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Ozone-Mediated Nitration of Phenylalkyl Ethers, Phenylacetic Esters, and Related Compounds with Nitrogen Dioxide. The Highest *Ortho* Substitution Observed in the Electrophilic Nitration of Arenes

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By the combined action of ozonized oxygen and nitrogen dioxide (the *kyodai*-nitration), the title compounds were smoothly nitrated in dichloromethane at subzero degrees with high *ortho* positional selectivity. Although the conventional nitration of phenylacetic acid and esters mainly produces *m*- and *p*-nitro derivatives, the present nitration offers a simple high-yield synthesis of *o*-nitro derivatives which are important as precursor in organic synthesis. The proportions of the *ortho* isomer in the nitration products from methyl 2-phenylethyl ether and methyl phenylacetate were 71 and 88%, respectively, the latter value being the highest *ortho* isomer proportion so far observed in the electrophilic aromatic nitration. The observed high *ortho* selectivity has been rationalized in terms of radical cation intermediate and six-membered cyclic transition state.

Introduction

The control of *ortho*−*para* isomer ratio in electrophilic aromatic substitution is an everlasting challenge to organic chemists. Low positional selectivity means the formation of large amounts of unwanted product or products, the disposal of which would often be problematic, bringing on economical loss or environmental concern. Steric bulkiness of reagent and/or substrate usually provides one solution for *para*-selective aromatic substitution. Thus the attachment of a bulky group such as *tert*-butyl onto aromatic substrate directs the entering electrophile to an unhindered site, favoring the substitution *para* to the blocking group. Some supported reagents and catalysts are also known to favor the *para* substitution.[1] However, is there any sort of promising means available to us when we need the *ortho* substitution products?

The nitration of benzylic ethers and phenylacetic esters has been studied in some detail because of the synthetic utilities of the products as well as mechanistic interest. A high proportion of the *o*-nitro derivatives observed in the nitration of these compounds with acetyl nitrate stands in marked contrast to the results obtained from the conventional nitration based on the use of nitric acid alone or nitric acid−sulfuric acid (mixed acid). This interesting phenonmenon has been explained in terms of an S_N2-type displacement reaction involving dinitrogen pentaoxide as the actual nitrating species.[2] The conventional nitration of these compounds proceeds in strong acid medium through a protonated or solvated species rather than a neutral one, while a special mechanism operates in the nitration with acetyl nitrate where the nitronium ion, generated *in situ* from dinitrogen pentaoxide, coordinates toward the oxygen function of side chain prior to the nuclear attack. A similar mechanism has also been proposed to explain the high *ortho* selectivity in the nitration of acetanilides.[2] The recently reported nitration of phenylacetic esters with nitric acid in dichloromethane has shown that the high *ortho* selectivity can be realized under appropriate substrate/reagent ratios. This finding was interpreted in terms of the precomplex formation between nitric acid and solvent employed.[3]

We report herein the ozone-mediated nitration of phenylalkyl ethers, phenylacetic esters, and some related compounds with nitrogen dioxide (the *kyodai*-nitration[4]), proposing an alternative mechanistic view based on radical cation intermediates for the observed high *ortho* selectivity. The classical nitration of phenylacetic acid and esters mainly produces *m*- and *p*-nitro derivatives, while our nitration offers a unique, simple high-yield synthesis of *o*-nitro derivatives which are important as precursors to oxindoles and derivatives.[5]

Results and Discussion

The *Kyodai*-Nitration of Ethers. Methyl phenylalkyl ethers **1** were smoothly nitrated by the *kyodai* method to give an isomeric mixture of nitro compounds in excellent yields (Table 1). The examination of methoxyalkyl groups of different chain length has revealed that the relative distance between the aromatic nucleus and the oxygen atom has a profound influence over the isomer composition of the products. Thus, when methyl 2-phenylethyl ether **1b** was subjected to this reaction at 0 °C, the *o*-nitro ether **2b** was obtained in a yield above 70%, the *o*/*p* isomer ratio being 2.73. A similar high *ortho* selectivity was reported for the nitration with acetyl nitrate in acetic anhydride ($o/p = 1.84$).[6] These results contrast to the nitration with mixed acid, where the major product is *p*-nitro derivative ($o/p = 0.3-0.5$).[7] When our reaction was carried out under much milder conditions, the *ortho* selectivity was further improved;

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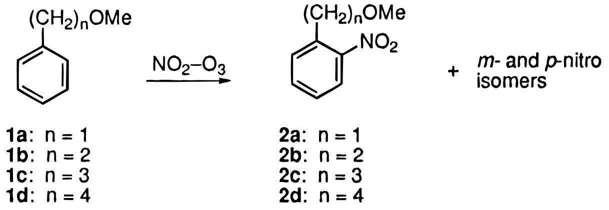
Table 1. The *Kyodai*-Nitrations of Methyl Phenylalkyl Ethers 1a–d and Phenylacetic Esters 3a–c[a]

substrate		E_p[b]	yield (%)[c]	isomer proportions *o*:*m*:*p* (%)
benzyl methyl ether	**1a**	2.76	>99	69:4:27
methyl 2-phenylethyl ether	**1b**	2.65	>99 (77)	71:3:26
			98[d]	79:2:19
			58[e]	81:6:13
methyl 3-phenylpropyl ether	**1c**	2.64	>99	38:3:59
methyl 4-phenylbutyl ether	**1d**	2.70	>99 (74)	54:3:43
tert-butyl 2-phenylethyl ether[f]		2.63	96 (77)	70:4:26
methyl phenylacetate	**3a**	2.70	85 (84)	88:4:8
ethyl phenylacetate	**3b**	2.79	78	87:5:8
isobutyl phenylacetate	**3c**	2.96	50	88:4:8
n-butylbenzene		2.66	>99	55:1:44

[a] All reactions were carried out for a substrate (5 mmol) in dichloromethane (20 mL) and nitrogen dioxide (1.0 mL) at 0 °C for 1 h, unless otherwise indicated. [b] V *vs* NHE. [c] GC yield. [d] Isolated yields after purification on silica gel are given in parentheses. [d] At −20 °C. [e] At −78 °C. [f] Reaction was carried out using a double amount of nitrogen dioxide.

Scheme 1



the reaction performed at −78 °C revealed as high as 81% of the *ortho* product. The *kyodai*-nitration of *n*-butylbenzene carried out under the same conditions showed the *o*/*p* isomer ratio of 1.25, demonstrating an important role of the ether function in the enhancement of the *ortho* substitution (Scheme 1).

The *ortho* selective substitution may be rationalized on a similar basis as has been discussed in a previous paper.[8] For example, the SET reaction between nitrogen trioxide and ether **1b** generates the radical cation **6** through a radical cation−nitrate anion pair **5** (Scheme 2).[9,10] Semiempirical MO calculation[11] for radical cation **6** revealed its radical susceptibility to be highest on the oxygen atom (Figure 1). Nitrogen dioxide combines with the oxygen atom of the radical cation to form the intermediate ion **7**, which then rearranges through an energetically favored, six-membered cyclic transition state to yield the *o*-nitro isomer **2b**.

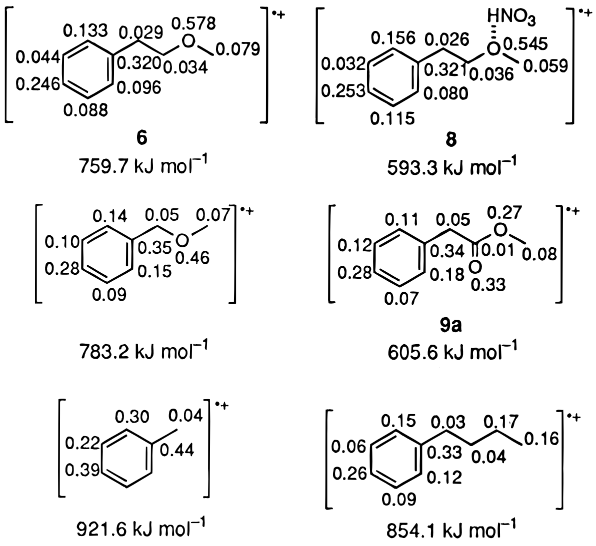


Figure 1. Frontier electron densities for the radical reaction, calculated by the PM3 method, of the radical cations derived from methyl 2-phenylethyl ether **6** and related compounds.

Scheme 2

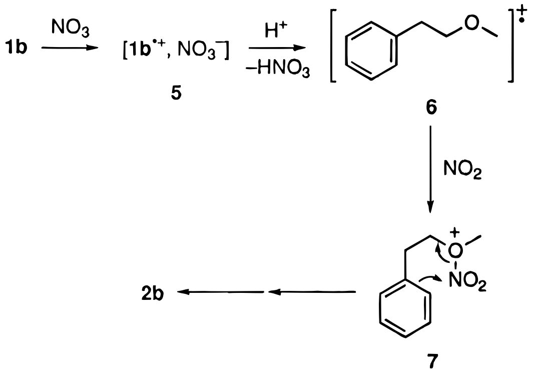


Table 2. Comparison of the Nitrations of Methyl 2-Phenylethyl Ether 1b under Various Conditions[a]

reagent	solvent	additive	conversion (%)	isomer proportions *o*:*m*:*p* (%)
NO_2-O_3	CH_2Cl_2	−	34	79:4:17
		$MeSO_3H$ (1 equiv)	26	70:2:28
		fum-HNO_3 (1 equiv)	41	64:1:35
	$MeNO_2$	−	37	66:3:31
	MeCN	−	38	65:4:31
	$CHCl_3$	−	14	76:4:20
	$ClCH_2CH_2Cl$	−	45	81:2:17
HNO_3−H_2SO_4			−	29:9:62[b]
$AcONO_2$−MeCN			−	66:4:30[b]

[a] All reactions were carried out for the substrate (5 mmol) in dichloromethane (20 mL) containing nitrogen dioxide (1.0 mL) at 0 °C for 10 min. [b] At 0 °C. See ref 2.

A similar *ortho* enhancement was observed in 1,2-dichloroethane, but in more polar solvents such as nitromethane and acetonitrile, or in the presence of a protic acid, the *ortho* selectivity decreased (Table 2). In order to see if the coordination of an acid molecule to the radical cation may lower the *ortho* selectivity, the semiempirical MO calculation was carried out for a model species **8** in which one molecule of nitric acid is associated to the radical cation **6** at the ether function (Figure 1). In this simple model, the radical susceptibility of the oxygen atom is lowered while that of the ring carbon atom at *para* position is slightly increased as compared with the noncoordinated species **6**. The ratios of the $c_{\text{oxygen}}/c_{p\text{-carbon}}$ coefficients are 2.35 and 2.15 for the relevant species **6** and **8**, respectively, which correspond to *ca.* 10% increase of the *p*-carbon selectivity. Association of multiple acid and/or solvent molecules to the radical cation would lead to much lower spin density on the oxygen atom, resulting in further decrease in *ortho* orientation.

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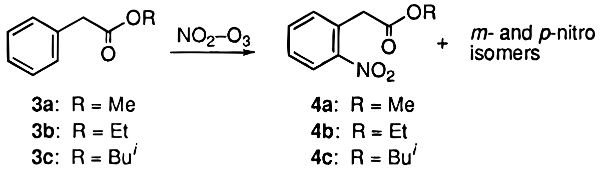
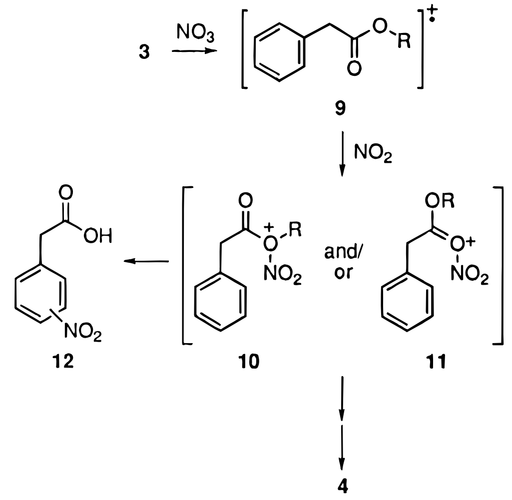
Scheme 3



Scheme 4



The *kyodai*-nitration in chloroform was found to be somewhat sluggish as compared with those carried out in the other solvents (Table 2). A similar anomaly observed in the *kyodai*-nitration of benzene in chloroform[10] was attributed to the fact that chloroform is 10 times more reactive toward nitrogen trioxide than dichloromethane.[12]

The *Kyodai*-Nitration of Esters. Under similar conditions, alkyl esters of phenylacetic acid **3** were also easily nitrated to give a high proportion of the *ortho* isomers **4** in good yields (Scheme 3; Table 1). The reactions proceeded more slowly as compared to the nitration of phenylalkyl ethers, and nitrophenylacetic acid **12** was obtained as a minor byproduct.

The high *ortho* orientation may be explained in a way similar to that made for the nitration of phenylethyl ether (Scheme 4). The oxonium ion intermediates **10** and/or **11** derived from the reaction of nitrogen dioxide and radical cation **9** undergo rearrangement through a six-membered cyclic transition state to afford the *ortho* nitro products **4**. The semiempirical MO calculation performed for the radical cation **9a** revealed the high radical susceptibility of both the alcoholic and carbonyl oxygen atoms (Figure 1). The value at the *ipso* position is also high, but the attachment of a nitrogen dioxide molecule to this carbon atom would be less favored by steric hindrance of the side chain. The side product **12** can be derived from the nitrogen dioxide adduct **10** by a loss of alkyl moiety. Diminished yield of the mononitration products according to the increase of steric bulk of alkyl groups may be a reflection of easier loss of the alkyl moiety as a cation (Table 1).

Partial Rate Factors. Relative rates and partial rate factors of the nitration are given for some selected substrates in Table 3. Partial rate factors for the *ortho* substitution of the compounds **1b** and **3a** are higher than those of toluene or compound **1c**.[7,13] The relative rate of **1b** is slightly lower than that of toluene ($k_{\text{toluene}}/k_{\text{benzene}} = 32^{9c}$), probably due to the electron-withdrawing nature of the oxygen function on the side chain. Noticeable rate enhancement is observed with those substrates which can take a six-membered cyclic transition state, *i.e.*, **1b** and **3a**. The nitration with mixed acid is slower, since the substrates are protonated to a considerable extent in a strong acid such as sulfuric acid.[7]

Table 3. Relative Rates and Partial Rate Factors for the *Kyodai*-Nitration of Some Selected Arenes Bearing the Methoxyalkyl or Alkoxycarbonylmethyl Substituents[a]

substrate	conditions	$k_{\text{PhR}}/k_{\text{PhH}}$[a]	f_o	f_m	f_p	reference
1b	$NO_2–O_3$	30	68	3	39	this work[b]
	$HNO_3–Ac_2O$	17	–	–	–	7
	$HNO_3–H_2SO_4$	1.8	–	–	–	7
1c	$NO_2–O_3$	31	56	3	71	this work[b]
	$HNO_3–Ac_2O$	29	–	–	–	7
	$HNO_3–H_2SO_4$	4	–	–	–	7
3a	$NO_2–O_3$	15	37	3	8	this work[b]
3b	$HNO_3–Ac_2O$	3.7	4.6	1.2	10	13

[a] Relative rate to benzene. [b] Determined at around 15% conversion in dichloromethane at 0 °C.

Conclusion

Methyl 2-phenylethyl ether and phenylacetic esters undergo the *kyodai*-nitration smoothly in dichloromethane at subzero degrees to produce a high proportion of the corresponding *ortho* isomers. The high *ortho* selectivity may be rationalized by the initial attachment of nitrogen dioxide to the oxygen atom of the substrate radical cation, followed by a rearrangement of the resulting oxonium ion intermediate through a six-membered cyclic transition state.

Experimental Section

General experimental details were given in previous papers.[8–10] All reagents and solvents used were reagent-grade commercial products. 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. An apparatus (Nippon Ozone Co. Ltd., type ON-1-2) was used for the generation of ozone. The machine produced ozone at a rate of 0.6 mmol min^{-1} with an oxygen flow of 10 L h^{-1} under an applied voltage of 80 V. Its efficiency was calibrated by iodometric titration. Methyl 2-phenylethyl ether and homologous ethers were prepared from the corresponding alcohols by standard methods.[2] *tert*-Butyl 2-phenylethyl ether was prepared according to the literature procedure.[14] Methyl, ethyl, and *sec*-butyl phenylacetates were used as obtained. All products were known and identified by ^{1}H-NMR, IR, GC-MS spectroscopies or by direct comparison with the authentic samples. Cyclic voltammetry was performed on a BAS-CV-50W electrochemical analyzer. Anodic peak potentials in the irreversible cyclic voltammograms were measured using a platinum electrode in dichloromethane containing 0.1 M $^n\text{Bu}_4\text{N}^+\text{PF}_6^-$ at a sweep rate of 100 mV s^{-1}. The Ag/AgNO$_3$ reference electrode was used and converted to the V *vs* NHE values by the relationship: $E(\text{NHE}) = E(\text{Ag/AgNO}_3) + 0.49$ V.

The *Kyodai*-Nitration of Methyl Phenylalkyl Ethers (1) and Phenylacetic Esters (3): Typical Procedure. Methyl 2-phenylethyl ether (**1b**) (0.68 g, 5 mmol) was dissolved in a freshly distilled dichloromethane (20 mL) containing nitrogen dioxide (1.0 mL), and the solution was placed in a three-necked flask fitted with a gas inlet tube and a vent which permitted waste gas to escape. The third neck was used for withdrawing an aliquot for monitoring. The mixture was

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cooled to 0 °C externally with a cooling bath (EYELA COOL ECS-1 with two thermocontrollers THS-40 and THD-50), while a stream of ozonized oxygen was introduced under vigorous magnetic stirring from the gas inlet tube, which should dip 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 conditions, the loss of nitrogen dioxide was not so significant. After 1 h the reaction was quenched by the addition of iced water, and excess nitrogen dioxide was expelled by blowing argon into the solution. The resulting mixture was neutralized with saturated aqueous sodium hydrogen carbonate (30 mL), and the organic phase was separated, washed successively with water (30 mL) and brine (30 mL), and dried over sodium sulfate. Removal of the solvent under reduced pressure left a mixture of unreacted substrate and isomeric nitro ethers as an oily residue. The isomer composition was determined by GLC using cyclododecane as an internal standard on a Shimadzu gas chromatograph instrument GC-14A, fitted with a fused silica capillary column (J&W Scientific, DB-5-30N-STD, 30 m × 0.25 mm i.d., 5% phenyl-methylsilicone, df = 0.25 mm) and a flame ionization detector. Peak areas were determined using a Shimadzu C-R5A Chromatopac computing integrator.

Molecular Orbital Calculations. All semiempirical calculations were carried out with the MOPAC[11] program using the PM3 Hamiltonian implemented on a Sony Tektronix CAChe system (versions 3.7 and 3.8). Unrestricted Hartree–Fock wave functions were employed, and the calculations were carried out by full optimization using an extra keyword PRECISE. The frontier electron densities for radical reactions were defined by Fukui *et al.* as a sum of the HOMO and SOMO coefficients.[15]

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