Ozone-mediated Nitration of Arenes with Nitrogen Dioxide: Change-over of the Orienting Influences of Alkyl, Alkoxyl and Halogen Substituent Groups from *Meta* to *Ortho-Para* Dominance

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In ozone-mediated nitration of toluene, anisole and chlorobenzene with nitrogen dioxide, the initial products have been found to be composed mainly of the *meta*-nitro derivatives, but the isomer distributions are rapidly replaced by the *ortho-para* isomers as the reaction proceeds, suggesting the operation of the electron transfer mechanism involving the nitrogen trioxide as initial electrophile.

Being a weak electrophile of radical character, nitrogen dioxide is not generally considered as a good nitrating agent for aromatic systems. In the presence of ozone, however, it is activated to act as a powerful nitrating agent, converting non- and even de-activated arenes into the corresponding mono- or poly-nitro derivatives in good yields.[1] The reaction, referred to as the kyodai-nitration,† appears to be an electrophilic aromatic process and is characterized by unique features such as the high *ortho*-directing trends of the acyl,[2] acylamino[3] and halogen substituents,[4] reversal of the *ortho-para* isomer ratio depending on the concentration of substrate,[4] and catalysis by some transition metal complexes.[5] We now report that the intrinsically *ortho-para* directing arenes such as toluene, anisole and chlorobenzene are nitrated by the present system in a quite unexpected way, giving mainly *meta*-nitro derivatives as the initial products of the reaction. With the progress of the reaction, however, the isomer distribution is rapidly restored to the normal pattern of *ortho-para* orientation.

During the course of monitoring the isomer proportion of the nitration product of chlorobenzene against the time elapsed from the start of the reaction, we were surprised to observe that the initial product was almost *m*-nitrochlorobenzene contrary to our belief that there should be *ortho*- and *para*-nitro derivatives (Table 1). The relative importance of the *meta*-isomer decreased rapidly as the reaction proceeded and at a later stage the isomeric composition bore the appearance of an ordinary aromatic nitration ($o:m:p$ = 30–53 : 0–3 : 47–67). When small amounts of methanesulfonic acid or nitric acid‡ were added at the initiation stage, such an anomaly was less noticeable or not observed. Changing the reaction medium from dichloromethane to the more polar nitromethane allowed the normal pattern of electrophilic substitution to be restored.

The conventional nitration of anisole has long been known to afford a mixture of *ortho*- and *para*-isomers, the *meta*-isomer. usually being slight or negligible.[6] When this compound was subjected to the kyodai-nitration in the presence of pyridine, the relative ratio of *meta*-nitroanisole was significant again at the initial stage and it rapidly decreased as the reaction proceeded. However, addition of pyridine delayed

Table 2 Kyodai-nitration of toluene, anisole and chlorobenzene in the presence of pyridine[a]

	Conditions			
Arene	Reaction time (t/h)	Amine base added/mmol[b]	Conv. (%)	Products (%)[c] $o:m:p$
Toluene	1	—	99	51: 6:43
	1	Py (10)	12	15:77: 8
	2	Py (30)	21	22:66:12
	3	Py (30)	80	41:36:23
Anisole	0.5	—	5[d]	61:—:39
	0.5	Py (10)	2	36:39:25
	1	Py (10)	28	53: 6:41
	1	Py (30)	3	25:54:21
	2	Py (10)	99	55: 1:44
	1	3,5-Me_2Py (30)	6	32:29:39
	1	2,6-Me_2Py (30)	23	44: 1:55
Chlorobenzene	1	Py (30)	2	7:91: 2
	2	Py (30)	6	9:86: 5

[a] All reactions were carried out in the presence of an excess nitrogen dioxide at 0 °C, using a mixture of arene (10 mmol) and dichloromethane (50 cm^3). Ozone was introduced at a rate of 10 mmol h^{-1}. [b] Py = Pyridine [c] Isomer proportion of products, determined by GLC. [d] Anisole (100 mmol) was employed.

Table 1 Effect of solvents and some additives on the isomer distribution at the initial stage of the kyodai-nitration of chlorobenzene[a]

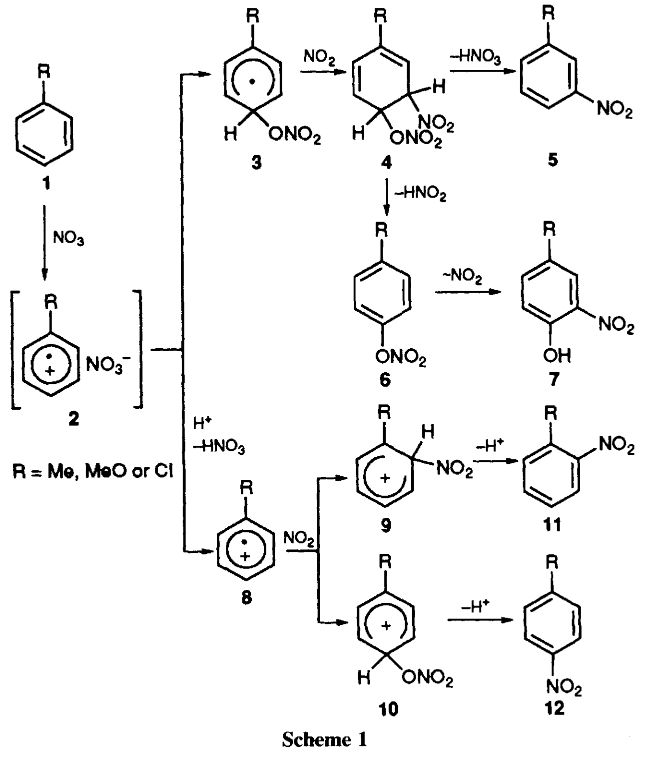
Solvent	Solvent parameters[b] π^*, $E_T(30)$, DN	Additive (equiv.)	Conversion (%)	Isomer proportion of products (%)[c] $o:m:p$
$MeNO_2$	0.85, 46.3, 2.7	—	3.5	27: 3:70
MeCN	0.75, 45.6, 14.1	—	0.18	15:44:41
$Cl(CH_2)_2Cl$	0.81, 41.3, 0.0	—	0.66	42: 7:51
CH_2Cl_2	0.82, 40.7, 1.0	—	0.05[e]	9:71:20
			0.13[f]	20:61:19
			0.33	21:46:33
			1.6[g]	30:17:53
		HNO_3[d] (0.1)	0.65	31:22:47
		HNO_3[d] (1.0)	1.6	49: 1:50
		$MeSO_3H$ (0.1)	3.0	30: 4:66
$CHCl_3$	0.58, 39.1, 4.0	—	0.15	8:88: 4
CCl_4	0.28, 32.4, 0.0	—	0.08	17:56:27
n-Hexane	−0.04, 31.0, 0.0	—	0.28	23: 5:72

[a] All reactions were carried out in the given solvent (50 cm^3) at 0 °C, ozone (3.0 mmol) being bubbled through for 5 min, unless otherwise indicated. Initial concentrations of chlorobenzene and nitrogen dioxide were 0.38 and 0.2 mol dm^{-3}, respectively. [b] Polarity/polarizability π^*, polarity $E_T(30)$ and donor number (DN) from ref. 11. [c] Determined by GLC on a Shimadzu GC 14A gas chromatograph using a CBP1-M25-025 fused silica capillary column. Cyclododecane was employed as an internal standard. [d] Nitric acid (d = 1.50) was added before starting the reaction. [e] Ozone (0.6 mmol) was introduced within 1 min. [f] Ozone (1.2 mmol) was introduced within 2 min. [g] Ozone (6.0 mmol) was introduced within 10 min.

the progress of the reaction considerably (Table 2). A similar phenomenon was also observed with toluene and chlorobenzene. When pyridine was introduced carefully in such a way so as to supply an amount equimolar to the anisole consumed, the proportion of the *meta* isomer could be raised as high as 60–70% at around 20% conversion. Pyridine could be replaced by 3,5-dimethylpyridine and pyridazine, but 2,6-dimethylpyridine and 4-(*N,N*-dimethylamino)pyridine were ineffective to enhance the *meta*-substitution.

In view of the current controversies over classical (electrophilic) and nonclassical (electron transfer) mechanisms of aromatic nitration,[7] our findings are of special interest. In the photoinduced reaction of *tert*-butylbenzene and bromobenzene with *N*-nitropyridinium salts in acetonitrile, Kochi and coworkers have observed a high proportion of *meta*-substitution at an early stage of the photochemical conversion and explained the unusual result by the addition–elimination mechanism involving the intermediary of a cyclohexadiene adduct.[8] Our observation of a similar anomaly in orientation may also be explained by assuming the nitrogen trioxide as the initial electrophile (Scheme 1). Ozone and nitrogen dioxide produces nitrogen trioxide, which oxidizes arene **1** to form cation radical-anion pair **2**. In the absence of protonic acid (*i.e.* at initial stage of the reaction), the ion-radical pair collapses into radical intermediate **3**.[¶] This intermediate is trapped by nitrogen dioxide at the *meta* position to give adduct **4**, which rearomatizes under the elimination of nitric acid to afford the *meta*-substitution product **5**. Loss of nitrous acid from the adduct eventually leads to phenolic products **7** *via* aryl nitrate **6**.[§] In the presence of protonic acid (*i.e.* as the reaction proceeds), however, the nitrate anion is removed from ion-radical pair **2** as nitric acid and the resulting cation radical **8** is trapped by nitrogen dioxide at the *ortho* and *para* positions to yield ordinary arenium ions **9** and **10**, thus leading to the *ortho*- and *para*-substitution products **11** and **12**.

Our finding poses a challenge to the general acceptance over the years that dinitrogen pentaoxide can react in two different modes; (*i*) in an ionic process involving the heterolytic cleavage of the pentaoxide to generate the nitronium ion, and (*ii*) in a molecular process in which the pentaoxide reacts *via* a polarized form.[9] Gaseous dinitrogen pentaoxide is known to exist in an equilibrium with nitrogen trioxide and nitrogen dioxide.[10] If we assume that dinitrogen pentaoxide can occur in chlorinated hydrocarbons, at least partly in an equilibrium, and that the electron transfer from arenes to nitrogen trioxide is rapid enough as compared with the molecular nitration by dinitrogen pentaoxide, then the reaction of dinitrogen pentaoxide with arenes would be expected to follow a reaction sequence similar to that shown in Scheme 1. This aspect of aromatic nitration remains to be elucidated.



Scheme 1

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Footnotes

[†] The nitration of arenes with lower nitrogen oxides using a combination of ozonized air and a third substance as the promoter is now the subject of industrially-based research to circumvent the problems arising from the classical methodologies based on the use of nitric acid–sulfuric acid. The prefix kyodai stands for Kyoto University, where the initial fundamental research was carried out.

[‡] Nitric acid is less effective than methanesulfonic acid in accelerating the reaction.

[§] Small to trace amounts of phenolic products always accompany the kyodai-nitration.

[¶] Although Titov earlier suggested the direct addition of nitrogen trioxide to arenes to form radical **3**,[12] we favour the two-stage process involving ion-radical pair **2** as the initial intermediate.

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