Electrophilic Aromatic Substitution. Part 23.[1] The Nitration of Phenol and the Cresols [2] in Aqueous Sulphuric Acid

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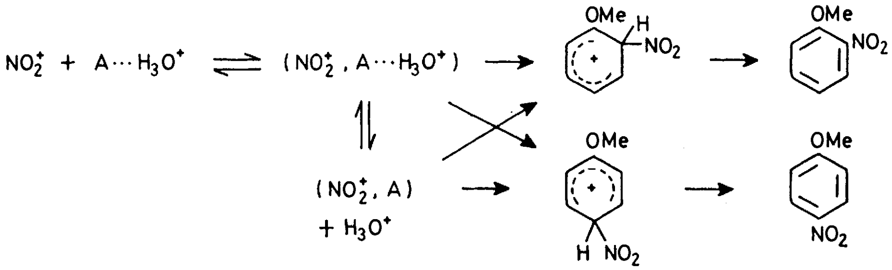
The quantitative mononitration of phenol and *o*-, *m*-, and *p*-cresol by nitric acid in 58—80% sulphuric acid involves reaction with the nitronium ion at or very close to the encounter-controlled rate. For phenol the *o* : *p* ratio changes smoothly from 2.4 to 0.9 over the range 56—83% sulphuric acid. For *o*-cresol the ratio of 2-methyl-6-nitrophenol to the 4-nitro isomer changes from 1.5 to 0.8 over 50—83% sulphuric acid, and for *m*-cresol the ratios of both 3-methyl-2- and 3-methyl-6-nitrophenol to the 4-nitro isomer fall over 58—81% sulphuric acid (0.6 to 0.2 and 1.5 to 0.7 respectively). These changes, and those for some related methyl ethers reported previously, are discussed. The nitration of *p*-cresol in 68—72% sulphuric acid involves *ca.* 40% *ipso* substitution at C–Me and the 4-methyl-4-nitrocyclohexadienone formed undergoes an acid-catalysed rearrangement to 4-methyl-2-nitrophenol. 2-Methyl-6-nitrophenol is established as an important product of nitration of *o*-methylanisole and a mechanism involving demethoxylation of a Wheland intermediate, formed by *ipso*-substitution at C–Me, and a subsequent specific 1,3-rearrangement is proposed.

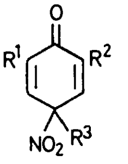
PREVIOUS papers in this series have drawn attention to the existence of medium effects on the ratio of the relative rates of attack of the nitronium ion at the various nuclear positions in the mononitration of aromatic compounds by nitric acid in aqueous sulphuric acid. Some such effects of alkylbenzenes were revealed [3] when the complications of *ipso*-substitution were unravelled, and were particularly large in the case of *o*-xylene. For anisole a very large change of isomer ratios with acidity was observed, and the mechanism outlined in Scheme 1 was presented as a tentative explanation.[4] In this Scheme the rate-limiting step is the formation of an encounter pair between the nitronium ion and a substrate molecule which is hydrogen bonded to a hydronium ion $(A\cdots H_3O^+)$. The Wheland intermediates (Ws) may then be formed, either directly from this encounter pair, or after loss of the hydrogen bond to form a nitronium ion–anisole ion pair. This latter pathway should compete more effectively at lower acidities. This medium effect was not apparent in the case of *p*-methylanisole, where *ipso*-substitution at C–Me played an important role, and it was suggested that this might be due to increased reactivity towards electrophiles, leading to W formation competing more effectively with loss of the hydrogen bonded hydronium ion. The situation concerning *o*-methylanisole was complicated by a drop in total yield of nitro-compounds at low acidities. The nitrations of anisole and 3,5-dimethylanisole in aqueous perchloric acid have also been reported.[5] The isomer ratio changes for anisole were similar to those in sulphuric acid, and the behaviour of 3,5-dimethylanisole was quite similar to that of anisole. The acidity at which equal amounts of the two detected products are formed, however, is lower (by *ca.* 6% w/w) for 3,5-dimethylanisole. This relatively small change in behaviour for a compound with two activating methyl groups is difficult to reconcile with the explanation advanced above for the behaviour of *p*-methylanisole.



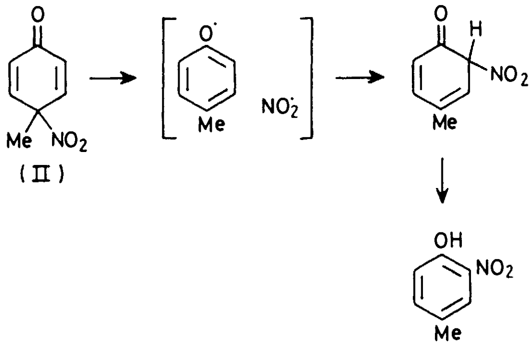
SCHEME 1

The present paper extends these studies to the nitrations of phenol and *o*-, *m*-, and *p*-cresol and defines the importance of medium effects and *ipso*-substitution at C–Me on the product distribution. The hydroxy, like the methoxy substituent, should ensure reaction at or near the encounter rate limit and allows also for the possibility of hydrogen bonding. The results are discussed in terms of the mechanism of Scheme 1, and those from the nitration of *o*-cresol led to a further study of the products of nitration of *o*-methylanisole and a reconsideration of the mechanistic pathways for this substrate.

The nitration of phenol has received surprisingly little specialized attention in the literature. As with anisole a marked decrease in *o* : *p*-ratio associated with the presence of nitrosating conditions, and usually presumed to involve nitrosation and subsequent oxidation, is well known.[6] With solutions of nitric acid in acetic anhydride the situation is complex and the differences may be due to a change in the nitrosating agent.[7] When nitrosation is precluded, phenol is nitrated by nitric acid at a rate a little less than the limiting rate set by encounter, as defined by the rate for mesitylene, in both sulphuric (68.3%) and perchloric acids, and in the latter medium (61.05%) an *o* : *p*-ratio of 1.86 has been reported.[8] In connection with the possibility of *ipso*-substitution at C–Me, which is to be expected for *o*- and *p*-cresol, it is relevant that cyclohexadienones are known as products of nitration of some phenols where reactive positions carry alkyl substituents. The nitration[9] of 2,4,6-trialkylphenols in organic media gave 2,4,6-trialkyl-4-nitrocyclohexa-2,5-dienones (I), and in many reactions dienones although not isolated are thought to be reaction intermediates.[10] A further claim,[11] however, to have observed such species in the nitration of 2,6-dialkylphenols is clearly erroneous. 4-Alkyl-4-nitrocyclohexa-2,5-dienones are also known as a consequence of nucleophilic intervention and elimination in the nitration of 4-X-*o*-xylenes and 5-X-hemimellitenes (X = Br, AcO, or MeO).[12] 4-Methyl-4-nitrocyclohexa-2,5-dienone (II) has also recently been isolated from the nitration of some 4-substituted toluenes, including *p*-methylanisole, by nitric acid in acetic anhydride.[13] Its rearrangement to 4-methyl-2-nitrophenol has been studied in various solvents and a radical dissociation–recombination mechanism (Scheme 2) has been established.[14]



(I)



SCHEME 2

EXPERIMENTAL

Materials.—98% Sulphuric acid, 70% nitric acid, acetic acid, urea, sulphamic acid, and sulphanilic acid were AnalaR reagents. Concentrations of diluted sulphuric acid solutions were determined from density measurements. Phenol, *o*-, *m*-, and *p*-nitrophenols, *o*-, *m*-, and *p*-cresols, 4-methyl-3-nitrophenol, 2-methyl-3- and -5-nitrophenols, 3-methyl-2-, -4-, -5-, and -6-nitrophenols, *o*- and *p*-methylanisole, and *m*-nitroanisole were commercial reagents redistilled or recrystallized as necessary. These compounds had physical properties corresponding to those in the literature. 4-Methyl-2-nitrophenol has been described previously,[4] as have 2-methyl-4- and -6-nitroanisoles, which were the gift of Professor K. Schofield.

2-*Methyl*-4-*nitrophenol*. This, m.p. 117—118 °C (lit.,[15] 119 °C), was prepared by diazotization of 2-methyl-4-nitroaniline followed by decomposition in acidic solution.

2-*Methyl*-6-*nitrophenol*. *o*-Toluidine (5.75 g) was dissolved in concentrated H_2SO_4 (10 cm^3). The solution was cooled to 15 °C and a solution of sodium nitrite (15 g) in water (50 cm^3) was added, gradually at first. The mixture was then poured into an excess of 50% H_2SO_4 and heated on a water-bath. After the vigorous evolution of nitrogen the mixture was steam distilled. The distillate contained 2-methyl-6-nitrophenol (80%) and 2-methyl-4,6-dinitrophenol (20%) which were separated on a preparative silica gel plate using 20% ethyl acetate–cyclohexane, and identified by ^1H n.m.r. spectroscopy. The former had m.p. 62—63 °C (lit.,[16] 65 °C).

Kinetic Measurements and Product Analyses.—These were in general as described previously.[4] A nitrous acid trap, usually sulphamic acid, was used in all reaction solutions. A pleated flask was not normally used as results were identical without this refinement. All nitro products were identified by comparison of their retention times on chromatographic analysis with those of independently identified authentic samples of the compounds. In the case of *o*-methylanisole the combined extracts from a series of reactions were concentrated and the 2-methyl-6-nitrophenol was separated by preparative t.l.c. as described above. Its identity was confirmed by its ^1H n.m.r. spectrum, τ 7.76 (3 H, s, ArCH_3), 3.12 (1 H, t, H-4, $J_{3.4} = J_{4.5} = 4$ Hz), 2.52 (1 H, d, H-3, $J_{3.4}$ 4 Hz), and 2.23 (1 H, d, H-6, $J_{4.5}$ 4 Hz), which was also identical to that of an authentic sample.

Various methods of quantitative product estimation were used as was appropriate. The final extinction curves in the u.v. region of reaction solutions of phenol and *o*-cresol were analysed by the method of Dewar and Urch.[17] The products of nitration of phenol (*o*-nitrophenol *only*) and *p*-cresol were analysed by g.l.c. under the conditions described in Table 1, using an authentic sample of the product from the other substrate as a reference standard. For phenol, *o*- and *m*-cresol, and *o*-methylanisole techniques involving high pressure liquid chromatography (h.p.l.c.) were used. In the case of phenol reaction solutions typically 4×10^{-3} mol dm^{-3} in substrate were used, and these were neutralized with ammonia solution (*d* 0.88) after addition of a solution of 4-methyl-2-nitrophenol in acetic acid as a reference standard. Samples (10 ml) of this solution were injected directly into the chromatograph (for conditions see Table 2). With *o*- and *m*-cresol and *o*-methylanisole product solutions were extracted with chloroform in the usual way and the concentrated extract was injected into the chromatograph.

TABLE 1

G.l.c. conditions [a]

Product [b]	Retention time (s)
o-Nitrophenol	252
4-Methyl-2-nitrophenol	340

[a] Pye 104 machine (flame ionisation detector); column 1 m × ¼ in, 5% PEG A on 1% phosphoric acid-washed Chromasorb W, 60—85 mesh; 118 °C; nitrogen carrier flow rate 60 cm^3 min^{-1}. [b] *p*-Nitrophenol and 4-methyl-3-nitrophenol were retained on the column.

Table 2

H.p.l.c. conditions [a]

Product	Column [b]	Flow rate (cm^3 min^{-1})	Solvent	λ [c]/nm	Retention time (s)
o-Nitrophenol	A	1	Water	320	414
p-Nitrophenol					588
4-Methyl-2-nitrophenol (reference standard)					870
2-Methyl-3-nitrophenol	B	2	*d*	320	596
2-Methyl-4-nitrophenol					700
2-Methyl-5-nitrophenol					360
2-Methyl-6-nitrophenol					142
m-Nitroanisole (reference standard)					220
3-Methyl-2-nitrophenol	B	2	*d*	300	252
3-Methyl-4-nitrophenol					870
3-Methyl-5-nitrophenol					600
3-Methyl-6-nitrophenol					162
2-Methyl-3-nitrophenol (reference standard)					690
4-Methyl-2-nitrophenol	C	1.3	*d*	280	93
4-Methyl-3-nitrophenol					180
2-Methyl-4-nitrophenol	B	2	*d*	300	664
2-Methyl-6-nitrophenol					144
2-Methyl-4-nitroanisole					255
2-Methyl-6-nitroanisole					195
m-Nitrophenol (reference standard)					535

[a] Waters Associates model 6000A pump, Cecil 272 detector at ambient temperature. [b] A, 1 m × $\frac{1}{8}$ in S.S. Permaphase E.T.H.; B, 25 cm × $\frac{1}{4}$ in Merkosorb SI 60; C, 1 m × $\frac{1}{8}$ in Corasil II. [c] Wavelength of detection. [d] 10% Ethyl acetate in cyclohexane. The differences in retention times for the same compound noted between the bracketed sets of compounds are due to the use of different batches of eluting solvent mixture.

RESULTS

Kinetics.—Second-order rate coefficients k_2(obs) for the nitration of the title compounds and some relevant mono-nitro-derivatives are given in Table 3, and rate profiles are in Figure 1, together with those of anisole,[4] mesitylene,[8,18] and benzene for comparison.[8] The experimental points are shown for the title compounds and a continuous line is given for each of the other substrates.

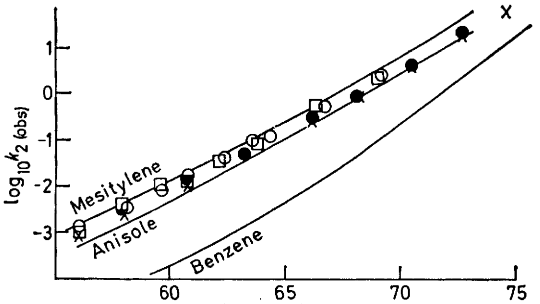


Figure 1 Rate profiles for nitration in aqueous sulphuric acid (×, phenol; ○, *o*-cresol; □, *m*-cresol; ●, *p*-cresol)

In all cases good straight line first-order kinetic plots were observed for individual runs, and except for *p*-cresol the u.v. extinction curves indicated an uncomplicated conversion of substrate into nitro products. For *p*-cresol in *ca.* 70% sulphuric acid, however, it was observed that an initial absorption occurred at between 230 and 255 nm and then disappeared slowly, indicating the presence of an intermediate species. The disturbance caused by the formation of this intermediate was apparently not sufficient to be noticed during the measurement of k_2(obs) for the substrate. It became clear that the rate of formation of the intermediate species was dependent on the concentration of nitric acid, but that its rate of disappearance was not. By increasing the concentration of nitric acid in the reaction mixture at a particular acidity, it was, therefore, possible to obtain the maximum absorbance due to the intermediate after *ca.* 120 s, corresponding to *ca.* 7 half-lives for the reaction the rate of which is recorded in Table 3. It was then possible to determine the first-order rate coefficients k_1 for the disappearance of the intermediate as a function of acidity, and these are given in Table 4. The occurrence of an appreciable rate of dinitration under these circumstances made it necessary to calculate the absorbance values at complete reaction in these cases, with an inevitable loss of accuracy. The calculation was possible on the knowledge (see below) that the sole initial reaction product of the intermediate was 4-methyl-2-nitrophenol, as the spectrum of this compound and the presence of an isosbestic point at 330 nm during its nitration were known. The overall spectral changes were also consistent with this hypothesis. Table 4 also includes values [19] of H_0 and it was found that a graph of $\log_{10}k_1$ *versus* $-H_0$ could be interpreted as a straight line of slope 0.9, although the range of acidity was small (4.6%).

A study of the change in the u.v. extinction curve during the nitration of *p*-methylanisole was carried out using sulphamic acid as the nitrous acid trap (25 °C; 70.5% H_2SO_4; [substrate] 1.1×10^{-4} mol dm^{-3}; [HNO_3] 5.5×10^{-2} mol dn.$^{-3}$; [HNO_3] 5.5×10^{-2} mol dm^{-3}; [sulphamic acid] 0.05 mol dm^{-3}). The characteristic behaviour, due to the presence of an intermediate species, also exhibited by *p*-cresol, was observed. The rate of subsequent disappearance of the intermediate was approximately determined at this acidity using an estimated value for the absorbance at complete reaction (k_1 *ca.* 4×10^{-3} s^{-1}).

Yields of Nitro Compounds.—These are given for the title compounds in Table 5.

Phenol. *o*- and *p*-Nitrophenols were formed in total quantitative yields over the range 56—83% sulphuric acid, the three methods of product estimation showing a gratifying agreement. The variation of yields with acidity is shown in Figure 2.

o-*Cresol*. 2-Methyl-6- and -4-nitrophenols were formed in total quantitative yield over the range 50—83% sulphuric acid. The 3- and 5-nitro isomers were not detected and were not present to >0.2%. The variation of yields with acidity is shown in Figure 3.

m-*Cresol*. 3-Methyl-2-, -4-, and -6-nitrophenols were formed in total quantitative yield over the range 58—81% sulphuric acid. The 5-nitro isomer would have been detected if present to the extent of >0.3%. The variation of yields with acidity is shown in Figure 3.

TABLE 3

Second-order rate coefficients for nitration in sulphuric acid at 25.0 ± 0.2 °C

H_2SO_4 (%) [a]	$10^2[HNO_3]$ [b,c]/ mol dm^{-3}	k_2(obs)/ dm^3 mol^{-1} s^{-1}
	Phenol [d]	
56.1	5.5	8.6×10^{-4}
58.1	5.5	2.5×10^{-3}
60.8	5.5	1.00×10^{-2}
63.2	5.5	2.6×10^{-2}
66.1	0.38	2.5×10^{-1}
68.0	0.09—0.17	7.7×10^{-1}
70.4	0.09	4.0
72.6	0.046	2.0
74.4	0.046	58
	o-Nitrophenol [e]	
75.5	5.5	8.0×10^{-3}
	p-Nitrophenol [f]	
75.5	5.5	2.0×10^{-2}
	o-Cresol [g]	
56.1	5.5	1.20×10^{-3}
58.1	5.5	3.6×10^{-3}
59.6	2.3	8.5×10^{-3}
60.8	0.67	1.69×10^{-2}
62.3	0.25	4.1×10^{-2}
63.6	0.25	9.9×10^{-2}
64.3	0.09	1.18×10^{-1}
66.6	0.09	5.8×10^{-1}
69.1	0.09	2.8
	2-Methyl-4-nitrophenol [h]	
80.8	5.5	2.5
	2-Methyl-6-nitrophenol [h]	
80.8	5.5	2.5
	m-Cresol [i]	
56.1	5.5	1.07×10^{-3}
58.1	5.5	4.0×10^{-3}
59.6	2.3	1.1×10^{-2}
62.2	2.3	3.8×10^{-2}
63.8	2.3	9.1×10^{-2}
66.3	0.09	6.0×10^{-1}
69.1	0.09	2.5
	3-Methyl-2-nitrophenol [j]	
80.8	5.5	2.7
	3-Methyl-4-nitrophenol [k]	
80.8	5.5	3.0
	3-Methyl-6-nitrophenol [h]	
80.8	5.5	2.9
	p-Cresol [l]	
56.1	5.5	2.1×10^{-3}
58.1	5.5	3.6×10^{-3}
60.8	5.5	1.28×10^{-2}
63.2	1.2—2.3	5.5×10^{-2}
66.1	0.38	3.0×10^{-1}
68.0	0.17	8.9×10^{-1}
70.4	0.09	4.3
72.6	0.09	19
	4-Methyl-2-nitrophenol [m]	
71.2	2.8	2.2×10^{-2}

[a] ±0.1%. [b] [Sulphamic acid] *ca.* 2—4 × 10^{-2} mol dm^{-3}. [c] [Substrate] *ca.* 1—2 × 10^{-4} mol dm^{-3}. [d] Measurement at 295 or 300 nm. [e] Measurement at 266 nm. [f] Measurement at 270 nm. [g] Measurement at 305 or 310 nm. [h] Measurement at 280 nm. [i] Measurement at 300, 305, or 310 nm. [j] Measurement at 273 nm. [k] Measurement at 278 nm. [l] Measurement at 286 nm. [m] Measurement at 258 nm, isosbestic point at 330 nm.

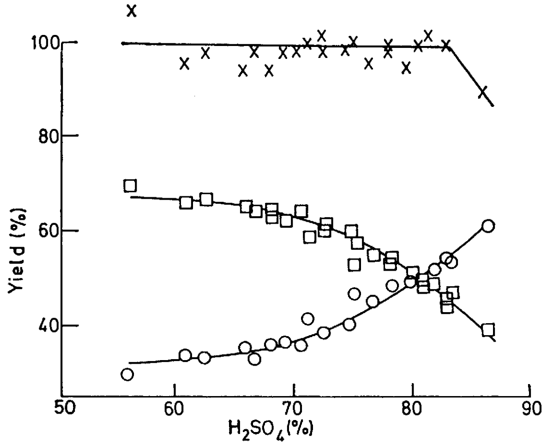


FIGURE 2 Nitration of phenol (□, *o*-nitrophenol; ○, *p*-nitrophenol; ×, total)

p-*Cresol*. When the nitration conditions used above were applied to this substrate, 4-methyl-2-nitrophenol was the sole product detected by g.l.c. and h.p.l.c. analysis under the conditions shown in Tables 1 and 2. Under these circumstances, however, the mass balance, although reproducible, varied over the range 52—100% in 60—80% sulphuric acid. That this was due to reaction involving the fortuitous presence of nitrous acid was confirmed by use of the more efficient nitrous acid trap sulphanilic acid, which was added to both nitric acid and substrate solutions. Under these reaction conditions the quantitative formation of 4-methyl-2-nitrophenol was found as recorded in Table 5. It was not

TABLE 4

First-order rate coefficients for the subsequent reaction of the intermediate formed in the nitration of *p*-cresol at 25.0 ± 0.2 °C [a,b]

H_2SO_4 (%)	$-H_0$	$10^2[HNO_3]$/ mol dm^{-3}	k_1/s^{-1}
67.9 [c]	5.50	5.5	9.8×10^{-4}
69.1 [d]	5.69	5.5	1.68×10^{-3}
71.2 [c]	6.00	1.2	3.4×10^{-3}
72.5 [d]	6.20	0.25	3.9×10^{-3}

[a] [Sulphamic acid] *ca.* 2—4 × 10^{-2} mol dm^{-3}. [b] Measurement at 380 nm. [c] [*p*-Cresol] = 1.23 × 10^{-3} mol dm^{-3}; 1 mm cell used. [d] [*p*-Cresol] = 1.23 × 10^{-4} mol dm^{-3}; 1 cm cell used.

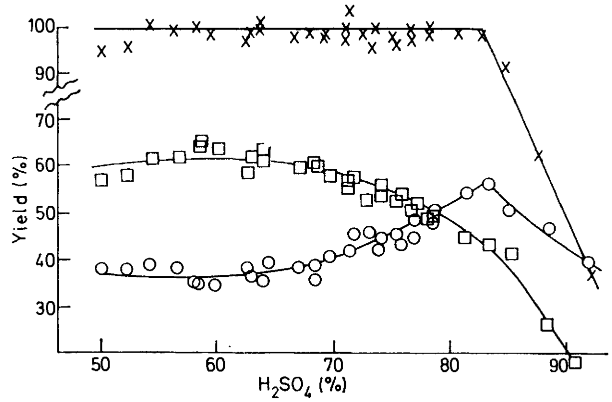


FIGURE 3 Nitration of *o*-cresol (○, 2-methyl-4-nitrophenol; □, 2-methyl-6-nitrophenol; ×, total)

possible to use sulphanilic acid in the u.v. studies of the intermediate species formed, as its absorption obscured the region of interest. Extrapolation of the kinetic plots for the disappearance of the intermediate species (which gave the results in Table 4) back to zero time enables estimates to be made of the proportions of 4-methyl-2-nitrophenol formed *via* the intermediate species and these are given in Table 6.

It was possible to construct the u.v. extinction curves appropriate to the intermediate from the initial spectra of the kinetic runs detailed in Table 4 by subtraction of the curve for 4-methyl-2-nitrophenol of the appropriate concentration. At both 67.9 and 71.2% sulphuric acid these had $\lambda_{max.}$ 240 ± 2 nm ($\varepsilon_{max.}$ *ca.* 10^4 mol^{-1} l cm^{-1}) but the value of $\varepsilon_{max.}$ was not constant over this narrow acidity range. A reasonable explanation of this difference is that it is due to the presence of a broad underlying absorption to

TABLE 5

Yields of nitro compounds from the nitration of phenol and the cresols in aqueous sulphuric acid at 25 °C

Compound	H_2SO_4 (%) [a]	Yield of products (%) Nitrophenols *o*	*p*	Mass balance (%)
Phenol [b]	56.1 [c,d]	70.6	29.4	107
	60.8 [c,d]	66.2	33.8	96
	62.5 [c,d]	66.8	33.2	98
	65.9 [c,d]	65.0	35.0	94
	66.6 [e,f]	64.2	33.8	98
	67.9 [g,d]	63.2		
	68.0 [c,d]	64.0	36.0	94
	70.3 [c,d]	64.2	35.8	98
	71.2 [e,f,h]	58.4	41.9	100
	72.5 [c,d]	61.3	38.6	102
	72.5 [e–g]	59.7	38.6	98
	74.6 [c,d]	59.7	40.3	99
	75.2 [e,f,h]	52.4	48.0	100
	75.2 [d,g,h]	57.0		
	76.6 [c,d,h]	54.8	45.2	96
	78.2 [c,d,h]	52.0	48.0	99
	78.2 [e,f,h]	52.7	46.8	99
	79.8 [c,d,h]	50.6	49.4	95
	80.8 [e,f,h]	47.3	52.7	100
	80.8 [g,d,h]	49.1		
	81.7 [c,d,h]	48.9	51.2	102
	82.8 [g,d,h]	45.8		
	83.8 [c,d,h]	46.7	53.3	100
	86.3 [c,d,h]	39.0	61.0	90
o-Cresol [b,f]		2-Methyl-6-nitrophenol	2-Methyl-4-nitrophenol [i]	
	49.8 [e]	56.2	38.3	95
	52.0 [e]	57.3	38.2	95
	53.9 [e]	60.8	39.6	100
	56.1 [e]	61.5	37.8	99
	58.1 [j]	64.7	35.2	100
	59.6 [e]	63.4	34.7	98
	62.4 [e]	58.4	38.3	97
	62.8 [j]	62.6	36.5	99
	63.6 [j]	64.5	35.4	100
	63.6 [e]	60.7	40.3	101
	66.6 [e]	59.7	38.2	98
	67.9 [e]	60.4	38.5	99
	69.1 [j]	61.7	36.1	98
	69.1 [e]	57.7	40.3	98
	70.8 [j]	57.5	42.3	100
	70.8 [e]	55.3	41.9	97
	71.1 [e,h]	57.5	45.8	103
	72.5 [e,h]	52.5	46.3	99
	73.5 [h,j]	53.6	42.7	96
	73.5 [e,h]	55.2	44.8	100
	75.2 [h,j]	52.5	45.8	98
	75.2 [e,h]	53.4	42.9	96
	76.6 [h,j]	51.4	44.1	95
	76.6 [e,h]	51.4	48.5	100
	78.2 [h,j]	49.6	49.2	99
	78.2 [e,h]	50.5	49.4	100
	80.8 [e,h]	45.1	53.9	99
	82.8 [e,h]	43.3	55.1	98
	84.6 [e,h]	41.4	50.1	91
	87.8 [e,h]	25.8	46.6	72
	91.3 [e,h]	18.1	38.9	57

TABLE 5 (*Continued*)

Compound	H_2SO_4 (%)	Yield of products (%) 3-Methyl-2-nitrophenol [k]	3-Methyl-4-nitrophenol [k]	3-Methyl-6-nitrophenol [k]	Mass balance (%)
m-Cresol [b,e,]	58.1	18.5	33.0	48.8	*100*
	59.6	19.5	33.1	46.6	99
	62.2	19.6	33.9	46.6	101
	63.8	18.9	33.2	46.3	100
	66.3	19.0	35.4	45.0	99
	68.5	15.3	35.9	46.7	100
	70.8	14.2	36.3	44.0	98
	73.4	13.3	38.1	43.8	95
	76.5	10.6	42.3	44.7	98
	77.6	12.8	44.5	39.9	97
	80.8	9.7	52.3	37.9	100
	82.8	8.0	40.6	35.2	83
	84.6	3.0	33.1	25.0	61
	87.8	1.6	18.2	12.4	32
p-Cresol [d,g,]			4-Methyl-2-nitrophenol [m]		
	56.1		100		
	58.1		100		
	60.8		101		
	62.5		100		
	64.3		99		
	66.6		99		
	67.9		101		
	71.2		99		
	72.5		99		
	75.2		99		
	76.6		100		
	78.2		99		
	80.8		86		
	81.7		81		
	84.6		58		
	87.8		51		
	91.3		32		

[a] $[HNO_3] = 2 \times 10^{-4}$—$5 \times 10^{-2}$ mol dm^{-3}. [b] [Sulphamic acid] *ca.* 2—4 × 10^{-2} mol dm^{-3}. [c] Dewar and Urch u.v. method (over 270—350 nm), yields of individual isomers normalized to 100%. [d] [ArH] *ca.* 1—2 × 10^{-4} mol dm^{-3}. [e] H.p.l.c. method. [f] $[ArH] = 4 \times 10^{-3}$ mol dm^{-3}. [g] G.l.c. method. [h] Equimolar proportions of ArH and HNO_3. [i] 2-Methyl-3- and -5-nitrophenols were not found (<0.2%). [j] Dewar and Urch u.v. method (over 270—390 nm). [k] 3-Methyl-5-nitrophenol was not found (<0.3%). [l] Sulphanilic acid (1×10^{-2} mol dm^{-3}) present in both the nitric acid and *p*-cresol solutions. [m] 4-Methyl-2-nitrophenol was the only product found; 0.2% of the 3-nitro isomer would have been detected by the h.p.l.c. analysis, which was carried out on selected reaction products.

TABLE 6

Proportions of 4-methyl-2-nitrophenol formed *via* the intermediate species in the nitration [a] of *p*-cresol in aqueous sulphuric acid at 25.0 ± 0.2 °C

H_2SO_4 (%)	Proportion (%)
67.9 [b]	45
69.1 [c]	43
71.2 [b]	41
72.5 [c]	39

[a] $[HNO_3] = 2.5 \times 10^{-3}$—$5.5 \times 10^{-2}$ mol dm^{-3}; [sulphamic acid] = 2×10^{-2} mol dm^{-3}. [b] [*p*-cresol] = 1.23×10^{-3} mol dm^{-3}. [c] [*p*-cresol] = 1.23×10^{-4} mol dm^{-3}.

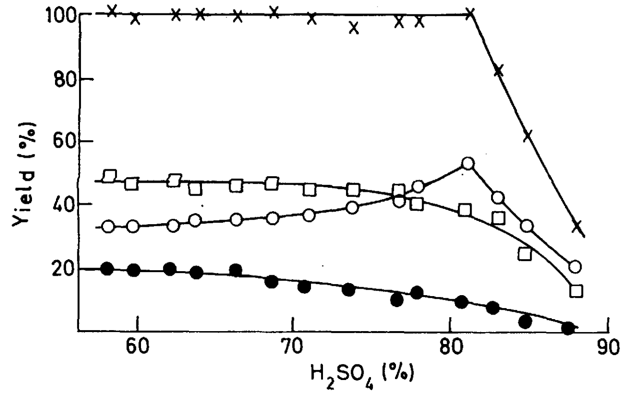


FIGURE 4 Nitration of *m*-cresol (●, 3-methyl-2-nitrophenol; ○, 3-methyl-4-nitrophenol; □, 3-methyl-6-nitrophenol; ×, total)

varying extents, associated with the fortuitous nitrosation which it has been found impossible to remove in the product studies using sulphamic acid.

Yields above 82—83% *Sulphuric Acid.*—In all cases where studies were pursued into this region the overall yield dropped giving a mass balance <100%.

o-*Methylanisole*. The products of nitration of this substrate were subject to an h.p.l.c. analysis (Table 2). 2-Methyl-6-nitrophenol was established as a product of the reaction although 2-methyl-4-nitrophenol was not detected and was not present to a greater extent than 0.1%. The yields of 2-methyl-6-nitrophenol are given in Table 7 together with yields of the methylnitroanisoles taken from the earlier study.[4] The mass balance given is the sum of the two sets of data. 2-Methyl-6-nitroanisole (3×10^{-3} mol dm^{-3}) was recovered essentially quantitatively (101%) from a solution in 58.1% sulphuric acid after 48 h at 25 °C.

TABLE 7

Yields of nitro compounds from the nitration [a] of *o*-methylanisole in aqueous sulphuric acid at 25 °C

	Yield of products (%)			
H_2SO_4 (%)	2-Methyl-6-nitrophenol [b]	2-Methyl-4-nitroanisole [c]	2-Methyl-6-nitroanisole [c]	Mass balance (%)
56.1	38.8	44	23	106
58.1	34.6	39	25	99
59.1	32.3	40	23	95
59.6	27.4	40	23	90
62.2	21.3	41	28	90

[a] [ArH] = 2.8×10^{-3} mol dm^{-3}; [HNO_3] = 2.3×10^{-2}—5.5×10^{-2} mol dm^{-3}; [sulphamic acid] = 2—4×10^{-2} mol dm^{-3}. [b] 2-Methyl-4-nitrophenol was not found (<0.1%). [c] Values from ref. 4.

DISCUSSION

Rate Profiles.—The behaviour of hydroxy and methoxy substituents in other electrophilic substitution reactions suggests that phenol and the cresols, in addition to anisole, should be reactive enough to be nitrated at the rate of encounter of the aromatic molecules with nitronium ions.

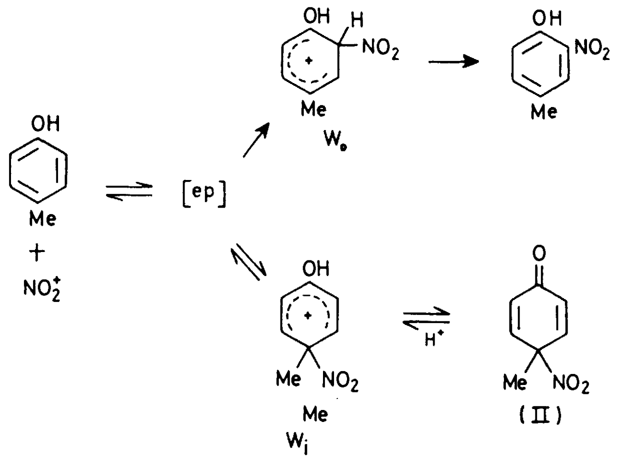
Mesitylene is typical of compounds which do react in this way, and the profile for anisole is almost parallel to that for mesitylene, and separated from it by a factor in rate of about two. The profiles for phenol and the cresols (Figure 1) lie between those for anisole and mesitylene and are of similar or slightly lower slope. A relatively small spread of observed rates of reaction of compounds sufficiently reactive to react at the encounter rate has been noted previously,[4,8] and the suggestion has been made that hydrogen bonding may be involved in some cases.[4] A point which may be usefully emphasized, however, is that the profiles of many of these reactive compounds have a significantly lower slope than those of less reactive compounds (*e.g.* benzene and the halogenobenzenes) where diffusion is not the rate-limiting step. This change in slope which has been attributed to the effect of changing viscosity of the medium on the limiting rate of encounter,[8] may provide a diagnostic test for substrates in the borderline region. For example, it seems to enable one to distinguish the behaviour of anisole, the profile of which is parallel to that of mesitylene and for which the reaction is encounter controlled, from that of toluene, for which the profile is parallel to that of benzene (in 63—68% sulphuric acid) and for which the reaction is not encounter controlled in this region. However, there are substrates (*e.g.* naphthalene) which are presumably encounter controlled and have steeper slopes, and an isotopic labelling experiment on the demethylative nitration of *p*-methylanisole has suggested that although the nitration of *p*-cresol occurs at the encounter limit in 71.3% sulphuric acid detectable return from the encounter pair occurs in 66.8% sulphuric acid.[20] We conclude that phenol and the cresols are reacting with the nitronium ion at or very near the rate of encounter.

Isomer Proportions.—In 56—83% sulphuric acid phenol is quantitatively mononitrated, and the *o* : *p* ratio varies from 2.1 to 0.88 (Table 5 and Figure 2), with the % of *para* substitution increasing from 30 to 53%. This behaviour is closely similar to that previously reported[4] for anisole, where the proportion of *para* substitution increased from 36 to 56%. A similar pattern also emerges for *o*- and *m*-cresols (Table 5 and Figures 3 and 4). For *o*-cresol the 6-nitro : 4-nitro product ratio changes from 1.5 to 0.8 over 50—83% sulphuric acid, and the proportion of substitution *para* to the hydroxy group increases from 38 to 55%, although the value is more constant over the range 50—68% sulphuric acid. In the case of *m*-cresol, where two products of *ortho*-substitution are observed, the proportion of *para*-substitution increases from 33 to 52% over the range 58—81% sulphuric acid.

Phenol is a molecule expected to be of similar reactivity to anisole and so, as the molecule is also susceptible to hydrogen-bonding interaction, the similarity in behaviour is not unexpected. In the cases of *o*- and *m*-cresol, however, the substrates have been activated to electrophilic substitution by the methyl group oriented either *meta* or *ortho* and *para* respectively to the position where substitution occurs. If the mechanism proposed in Scheme 1 is applicable to these substrates, it might be expected that the increased reactivity would lead to W formation competing more effectively with loss of the hydrogen-bonded hydronium ion. It would, therefore, be expected that isomer ratios resulting from reaction of the hydrogen-bonded encounter pair would persist to lower acidities the more activated the substrate, and that the acidity range where changes of isomer ratio occurred would also move to lower values of acidity. The picture that emerges, however, is of a qualitatively similar change in isomer ratios over the same range of acidity for anisole, phenol, and *o*- and *m*-cresol. These changes are much larger than those usually present for the nitration of alkylbenzenes (*e.g.* toluene,[3] ethylbenzene,[21] *o*-diethylbenzene [22]), although *o*-xylene is anomalous in this regard, and appear to require a special explanation.[3,22] If the mechanism of Scheme 1 is indeed applicable to these systems it follows that the increased reactivity to electrophilic substitution conferred by the additional methyl group has had an effect which is too small to be detected. This could be consistent with the observation that the region of isomer ratio change has only shifted marginally to lower acidities in the case of the comparison between 3,5-dimethylanisole and anisole in perchloric acid.[5] The effect of the substituents on the rate of loss of the hydrogen bond may be relevant to this conclusion and it is also conceivable that an equilibrium is set up between the two encounter pairs of Scheme 1.

This observation of a general medium effect on the isomer ratios from the nitration of hydroxy- and methoxy-substituted compounds of this type is, however, apparently at variance with the earlier results on the nitration of *p*-methylanisole.[4] In this case the ratio of substitution *para* to the methoxy group to that *ortho* was approximately constant over the range 46—80% sulphuric acid (see Figure 4 in ref. 4). However, *para*-substitution (*ipso* to C–Me) was measured by the amount of a demethylated product formed (see Scheme 3 in ref. 4), and in the region 80—82% sulphuric acid this fell rapidly, to be replaced by the *ortho*-substituted product, presumably as the rate of demethoxylation failed to compete effectively with the return of the *ipso*-substituted W to the encounter pair. This effect may, however, occur over a wider range of acidity and over the range *ca.* 70—80% sulphuric acid the amount of demethylated product may be progressively lowered to be replaced by the *ortho*-substituted product. This trend would be the opposite of that expected by the general medium effect described above and it is possible that the combination of the two phenomena gives fortuitously an approximately constant ratio of the two products.

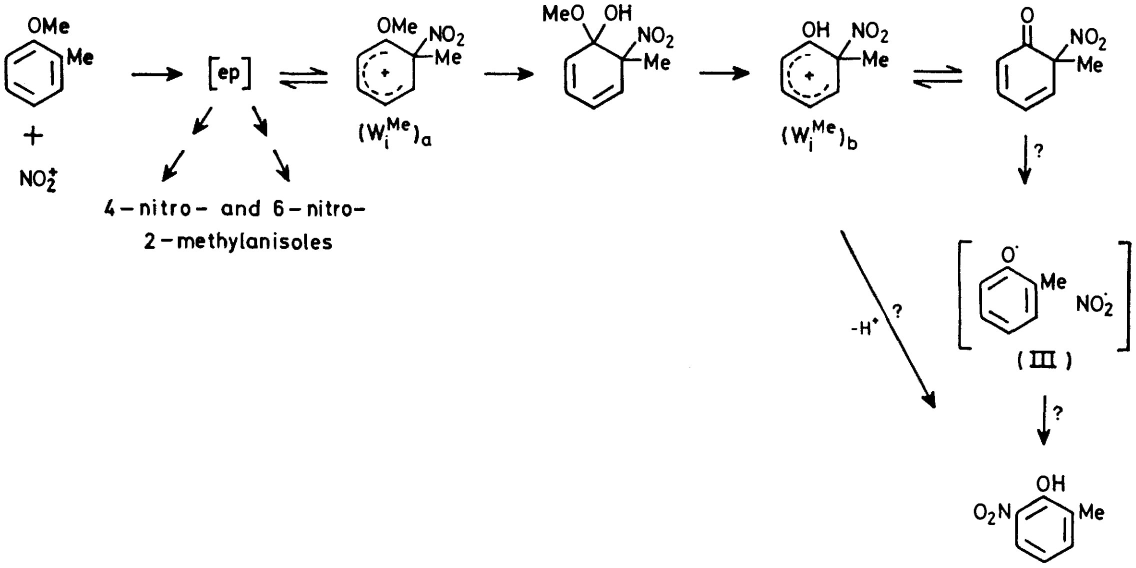
The studies of the nitration of *p*-cresol indicate that in the absence of nitrous acid catalysis the final product of reaction is 4-methyl-2-nitrophenol, but that this is formed by two routes, either directly (*via* W_0, Scheme 3) or *via* an acid catalysed reaction of an intermediate species. The intermediate, $\lambda_{max.}$ 240 ± 2 nm ($\varepsilon_{max.}$ *ca.* 10^4 mol^{-1} l cm^{-1}), was formed to the extent of 39—45% in the initial nitration reaction (Table 6). Consideration of the u.v. spectrum [*cf.* 220 nm ($\varepsilon_{max.}$ 15 700 mol^{-1} l cm^{-1}) for (II) in trifluoroethanol;[13] 241—251 nm ($\varepsilon_{max.}$ *ca.* 10^4 mol^{-1} l cm^{-1}) for alkyl-substituted analogues in cyclohexene [9]] and of the results of the recent studies of the nitration of *para*-substituted toluenes[13,14] indicate that the intermediate species is 4-methyl-4-nitrocyclohexadienone (II), formed by *ipso*-attack at C–Me (see Scheme 3). The acidity dependence of the rate of conversion of (II) into 4-methyl-2-nitrophenol implies that the rate-limiting stage involves reaction of the protonated cyclohexadienone (W_i^{Me}). This reaction contrasts with that of the unprotonated species (II) established [14] in less acidic media (Scheme 2). We suggest that this faster reaction of the protonated species involves rate-limiting reversion to the encounter pair, with heterolytic fission of the C–N bond of W_i^{Me}, and subsequent fast W_0 formation and proton loss. Consideration of homolytic fission of the C–N bond of W_i^{Me} would be tantamount to a discussion of the possibility of complete electron transfer being involved in the ' encounter pair ' structure. This is a suggestion [23] for which we can see no compelling evidence. We conclude that the rearrangement of (II) *via* W_i^{Me} supplants the dissociation–recombination mechanism from the unprotonated (II) in sufficiently acidic media.



SCHEME 3

This mechanism for the conversion of W_i^{Me} into 4-methyl-2-nitrophenol has been postulated previously,[4,20] for the demethylative nitration of *p*-methylanisole, and so (II) should also be observed as an intermediate in this reaction. The evidence presented in the results section shows that indeed this is so, and that the rate of decomposition of the intermediate (II) formed in this way is acceptably close to that of (II) formed in the nitration of *p*-cresol. In the earlier study the u.v. absorption due to (II) had been obscured by the sulphanilic acid used as the nitrous acid trap.

The pattern of products from *o*-cresol contrasts with that from *o*-methylanisole (Table 3 and Figure 3 of ref. 4), where the total yield of nitro compounds was not quantitative in media below 70% sulphuric acid. In both cases *ipso*-substitution at C–Me is to be expected. The reinvestigation of the nitration of *o*-methylanisole establishes that 2-methyl-6-nitrophenol, but not the 4-nitro isomer, is an additional product of the reaction. With the recognition of this product the yields become reasonably quantitative (Table 7). Demethylation prior to nitration seems unlikely and is ruled out by the absence of the 4-nitro isomer, which would have been formed from *o*-cresol. The previous observation that 2-methyl-6-nitroanisole is stable for the duration of a nitration experiment was also confirmed. It is suggested then, that this demethylation is the consequence of *ipso*-substitution at C–Me (Scheme 4). This forms $(\mathrm{W_i^{Me}})_a$ which is captured by water at low acidities to form $(\mathrm{W_i^{Me}})_b$, protonated 2-methyl-2-nitrocyclohexadienone, by demethoxylation. The pathway by which the 2-methyl-6-nitrophenol is then formed is speculative. Heterolytic fission of the C–N bond in $(\mathrm{W_i^{Me}})_b$ to form an *o*-cresol–nitronium ion encounter pair can be ruled out as some 2-methyl-4-nitrophenol would then be formed. Any postulated heterolytic route must involve a specific 1,3-rearrangement. Homolytic fission in the unprotonated 2-methyl-2-nitrocyclohexadienone to give (III) (see Scheme 4) is another possibility to be considered, and it may be that the specific 1,3-rearrangement of the nitro group to the 6-position is associated with the presence of the oxygen substituent facilitating the process, perhaps by involving phenyl nitrate as an intermediate.



Scheme 4

Either of these mechanisms imply that a significant but unquantified amount of the 2-methyl-6-nitrophenol formed during the nitration of *o*-cresol itself, in at least up to 70% sulphuric acid, involves *ipso*-substitution at C–Me, proton loss, and rearrangement.

If the fate of $(\mathrm{W_i^{Me}})_a$, when demethoxylation does not occur, is to return to the encounter pair, then the ratio of 2-methyl-6-nitroanisole to the 4-nitro isomer does not vary in the way expected from the general medium effect on these compounds. However, if it is assumed that *ipso*-substitution can only result in demethoxylation or the formation of 2-methyl-6-nitroanisole, then the behaviour of the substrate is quite similar to that of anisole, phenol, and *o*- and *m*-cresol; the proportion of *para*-substitution, for example, increases from 39 to 57% in from 58 to 80% sulphuric acid, although the changes seem displaced a little to lower acidity. The similarity suggests that the consequence of *ipso*-substitution, in the absence of demethoxylation, may be the formation of 2-methyl-6-nitroanisole, by another specific and unusual rearrangement. In contrast to the rearrangement of the demethylated compound, reaction of a cyclohexadienone species is not possible here, and these considerations may strengthen the possibility that the formation of 2-methyl-6-nitrophenol involves a specific heterolytic process.

It is noteworthy that nucleophilic trapping of *ipso*-Ws in any of these compounds leading to other than demethoxylated products has not been observed. This contrasts with the situation for alkylated benzenes.

As before a drop in total yield in above *ca.* 82% sulphuric acid occurs for all substrates studied in this region. In the case of anisole, dinitration was shown to be only partly responsible for this,[4] and in the cases of phenol and *o*- and *m*-cresol, where the mononitration products are less reactive than those of anisole, this is presumably also the case. 4-Methyl-2-nitrophenol is, however, nitrated about ten times faster than the nitroanisoles. The redetermined 'zeroth-order' rates of nitration for reactive compounds at high acidities [24] do not alter significantly the calculations [4] which suggest that nitration is very much faster than sulphonation under the reaction conditions. Most of the lowered yields at high acidity therefore remain unaccounted for.

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