Electrophilic Aromatic Substitution. Part 28.[1] The Mechanism of Nitration of Some 4-Substituted Anisoles and Phenols, and of Rearrangement of the Intermediate 4-Nitro-4-substituted-cyclohexa-2,5-dienones

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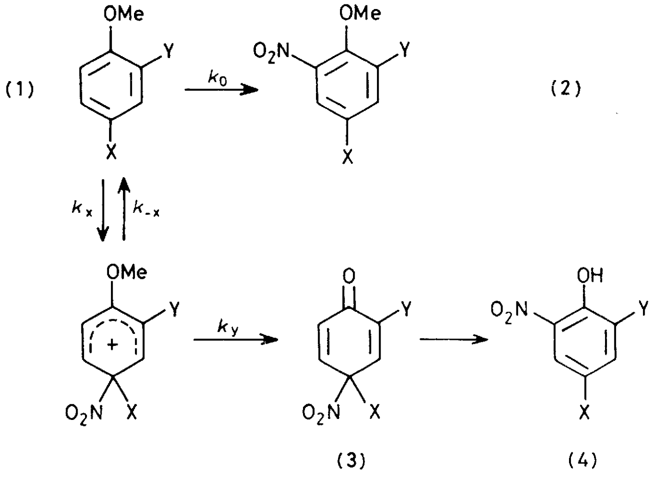
The kinetics of nitration in sulphuric acid of 2-chloro-4-methyl-, 4-chloro-, 2,4-dichloro-, and 4-fluoro-anisole and of the corresponding phenols have been determined. The reaction products from the anisoles and from 2-chloro-4-methyl- and 4-fluoro-phenol have been determined. Results for 4-methylanisole supplementary to earlier ones are also reported. Generally the anisoles give the 2-nitro-derivatives and the 2-nitrophenols, and from 2-chloro-4-methylanisole, 2-chloro-4-methyl-4-nitrocyclohexa-2,5-dienone was formed as an intermediate. The decomposition of this dienone in sulphuric acid, like those of others, changes from a non-acid-catalysed to an acid-catalysed form with increasing acidity. The first form is regarded as a decomposition into an aryloxyl radical and nitrogen dioxide which can recombine to give the 2-nitrophenol. The formation of a small amount of 2-(4-fluorophenoxy)-4-fluorophenol in the nitration of 4-fluorophenol is seen as support for this view. The acid-catalysed form is regarded as the decomposition of the protonated dienone into a phenol–nitronium ion encounter-pair which can give the nitrophenol. A consequence of the mechanism is that if the phenol were nitrated at less than the encounter rate, the phenol itself would in appropriate conditions be a product of the *ipso*-nitration of the original anisole. 4-Methyl-, 2-chloro-4-methyl-, and 4-chloro-phenol have been so identified. Quantitative analysis of the results allows evaluation of the partitioning of dienone decomposition between the two modes. The mechanism accounts for the formation from 2,4-dichloro-anisole of both 2,4-dichloro-6- and 2,4-dichloro-5-nitroanisole, but only 2,4-dichloro-6-nitrophenol.

Nitration of *para*-substituted anisoles can give rise to nitrophenols;[2] thus (1a) gives a mixture of (2a) and (4a).[3] (1c) Behaves similarly.[4] The phenolic products arise from *ipso*-attack, demethoxylation to give the dienone intermediate (3) in equilibrium with its conjugate acid, and rearrangement (Scheme 1). In order to gain more information about this reaction, and particularly about the rearrangement step (3) ⟶ (4), we studied the kinetics and products of nitration in aqueous sulphuric acid of the anisoles (1a—f) and of the corresponding phenols (5a—f).

The dienone (3a) has been shown to rearrange to the nitrophenol (4a) in a number of solvents by a radical mechanism.[5] A change in mechanism with increasing acidity is indicated by the onset of acid catalysis at the acidity represented by 60% H_2SO_4.[6,7] This acid-catalysed reaction might occur as in Scheme 2 through dissociation of the conjugate acid of the dienone into a solvent-caged pair (e.p.) of the phenol (5) and nitronium ion. It is possible to estimate approximately the extent of leakage from such a pair [which is the same as the encounter pair formed in the nitration of (5)] because it is related to the closeness of the rate coefficient for nitration of (5) to the rate coefficient for an encounter controlled nitration in the same medium.[8,9] The extent of leakage is measurable because it leads to the formation of (5) in the nitration of (1), either as an intermediate (when nitric acid is taken in excess) or as a product [when the anisole (1) is taken in excess and can act as a scavenger for nitronium ion formed through leakage]. Taken together, these observations can therefore lead to an estimate of the fraction of the rearrangement of the dienone (3) which takes place *via* the nitronium ion–phenol encounter pair. Such studies are described in this paper.

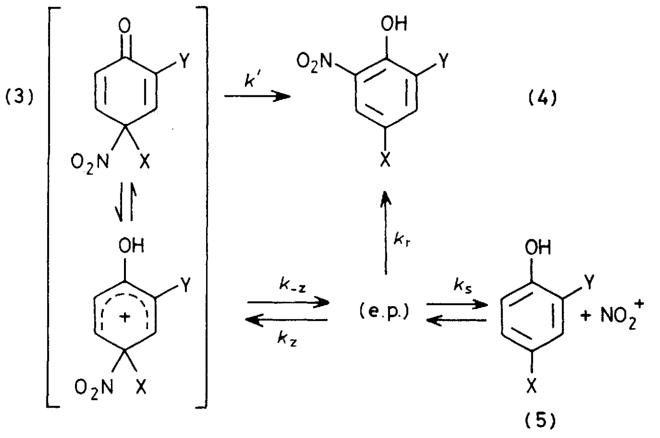


a; X = Me, Y = H
b; X = Me, Y = Cl
c; X = Cl, Y = H
d; X = Y = Cl
e; X = F, Y = H
f; X = F, Y = D

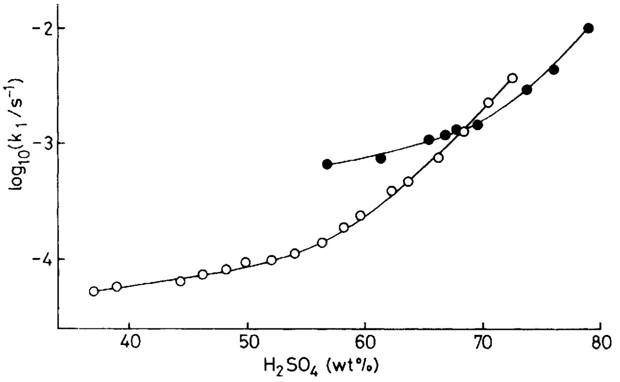
Scheme 1

Results

Kinetics.—Second-order rate coefficients for nitration, $k_{2obs.}$, in aqueous sulphuric acid are in Table 1. In the nitration of (1b) and (5b) an intermediate was detectable spectroscopically. It was possible by suitable choice of conditions and method of observation to obtain rate coefficients both for nitration, and for further reaction of the intermediate. The disappearance of (1b) due to nitration was followed by g.c. analysis of quenched and extracted samples. Rate coefficients for nitration of (5b) were obtained spectrophotometrically, either using concentrations of nitric acid which were low enough for formation of the intermediate to be much



Scheme 2



The kinetics of decomposition of cyclohexadienones (3) in sulphuric acid: ○, (3a); ●, (3b)

slower than its further reaction, or making use of the isosbestic point (263 nm) between intermediate and product.

Rate coefficients, k_1, for the further reaction of the intermediate formed in the nitration of (5b) in 65—75% H_2SO_4 were obtained using relatively high concentrations of nitric acid. Under these conditions the formation of the intermediate was much faster than its decomposition; the slow change in absorbance which followed the fast initial change was monitored. Values of k_1 are in Table 2. The rate coefficients for further reaction of the intermediate formed in the nitration of (1b) in 66.7 and 68.1% H_2SO_4 were measured in the same way and are closely similar (Table 2) in accord with the conclusion [drawn by analogy with the reaction of (1a) and (5a) [6]] that the same intermediate (3b) is present in both reactions. Its further reaction, as the product studies below confirm, is largely but not entirely rearrangement to give (4b).

To avoid problems with dinitration, values of k_1 for rearrangement of (3b) in >75% H_2SO_4 were obtained taking (5b) in excess over nitric acid. Extending the rate profile to acidities lower than that represented by 65% H_2SO_4 also presented problems; it was not possible to achieve nitric acid concentrations high enough for the initial nitration step to be comparatively fast. The intermediate was therefore preformed in 70—74% H_2SO_4 and the acid was then diluted to the required acidity. Rate profiles for rearrangement of (3a) [7] and (3b) are compared in the Figure.

We were unable spectroscopically to detect dienones (3c—e) in the nitration of (1c—e) and (5c—e). However their intermediacy may be inferred from the product studies described below. Presumably the ratio of first-order rate constants for formation and decomposition of these intermediates was always small.

Table 1. Rate coefficients $k_{2obs.}$ for nitration in aqueous sulphuric acid [a] at 25 °C

Substrate [b] (λ/nm) [c]	Acid (%)	10^3 [HNO_3]/mol dm^{-3}	$k_{2obs.}$/dm^3 mol^{-1} s^{-1}
(1b) (g.c.) [d]	68.1	1.2—26 [d]	0.40
(5b) (360)	58.9 [e]	27.2	2.1×10^{-3}
	66.7 [e]	0.132	0.186
	71.4 [e]	0.082	7.1
	73.5 [f]	0.49	51
(1c) (360)	61.5	150	3.4×10^{-3}
	62.6	180	7.2×10^{-3}
	64.3	190	2.0×10^{-2}
	66.5	60	8.4×10^{-2}
	69.1	6.7	0.46
	70.2	5.0	1.10
	72.4	0.85	8.5
(5c) (370)	60.3	200	3.4×10^{-3}
	62.6	200	1.2×10^{-2}
	64.3	47	3.2×10^{-2}
	66.2	11	1.5×10^{-1}
	67.3	1.3	2.4×10^{-1}
	70.0	2.2	1.7
	70.3	4.4	2.2
(1d) (350)	64.3	190	7.0×10^{-4}
	67.3	130	7.6×10^{-3}
	70.0	54	6.6×10^{-2}
(5d) (370)	62.6	200	1.1×10^{-3}
	64.3	180	3.3×10^{-3}
	66.2	110	1.3×10^{-2}
	67.3	130	2.6×10^{-2}
	70.0	24	0.190
	70.3	45	0.28
	72.6	4.9	1.20
	73.9	4.2	4.4
(1e) (350)	60.2	20	1.60×10^{-3}
	62.0	18.3	5.6×10^{-3}
	64.8	21	3.6×10^{-2}
	67.1	16.4	0.126
	71.0	6.7	2.5
	72.5	3.2	7.1
	75.4	0.26	112
(5e) (340)	62.6	64	1.22×10^{-2}
	68.8	14.6	0.68
	72.2	3.0	7.9
	75.8	0.23	110

[a] Containing sulphanilic acid as a nitrous trap, $(0.3—2) \times 10^{-2}$ mol dm^{-3}. [b] Substrate concentration *ca.* 2×10^{-4} mol dm^{-3} unless otherwise indicated. [c] Wavelength used for observation, unless otherwise indicated. [d] This substrate only was studied by g.c. analysis for unchanged substrate of six samples left for various extents of reaction. [e] Substrate concentration *ca.* 1×10^{-5} mol dm^{-3}. [f] Substrate concentration 3.8×10^{-5} mol dm^{-3}. λ 263 nm.

Products of Nitration of (1a).—Our results were obtained taking aromatic in excess, and supplement those previously reported [6] where nitric acid was taken in excess. Yields are compared in Table 3. The sum of the yields of the two nitro-compounds (2a) + (4a) (based on the nitric acid used) is again within experimental error quantitative, but relatively more (2a) is formed and some (5a) is also formed. These observations are in agreement with the conclusion drawn from (intrinsically less accurate) studies of oxygen isotope uptake [4] that the acid catalysed rearrangement of (3a) takes place in whole or in part through a *p*-cresol–nitronium ion encounter pair (e.p. in Scheme 2) from which

Table 2. Rate coefficients k_1 for rearrangement of dienone (3b) in sulphuric acid [a] at 25 °C

Acid (%)	10^3 [Ar] [b] / mol dm^{-3}	10^3 [HNO_3] [a] / mol dm^{-3}	10^3 k_1/s^{-1}	100 (A_∞ − A_1)/A_∞ [c]
56.8 [d]	0.093	3.5	1.08	
61.3 [d]	0.098	1.21	1.19	
65.4	0.125	200	1.60	50
66.7	0.142 [e]	177	1.90	
66.7	0.095	180	1.80	48
68.1	0.125 [e]	200	2.2	
68.1	0.125	200	2.2	48
69.5	0.125	70	2.3	50
71.4	0.125	13.0	3.8	46
71.4	0.125	30	3.8	
73.7	0.025	12.0	4.6	43
76.0	0.025	1.01	6.3	40
78.9	0.125	0.020	17	

[a] Containing sulphanilic acid as a nitrous trap, (2—6) × 10^{-2} mol dm^{-3}. Measurements at 320 nm unless otherwise indicated. [b] The aromatic substrate was (5b) unless otherwise indicated. [c] Approximately the percentage of initial *ipso*-attack. See text. [d] Reaction started in 70—74% H_2SO_4. See text. [e] The aromatic substrate was (1b).

there is some leakage. Any such leakage should lead to competitive reaction of (1a) and (5a) with the nitronium ion. In view of the similar reactivities [6] and vastly different concentrations {[(5a)]/[(1a)] goes from 0 to *ca.* 0.03 as reaction proceeds}, further reaction of (5a) in this way can be neglected.

Products of Nitration of (1b) *and* (5b).—Nitration of (1b) with nitric acid in excess gave (2b) and (4b) (Table 4); the phenolic product was the major one. In these experiments, products were extracted after >10 half-lives for nitration and usually >10 half-lives for further reaction of the dienone (3b). Yields were less than quantitative. In one case the products were extracted after 10 half-lives for nitration but before significant decomposition of (3b). In this case only, a quantitative yield was obtained. It is likely that (3b), like [5] (3a), is unstable and rearranges to (4b) in the dichloromethane extract, during the concentration of the latter prior to g.c. analysis. It appears therefore that allowing the rearrangement of (3b) to proceed in sulphuric acid leads to some loss of yield. [The very low yields at the highest acidities, *viz.* 78.9 and 83.5% H_2SO_4 (Table 4) cannot be so explained. Loss of total yield in nitration of anisoles at high acidities is a general feature [3] which has been discussed.[6]]

Nitration of (5b) gives (4b) as the only detected product, but again in less than quantitative yield (Table 4). Some of the product arises from direct nitration, and some *via* (3b) and its rearrangement. The percentage which arises *via* (3b) is given by (A_∞ − A_1)/A_∞ (Table 2). A_1 is the absorbance at the end of the fast initial change, and A_∞ the final absorbance, at a wavelength at which only the product absorbs and under conditions where formation of the intermediate is much faster than its further reaction. This represents the percentage of initial *ipso*-attack in (5b), and in view of the less than quantitative overall yield, can only be regarded as approximate. It can be compared with the yield of (4b) in the nitration of (1b) (Table 4) which is a minimum value for the percentage of initial *ipso*-attack in (1b). *ipso*-Attack appears to be somewhat more prevalent in (1b) than in (5b).

Nitration of (1b) with aromatic in excess gave (2b) and (4b), in less than quantitative yield based on the nitric acid used. Some (5b) was formed.

Table 3. Yields [a] of products from the nitration of (1a) in sulphuric acid [b] at 25 °C

Acid (%)	Yields (%) [c] with [Ar] in excess			Yields (%) [d] with [HNO_3] in excess	
	(2a)	(4a)	(5a)	(2a)	(4a)
64.5	68.8 [e]	31.2 [e]	8.1 [e]	63.0	35.0
67.1	67.8	32.5	8.2	64.5	36.0
78.9	73.0	28.4	7.3	64.5	37.5

[a] ±2%. [b] [Sulphanilic acid] 2 × 10^{-2} mol dm^{-3}. [c] [Ar] 1.1 × 10^{-3} mol dm^{-3}, in tenfold excess of [HNO_3]. Yields based on HNO_3. [d] From ref. 6. [e] Reaction quenched after three half-lives; reported yields were obtained from the observed values by division by 0.87.

Products from the Nitration of (1c).—The yield (2c) + (4c) was quantitative (Table 5) when nitric acid was taken in excess, and the ratio (2c) : (4c) increased markedly with acidity. When the aromatic compound was in excess, (5c) was an additional product. It was necessary to use very low aromatic concentrations (<10^{-3} mol dm^{-3}) in these experiments, because higher concentrations led to loss in relative yield of (5c) probably for reasons of low solubility. Reaction times were therefore inconveniently long, and except at the highest acidity studied reaction was quenched before completion. It was not thought worthwhile to conduct product studies from runs with aromatic in excess at acidities higher than that represented by 70% H_2SO_4, because yields of phenolic products were very low (Table 5). (5c) Was detected as an intermediate during the nitration of (1c) with nitric acid taken in excess (Table 6).

Products from the Nitration of (1d).—Low solubility precluded experiments in which the aromatic compound was taken in excess. With nitric acid in excess no (5d) could be detected as an intermediate. Products were (2d), (4d), and 2,4-dichloro-5-nitroanisole, in quantitative yield (Table 7).

Products from the Nitration of (1e) *and* (5e).—No (5e) could be detected as an intermediate or as a product in the nitration of (1e). The yield (2e) + (4e) was quantitative (Table 8). (5e) Gave (4e) approximately quantitatively, but when aromatic was taken in excess there was formed also a small amount of an additional product (probably <2%), shown by g.c.m.s. to be a ' dimeric ' species, molar mass corresponding to $(FC_6H_3OH)_2$. This was shown by comparison with an authentic sample to be 2-(4-fluorophenoxy)-4-fluorophenol.

Products from the Nitration of (1f).—The observation [10] that proton loss from the 2-position is rate determining under certain conditions in the similar rearrangement (6) ⟶ (7) led us to seek a product isotope effect in the rearrangement of (3f). The phenolic products from the nitration of (1f) arise solely from (3f), as in Scheme 1. As described in the Experimental section after correction for the small but not negligible extent of proton exchange prior to nitration, the product isotope effects in Table 9 were obtained. The small, inverse, isotope effect is just outside experimental error. There is no primary kinetic isotope effect in the rearrangement, showing that proton loss is not rate-determining.

Discussion

We discuss first the evidence concerning the mechanism for the rearrangement of the dienone (3). In Scheme 2 a mechanism is put forward in which the dienone proceeds *via* its conjugate

Table 4. Yields [a] of products from the nitration of (1b) and (5b) in sulphuric acid [b] at 25 °C

Substrate	Acid (%)	Yields (%) [c] with [Ar] in excess			Yields (%) [d] with $[HNO_3]$ in excess		Total yield (%)
		(2b)	(4b)	(5b)	(2b)	(4b)	
(1b)	58.9				20.7	70.6	91.3
	64.3				20.2	72.8	93.0
	68.1				20.5	70.4	90.9
	68.1 [e]				21.9	77.9	99.8
	69.2	24.4	68.4	12.1			92.8
	71.4				20.0	69.7	89.7
	73.7				20.2	68.7	88.9
	75.5				21.0	65.5	86.5
	76.4	27.4	63.8	12.2			91.2
	78.9 [f]				24.3	42.3	66.6
	83.5 [f]				30.8	3.8	31.6
(5b)	58.9					91.4	91.4
	68.1					91.1	91.1
	73.7					92.6	92.6

[a] ±2%. [b] [Sulphanilic acid] 2×10^{-2} mol dm^{-3}. [c] [Ar] 2.4×10^{-4} mol dm^{-3} in ten-fold excess of $[HNO_3]$. Yields based on HNO_3. [d] [Ar] 2×10^{-4} mol dm^{-3}, $[HNO_3]$ at least ten-fold larger unless otherwise stated. [e] $[HNO_3]$ 0.2 mol dm^{-3}. Reaction quenched before decomposition of the dienone. [f] Equimolar conditions, [Ar] = $[HNO_3]$.

Table 5. Yields [a] of products from the nitration of (1c) in sulphuric acid [b] at 25 °C

Acid (%)	Yields (%) [c] with [Ar] in excess			Yields (%) [d] with $[HNO_3]$ in excess		Total yield (%)
	(2c)	(4c)	(5c)	(2c)	(4c)	
57.6				59.0	39.4	98.5
60.3				59.6	39.8	99.4
62.6				61.8	37.9	99.7
63.7	65.4 [e]	28.0 [e]	9.2 [e]			93.4 [g]
64.3				63.1	36.5	99.6
66.1	53.2 [e]	22.8 [e]	6.2 [e]			76.0 [g]
66.1	58.5 [f]	24.6 [f]	7.5 [f]			83.1 [g]
67.3				69.2	29.2	98.4
70.0	83.4	17.5	5.4			101 [g]
70.5				79.3	19.8	99.1
73.9				90.2	9.6	99.8
76.4				95.2	4.0	99.2
78.4				98.0	2.1	100.1
80.3				98.9	0.6	99.5
83.1				90.0	0.1	90.1

[a] ±2%. [b] [Sulphanilic acid] 10^{-2} mol dm^{-3}. [c] [Ar] $(0.5—1) \times 10^{-3}$ mol dm^{-3}, in at least eight-fold excess of $[HNO_3]$. Yields based on $[HNO_3]$. Reaction quenched after at least 10 half-lives unless otherwise stated. [d] [Ar] $1—5 \times 10^{-4}$ mol dm^{-3}, $[HNO_3]$ at least eight-fold larger, reaction quenched after at least 10 half-lives, unless otherwise stated. [e] Reaction quenched after one half-life; observed yields have therefore been doubled. [f] Reaction quenched after three half-lives; observed yields have therefore been divided by 0.87. [g] Total yield of nitro-compounds.

Table 6. The detection of (5c) as an intermediate in the nitration of (1c) in sulphuric acid at 25 °C

Acid (%)	10^3 [Ar] / mol dm^{-3}	10^3 $[HNO_3]$ / mol dm^{-3}	Extent of reaction (%)	Yield (%) [a] of (5c)
61.5	0.46	103	19	0.9
61.5	0.46	103	35	1.4
61.5	0.46	103	47	1.7
63.7	0.45	64	51	2.1
66.2	0.45	15	50	2.1
67.3	0.45	15	50	1.8

[a] Based on initial aromatic concentration.

Table 7. Yields [a] of products from the nitration of (1d) in sulphuric acid [b] at 25 °C

Acid (%)	Yields (%)			
	(2d)	(4d)	2,4-Dichloro-5-nitroanisole	Total yield (%)
61.5	29.6	67.6	1.2	98.4
64.5	38.7	58.1	1.9	98.7
67.1	48.5	48.9	3.6	101.0
71.4	70.5	26.1	5.8	102.4
76.2	78.8	10.0	9.1	97.9
83.2	85.7	0.0	12.1	97.8

[a] ±2%. Normalised for any unreacted starting material. [b] [Sulphanilic acid] 2×10^{-2} mol dm^{-3}; [Ar] 1×10^{-4} mol dm^{-3}; $[HNO_3]$ in at least ten-fold excess over [Ar].

acid to the encounter pair (e.p.) of substituted phenol (5) and nitronium ion. The encounter pair may 'leak' to give (5), or produce the nitrophenol (4). Kinetic analysis permits an estimate to be made of the extent of the leakage.

The conventional experimental second-order rate coefficient for the nitration of phenol (5) is defined by $k_2{}^5{}_{obs.}$ = Rate/[(5)]$[HNO_3]$. A similar definition applies for each of the coefficients $k_2{}^1{}_{obs.}$ and $k_2{}^M{}_{obs.}$, relating to the anisole (1) and to mesitylene, respectively. The nitration of mesitylene is thought to be entirely encounter-controlled.[8]

The fraction, f, of the encounter pair which leaks is related to the closeness of the rate constant for the nitration of (5) to the rate constant for encounter-controlled nitration in the same medium. If the nitration of (5) were wholly encounter-controlled then there would be no leakage ($f = 0$). Otherwise, and assuming that the rate constants for the diffusion steps, (5) meets nitronium ion and mesitylene meets nitronium ion, are equal, then f is given by equation (1).

$$f = 1 - (k_2{}^5{}_{obs.}/k_2{}^M{}_{obs.}) \qquad (1)$$

Application of the steady-state approximation to [(3)] and [e.p.] in Scheme 2 shows that f is defined by equation (2).

$$f = k_s/[k_s + k_r + \{k'k_z/(k' + k_z)\}] \qquad (2)$$

Table 8. Yields [a] of products from the nitration of (1e) and (5e) in sulphuric acid [b] at 25 °C

Substrate	Acid (%)	Yields (%) (2e)	Yields (%) (4e)	Total yield (%)
(1e) [c]	57.5	78.8	20.7	99.5
	60.2	78.0	20.5	98.5
	64.8	76.2	23.1	99.3
	67.1	78.9 [d]	21.1 [d]	100.0 [d]
	70.9	77.4	22.2	99.4
	72.5	77.7	22.5	100.2
	73.7	78.4 [d]	22.9 [d]	101.3 [d]
	75.4	78.4	22.1	100.5
	75.5	77.8 [d]	21.1 [d]	98.9 [d]
	78.4	81.0 [e]	21.0 [e]	102.0 [e]
	83.1	90.9 [e]	6.7 [e]	97.6 [e]
(5e)	62.6		99.6	99.6
	68.8		98.7	98.7
	71.9		98.6	98.6
	75.8		101.5	101.5

[a] ±2%, [Ar] 6×10^{-4} mol dm^{-3}; [HNO$_3$] at least ten-fold larger, unless otherwise stated. [b] [Sulphanilic acid] $(0.3—2) \times 10^{-2}$ mol dm^{-3}. [c] A very small amount of 2-(4-fluorophenoxy)-4-fluorophenol was observed amongst the products from this reaction in 71.9% and 72.2% H_2SO_4. See text. [d] [Ar] 1×10^{-3} mol dm^{-3}, [HNO$_3$] 1×10^{-4} mol dm^{-3}. [e] Equimolar concentrations used.

Table 9. Product isotope effects in the nitration of (1f) in sulphuric acid at 25 °C

Acid (%)	R [a]	k_H/k_D [b]
64.8	0.022	0.92
68.8	0.041	0.93
75.8	0.013	0.92

[a] Correction for concurrent exchange [equation (7)]. [b] Rate constants as in Scheme 5. Error in ratio estimated to be ±0.05.

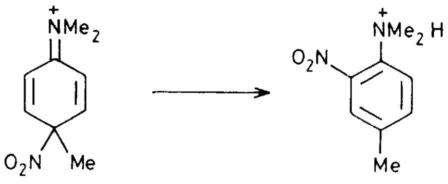
In Scheme 2 the fraction of (3) which gives (5) is the product fg, in which f is the quantity defined above, and $g = k_{-z}/(k' + k_{-z})$ is the fraction of (3) taking the encounter pathway. The product fg can be evaluated from equations (3) and (4) which again follow from application of the steady-state approximation. Y_5^{∞} and Y_4^{∞} are yields of (5) and (4) at the end of the reaction, and Y_5^{t} is the yield of (5) at time t. Equation (3) applies when the aromatic compound is taken in excess over nitric acid (preventing the freed phenol from being nitrated), and equation (4) applies when nitric acid is taken in excess.

$$fg = Y_5^{\infty}/(Y_5^{\infty} + Y_4^{\infty}) \qquad (3)$$

$$fg = \left(\frac{Y_5^{t}}{Y_4^{\infty}}\right)\left(\frac{k_2{}^5{}_{\text{obs.}} - k_2{}^1{}_{\text{obs.}}}{k_2{}^1{}_{\text{obs.}}}\right)(e^{-k_2{}^1{}_{\text{obs.}}[\text{HNO}_3]t} - e^{-k_2{}^5{}_{\text{obs.}}[\text{HNO}_3]t})^{-1} \qquad (4)$$

If it be acknowledged that diffusion-rate constants for different aromatic compounds meeting nitronium ion vary over a small range, and if a factor of 2 be adopted to cover the range of values, we can modify equation (1) to give a minimum value of f, as in equation (5). Values of fg, f, and $f_{\text{min.}}$, with the consequent values of g and $g_{\text{max.}}$ are in Table 10. That $g_{\text{max.}}$ is most often less than unity justifies the inclusion of the step with rate constant k' in Scheme 2.

$$f_{\text{min.}} = 1 - 2(k_2{}^5{}_{\text{obs.}}/k_2{}^{\text{M}}{}_{\text{obs.}}) \qquad (5)$$



(6) (7)

Scheme 3

The significant points, as they relate to the individual species, are these. For (3a) $g_{\text{max.}}$ is 1, which suggests that (3a) may proceed to (4a) entirely by the encounter pair route. Such leakage as there is may arise because *p*-cresol is not quite reactive enough to react entirely upon encounter, a surprising conclusion which has been discussed before and attributed to hydrogen bonding.[4,6] The same can be said of dienone (3b) rearranging in 76.4% H_2SO_4, because $g_{\text{max.}}$ is 1. However in 69.2% H_2SO_4, $g_{\text{max.}}$ for (3b) is only 0.26; thus not more than about a quarter of the reaction of (3b) takes place through the encounter pair; the alternative k' pathway predominates. Reference to the rate profile for this rearrangement (Figure) suggests that the results could be explained satisfactorily if the k' pathway is the non-acid-catalysed reaction observed at low acidities, and the acid-catalysed decomposition takes place, largely though not necessarily completely, through the encounter pair route. If the above conclusions apply also to the dienone (3c) formed from 4-chloroanisole (1c), an increase in g with increasing acidity might be expected. There is some indication that this happens (Table 10) but the uncertainties arising from small yields and long reaction times preclude firm conclusions. It is clear however that the encounter pair pathway accounts for less than half the rearrangement at all acidities studied.

Dienones formed from (1d and e) give no detectable yields of phenols; <2% of each of these reactions proceeds *via* the encounter pair.

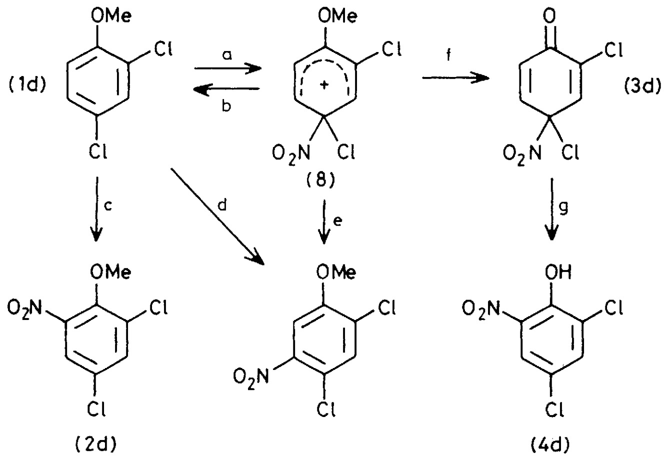
The effects of medium and substituents on the fraction g (*i.e.* on the relative importance of the encounter pair, as opposed to the k' pathway) can now be summarised. g Increases with acidity; 2-chloro substituents reduce g [compare (1a) with (1b), and (1c) with (1d), in Table 10]. g Decreases as the 4-substituent is changed from methyl to chloro to fluoro [compare (1a), (1c), and (1e) in Table 10].

Our results give little information on the nature of the k' pathway, but by analogy with the conclusions of previous workers on similar reactions,[5,10] a radical mechanism seems likely. The observation that nitration of (5e) (a reaction which proceeds entirely by the k' pathway) leads to the formation of a small amount of 2-(4-fluorophenoxy)-4-fluorophenol is in accord with such a conclusion, for the ' dimer ' could arise from the reaction of the 4-fluorophenoxyl radical with 4-fluorophenol. An alternative source of 2-(4-fluorophenoxy)-4-fluorophenol would be the reaction with 4-fluorophenol of 4-fluorophenoxenium ion, formed by loss of nitrite ion from (3e). However such a reaction would be expected to give also the products of C–C coupling.[11] Heterolysis of (3) in this way would be favoured by electron-releasing substituents, yet the reverse is true for k'. These two observations argue against the alternative view that the k' pathway proceeds by nitrite loss from (3). Our view is then that the k' pathway probably involves formation of a solvent caged, aryloxyl radical–nitrogen dioxide pair, from which there can be some leakage. The possibility arises that the free aryloxyl radical can then be reduced to the phenol. There is no evidence for this, and

Table 10. Partitioning in the rearrangement in Scheme 2

Aromatic	H_2SO_4 (%)	fg [a]	$k_2{}^5{}_{obs.}/k_2{}^M{}_{obs.}$ [b]	f	$f_{min.}$ [c]	g	$g_{max.}$
(1a)	64.5	0.21 [d]	0.56	0.44	(0.21)	0.48	1
	67.1	0.20 [d]	0.56	0.44	(0.20)	0.48	1
(1b)	69.2	0.14 [d]	0.23	0.77	0.54	0.18	0.26
	76.4	0.15 [d]	*ca.* 15	*ca.* 0	(0.15)	*ca.* 1	1
(1c)	61.5	0.17 [e]	0.19	0.81	0.62	0.21	0.27
	63.7	0.25 [d]	0.19	0.81	0.62	0.31	0.40
	63.7	0.20 [e]	0.19	0.81	0.62	0.25	0.32
	66.1	0.21 [d]	0.21	0.79	0.59	0.27	0.36
	66.2	0.23 [e]	0.21	0.79	0.59	0.29	0.39
	67.3	0.24 [e]	0.21	0.79	0.59	0.30	0.41
	70.0	0.23 [d]	0.24	0.76	0.52	0.30	0.44
(1d)	64.5	<0.01 [d,f]	0.02	0.98	0.96	<0.01	0.01
(1e)	67.1	<0.01 [d,f]	0.22	0.78	0.56	<0.01	0.02
	73.7	<0.01 [d,f]	0.26	0.74	0.47	<0.01	0.02

[a] For definitions of f and g, see text. [b] For definitions see text. [c] Figures in parentheses result from the constraint $g \leqslant 1$ Otherwise values are obtained as described in the text. [d] From equation (3). [e] From equation (4). [f] Based on the estimate that >0.2% of (5) would have been detected. [g] By extrapolation of rate data for (5b).



Scheme 4

in any case it would not alter the status of $g_{max.}$ in the foregoing discussion.

Unlike the similar rearrangement (6) ⟶ (7),[10] (3e) ⟶ (4e) is not rate limited by proton loss, as the product isotope effects (Table 9) testify. This is in accord with the suggestion [12] that steric hindrance from the NMe_2 group is to some extent responsible for proton loss being rate determining in (6) ⟶ (7).

The rearrangement of (5d) gives no leakage and therefore proceeds by the k' pathway. The products from reaction of (1d) include 2,4-dichloro-5-nitroanisole (the yield of which increases with increasing acidity) but no 2,4-dichloro-5-nitrophenol (Table 7). Scheme 4 accounts for these observations. The 2,4-dichloro-5-nitroanisole is seen to arise from the *ipso*-Wheland intermediate (8) formed at C-4, by 1,2-migration of the nitro-group (path e). This process, together with reversal by loss of nitronium ion (path b) competes more effectively with demethoxylation mediated by water (path f) as the acidity increases. [The very low yield of 2,4-dichloro-5-nitroanisole at low acidities suggests that direct nitration at C-5 (path d) is insignificant.] It is noteworthy that (8) gives the products of both formal 1,2- and 1,3-migration, but (3d) gives only that of 1,3-migration. This contrast suggests that the k' pathway is not acid-catalysed, for protonated (3d) is closely similar in structure to (8).

Experimental

Materials.—Comments on some materials used have been given in earlier Parts.[3] *p*-Cresol and 4-methylanisole and their nitro-derivatives have also been mentioned earlier.[3,6] 4-Chlorophenol (b.p. 217 °C), 4-chloroanisole (b.p. 198 °C), 4-fluorophenol (b.p. 185 °C), 4-fluoroanisole (b.p. 157 °C), 2,4-dichlorophenol (b.p. 210 °C), and 2,4-dichloroanisole (b.p. 233 °C) were commercial specimens and were distilled before use. 4-Chloro-2-nitrophenol (m.p. 87 °C), a commercial specimen, and 4-chloro-2-nitroanisole (m.p. 97 °C) (prepared from the phenol [13]) were both recrystallised from ethanol. 2-Chloro-4-methylanisole [b.p. 111 °C at 15 mmHg; δ_H ($CDCl_3$) 2.24 (3 H, s), 3.84 (3 H, s), and 6.90 (3 H, m)] and 2-chloro-4-methyl-6-nitroanisole [m.p. 41 °C after crystallisation from methanol; $\delta_H(CDCl_3)$ 2.40 (3 H, s), 4.00 (3 H, s), 7.42 (1 H, d), and 7.49 (1 H, d); J_{meta} 2.2 Hz] were prepared by methylating the corresponding phenols.[14] 2-Chloro-4-methylphenol, obtained by chlorinating *p*-cresol [15] was distilled, b.p. 199—200 °C at 751 mmHg; $\delta_H(CDCl_3)$ 2.24 (3 H, s, CH_3), 5.40 (1 H, s, OH), and 7.00 (3 H, m).

2-*Chloro*-4-*methyl*-6-*nitrophenol.*—A solution of fuming nitric acid (3 ml) in chloroform (10 ml) and 98% H_2SO_4 (0.1 ml) was added to one of 2-chloro-4-methylphenol (10 ml) in chloroform (100 ml) with vigorous shaking. After 1 h the solution was washed with water and dried ($MgSO_4$). Removal of the solvent and crystallisation from aqueous ethanol gave the nitrophenol, m.p. 64 °C; $\delta_H(CDCl_3)$ 2.44 (3 H, s, CH_3), 7.58 (1 H, d), 7.90 (1 H, d) (J_{meta} 2.0 Hz), and 10.80 (1 H, s, OH); *m*/*e* 189 (30%), 187 (100), 162 (2), 160 (1), 157 (11), 142 (10), 140 (9), 129 (8), and 113 (15).

4-*Fluoro*-2-*nitrophenol.*—Nitric acid (1.42 g) in acetic acid (10 ml) was added to a solution of 4-fluorophenol (2.37 g) in acetic acid (30 ml) at 16 °C. After 2 min the solution was poured onto ice. Extraction with dichloromethane (1 × 50 ml, 4 × 20 ml), drying of the extract ($MgSO_4$), and removal of the solvent gave the product (95%) which after crystallisation from ethanol had m.p. 74 °C; *m*/*e* 157 (100%), 140 (5), 127 (11), 110 (7), 99 (8), 83 (19), and 82 (18).

4-*Fluoro*-2-*nitroanisole.*—A solution of 4-fluoroanisole (12 g) in acetic acid (17 g) and acetic anhydride (12.6 g) at 0 °C was stirred and treated with nitric acid (10.5 ml) in acetic acid (30 ml), added over 30 min. The solution was

Table 11. G.c. and h.p.l.c. conditions

Substance	Ref. standard	Response factor [a]	R_t/s of substance (of standard)	Column temperature (°C)
4-Methyl-2-nitroanisole [b]	2-Bromo-4-nitrotoluene	0.870	410 (250)	145
4-Methyl-2-nitrophenol [b]	2-Bromo-4-nitrotoluene	0.857	400 (1 100)	110
4-Methylphenol [b]	2-Bromo-4-nitrotoluene	0.921	540 (1 100)	110
2-Chloro-4-methyl-6-nitroanisole [b]	2-Bromo-4-nitrotoluene	1.004	570 (430)	135
2-Chloro-4-methyl-6-nitrophenol [b]	2-Bromo-4-nitrotoluene	0.803	665 (430)	135
2-Chloro-4-methylphenol [b]	2,4-Dichloroanisole	1.017	480 (580)	100
4-Chloro-2-nitroanisole [b]	2-Bromo-5-nitroanisole	1.092	1 470 (1 890)	130
4-Chloro-2-nitrophenol [b]	2-Bromo-5-nitroanisole	0.802	302 (1 890)	130
4-Chlorophenol [b]	2-Bromo-5-nitroanisole	0.802	850 (1 890)	130
2,4-Dichloro-6-nitroanisole [c]	2-Bromo-5-nitroanisole	0.189	1 340 (1 010)	Room temp.
2,4-Dichloro-5-nitroanisole [c]	2-Bromo-5-nitroanisole	0.320	1 360 (1 010)	Room temp.
2,4-Dichloro-6-nitrophenol [c]	2-Bromo-5-nitroanisole	0.480	350 (1 010)	Room temp.
2,4-Dichlorophenol [c]	2-Bromo-5-nitroanisole	0.190	875 (1 010)	Room temp.
4-Fluoro-2-nitroanisole [b,d]	4-Nitrotoluene	0.868	690 (550)	155
4-Fluoro-2-nitrophenol [b,d]	4-Nitrotoluene	0.687	315 (550)	155
4-Fluorophenol [b,d]	4-Nitrotoluene	0.757	740 (2 440)	100
4,4′-Difluoro-2,2′-dihydroxybiphenyl [b,d]	None		2 250	170
2-(4-Fluorophenoxy)-4-fluorophenol [b,d]	None		1 250	170
2-(4-Fluorophenoxy)-4-fluorophenol [b,e]	None		580	185

[a] (Area ratio/mol ratio), both for (substance/ref. standard). [b] By g.c.; Pye 104 instrument with flame ionisation detector and computing integrator (Disc DP88 or Datalab 308). All on Chromasorb WAW, nitrogen flow rate 40 ml min^{-1}, 5% polyethyleneglycol adipate (PEGA) unless otherwise stated. [c] By h.p.l.c.; Spherisorb ODS 5μ analytical column; Pye Unicam LC3 u.v. detector, flow rate 0.4 ml min^{-1}, solvent system MeOH : H_2O; 3 : 1. Wavelength 280 nm. [d] 15% SE30, not 5% PEGA. [e] 10% Dexsil 400 GC, not 5% PEGA.

allowed to warm to 25 °C and kept for 45 min. Quenching, extraction with dichloromethane, processing as usual, and crystallising from ethanol gave the nitro-compound, m.p. 61 °C, *m*/*e* 171 (60%), 141 (46), 124 (86), 113 (14), 111 (20), 110 (43), and 95 (100).

2,4-*Dichloro*-5- *and* -6-*nitroanisole*.—Fuming nitric acid (3 ml) in chloroform (10 ml) was added to a solution of 2,4-dichloroanisole (10 ml) in chloroform (100 ml) and the solution was vigorously shaken. After 1 h the solution was washed with water and after drying ($MgSO_4$) the chloroform was removed. G.l.c. analysis of the product on a preparative column (1.7 m packed with 15% SE30 on Chromosorb W and fitted to a Pye 105 instrument, oven temperature 190 °C, nitrogen flow rate 60 ml min^{-1}) showed the presence of starting material and three nitroanisoles, one, the 3-nitro-isomer being present to the extent of <0.1%. The two major isomers were separated and their ^1H n.m.r. spectra recorded ($CDCl_3$). 2,4-Dichloro-6-nitroanisole had δ 4.02 (3 H, s, OCH_3), 7.62 (1 H, d), and 7.71 (1 H, d) (J_{meta} 2.6 Hz); 2,4-dichloro-5-nitroanisole had δ 3.97 (3 H, s, OCH_3), 7.49 (1 H, d), and 7.57 (1 H, d) (J_{para} < 0.5 Hz). The 6-nitro-compound was the major product.

4-*Fluoro*-2-*deuterioanisole*.—4-Fluoro-2-nitroanisole (6 g) in ethanol (100 ml), with 5% palladised charcoal (0.5 g) was shaken with hydrogen. The product in light petroleum (b.p. 40—60 °C) was subjected to chromatography on neutral alumina (130 g), elution being effected with a 60 : 40 mixture of light petroleum and chloroform. 2-Amino-4-fluoroanisole was recovered as an oil.

A solution of amine (2.4 g) in deuterium chloride (>98 atom % in D_2O; 18.3% w/w; 10.5 g) was cooled to 0 °C and diazotised under a stream of dry air with a solution of sodium nitrite (2.03 g AnalaR, dried at 70 °C and 0.1 mmHg) in deuterium oxide (3.6 ml). The diazonium solution was cooled to −10 °C and added slowly to deuteriohypophosphorous acid (31.2 ml; 50% w/w D_3PO_2 in D_2O) at −10 °C, the solution being kept under dry air. The mixture was allowed to warm to 20 °C (3 h) and stirred for a further 14 h. Extraction with dichloromethane (1 × 50 ml, 5 × 20 ml) and concentration of the dried ($MgSO_4$) extract gave the crude product (1.05 g). The product was passed over neutral alumina (130 g) in 80 : 20 chloroform–light petroleum (b.p. 40—60 °C), and then over a similar column using for elution a solvent which was changed continuously from 20 : 80 to 65 : 35 chloroform–light petroleum. The oil so obtained showed >99.5% deuterium incorporation at the *o*-position, *m*/*e* 127 (100%), 112 112 (59), and 84 (45).

4,4′-*Difluoro*-2,2′-*dihydroxybiphenyl*.—This compound and its dimethyl ether have been reported[16] without details of their preparation.

Activated copper bronze (15 g) was added slowly to a stirred mixture of 4-fluoro-2-iodoanisole (15 g) and sand (30 g), maintained at 200 °C, over 40 min. Heating was continued for 3.5 h more. The hot mixture was poured on to sand (100 g), mixed, and allowed to cool. Extraction with boiling ethanol (2 × 100 ml), filtration, and concentration, followed by recrystallisation from ethanol gave the methoxy-compound, m.p. 123 °C (3.2 g).

This (2.2 g) and pyridine hydrochloride (22 g) were heated under reflux for 1.75 h. The cooled mixture was diluted with water, and the solution was extracted with dichloromethane. The dichloromethane solution was extracted with sodium hydroxide solution (20 g in 100 ml of water), the aqueous layer was acidified (pH 1) in the presence of dichloromethane and the dichloromethane solution was washed with water (2 × 250 ml) and dried ($MgSO_4$). Removal of the solvent and recrystallisation from ligroin (b.p. 60—80 °C) gave the phenol, m.p. 139—140 °C (1.0 g). This compound differed from the ' dimeric ' product formed in the nitration of 4-fluorophenol, as was shown by g.c. (Table 11).

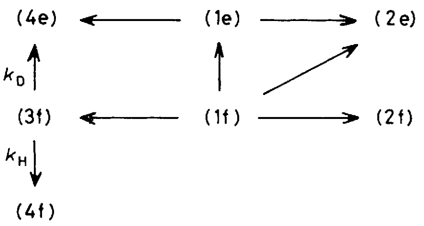
2-(4-*Fluorophenoxy*)-4-*fluorophenol*.—4-Fluoro-2-iodoanisole (15.5 g), 4-fluorophenol (12.8 g), anhydrous potassium carbonate (6.1 g), pyridine (1.2 ml), and precipitated copper (1.2 g) were heated at 170 °C for 1.5 h. More pyridine (1.3 ml) and copper (1.25 g) were added and heating was continued for a further 3 h. The mixture was diluted with 1M-hydrochloric acid and extracted with ether. The extract was washed with sodium hydroxide solution, sodium hydrogensulphite solution, and water, and after drying ($MgSO_4$) was boiled with a little decolourising charcoal. Distillation gave the methoxy-compound (3.1 g), b.p. 122 °C at 1.0 mmHg.

Powdered anhydrous aluminium chloride (6.0 g) was added in small portions to the methoxy-compound (3.1 g) in dry benzene (50 ml) and the mixture was heated for 1 h at 115—125 °C. After quenching on ice the mixture was extracted with ether. Concentration of the dried ($MgSO_4$) extract and sublimation (10^{-4} mmHg; bath temperature 60—70 °C followed by crystallisation from ligroin (b.p. 60—80 °C) gave the phenol, m.p. 43.5 °C (C, 64.95; H, 3.5. Calc. for $C_{12}H_8F_2O_2$: C, 64.9; H, 3.6%), δ_H ($CDCl_3$) 5.10 (1 H, s, OH); the aromatic region was complex, δ 6.46 (d, J 3.0 Hz), 6.55 (d, J 3.0 Hz), 6.70 (d, J 3.0 Hz), 6.78 (d, J 3.0 Hz), 6.89 (s), 6.94 (s), 7.05 (d, J 1.8 Hz), and 6.99 (s) (total 7 H); m/e 223 (11%), 222 (100), 206 (2), 193 (2), 184 (3), 165 (3), 146 (3), 141 (3), 127 (2). The compound was identical chromatographically with the ' dimer ' from the nitration of 4-fluorophenol (Table 11).

2,4-*Dichloro*-6-*nitrophenol*.—2,4-Dichlorophenol (1 g) in acetic acid (2.5 ml) was added to concentrated sulphuric acid (10 ml). The solution was cooled in ice and a solution of concentrated nitric acid (0.5 ml) in concentrated sulphuric acid (2 ml) was added over 30 min. The mixture was kept for 2 h at 25 °C and then poured into iced water (100 ml). Steam-distillation, extraction of the distillate with dichloromethane (4 × 20 ml), and concentration of the dried ($MgSO_4$) extract gave the product (0.6 g). Recrystallisation from acetic acid gave yellow leaflets, m.p. 122—123 °C.

Product Studies and Analytical Techniques.—These were carried out as previously,[17] except that for runs of >2 h, reaction vessels were kept in the dark. Separate experiments were used to establish that the compounds were stable in, and quantitatively recoverable from, aqueous acids after periods comparable with the length of the nitration experiments. Recoveries were 99—100% except in the following cases: (5a), (80%); (5b), (94%); (5c), (72—82% depending on acidity); (5e), (94—96%). Yields of (5a—c) in Tables 3—5 have been corrected for incomplete extraction. Products were analysed by g.c. or h.p.l.c.; details are in Table 11.

The products from the nitration of 1-deuterio-4-fluoroanisole (1f) were analysed by g.c.m.s.; g.c. conditions were as for the corresponding undeuteriated compounds. Extents of isotopic exchange in the absence of nitric acid but otherwise under the same condition as for the nitration experiments were separately determined. Ratios of rate constants, k_H/k_D, for (3f) ⟶ (4f) and (3f) ⟶ (4d) (Scheme 5), were derived from the ratio of yields Y of the two products using equation (6), which follows from Scheme 4 is secondary isotope effects are ignored in estimating the small corrections for concurrent exchange.



Scheme 5

$$Y_{(4e)}/Y_{(4f)} = k_D(1 + R)/k_H + R \qquad (6)$$

$$R = \frac{\text{rate constant for exchange}}{\text{pseudo-first-order rate constant for nitration}} \qquad (7)$$

Kinetic Methods.—These were essentially as previously described.[9]

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