Ozone-mediated Nitration of Chloro- and Bromo-benzenes and Some Methyl Derivatives with Nitrogen Dioxide. High *ortho*-Directing Trends of the Chlorine and Bromine Substituents

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In the presence of ozone, chloro- and bromo-benzenes are nitrated smoothly with nitrogen dioxide at low temperatures, giving a mixture of the corresponding nitro derivatives in nearly quantitative yield. The nitration products are generally *ortho*-rich as compared with those obtained by the conventional procedures based on the use of nitric acid or mixed acid. Interestingly, the *ortho*:*para* isomer ratios of the products can be reversed from *ortho*-rich (*o*:*p* = 1.14 and 1.09) to *para*-predominant (*o*:*p* = 0.45 and 0.68) simply by altering the initial concentration of the substrate. This enigmatic phenomenon has been interpreted in terms of the equilibrium between the monomer and the dimer forms of the cation radical derived from a halogenobenzene and the difference in their relative reactivity toward nitrogen dioxide. Similar preference for substitution *ortho* to the halogen substituent has been observed with 4-chloro- and 4-bromo-toluenes, which concurrently suffer extensive *ipso* attack by the present reagent system, leading to the formation of 4-methyl-2-nitrophenol as a common side product.

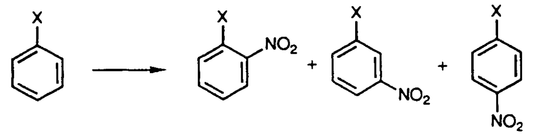
Of a wide variety of nitrobenzene derivatives which find uses in industry, 2- and 4-chloronitrobenzenes **2a** and **4a** are most important as precursors for chemical products. Many tens of thousands of tons of these compounds are used annually for the manufacture of dyestuffs, pharmaceuticals, agrochemicals, synthetic fibres, constituents of rubbers, and other commodities.[†] Commercial production of chloronitrobenzenes **2a** and **4a** involves direct treatment of chlorobenzene **1a** with concentrated nitric acid or mixed acid. This classical methodology was introduced as early as the first half of the last century, but it is, as yet, the only one we can usefully employ.[1]

The reaction of chlorobenzene **1a** with nitric acid or mixed acid has been investigated in detail by several groups.[2–9] The *ortho*:*para* isomer ratios can be varied to some extent according to the nitrating agent and solvent system employed, but modification of other circumstantial factors such as temperature, concentration, reaction time, and reagent: substrate ratio does not usually exert a significant influence on the isomer composition of the products under kinetically controlled conditions.

In a recent communication,[10] we have reported that chloro- and bromo-benzenes **1a** and **1b** are nitrated smoothly with nitrogen dioxide in the presence of ozone to produce the products of nitration rich in the *ortho* isomer, and that the *ortho*:*para* isomer ratios of the nitration products can be reversed from *ortho*-rich (*o*:*p* = 1.10 and 1.09) to *para*-predominant (*o*:*p* = 0.45 and 0.68) simply by altering the initial concentration of the substrate. This paper describes a further study of the nitration of chloro- and bromo-benzenes and some of the methyl derivatives with nitrogen dioxide. Based on the results obtained, a tentative nitration mechanism has been proposed in which a radical cation is generated from a halogenobenzene *via* the one-electron transfer oxidation with nitrogen trioxide, the capture of the cation radical species by nitrogen dioxide to form ordinary benzenium ion intermediates being followed by proton release, finally leading to the expected nitration products.

Results and Discussion

The nitration of chlorobenzene **1a** has been much studied using nitric acid,[2,3] mixed acid,[2,4,5] acetyl nitrate,[4,6,7] nitronium tetrafluoroborate[8] or nitrate salt–trifluoroacetic acid.[9] The isomer distributions reported are in the ranges *ortho* 20–36%, *meta* < 0.9% and *para* 63–80%. Compound **1a** was easily nitrated with nitrogen dioxide in the presence of ozone to give a mixture of three isomeric chloronitrobenzenes **2a**, **3a** and **4a** in nearly quantitative yield (Scheme 1). The isomer composition of the products was generally rich in the *ortho* isomer compared with those obtained by conventional procedures (Table 1).[2–9] Quite unexpectedly, the proportion of *meta* isomer was unusually high (8.5% at 6% conversion) at the initiation stage, but its relative importance rapidly decreased to 2–3% as the reaction proceeded (Table 2). On a 20 mmol scale experiment in dichloromethane (50 cm^3), the *o*:*p* ratio was 0.61 at 6% conversion, steadily increasing to 0.77 near completion. This increase in the *o*:*p* ratios may be due to the change in solvent polarity caused by the nitric acid concurrently formed. Indeed, the initial addition of an equimolar amount of nitric acid to the reaction system resulted in both the acceleration of the nitration and the increase in the *o*:*p* ratio.



1 **2** **3** **4**

a X = Cl
b X = Br
c X = F

Scheme 1 *Reagents and conditions:* NO_2–O_3, CH_2Cl_2, 0 °C

The most interesting feature of the present nitration is the reversal of the *ortho*:*para* isomer ratios of the nitration products depending on the initial concentration of the substrate (Fig. 1). A high *o*:*p* ratio 1.14 was observed at low concentration in dichloromethane (chlorobenzene–dichloromethane = 0.1 mmol/50 cm^3; 2×10^{-3} mol dm^{-3}), while a low value 0.45 was obtained in the absence of solvent. In contrast, little or no

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[†] Demands in Japan in 1989–1990 for 2- and 4-chloronitrobenzenes were estimated at 20,900 and 23,400 tons, respectively, according to a market survey of Nissan Chemical Industries, Ltd.

Table 1 Comparison of the nitrations of chloro-, bromo- and fluoro-benzenes with a variety of nitrating systems

Substrate	Nitrating conditions	Isomer proportion (%) *ortho*:*meta*:*para*	*o*:*p* Ratio
1a	HNO_3–74% H_2SO_4, 25 °C	36:0.9:63	0.57[b]
	$AcONO_2$–$MeNO_2$, 25 °C	29.6:0.9:69.5	0.43[c]
	NO_2BF_4–sulfolane, 25 °C	22.7:0.7:76.6	0.30[d]
	NH_4NO_3–CF_3CO_2H, 25 °C	20:—:80	0.25[e]
	NO_2–O_3, CH_2Cl_2, 0 °C	30.0 ~ 52.9:2.9 ~ 0.0:67.1 ~ 46.6	0.45 ~ 1.14[a]
1b	HNO_3–74% H_2SO_4, 25 °C	43:0.8:56	0.77[b]
	$AcONO_2$–$MeNO_2$, 25 °C	36.5:1.2:62.4	0.58[c]
	NO_2BF_4–sulfolane, 25 °C	25.7:1.1:73.2	0.35[d]
	NO_2–O_3, CH_2Cl_2, 0 °C	39.1 ~ 50.7:3.5 ~ 2.9:57.4 ~ 46.4	0.68 ~ 1.09[a]
1c	HNO_3–74% H_2SO_4, 25 °C	13:0.6:86	0.15[b]
	HNO_3–Ac_2O, 25 °C	8.7:—:91.3	0.10[f]
	NO_2BF_4–sulfolane, 25 °C	8.5:—:91.5	0.09[d]
	NO_2–O_3, CH_2Cl_2, 0 °C	10.0 ~ 14.0:—:90.0 ~ 86.0	0.11 ~ 0.16[a]

[a] Present work. Ranges of the isomer ratios may be further extended under optimized conditions. [b] Ref. 4. [c] Ref. 7. [d] Ref. 8. [e] Ref. 9. [f] Ref. 5.

Table 2 Nitration of chlorobenzene **1a** with NO_2–O_3. Effect of amount of added NO_2[a]

Volume of added NO_2/cm^3[b]	Reaction time (*t*/h)	Conversion (%)	Isomer proportion (%) *ortho*:*meta*:*para*	*o*:*p* Ratio
0.3	3	82	40.7:3.0:56.3	0.72
0.5	0.5	6	34.8:8.5:56.7	0.61
0.5	1	19	37.2:5.0:57.8	0.64
0.5	2	58	40.2:2.6:57.2	0.70
0.5	3	97	43.0:1.1:55.9	0.77
0.5[c]	2	67	47.4:0.3:52.3	0.91
0.5[d]	2	>99	31.7:0.8:67.5	0.77
0.5[e]	2	59	20.4:1.3:78.3	0.26
1.0	3	84	39.6:2.0:58.4	0.68

[a] All reactions were carried out using 20 mmol of substrate in dichloromethane (50 cm^3) at 0 °C. [b] The indicated volume of liquid nitrogen dioxide was added at intervals of 0.5 h. [c] An equimolar amount of nitric acid (20 mmol) was added before starting the reaction. [d] An equimolar amount of methanesulfonic acid (20 mmol) was added before starting the reaction. [e] The reaction was carried out in carbon tetrachloride (50 cm^3) at 0 °C.

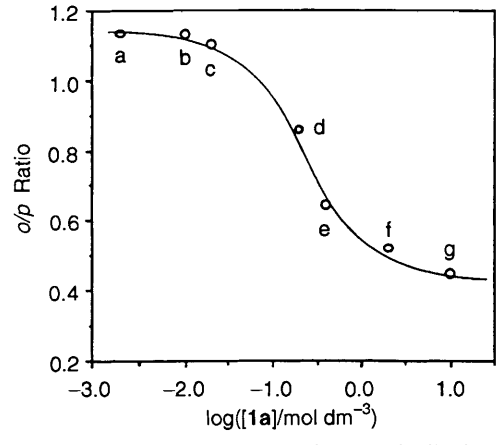

Fig. 1 Dependence of the *ortho*:*para*-isomer distributions on the initial concentration of chlorobenzene. Reactions were performed for solutions [dichloromethane (50 cm^3); 40 cm^3 was used for a 100 mmol scale experiment **f**] or on the neat substrate at 0 °C in the presence of an excess of nitrogen dioxide. Isomer proportions were determined 1 h after starting. PhCl, **a**, 0.1 mmol; **b**, 0.5 mmol; **c**, 1 mmol; **d**, 10 mmol; **e**, 20 mmol; **f**, 100 mmol; **g**, 500 mmol (neat).

comparable variations of the *o*:*p* values were observed in the conventional nitration of compound **1a** with mixed acid; the isomer proportions obtained under similar conditions, HNO_3–80% H_2SO_4; 0 °C, 20 h; 10 mmol in dichloromethane (50 cm^3) and 500 mmol (neat), were *ortho*:*meta*:*para* = 33.0:0:67.0 and 32.0:0.3:67.4, the *o*:*p* ratio being 0.49 and 0.48, respectively. This significant dependence of the product ratios on the initial concentration of a substrate was observed only for those reactions carried out in chlorinated hydrocarbons such as dichloromethane and 1,2-dichloroethane. In more polar solvents such as acetonitrile or nitromethane and in less polar solvents such as carbon tetrachloride or *n*-hexane, the variation of isomer distribution became less prominent (Table 3).

A similar change in the *o*:*p* values was observed with bromobenzene **1b** (Table 4). The *ortho*:*para* ratios were as high as 1.11 at low concentration in 1,2-dichloroethane and 0.68 in the absence of solvent. The isomer proportions reported in the literature are in the ranges *ortho* 26–43%, *meta* 0.8–1.2% and *para* 56–73%, the *o*:*p* ratios varying from 0.35 to 0.77.[2–9] In contrast with chloro- and bromo-benzenes **1a** and **1b**, the dependence of the isomer ratio on the initial concentration was not so marked with fluorobenzene **1c**. The *o*:*p* ratios varied in a narrow range from 0.16 to 0.11.

In a previous paper of this series,[12] we have suggested a single-electron transfer mechanism for the nitration of alkylbenzenes with nitrogen dioxide in the presence of ozone. Nitrogen dioxide reacts rapidly with ozone to give nitrogen trioxide [eqn. (1)], which, in the absence of an appropriate oxidizable substrate, is trapped by another molecule of nitrogen dioxide to form dinitrogen pentaoxide [eqn. (2)]. The former step is a rapid rate-determining process.[13] The nitrogen trioxide is highly electron-deficient and therefore a strong oxidizing species,[14,15] especially in solution.[16]

$$NO_2 + O_3 \longrightarrow [NO_2{\cdot}O_3] \longrightarrow NO_3 + O_2 \qquad (1)$$

$$NO_3 + NO_2 \longrightarrow N_2O_5 \qquad (2)$$

Table 3 Effect of solvents on isomer proportion in the nitration of chlorobenzene with nitrogen dioxide[a]

Solvent	E_T value[b]	Amount of substrate/mmol	Isomer proportion (%)[c] *ortho*:*meta*:*para*	*o*:*p* Ratio
$MeNO_2$	46.3	1	31.1:0:68.9	0.45
		10	27.9:0.9:71.2	0.39
MeCN	46.0	1	26.7:1.6:71.7	0.37
		10	26.5:1.4:72.1	0.37
$ClCH_2CH_2Cl$	41.9	1	50.6:0:49.4	1.02
		10	46.1:0.5:53.4	0.86
CH_2Cl_2	41.1	1	52.4:0:47.6	1.10
		10	45.9:0.7:53.4	0.86
$CHCl_3$	39.1	10	31.6:1.6:66.8	0.47
PhCl[d]	37.5	(Neat)	30.0:3.0:67.0	0.45
CCl_4	33.6	1	19.5:1.4:79.2	0.25
		10	20.8:0.8:78.4	0.27
n-C_6H_{14}[e]	33.1	10	26.9:0:73.1	0.37

[a] All reactions were carried out in the given solvent (50 cm^3) at 0 °C. [b] Ref. 11. [c] Isomer proportions were determined at > 98% completion of the reaction except for when PhCl was the solvent. [d] Reaction was carried out for neat chlorobenzene and the isomer ratio was determined after *ca.* 1% conversion. [e] This solvent was attacked to a small extent by the NO_2–O_3 system.

Table 4 Nitration of halogenobenzenes **1a–c** with NO_2–O_3[a]

Substrate	Amount of substrate/mmol	Reaction time (t/h)	Conversion (%)	Isomer proportion (%)[b] *ortho*:*meta*:*para*	*o*:*p* Ratio
1a	0.1	1	>99	52.9:0.5:46.6	1.14
	0.5	1	>99	52.8:0.5:46.7	1.13
	1	1	87	52.4:0:47.6	1.10
	10	0.5	43	43.9:1.1:55.0	0.80
	10	1	92	45.9:0.7:53.4	0.86
	10[c]	1	76	29.6:0.5:69.9	0.42
	100[d]	1	5	32.8:4.4:62.9	0.52
	500[e]	1	2	30.0:3.0:67.0	0.45
1b	1[f]	1	>99	51.6:1.7:46.7	1.11
	10	0.5	20	49.3:2.9:47.8	1.03
		1	65	50.7:2.9:46.4	1.09
	10[c]	0.5	30	32.8:3.4:63.8	0.51
	500[e]	0.5	2	37.4:7.7:54.9[g]	0.68
1c	10	1	81	14.0:—:86.0	0.16
	10[c]	1	72	8.2:—:91.8	0.09
	500[e]	1	2	10.0:—:90.0	0.10

[a] All reactions were carried out in dichloromethane (50 cm^3) at 0 °C unless otherwise indicated. [b] Isomer distributions were determined for substrates **1a** and **1c** by GLC and for substrate **1b** by HPLC. [c] An equimolar amount of methanesulfonic acid (10 mmol) was added before starting the reaction. [d] Reaction was carried out in 40 cm^3 of dichloromethane. [e] Reaction was carried out for the neat substrate. [f] Reaction was carried out in 1,2-dichloroethane (50 cm^3). [g] Trace amounts of nitrobenzene, 1,2- and 1,4-dibromobenzenes were also detected.

In the ozone-mediated nitration of aromatic halogen compounds with nitrogen dioxide (for brevity, this reaction process will often be referred to as the *kyodai*-nitration process, hereafter),* it is tempting to assume compounds **1a** and **1b** to be oxidized by nitrogen trioxide to generate a cation radical **9**, which would subsequently undergo a coupling reaction with nitrogen dioxide to furnish ordinary arenium ion intermediates **11–14** (Scheme 2). Formation of a cation radical **9** from chloro- or bromo-benzene and nitrogen trioxide has been observed by spectroscopy.[15,†] If we assume the generation of a radical cation as the initial step of the present nitration, the reversal of the *ortho*:*para* isomer ratios depending on the initial concentration of a substrate may be interpreted in terms of the equilibrium between the cation radical **9** and its dimeric form **10**, and the difference in their relative reactivity toward nitrogen dioxide. The stabilization of the cation radical of halogenobenzene as a parallel dimeric form **10** in concentrated solutions has previously been confirmed by an EPR technique.[17,18] PM3 calculations[19] carried out for the radical cation **9** and its dimer **10** revealed that the frontier electron density involved in a

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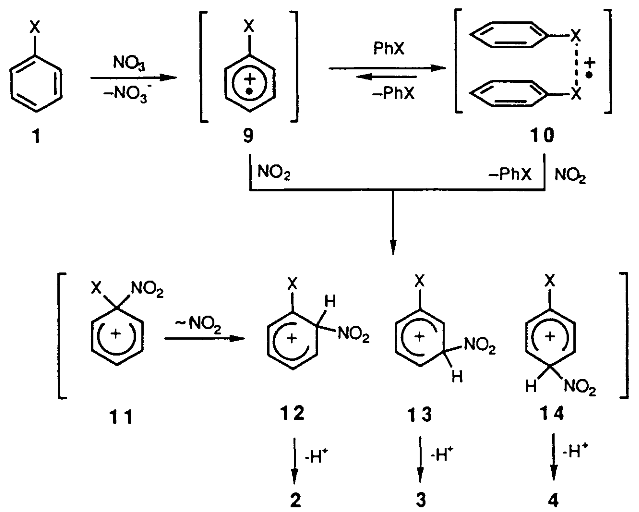
* The nitration of arenes with lower oxides of nitrogen using a combination of ozonized air and some third substance as the promoter is now the subject of much industrial effort to put it into practice as a means to circumvent the problems arising from the classical methodologies based on the use of nitric acid/sulfuric acid. The prefix *kyodai* is the Japanese abbreviation of Kyoto University.

† Cation radicals from **1a** and **1b** absorb at λ = 490–550 nm.[16]

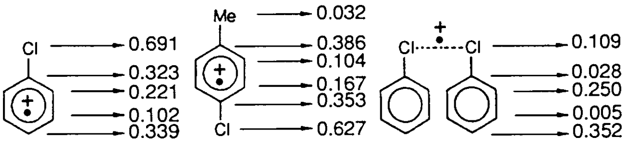
Table 5 Nitrations of 4-chlorotoluene **5b** with NO_2–O_3[a] and other nitrating systems

Reagent	Amount of substrate/mmol	t/h (T/°C)	Conversion (%)	Proportion of products (%)[b] **6b**:**5e**:**8**	3-Nitro: 2-nitro ratio
NO_2–O_3	500[c]	1 (7–9)	1	28.7:53.5:17.8	1.9
		3 (7–9)	4	36.2:47.6:6.2	1.3
	20	1 (0)	32	30.3:50.2:19.5	1.4
		2 (0)	77	36.5:52.3:11.2	1.4
	20[d]	1 (0)	55	65.8:33.5:0.7	0.51
	1	0.5 (0)	65	9.3:64.7:26.0	7.0
HNO_3–80% H_2SO_4[e]	20	20 (0–r.t.)	45	65.5:34.5:—	0.53
HNO_3–85.0% H_2SO_4[f]	—	— (25)	—	61.5:35.3:—	0.57
HNO_3–63.1% H_2SO_4[g]	—	— (25)	—	39.1:31.0:9.3	0.79

[a] See footnote in Table 4. [b] Values ±0.4%. [c] Reaction was carried out for neat substrate. [d] An equimolar amount of methanesulfonic acid (20 mmol) was added before starting the reaction. [e] Present work. See the Experimental section. [f] Ref. 25. [g] Ref. 26.



Scheme 2

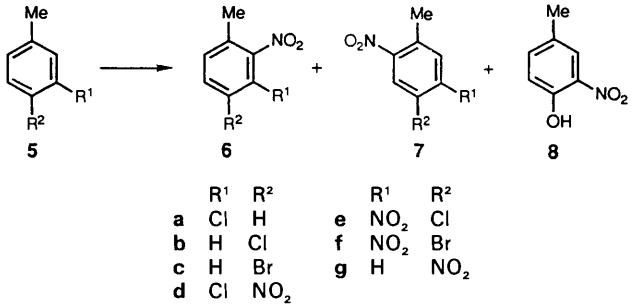


9a 15a 10a

Fig. 2 Frontier electron densities calculated by the PM3 method for the radical substitution reaction of the monomeric and dimeric forms of radical cations derived from chlorobenzene **1a** and 4-chlorotoluene **5b**

radical substitution reaction[20] is highest on the chlorine atom in the monomer form, while it is most important at the *para*-carbon atom in the dimer form (Fig. 2). In dilute solution, the *hot* radical cation **9** would be rapidly trapped by nitrogen dioxide present in large excess *via* the electronic interaction with the chlorine substituent, leading to the arenium ion intermediates **11** and **12**. Such a process would work favourably for the *ortho* substitution. In concentrated solution, however, the cation radical **9** can be partially stabilized through coordination toward the chlorine atom of another chlorobenzene molecule to give a dimeric form **10**, in which the frontier electron would be extensively spread over the whole dimeric molecule. Under these circumstances, nitrogen dioxide could react in a more regioselective manner, resulting in the predominant substitution at the *para* position.

In order to examine the validity of the proposed mechanism, some halogenotoluenes were nitrated with nitrogen dioxide as described above. The *kyodai*-nitration of 4-chlorotoluene **5b** gave a mixture of two isomeric nitro derivatives **6b** and **5e** and 4-methyl-2-nitrophenol **8** (Scheme 3). Preference for a position *ortho* to the chlorine atom was again prominent, especially in dilute solution (Table 5). Neglecting the accompanying phenol **8**, the 3-nitro:2-nitro (**5e**:**6b**) ratios decreased from 7.0 to 1.4 as the initial concentration of the substrate increased. Similar nitration of 4-bromotoluene **5c** produced two bromonitrotoluenes **6c** and **5f**, the nitrophenol **8** and 4-nitrotoluene **5g** (Table 6). Neglecting the last two side products, the 3-nitro:2-nitro (**5f**:**6c**) isomer ratios varied from 4.2 to 1.3 depending on the initial concentration of compound **5c**. The formation of phenolic product **8** was considerable in dilute solution, while the nitrodebromination became noticeable as the initial concentration of the substrate increased. In the presence of an acid catalyst, the amount of phenol **8** decreased significantly, suggesting a change-over of the reaction mode from homolytic to heterolytic. The isomer proportion of the product was, in this case, close to that obtained by nitration with mixed acid. Thus, we can switch at will the main product from 3-nitro to 2-nitro or *vice versa*.



Scheme 3 *Reagents and conditions:* NO_2–O_3, CH_2Cl_2, 0 °C

The nitration of halogenotoluenes has been investigated by many workers using nitric acid or mixed acid, but most of early works are of no quantitative significance.[21] The isomer compositions of the nitration products from 4-chloro- and 4-bromo-toluenes **5b**[3,22–26] and **5c**[3,25–28] are in the ranges 2-nitro 58–64% and 3-nitro 35–42% for compound **5b**, and 2-nitro 36–44% and 3-nitro 56–64% for compound **5c**, the 3-nitro:2-nitro ratio being 0.55–0.72 for the former compound and 0.39–0.77 for the latter. In our reaction, therefore, the preferred attack on a position next to the halogen atom was again confirmed.

The *kyodai*-nitration of 3-chlorotoluene **5a** provides a further

Table 6 Nitrations of 4-bromotoluene **5c** with NO_2–O_3[a] and other nitrating systems

Reagent	Amount of substrate/mmol	*t*/h (*T*/°C)	Conversion (%)	Proportion of products (%)[b] **6c**:**5f**:**8**:**5g**	3-Nitro: 2-nitro ratio
NO_2–O_3	20	1 (0)	34	34.2:50.7:5.7:9.4[d]	1.8
		2 (0)	88	36.6:47.4:8.1:7.9[d]	1.3
	20[c]	1 (0)	64	64.9:29.2:0.7:5.2[d]	0.45
	1	0.5 (0)	52	15.3:64.5:16.9:3.3[d]	4.2
HNO_3–80% H_2SO_4[e]	20	22 (0–r.t.)	67	59.7:40.3:—:—	0.68
HNO_3–82.7% H_2SO_4[f]	—	— (25)	—	60.9:39.1:—:—	0.64
HNO_3–63.0% H_2SO_4[f]	—	— (25)	—	45.5:17.7:—:13.3	0.39
HNO_3–Ac_2O[g]	—	— (0)	—	—:48:40:—	—

[a] See footnote in Table 4. [b] Values ±0.4%. [c] An equimolar amount of methanesulfonic acid (20 mmol) was added before starting the reaction. [d] Trace amounts of 2,4- and 3,4-dibromotoluenes were also detected. [e] Present work. See the Experimental section. [f] Ref. 25. [g] Ref. 28.

Table 7 Nitrations of 3-chlorotoluene **5a** with NO_2–O_3[a] and other nitrating systems

Reagent	Amount of substrate/mmol	*t*/h (*T*/°C)	Conversion (%)	Proportion of products (%)[b] **7a**:**5d**:**6a**	4-Nitro: 6-nitro ratio
NO_2–O_3	20	1 (0)	49	49.1:43.4:7.5	0.88
		2 (0)	90	47.1:44.6:8.3	0.95
	1	0.5 (0)	95	46.9:45.3:7.8	0.97
HNO_3–80% H_2SO_4[c]	20	19 (0–r.t.)	43	59.1:31.6:9.3	0.53
$MeONO_2$–BF_3[d]	—	0.8 (25)	—	67.9:25.7:6.4	0.38

[a] See footnote in Table 4. [b] Values ±0.4%. [c] Present work. See the Experimental section. [d] Ref. 29.

example of *ortho* enhancement by the chlorine substituent. The reaction of this compound with fuming nitric acid (d = 1.52) was reported early on to give 2-nitro, 4-nitro and 6-nitro derivatives **6a**, **5d** and **7a** in 8.8, 32.3 and 58.9% relative yields, respectively.[23] As may be easily understood from the figures, the *para*-directing power of the chlorine atom is twice as effective as the methyl group. When compound **5a** was subjected to the present nitration, the proportion of 2-, 4- and 6-nitro derivatives was 7.8, 45.3 and 46.9%, respectively, in dilute solution, while it was 8.3, 44.6 and 47.1% in more concentrated solution (Table 7). The relative yield of 4-nitro isomer increased at the expense of 6-nitro isomer in accordance with the *ortho*-directing trends of the chlorine substituent towards the entering nitro group.

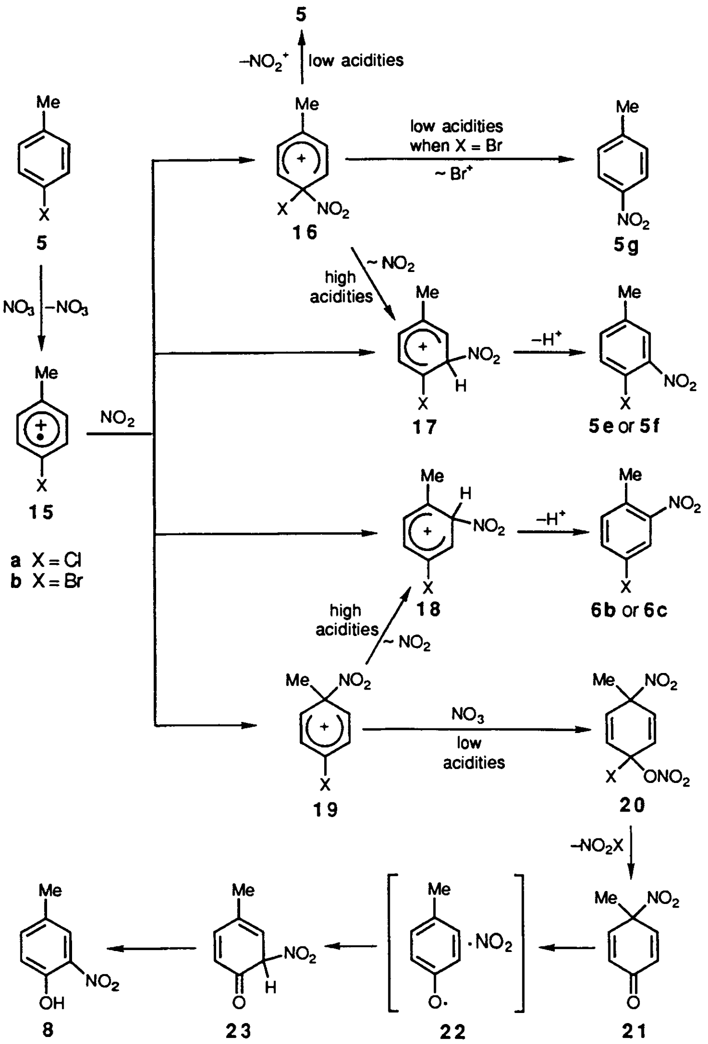
The formation of phenol **8** and nitrotoluene **5g** as by-products is also worthy of a brief mention. Both products are likely to arise from the coupling of the radical cation and nitrogen dioxide at the *ipso* position as shown in Scheme 4. Nitrodienone **21** derived from adduct **20** would aromatize into the phenol **8** *via* a dissociation–recombination mechanism.[30] Nitrodehalogenation observed with compounds **5c** and **1b** is in accord with the migratory aptitude of the cationic species $Cl^+ < NO_2^+ < Br^+$.[31] With increased acidity of the reaction system, *i.e.*, in the presence of an acid catalyst, these side reactions have been suppressed in favour of the 1,2-rearrangement of the *ipso* ions **16** and **19** to form ordinary arenium ions **17** and **18**.[32] Both types of side reaction have many precedents in aromatic nitration.[1,33]

In summary, the *kyodai*-nitration of chloro- and bromobenzenes and some of the methyl derivatives proceeded with ease, giving the corresponding nitro derivatives in good yields. The introduction of the nitro group occurred preferentially at a position next to the halogen substituent, and this characteristic feature was especially prominent in a dilute solution. The proportion of *meta* substitution was found to be unusually high at the initiation stage. The reaction was accelerated by the presence of an appropriate acid catalyst. Dichlorobenzenes, trichlorobenzenes and higher polychlorobenzenes were all smoothly nitrated, especially in the presence of an acid catalyst under similar conditions, the details of which will be reported in a forthcoming paper.

Experimental

General experimental details were given in a previous paper of this series.[12] All reagents and solvents were obtained from commercial sources. Dichloromethane was dried by distillation from calcium hydride. Nitrogen dioxide (99% pure) was obtained in a cylinder from Sumitomo Seika Co. Ltd. and used after transfer distillation. A Nippon Ozone Co. Ltd., type ON-1-2 apparatus was used for the generation of ozone. The machine produced ozone at a rate of 10 mmol h^{-1}, and its efficiency was calibrated by iodimetric titration. Chlorobenzene, bromobenzene, fluorobenzene and 3- and 4-chlorotoluenes were all distilled prior to use, and 4-bromotoluene was purified by recrystallization from ethanol. All products were known and identified by IR, ^1H NMR, GC–MS or by direct comparison with the authentic samples.

Typical Procedures for Nitration.—(*a*) *Nitrogen dioxide and ozone* (kyodai-*nitration*). 4-Chlorotoluene **5b** (2.53 g, 20 mmol) was dissolved in a 1:10 v/v mixture of liquid nitrogen dioxide (5 cm^3) and freshly distilled dichloromethane (50 cm^3) and the solution was placed in a three-necked 50 cm^3 flask fitted with a gas inlet tube and a vent which permitted waste gas to escape. The mixture was cooled to 0 °C in an ice bath, while a stream of ozonized oxygen was introduced with vigorous stirring through the gas inlet tube, which dipped just below the surface of the liquid in the flask. Throughout the reaction, ozonized oxygen was fed continuously at a low flow rate. Under these reaction



Scheme 4

conditions, the loss of nitrogen dioxide was not significant. The progress of the reaction was monitored intermittently by GLC. After 3 h the reaction was almost complete at the mononitration stage. The cooling bath was removed and the excess of nitrogen dioxide was expelled by blowing air into the solution. The reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate and the organic phase was separated, washed with water, and dried over sodium sulfate. Removal of the solvent under reduced pressure left a mixture of chloronitrotoluenes **6b** and **5b** and the phenol **8** as a solid residue. The product composition was determined using *n*-decane as an internal standard on a Shimadzu gas chromatograph instrument GC-14A, fitted with a fused silica capillary column (Shimadzu CBP1-M25-025) and a flame ionization detector. Peak areas were determined using a Shimadzu C-R5A Chromatopac computing integrator.

(*b*) *Nitric Acid and Sulfuric Acid.* To a mixture of 3-chlorotoluene **5a** (2.53 g, 20 mmol), 97% sulfuric acid (30 cm^3) and water (11.7 cm^3) was added dropwise a mixture of 61% nitric acid (1.3 g) and 97% sulfuric acid (5.9 g) with vigorous stirring at 0 °C. After 22 h the reaction mixture was diluted with iced water (200 cm^3) and organic phase was extracted with dichloromethane (2 × 50 cm^3). The combined extracts were washed with aqueous sodium hydrogen carbonate (2 × 100 cm^3) and water (2 × 100 cm^3), and dried over sodium sulfate. Removal of the solvent under reduced pressure left an oily residue, the composition of which was analysed by GLC using 1,3-dinitrobenzene as an internal standard.

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