Nitrosation and Nitrous Acid-catalysed Nitration of Anisole and 2,6-Dimethylanisole

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Rate–acidity profiles have been obtained for the nitrosation of anisole, 2,6-dimethylanisole (DMA), and 2,6-dimethylphenol (DMP) in aqueous sulphuric acid. The phenol is more reactive than the corresponding anisole, and DMA has a more shallow profile than anisole. A deuterium kinetic isotope effect (k_H/k_D) of 4.0 for [4-^{2}H]anisole indicates that the product of nitrosation of anisole in 46.5% sulphuric acid (*p*-nitrosophenol) is formed by slow proton loss from the Wheland intermediate. Intense colours were associated with the nitrosation of these compounds when nitrous acid was in excess.

The kinetics of nitrous acid-catalysed nitration of anisole were studied in 43.0 and 47.0% sulphuric acid; the product is *p*-nitrophenol. Nitrosation followed by oxidation by N^V was the major pathway at these acidities. The other pathway has a kinetic form given by $k_C = k_3[N^{III}][N^V]$, consistent with a process where oxidation by N^V is rate-limiting. Product studies show that *p*-nitrophenol is formed at lower acidities and *o*- and *p*-nitroanisole at higher acidities. A mechanism is suggested involving a radical cation species, which would predominate at higher acidities and account for the k_C pathway at lower acidities.

The nitrous acid-catalysed nitration of DMA gives 2,6-dimethyl-4-nitroanisole in higher yield as the acidity increases.

The nitrous acid-catalysed nitration of anisole has been studied under a variety of conditions, and similar conclusions about the mechanism of the reaction have been reached in each case. In nitric acid solution,[1] nitration of anisole is found to proceed swiftly if nitrous acid is present, giving a mixture of nitrophenols and nitroanisoles, with the nitroanisoles predominating at higher acidities. Similar products were obtained in the nitration of *p*-nitrosoanisole under the same conditions. Partial dealkylation of reagents during nitration has been reported also in work on diaryl ethers[2] and dialkylanilines.[3] Ingold[4] and his co-workers studied the kinetics of nitrous acid-catalysed nitration in acetic acid solution and proposed a mechanism involving initial slow nitrosation followed by rapid proton loss and oxidation by nitric acid to give the *p*-nitro compound. A feature of nitrous acid-catalysed nitration of anisole seems to be a strong tendency for *para*-nitration, with low *ortho*:*para* ratio (only a small amount of *m*-nitroanisole is detected). Hoggett and his co-workers[5] obtained almost complete conversion of anisole into *p*-nitroanisole when catalysed nitration was carried out in aqueous sulphuric acid. Studies of nitration of anisole by dinitrogen tetraoxide in chloroform also show a low *ortho*:*para* ratio for the products.[6] Anisole therefore appears to undergo *para*-nitrosation, and this is supported by the work of Challis[7] and the present authors. The nitrous acid-catalysed nitration of anisole and 2,6-dimethylanisole in aqueous sulphuric acid is considered in the present paper. This solvent is convenient to use because anticatalytic effects[8] due to nitrous acid are not observed and the catalysed nitration mechanism can be separated from the non-catalysed nitronium ion nitration mechanism over a substantial acidity range.

Results and Discussion

Nitrosation.—Since previous work indicates that nitrous acid-catalysed nitration of anisole involves a nitrosation–oxidation pathway, a study of the nitrosation of anisole is necessary.

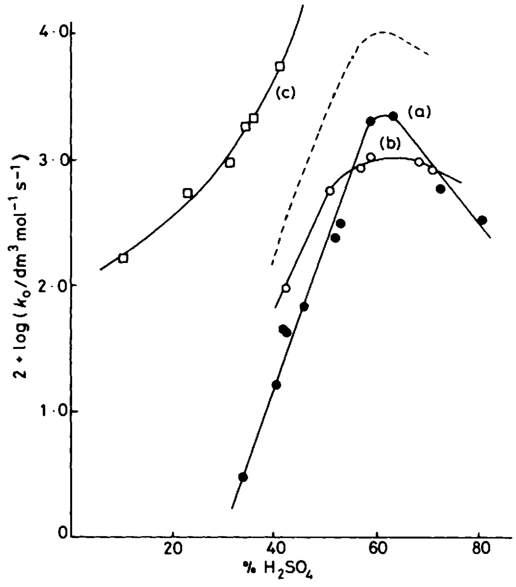

Figure 1. Rate–acidity profiles for nitrosation in sulphuric acid at 25.0 °C: (a) anisole, (b) 2,6-dimethylanisole, (c) 2,6-dimethylphenol, (d) phenol (data from ref. 6)

Challis[7,9,10] has studied this reaction under rather different conditions from those employed for studies of catalysed nitration in the present work. The rate–acidity profile for the nitrosation of anisole at 25.0 °C (Figure 1) is similar to that obtained[7] for reaction in perchloric acid at *ca.* 0 °C. Second-order rate coefficients, k_0, are given in Table 1. The profile for phenol[11] is presented for comparison. U.v. absorbance measurements in 46.5% sulphuric acid show that there is 98.4% conversion of anisole into *p*-nitrosophenol under these conditions. A primary deuterium kinetic isotope effect (k_H/k_D) of 4.0 ($\pm$0.4) for [$^2H_5$]anisole indicates that proton loss from the Wheland intermediate is slow compared with loss of

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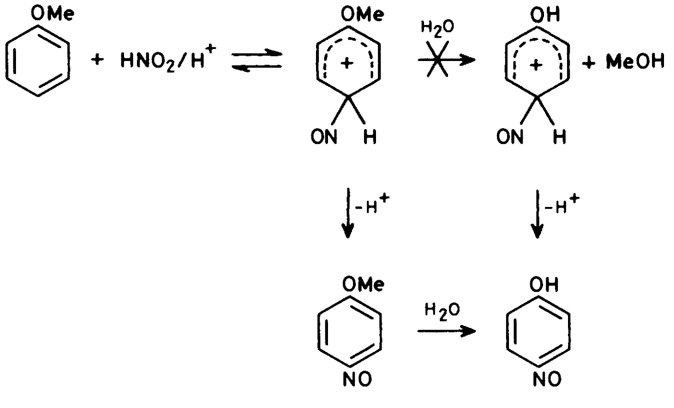
Table 1. Second-order rate coefficients, k_0, for nitrosation at 25.0 (±0.1) °C.

H_2SO_4 (%)	$10^4[N^{III}]$/ mol dm^{-3}	10^4[substrate]/ mol dm^{-3}	k_0/ dm^3 mol^{-1} s^{-1}
Anisole			
34.1	49.8	1.7	0.03
40.1	49.8	1.7	0.16
41.9	1.3	20.8	0.43
42.3	38.3	2.6	0.41
42.3	38.3	2.5	0.10^a
46.0	49.8	1.7	0.67
51.8	1.3	20.8	2.37
53.0	0.6	18.9	3.04
58.6	0.6	18.9	19.57
63.2	0.6	18.9	21.48
72.3	0.6	18.9	5.71
80.7	0.6	18.9	3.27
DMA			
40.1	53.4	2.02	0.02
42.4	0.21	16.0	0.94
46.0	53.4	2.02	0.04
50.5	0.21	16.0	5.50
50.7	21.4	2.02	0.24
57.0	0.21	16.0	8.00
58.9	0.21	16.0	10.37
68.3	0.21	16.0	9.37
72.2	0.21	16.0	7.94
DMP			
10.3	7.55	0.51	1.69
23.1	7.55	0.51	5.33
31.4	7.55	0.51	9.40
34.2	7.55	0.51	18.14
35.7	7.55	0.51	20.13
41.0	7.55	0.51	52.98

^{a} Substrate $[^2H_5]$ anisole.



Scheme 1.

nitrosonium ion and must occur in preference to irreversible dealkylation (Scheme 1). The dealkylation step therefore appears to involve nucleophilic attack by water on *p*-nitrosoanisole, which is known[12] to be unstable in acidic solution although no kinetic studies on the conversion of *p*-nitrosoanisole into *p*-nitrosophenol have been reported.

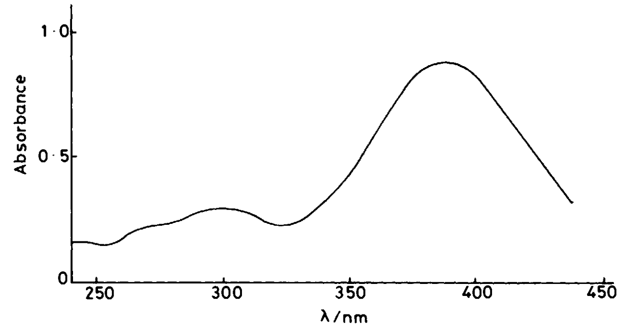


Figure 2. Spectrum of coloured species formed by anisole with sodium nitrite in 70% sulphuric acid

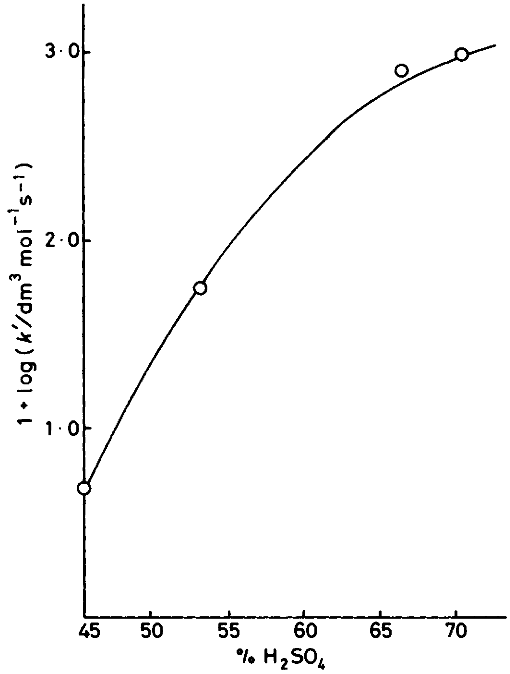


Figure 3. Rate–acidity profile for formation of coloured species at 400 nm

A number of kinetic runs were carried out with nitrous acid in excess over anisole; the runs at lower acidity were in good agreement with those under reversed conditions. At acidities greater than 50% sulphuric acid an intense brown colour was formed, the absorbance of which completely swamped the wavelength region used to follow the kinetics of nitrosation. The colour gradually fades, and has a wavelength maximum at 400 nm (Figure 2). The minor peak at 300 nm is probably due to *p*-nitrosophenol. The formation of the colour was acid-catalysed and slow enough to be followed by conventional spectrophotometry. A rate–acidity profile was obtained (Figure 3); the bimolecular rate constants, *k'*, for formation of the colour are given in Table 2. The profile shows a levelling off in rate at *ca.* 60% sulphuric acid, which corresponds[13] to quantitative conversion of nitrous acid into the nitrosonium ion, NO^+. It is not clear why this intense colour is formed when the other reagent is used in excess, and the origin of the intense colour remains unknown. The possibility of a charge-transfer species (a π-complex) giving rise to the intense absorption is ruled out here because the formation of the coloured species is too slow.

The nitrosation of 2,6-dimethylanisole (DMA) was also studied in a range of sulphuric acid strengths (40—70%); the results are included in Table 1. The runs with nitrous acid in excess are much slower than those under the reverse conditions. In these runs also, an intense brown colour was formed, as with anisole. The reason for the large difference in rates between the two conditions is not clear and needs further investigation. No such complications occur with DMA in excess over nitrous acid and the rate profile from these runs is given in Figure 1. As would be expected, the rate of nitrosation of DMA up to the rate maximum is greater than that of anisole.

The nitrosation profile of 2,6-dimethylphenol (DMP) has been obtained for comparison (Figure 1 and Table 1). This substance is more reactive than DMA by a factor of 50 in 40% sulphuric acid; this difference in rates is similar to that between phenol and anisole. It is interesting that a coloured species is formed at higher acidities in the same way as with anisole and DMA; furthermore DMP forms a coloured species with wavelength maximum at 454 nm in 70% sulphuric acid with no added reagents. This has not been investigated further.

Nitrous Acid-catalysed Nitration.—The kinetics of nitration of anisole in the presence of added sodium nitrite have been studied in 43.0 and 47.0% sulphuric acid. Under these conditions nitration by nitronium ion is negligible[14] and the product of catalysed nitration in 45.4% sulphuric acid is 93.2% *p*-nitrophenol under conditions similar to those in the kinetic runs. The kinetics may be followed by observing the formation of *p*-nitrophenol at an isobestic point formed between the spectra for *p*-nitrophenol and for *p*-nitrosophenol. If the reaction were to involve initial formation of *p*-nitrosophenol followed by oxidation[15] to *p*-nitrophenol, then observation of the kinetics at the isobestic point would not show the oxidation step. The observed rate constant, k, is then made up of two components; due to the nitrosation step (k_N) and the catalysed nitration step (k_C) [equation (1)].

$$k = k_N + k_C \qquad (1)$$

This method has been used in studying the kinetics of catalysed nitration of phenol;[11] k_N is determined from the data for the nitrosation of anisole and it is assumed that the rate of nitrosation is unaffected by the presence of nitric acid. A value for k_C is therefore easily obtained and represents the 'catalysed nitration' rate, *i.e.* nitration by a pathway other than nitrosation–oxidation. Unlike the catalysed nitration of phenol,[11] with anisole k_C always represented the minimum pathway; values of k_C/k higher than 0.5 could not be achieved (Table 3). This limits the accuracy of the values of k_C obtained. In further contrast to phenol, the values of k_C were found within experimental error to depend upon the product of the concentrations of N^{III} and N^{V} [equation (2); Table 3 and Figure 4]. In

$$k_C = k_3[N^{III}][N^{V}] \qquad (2)$$

43.0% sulphuric acid, k_3 is 0.57 ± 0.04 dm^6 mol^{-2} s^{-1}, and the value in 47.0% sulphuric acid is 2.17 ± 0.53 dm^6 mol^{-2} s^{-1}. This is clearly an acidity dependence in this narrow range (40—50% sulphuric acid). Kinetic studies were limited to this range because of the slowness of the reaction, complicated by decomposition of the nitrous acid at lower acidities, and interference from the intensely coloured species formed at higher acidities (as already mentioned). The results show that the nitrosation–oxidation pathway gains in importance as the nitric acid concentration decreases and as acidity decreases (measured by the decreasing k_C/k value).

Table 2. Bimolecular rate constant, k', for formation of intense colour with anisole and nitrous acid at 400 nm and 25(±0.1) °C

H_2SO_4 (%)	$10^4[N^{III}]$/ mol dm^{-3}	10^4[anisole]/ mol dm^{-3}	k'/ dm^3 mol^{-1} s^{-1}
45.4	32.6	0.65	0.47
53	32.6	0.65	5.40
66.1	16.3	0.65	79.75
69.8	12.7	1.85	102.40

Table 4. Products (determined by g.l.c.) of nitrous acid-catalysed nitration

% H_2SO_4	10^3[nitrous acid]/ mol dm^{-3}	10^3[nitric acid]/ mol dm^{-3}	Nitroanisoles % *para*-	 % *ortho*-
Anisole				
62.8	6.5	160	63.2	32.3
62.8	35	160	31.2	9.3
62.0	43	420	47.7	2.8
56.0	42	50	38.4	0
54.0	6.5	160	18.9	17.8
47.0	20	1 000	12.5	3.0
46.0	30	100	0	0
40.3	54	160	0	0
	[anisole] = 3.8 × 10^{-3} mol dm^{-3}			
DMA				
38.8	41.5	200	13.6	
55.1	41.5	200	64.1	
61.1	41.5	200	67.6	
	[DMA] = 7.76 × 10^{-3} mol dm^{-3}			

Table 3. Kinetics of nitrous acid-catalysed nitration of anisole at 25(±0.1) °C[a]

H_2SO_4 (%)	$10^3[N^{III}]$/ mol dm^{-3}	$10^3[N^{V}]$/ mol dm^{-3}	$10^3[N^{III}][N^{V}]$/ mol^2 dm^{-6}	10^3 k/ s^{-1}	10^3 k_C/ s^{-1}	k_C/k
43.0	4.33	190	0.823	1.53	0.43	0.27
	4.33	95	0.411	1.34	0.23	0.17
	4.33	381	1.650	2.00	0.88	0.44
	2.16	381	0.823	1.00	0.45	0.45
	1.30	381	0.495	0.65	0.32	0.49
	5.78	381	2.202	2.80	1.32	0.47
47.0	3.30	170	0.561	5.73	1.34	0.23
	3.30	127	0.419	5.00	0.60	0.12
	1.98	110	0.218	2.97	0.34	0.11
	1.32	110	0.145	2.02	0.26	0.13
	3.30	63.5	0.209	5.00	0.61	0.12

[a] In all runs [anisole] = 1 × 10^{-4} mol dm^{-3}.

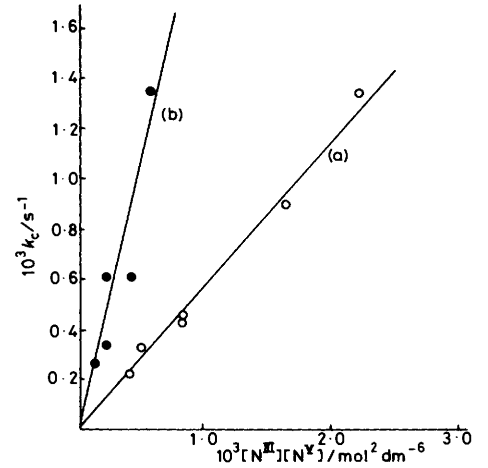
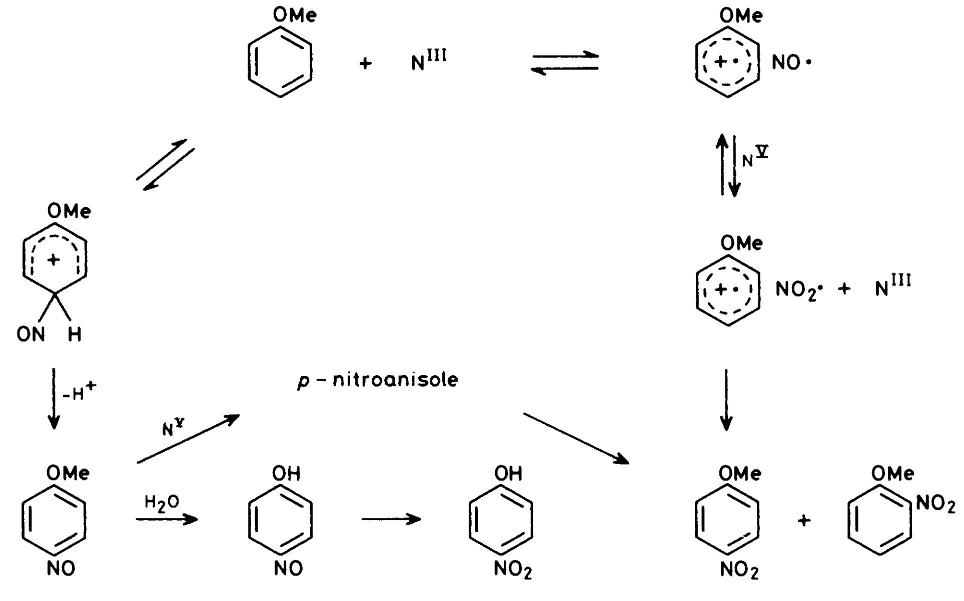


Figure 4. Variation of first-order rate constants for catalysed nitration, k_C, with $[N^{III}]$ $[N^{V}]$: (a) in 43% H_2SO_4, (b) in 47% H_2SO_4



Scheme 2.

Product studies were carried out over a wider range of acidities; the results are given in Table 4. The yield of nitroanisoles and the *ortho*:*para* ratio depend very much upon reaction conditions. The total yield of nitroanisoles decreases with acidity, and as $[N^{III}]/[N^{V}]$ increases, the yield of nitroanisoles decreases. The *o*:*p* ratios tend to decrease as $[N^{III}]/[N^{V}]$ increases although the decrease is not regular for these results.

As already mentioned, the major product at lower acidities is *p*-nitrophenol. On the basis of the foregoing results, the mechanism outlined in Scheme 2 is proposed. This involves a nitrosation–oxidation pathway at low acidities giving *p*-nitrophenol as the major product. At higher acidities, a pathway involving a radical cation species produces the nitroanisoles. The kinetic form [equation (2)] shows that in this process the step in which N^{V} acts as an oxidant can be rate-limiting. This is in contrast to the situation which obtains in the catalysed nitration of phenol,[11] presumably because the phenolic proton has been lost at this stage, making the reverse of the electron-transfer step much less likely. *p*-Nitroanisole also results from the nitrosation–oxidation pathway, by oxidation of *p*-nitrosoanisole prior to dealkylation. It could be argued that the latter would account for some of the *p*-nitroanisole obtained, and that *o*-nitroanisole would be formed by direct nitration by nitronium ion at the higher acidities (>60% H_2SO_4). However, a consideration of the rates of nitration of anisole in the absence of nitrous acid[14] under these conditions suggests that only a small fraction (<10%) of the *ortho*-isomer actually obtained comes *via* nitration by nitronium ion.

Therefore *o*-nitroanisole must come from another source, probably from the radical-cation mechanism in Scheme 2, which would gain in importance at high acidities. The mechanism is similar to that proposed for the catalysed nitration of *N*,*N*-dimethylaniline under similar conditions.[16,17]

The catalysed nitration of 2,6-dimethylanisole was also studied. Reliable kinetic data could not be obtained for this substance owing to problems related to the formation of coloured species as already explained. The products of reactions in 38—62% sulphuric acid were examined; 2,6-dimethyl-4-nitroanisole and 2,6-dimethyl-4-nitrophenol were the major ones. The nitroanisole persists down to lower acidities than for the unsubstituted anisole, even with a comparatively high nitrous acid concentration (see Table 4). The steric inhibition of the dealkylation step by the methyl groups may account for this, *i.e.* oxidation of 2,6-dimethyl-4-nitrosoanisole competes successfully with the dealkylation step. On the other hand, formation of a radical cation species from DMA and nitrous acid should be more favoured and so catalysed nitration would be found at lower acidities than that observed for anisole.

Experimental

Materials.—Nitric acid was prepared by distillation of fuming nitric acid from concentrated H_2SO_4 under vacuum. Concentrations of sulphuric acid were obtained from density measurements with a Paar DMA46 density meter. $[^2H_5]$Anisole was obtained by deuteriation of anisole with D_2O containing fluoroacetic anhydride. 2,6-Dimethyl-4-nitroanisole was prepared by nitration of DMA in acetic acid. All other reagents were of AnalaR grade and were purified before use when appropriate.

Kinetic Studies.—A small volume of aqueous sodium nitrite was injected into a mixture of reagents in sulphuric acid at 25.0 °C; the solution was shaken, and rapidly transferred to a u.v. cell. A Unicam SP 1800 spectrophotometer interfaced to a microcomputer was used to obtain first-order rate coefficients over 4—6 half-lives. Wavelengths used in this work were in the region 300—400 nm.

Product Studies.—Runs usually proceeded for 4 h, which in most cases corresponded to more than 7 half-lives. Nitroanisoles were determined by g.l.c. Solutions were extracted with dichloromethane (7×15 cm^3) after dilution with iced water. The extracts were dried over magnesium sulphate and filtered. The reference (4-nitro-1,2-xylene) was added as a solution in dichloromethane. In some cases it was necessary to reduce the volume of solution by distillation; however, this was generally avoided in view of the volatility of nitroanisoles. The solutions were analysed with Pye Unicam GCD Chromatograph (flame ionization detector; 2 m, 5% PEGA on Chromosorb W; N_2 flow rate 40 cm^3 min^{-1}). Retention times were; *o*-nitroanisole 886, *p*-nitroanisole 1 000, reference 485 s at 126 °C; 2,6-dimethyl-4-nitroanisole 485, reference 230 s at 145 °C.

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