

## Reversal of the *ortho*–*para*-Isomer Ratios by altering the Initial Concentration of Substrate in the Ozone-mediated Nitration of Chloro- and Bromo-benzenes

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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 in the ozone-mediated reaction of chloro- and bromo-benzenes with nitrogen dioxide.

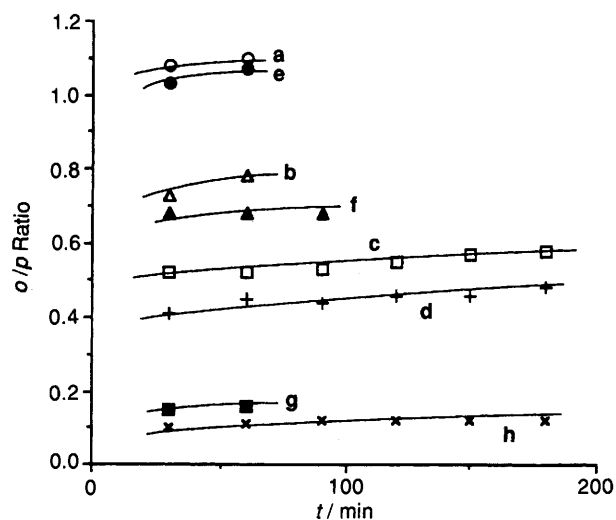
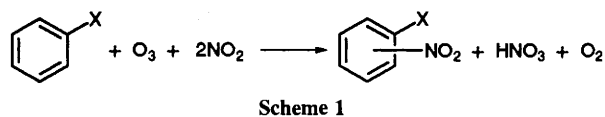
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Halogenonitrobenzenes are important as chemical precursors in organic synthesis. Thus chlorobenzene is mononitrated on a large scale in industry to produce *o*- and *p*-chloronitrobenzenes, many thousands of tons of which are used annually for the manufacture of dyestuffs, pharmaceuticals, agrochemicals

and constituents of rubber.† Since the market for the

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



**Fig. 1** Dependence of *ortho-para*-isomer distributions on the initial concentration of halogenobenzenes. Reactions were performed for solutions (dichloromethane; 50 cm<sup>3</sup>) or on the neat substrate at 0 °C in the presence of an excess of nitrogen dioxide. PhCl, **a**, 1 mmol; **b** 10 mmol; **c** 100 mmol; **d** 500 mmol (neat); PhBr, **e** 10 mmol; **f** 500 mmol (neat); PhF, **g** 10 mmol; **h**, 500 mmol (neat).

respective isomers varies from year to year, a means of controlling the percentage of the desired isomer would be beneficial for their industrial production. However, the orientation in electrophilic aromatic substitution is largely governed by the electronic and steric requirements of the electrophile and of the substituent on the aromatic ring.<sup>1</sup> Modification of circumstantial factors such as concentration, temperature and reaction time usually does not exert a significant influence on the isomer composition of the products under kinetically controlled conditions. We report here that the *ortho-para*-isomer ratio in the nitration products can be reversed from *ortho*-rich to *para*-predominant simply by altering the initial concentration of the substrate in the ozone-mediated reaction of chloro- and bromo-benzenes (**1** and **2**) with nitrogen dioxide.<sup>2</sup>

The general procedure was as follows: the halogenobenzene was mixed with a slight molar excess of liquid nitrogen dioxide in dichloromethane (50 ml), and ozonized oxygen was bubbled slowly (O<sub>3</sub>, 10 mmol h<sup>-1</sup>) through the stirred mixture at ca. 0 °C until the reaction was almost complete at the mononitration stage. The reaction was clean and no oxidative degradation was observed. Nitration was rapid and after the usual work-up the nitro compounds were obtained as an isomeric mixture in nearly quantitative yield. Under these uncatalysed conditions, the reaction at early stages was stoichiometric in ozone, one mole of ozone and one mole of arene producing one mole of nitration product as shown in Scheme 1.

The *ortho-para* isomer ratio of the nitration products slightly increased as the reaction proceeded (Fig. 1). Under conditions of continuous feeding of nitrogen dioxide, the final ratio was around 0.78 for **1** on a 10 mmol scale experiment. In the presence of an acid catalyst, the ratios remained almost unaffected throughout the reaction (from 0.43 to 0.45 for methanesulfonic acid and from 0.78 to 0.80 for nitric acid). Isomer distributions previously reported for the mononitra-

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

Substrate	Nitrating conditions <sup>b</sup>	Isomer proportion			<i>o/p</i> ratio
		<i>ortho</i> : <i>meta</i> : <i>para</i>			
PhCl	A	36 : 0.9 : 63			0.57 <sup>c</sup>
	B	29.6 : 0.9 : 69.5			0.43 <sup>d</sup>
	C	22.7 : 0.7 : 76.6			0.30 <sup>e</sup>
	D	20 : — : 80			0.25 <sup>f</sup>
	F	30.0–52.4 : 2.9–0.0 : 67.1–47.6			0.45–1.10 <sup>a</sup>
	PhBr	A	43 : 0.8 : 56		
B		36.5 : 1.2 : 62.4			0.58 <sup>d</sup>
C		25.7 : 1.1 : 73.2			0.35 <sup>e</sup>
F		39.1–50.7 : 3.5–2.9 : 57.4–46.4			0.68–1.09 <sup>a</sup>
PhF	A	13 : 0.6 : 86			0.15 <sup>c</sup>
	E	8.7 : — : 91.3			0.10 <sup>g</sup>
	C	8.5 : — : 91.5			0.09 <sup>e</sup>
	F	10.0–14.0 : — : 90.0–86.0			0.11–0.16 <sup>a</sup>

<sup>a</sup> Present work. Optimisation of conditions may lead to improvements. <sup>b</sup> Conditions for the nitration are: A HNO<sub>3</sub>–74% H<sub>2</sub>SO<sub>4</sub>, 25 °C; B AcONO<sub>2</sub>–MeNO<sub>2</sub>, 25 °C; C NO<sub>2</sub>BF<sub>4</sub>–sulfolane, 25 °C; D NH<sub>4</sub>NO<sub>3</sub>–CF<sub>3</sub>CO<sub>2</sub>H, 25 °C; E HNO<sub>3</sub>–Ac<sub>2</sub>O, 25 °C; F NO<sub>2</sub>–O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C. <sup>c</sup> Ref. 3. <sup>d</sup> Ref. 4. <sup>e</sup> Ref. 5. <sup>f</sup> Ref. 7. <sup>g</sup> Ref. 6.

**Table 2** Effect of solvents on isomer proportion in the nitration of chlorobenzene with nitrogen dioxide<sup>a</sup>

Solvent	<i>E</i> <sub>T</sub> value <sup>c</sup>	Amount of substrate/ mmol	Isomer proportion <sup>b</sup>		<i>o/p</i> ratio
			<i>ortho</i> : <i>meta</i> : <i>para</i>		
MeNO <sub>2</sub>	46.3	1	31 : 0 : 69		0.45
		10	28 : 1 : 71		0.39
MeCN	46.0	1	27 : 1 : 72		0.37
		10	26 : 1 : 73		0.36
ClCH <sub>2</sub> CH <sub>2</sub> Cl	41.9	1	50 : 0 : 50		1.00
		10	46 : 0 : 54		0.85
CH <sub>2</sub> Cl <sub>2</sub>	41.1	1	52 : 0 : 48		1.10
		10	42 : 1 : 57		0.74
CHCl <sub>3</sub>	39.1	10	32 : 1 : 67		0.48
PhCl <sup>c</sup>	37.5	(Neat)	30 : 3 : 67		0.45
CCl <sub>4</sub>	33.6	1	20 : 1 : 79		0.25
		10	21 : 0 : 79		0.27
<i>n</i> -C <sub>6</sub> H <sub>14</sub> <sup>d</sup>	33.1	10	27 : 0 : 73		0.37

<sup>a</sup> All reactions were carried out in the given solvent (50 cm<sup>3</sup>) at 0 °C.

<sup>b</sup> Isomer proportions were determined at >98% completion of the reaction except for PhCl as solvent. <sup>c</sup> Reaction was carried out in neat chlorobenzene and the isomer proportion was determined after ca. 1% conversion. <sup>d</sup> This solvent was slightly attacked by the NO<sub>2</sub>–O<sub>3</sub> system. <sup>e</sup> Ref. 8.

tion of halogenobenzenes are compared with the results of the present work in Table 1.

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). High *o/p* ratios (1.10 for **1** and 1.09 for **2**) were observed at low concentration in dichloromethane, while lower values (0.45 for **1** and 0.68 for **2**) were obtained in the absence of solvent. Little or no comparable variations of the *ortho-para*-isomer ratios were observed in the conventional nitration of halogenobenzenes based on the use of mixed acids.‡

‡ Isomer proportions obtained from experiments with chlorobenzene under similar conditions (HNO<sub>3</sub>–80% H<sub>2</sub>SO<sub>4</sub>; 0 °C, 20 h): 10 mmol in CH<sub>2</sub>Cl<sub>2</sub> (50 cm<sup>3</sup>) and 500 mmol (neat), were *ortho* : *meta* : *para* = 33.0 : 0 : 67.0 and 32.3 : 0.3 : 67.4, the *o/p* ratio being 0.49 and 0.48, respectively.

The dependence of isomer ratio on the initial concentration was not so marked with fluorobenzene (*o/p* ratios varied in the range 0.16–0.11). A significant change in the product ratios 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 hexane, the variation of isomer distribution became less prominent (Table 2).

We are not in a position to comment on the reason for the concentration-dependent variation of the *ortho-para*-isomer ratios, but one possible answer to this peculiar phenomenon is the changeover of the nitration mechanism depending on the initial concentration of the substrate, although the reaction pathway itself is not clear at present. Isomer control is of perennial concern from the preparative point of view, and further research may shed light on this interesting aspect of aromatic nitration.

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## References

- 1 For a general survey of nitration of halogenobenzenes, see: G. A. Olah, R. Malhotra and S. C. Narang, *Nitration, Methods and Mechanisms*, VCH, New York, 1989; K. Schofield, *Aromatic Nitration*, Cambridge University Press, London, 1980; J. G. Hoggett, R. B. Moodie, J. R. Penton and K. Schofield, *Nitration & Aromatic Reactivity*, Cambridge University Press, London, 1971; P. B. D. de la Mare and J. H. Ridd, *Aromatic Substitution, Nitration and Halogenation*, Butterworths, London, 1959.
- 2 For further information on this new methodology of aromatic nitration, see: H. Suzuki, T. Murashima, K. Shimizu and K. Tsukamoto, *J. Chem. Soc., Chem. Commun.*, 1991, 1049; H. Suzuki, T. Murashima, I. Kozai and T. Mori, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1591.
- 3 J. D. Roberts, J. K. Sanford, F. L. J. Sixma, H. Cerfontain and R. Zagt, *J. Am. Chem. Soc.*, 1954, **76**, 4525.
- 4 J. R. Knowles, R. O. C. Norman and G. K. Radda, *J. Chem. Soc.*, 1960, 4885.
- 5 G. A. Olah, S. J. Kuhn and S. H. Flood, *J. Am. Chem. Soc.*, 1961, **83**, 4581.
- 6 R. G. Coombes, D. H. G. Crout, J. G. Hoggett, R. B. Moodie and K. Schofield, *J. Chem. Soc. B*, 1970, 347.
- 7 J. V. Crivello, *J. Org. Chem.*, 1981, **46**, 3056.
- 8 C. Reichardt, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 98.