl-2-methylaminopyridinium [s]	78.4—82.0	0.611 3	−5.599 2	0.998 7
1,2-Dihydro-5-methyl-4-nitro-2-phenylpyrazol-3-one [37]	71.9—77.5	0.834 4	−1.362 7	0.999 2
3-Methyl-1-phenylpyrazole [o]	79.2—82.1	0.868 7	−3.786 7	1.000 3
1-Methylpyrazole 2-oxide [t]	65.8—75.5	0.569 0	−1.200 5	0.999 4
1-Methylquinolinium †,[r]	79.6—81.3	0.873 3	−7.893 7	0.999 9
1-Methyl-4-quinolone †,[q]	77.4—81.4	0.789 2	−5.532 0	1.000 0
4-Methylthiazole-2(3*H*)-one [38]	76.8—80.8	0.481 5	0.037 2	0.991 4
free base [38]	76.8—80.8	0.687 9	0.698 4	0.990 1
1-Phenylimidazole [o]	68.6—80.4	0.881 8	−4.495 2	0.998 8
1-Phenylpyrazole [o]	77.7—82.1	0.771 1	−4.246 6	0.997 6
2-Phenylpyridine [u]	78.0—80.9	1.017 3	−4.850 0	0.996 6
4-Phenylpyridine (24.8 °C) [m]	75.1—80.1	0.948 5	−3.497 0	0.999 1
2-Phenylpyridine 1-oxide [u]	74.7—78.6	1.005 3	−4.300 1	0.999 5
2-Pyridone (observed) [38]	75.2—81.2	0.385 4	5.747 0	0.999 0
free base [38]	75.2—81.2	0.638 9	−0.996 3	1.000 1
Quinoline 1-oxide (25.2 °C) [v]	73.0—82.0	0.454 6	−5.640 0	0.999 9
Quinolinium †,[r]	79.6—81.3	0.680 0	−6.513 4	1.000 0
1,2,3,5-Tetramethylpyrazolium (24.3 °C) [w]	75.6—81.7	0.867 6	−6.037 9	0.995 7
1-(*o*-Tolyl)pyrazole [o]	79.2—82.1	0.862 5	−4.053 6	0.999 2
1,4,5-Trimethylimidazole 3-oxide [t]	73.3—81.7	0.479 0	−2.648 0	0.998 3
1,3,5-Trimethylpyrazole (20.9 °C) [w]	73.3—81.6	0.970 0	−6.551 0	0.973 5
Ethers and carbonyl compounds				
Acetophenone [z]	75.5—81.4	0.646 8	−4.261 8	0.994 4
free base [y]	75.5—81.4	0.849 5	−3.779	0.996 4
Benzoic acid [x]	78.0—81.4	0.721 7	−3.628 7	0.999 2
free base [y]	78.0—81.4	0.809 9	−3.338 1	0.999 5
Benzyl methyl ether [2]	67.7—72.9	0.911 1	−0.980 4	0.999 8
Methyl phenethyl ether [2]	67.7—80.9	0.941 7	0.102 1	0.995 1
Methyl 3-phenylpropyl ether [2]	65.7—80.9	0.933 3	0.623 4	0.998 6
Anilides and related compounds				
1-Acetamidonaphthalene [z]	65.8—75.5	0.849 0	0.297 3	0.999 6
Acetanilide [2]	65.8—80.9	0.809 0	−2.018 6	0.998 7
free base ¶,[2]	65.8—80.9	0.998 9	0.500 2	0.999 2
free base **,[2]	65.8—80.9	1.021 9	0.471 4	0.999 3
α-Chloroacetanilide [2]	65.8—80.4	0.674 5	−1.053 6	0.999 3
free base [2]	65.8—80.4	0.851 9	−0.239 0	0.997 8
3,4-Dihydroquinolin-2(1*H*)-one §	65.8—79.4	0.791 0	−1.426 8	0.999 0
free base §	65.8—79.4	0.989 2	0.551 1	0.998 5
p-Methoxyacetanilide §	66.1—73.3	0.771 2	−0.306 0	0.999 7
Methyl *N*-*p*-methoxyphenyl acetimidate §	65.9—75.7	0.877 9	−1.137 7	0.998 3
Methyl *N*-phenylacetimidate §	75.8—80.2	0.909 7	−1.159 3	0.998 5
Methyl *N*-phenylcarbamate §	63.3—74.3	0.807 3	0.299 6	0.997 1
free base §	63.3—74.3	0.888 8	0.538 3	0.999 2
N-Methylsulphonylaniline [2]	65.8—80.4	0.926 5	0.228 3	0.999 7
Indolin-2-one §	65.8—79.4	0.710 9	−0.925 0	0.999 0
free base §	65.8—79.4	0.903 5	0.360 7	0.998 3
ααα-Trifluoroacetanilide [2]	65.8—80.9	0.832 7	−0.866 5	0.999 6

* Calculations were made on a Sony Sobax 2550 calculator using a least-squares program which assumed that the error lay equally on the values of both log k_1^{AR}(obs.) and log k_2^{bz} (observed). † Slope calculated from two points only. ‡ Results at 25 °C obtained by extrapolation of Arrhenius plots, range 65—95 °C. § This work. ¶ Corrected using data from ref. 22. ** Corrected using data from ref. 23.

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It is likely that the ambiguous performance of acetanilide is caused by hydrogen bonding which, as already seen, affects the orientation of nitration substantially. In this connection, the behaviour of some heterocyclic compounds containing oxygen functions is interesting. 2-Pyridone, a compound for which the ratio of isomers formed in nitration depends markedly on acidity, gives a notably low value of $d[\log k_2(\text{obs.})]/d[-(H_R + \log a_{H_2O})]$ even after correction for ionisation.[37] Low slopes are found also for thiazolones, but most strikingly with 1,2-dihydro-1,5-dimethyl-4-nitro-2-phenylpyrazol-3-one (3) and 1,2-dihydro-1,5-methyl-2-*p*-nitrophenylpyrazol-3-one (4).[38] In all these cases hydrogen bonding is probably important.

Clearly, with weak bases being nitrated in strongly acidic media the dichotomy of mechanism between reaction of free base and reaction of cation is too simple, neglecting the influence of hydrogen-bonding; when the free base, modified by this phenomenon, is the reacting species ambiguous or anomalous slopes of rate profiles must be expected, and where the structure permits, marked medium dependence of isomer ratios.

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