Unusual Isomer Distribution of Dinitrobenzenes and Nitrophenols Formed as Side Products during the Ozone-mediated Nitration of Benzene with Nitrogen Dioxide. Further Evidence for the Alternative Mechanism of Electrophilic Nitration of Arenes

Hitomi Suzuki* and Tadashi Mori
Department of Chemistry, Faculty of Science, Kyoto University, Kitashirakawa, Sakyo-ku, Kyoto 606-01, Japan

Dinitrobenzenes and nitrophenols formed as side products in the title reaction leading to nitrobenzene show an isomer distribution that is significantly different from those observed in the conventional nitration using nitric acid or nitric acid–sulfuric acid, suggesting the operation of a non-classical nitration mechanism involving nitrogen trioxide as the initial electrophile.

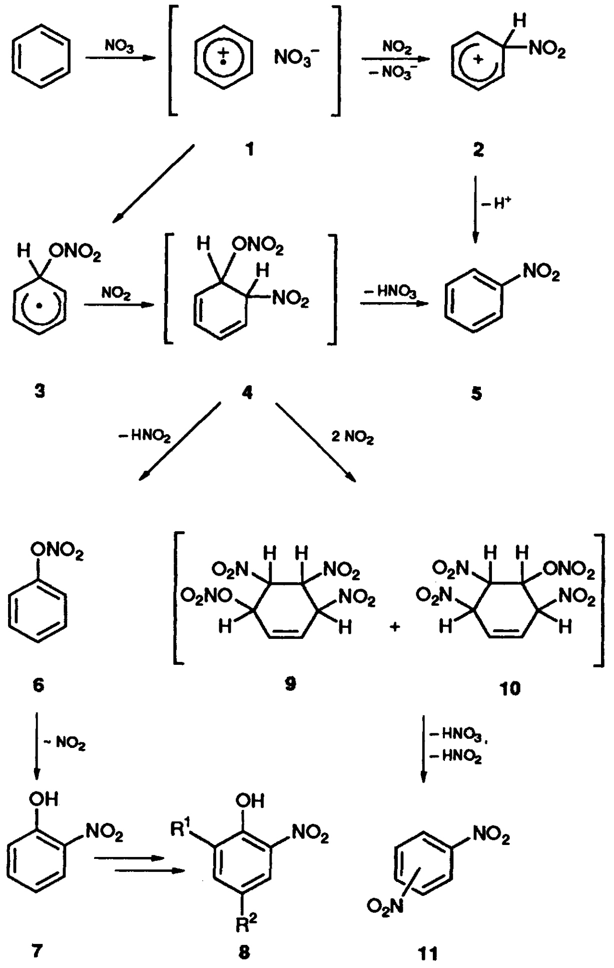
Thanks to thorough studies by British chemists, various aspects of electrophilic aromatic nitration are now well understood in terms of a single reaction mechanism involving the nitronium ion (NO_2^+) as the universal electrophile.[1] Since it is a strong Lewis acid, the nitronium ion requires *acidic* conditions for its generation and therefore, conventional aromatic nitration has been carried out using nitric acid or nitric acid–sulfuric acid (mixed acid) as the nitrating agent. Recently we have reported an alternative type of electrophilic aromatic nitration which can be conducted satisfactorily under *neutral* conditions, *i.e.*, the ozone-mediated nitration of arenes with lower oxides of nitrogen (*kyodai* nitration).[2–6] The reaction is most likely to proceed *via* nitrogen trioxide (NO_3) as initial electrophile,[2–4] which is a highly electron-deficient radical species not requiring acidic conditions for its generation. In this paper, we provide further evidence which endorses the possible role of nitrogen trioxide as the electrophile for the *kyodai* nitration of non-activated arenes, represented herein by benzene.

Results and Discussion

Lower oxides of nitrogen show little or no nitrating ability towards benzene at ordinary temperature. Only under forcing conditions, *i.e.*, at elevated temperature,[7] under irradiation[8] or in the presence of strong acid catalyst,[9] do such nitrogen oxides react with benzene to form nitrobenzene, usually accompanied by varying amounts of side products arising from concurrent oxidation, addition, condensation and/or coupling reactions. Because of the complex nature of the product, most of the reported reactions appear to be of no practical significance.

In the presence of ozone, however, lower nitrogen oxides such as nitrogen monoxide, dinitrogen trioxide and nitrogen dioxide are activated to act as excellent nitrating agents for aromatic systems.† Thus, when a stream of ozonized oxygen was introduced into a solution of benzene in dry dichloromethane in the presence of excess of nitrogen dioxide at 0 °C, the substrate was rapidly nitrated to afford nitrobenzene **5** as the major product. The yield of the product increased linearly with time over a wide range of reaction times until the substrate had been completely consumed. Since the rate of introduction of ozone was kept constant throughout the reaction (see Experimental section), the linear profile could be regarded as showing a quasi-zero-order reaction, the effective concentration of ozone in the reaction system being the rate-determinant.

Careful examination of the side products by GLC, HPLC and GC–MS revealed the presence of three isomeric dinitrobenzenes **11**, 2-nitrophenol **7**, and 2,4- and 2,6-dinitrophenols **8a** and **8b**. The relative ratios of these products varied



a $R^1 = H$; $R^2 = NO_2$
b $R^1 = NO_2$; $R^2 = H$

Scheme 1

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† A combination of nitrogen monoxide (nitric oxide), nitrogen dioxide (dinitrogen tetraoxide) and oxygen has recently been found to show good nitrating ability towards alkylbenzenes under certain conditions.[10] Nitrogen trioxide (NO_3), derived from nitrogen monoxide and oxygen *via asym*-nitrogen trioxide (ONOO),[11] is considered to be responsible for this reaction also.

Table 1 Effect of the substrate–reagent ratio on the products distribution of the *kyodai* nitration of benzene[a]

Initial concentration/mol dm^{-3}		Reaction time (t/min)	Yield (%)	Product distribution (%)[b] **5**:**11**(o:m:p):**7**
C_6H_6	NO_2			
0.31	11	10	12.4	88.0:11.0 (9:67:24):1.0
0.36	3.1	10	9.9	86.0:12.1 (7:63:30):1.9
0.37	3.1	60	60.6	93.7:2.7 (4:64:32):3.6[c]
0.37	3.1	120	97.6	91.7:2.5 (2:56:42):5.8[d]
0.37	3.1	60	4.3[e]	48.1:—[f] (—):51.9[c]
0.38	1.1	10	7.1	90.5:6.6 (6:57:37):2.9
0.097	1.1	10	27.5	89.2:9.2 (7:59:34):1.6
0.020	1.1	10	55.2	90.2:8.8 (7:65:28):1.0
11[g]	1.1	10	0.4	87.9:9.2 (11:55:34):2.9
2.9	0.83	10	1.0	86.7:9.9 (7:60:33):3.4
1.7	0.95	10	1.9	90.8:6.0 (6:61:33):3.2
0.38	0.55	10	6.3	90.5:5.8 (7:69:24):3.7
0.39	0.22	10	4.0	87.2:5.8 (13:60:27):7.0
0.39	0.055	10	0.5	86.3:—[f] (—):13.7

[a] All reactions were carried out in dichloromethane (50 cm^3) at 0 °C, unless otherwise indicated. [b] Determined by GLC. [c] A mixture of nitrophenols **7** and **8** (4:6) was obtained. [d] Only dinitrophenols **8a** and **8b** (9:1) were obtained. [e] Reaction was carried out at −78 °C. [f] Not detected. [g] Reaction was carried out for neat benzene.

Table 2 Effect of solvent and additives on the product distribution in the *kyodai* nitration of benzene at low conversion[a]

Solvent	Solvent parameters[b] π^*, $E_T(30)$, DN	Additive (equiv.)	Yield (%)	Product distribution (%)[c] **5**:**11**(o:m:p):**7**
$MeNO_2$	0.85, 46.3, 2.7	—	10.9	98.1:0.7 (14:69:17):1.2
MeCN	0.75, 45.6, 14.1	—	10.2	87.7:2.3 (16:51:33):10.0[d]
$(CH_2Cl)_2$	0.81, 41.3, 0.0	—	9.1	92.1:6.0 (8:63:29):1.9
CH_2Cl_2	0.82, 40.7, 1.0	—	7.1	90.5:6.6 (6:57:37):2.9
		HNO_3[e] (0.1)	7.5	89.0:1.3 (8:59:33):9.7[f]
		HNO_3[e] (1.0)	11.4	85.5:7.3 (5:60:35):7.2[f]
		$MeSO_3H$ (0.1)	8.5	88.8:1.5 (8:64:28):9.7[g]
$CHCl_3$	0.58, 39.1, 4.0	—	1.5	58.5:21.0 (5:66:29):20.5
CCl_4	0.28, 32.4, 0.0	—	3.7	91.4:4.4 (9:63:28):4.2
n-C_6H_{14}	−0.04, 31.0, 0.0	—	12.9	98.6:0.6 (14:61:25):0.8

[a] All reactions were carried out in the given solvent (50 cm^3) at 0 °C, ozone (6 mmol) being bubbled through for 10 min. Initial concentrations of benzene and nitrogen dioxide were 0.38 and 1.1 mol dm^{-3}, respectively. [b] Polarity/polarizability π^*, polarity $E_T(30)$ and donor number (DN) from ref. 25. [c] Determined by GLC. [d] A mixture of nitrophenols **7** and **8** (3:7) was obtained. [e] Fuming nitric acid (d = 1.50) was added before starting the reaction. [f] A mixture of nitrophenols **7** and **8** (6:4) was obtained. [g] A mixture of nitrophenols **7** and **8** (4:6) was obtained.

considerably depending on the reaction conditions employed (Tables 1 and 2). The formation of compounds **7** and **11** was observed from the beginning of the reaction, but polynitrophenols **8** were formed gradually as the reaction proceeded. The isomer composition of dinitrobenzenes obtained (o:m:p = 2–13:55–67:27–42) was significantly different from the corresponding composition (o:m:p = 4–10:87–94:1–3) observed in the conventional nitrations based on the use of nitric acid, mixed acid or nitronium salt.[12–15] In view of the exceptionally high proportion (up to 42%) of the *para*-isomer and the reluctance of nitrobenzene **5** to undergo the *kyodai* nitration in the absence of acid catalyst, it is unlikely that the dinitrobenzenes **11** were derived from the further nitration of the initially formed nitro-compound **5**. In the presence of methanesulfonic acid as a catalyst, nitrobenzene was smoothly converted into dinitrobenzenes by the *kyodai* nitration, the isomer proportion being o:m:p = 8:91:1, while the isomer composition of compound **11** obtained by the direct dinitration of benzene in dichloromethane using a large excess of HNO_3–H_2SO_4 (8:2) at 0 °C was o:m:p = 5:94:1, with little or no phenolic products.

The *kyodai* nitration of benzene has been carried out in several different solvent systems, but the results obtained did not show any definite relationship between the unusual isomer composition and common solvent parameters (Table 2). Addition of protonic acid accelerated the reaction only slightly, but increased the amount of the phenolic products considerably. Under these conditions, 2-nitrophenol **7** was further nitrated to give dinitrophenols **8**. When nitromethane or *n*-hexane was used as the solvent, the proportion of nitrobenzene increased at the expense of side products **7** and **11**. Interestingly, the reaction was quite sluggish in chloroform and the relative amounts of dinitrobenzenes and phenolic products were increased. The slowing of the reaction may be a reflection of a recent finding that chloroform reacts with nitrogen trioxide more than ten times as rapidly as dichloromethane.[16]

Formation of phenolic by-products during aromatic nitration has long been known.[17] In the nitration of benzene and nitrobenzene with mixed acid, 2,4-dinitrophenol **8a** and 2,4,6-trinitroresorcinol are formed as the respective phenolic by-products.[18] These findings contrast with our results where 2-nitrophenol **7** is the sole mononitrophenol and 2,6-dinitrophenol **8b** is an important component of the dinitrophenols obtained. Possible formation of compound **7** from phenyl nitrate **6** *via* the coupling of the phenoxyl radical–nitrogen dioxide pair is supported by the absence of 4-nitrophenol in the product mixture.[19] At low temperatures, the formation of nitrophenol was markedly enhanced, although the reaction became quite slow; at −78 °C the proportion of compound **7** was as high as 52% at 4% conversion. As discussed later, this finding suggests that nitric acid is more easily eliminated from adduct **4** than nitrous acid as the temperature increases.

The unusual isomer distributions of dinitrobenzenes and nitrophenols may be rationalized by the addition–elimination sequence,[4] in which the nitrogen trioxide is involved as the initial electrophile (Scheme 1). A rapid reaction between nitrogen dioxide and ozone produces nitrogen trioxide, which is highly electron-deficient and a strongly oxidizing species, especially in solution.[20] The addition–elimination mechanism for aromatic nitration was proposed earlier by Titov to explain the formation of polynitro and phenolic compounds in the reaction of arenes with nitrogen dioxide at elevated temperatures,[21] where he assumed the direct attachment of radical species to the unsaturated bond of aromatic systems. In our case, however, we favour the view that the single-electron-transfer oxidation of the arene by nitrogen trioxide is followed by coupling between the nitrate anion and the cation radical of benzene to form the primary adduct. The reaction between radical cations and nucleophiles is known to be much faster than the coupling between arene cation radicals and nitrogen dioxide.[22] Thus, Eberson and associates were successful in isolating such an adduct in low yield, which arose from the photochemical electron-transfer reaction between benzene and tetranitromethane.[23] In the present case, benzene would be oxidized by nitrogen trioxide to generate the cation radical–anion pair **1**, which is then trapped by nitrogen dioxide to give the arenium ion **2** and subsequently nitrobenzene **5** *via* proton loss. The ion-radical pair **1** may in part collapse into the radical intermediate **3**, which is converted into adduct **4** and subsequently rearomatizes with elimination of nitric acid to afford compound **5**. Loss of nitrous acid from adduct **4** leads to phenolic product **7** *via* aryl nitrate **6**.[19] The adduct **4** may take up further molecules of nitrogen dioxide to form cyclohexene derivatives **9** and **10**. Elemination of nitric and nitrous acid molecules from these adducts eventually leads to dinitrobenzenes **11**. These higher adducts may also be responsible in part for the formation of phenolic products.

Semi-empirical PM3 calculations carried out for adducts **4** have shown that formation of the *trans*-isomer is favoured over the *cis*-isomer, calculated standard enthalpies for the formation of *trans*- and *cis*-isomers being 8.7 and 16.8 kJ mol^{-1}. respectively. This means that the addition of nitrogen dioxide to radical intermediate **3** would proceed predominantly in a *trans*-mode. If we assume such a *trans*-1,2-addition predominates in subsequent reaction of the primary adduct **4** with nitrogen dioxide, all-*trans* types of adducts **9** and **10** would result, the enthalpies of formation of which are calculated to be −49.1 and −56.0 kJ mol^{-1}, respectively. Under protonic acid catalysis, the adducts **9** and **10** would decompose by loss of nitric acid followed by nitrous acid *via* two successive 1,2-eliminations, giving a mixture of isomeric dinitrobenzenes **11**. Although no information is available in literature on the aromatization mode of these adducts, the more favoured adduct **10** is expected mainly to lead to the *meta*- and *para*-isomers, while the less favoured adduct **9** will lead to the *ortho*- and *meta*-isomers. The unusually high proportion of *p*-dinitrobenzene observed in the present reaction may be a reflection of the importance of adduct **10** over **9** as an intermediate for the formation of dinitrobenzenes.

In summary, benzene reacts easily with nitrogen dioxide in the presence of ozone at low temperature to give nitrobenzene as the major product, along with isomeric dinitrobenzenes and nitrophenols as minor products. The observed isomer proportion of dinitrobenzenes, $o:m:p$ = *ca.* 1:6:3, is incompatible with the classical electrophilic mechanism based on the nitronium ion as electrophile. The *kyodai* nitration can be rationalized by an alternative electrophilic mechanism which involves the electron-transfer and addition–elimination sequences with nitrogen trioxide being the initial electrophile. The nitration of arenes has long been carried out under acidic conditions using nitric acid as the sole source of the nitro group.

Experimental

General experimental details were as given previously.[2] All reagents and solvents used were reagent-grade, obtained from commercial sources. Dichloromethane was dried by distillation from calcium hydride. Nitrogen dioxide (99% pure) was obtained in a cyclinder 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. This apparatus produced ozone at a rate of 0.6 mmol min^{-1} with an oxygen supply of 10 dm^3 h^{-1} under an applied voltage of 80 V. Its efficiency was calibrated by iodometric titration. Benzene was distilled from calcium hydride prior to use. Products were identified by IR and ^1H NMR spectroscopy, GC–MS or direct comparison with the authentic samples.

General Procedure for the Kyodai *Nitration of Benzene.*—Benzene and nitrogen dioxide were dissolved in an appropriate molar ratio in freshly distilled dichloromethane (50 cm^3) and the solution was placed in a 50 cm^3 flask fitted with a gas inlet tube and a vent for waste gas. The mixture was cooled to 0 °C in a bath, while a stream of ozonized oxygen was introduced with vigorous stirring through the inlet tube, which dipped just below the surface of the liquid. Throughout the reaction, ozonized oxygen was fed continuously at a low flow rate. Under these conditions, the loss of nitrogen dioxide was not significant. The progress of the reaction and the product composition were intermittently monitored by GLC using cyclododecane 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. After the lapse of an appropriate time, the reaction was quenched and excess of nitrogen dioxide was expelled by blowing air through 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 nitrobenzenes and phenolic products as an oily residue.

Molecular orbital calculations were carried out with the MOPAC[24] program (version 6.10) using the semi-empirical PM3 method implemented on a Sony Tektronix CAChe system (version 3.5). Unrestricted Hartree–Fock wave functions were employed and the calculations were carried out by full optimization using the extra keyword PRECISE.

Acknowledgements

We acknowledge support of this work by a Grant-in-Aid for Scientific Research No. 05554023 from the Ministry of Education, Science and Culture.

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Paper 4/04875J
Received 8*th August* 1994
Accepted 9*th September* 1994