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Ortho Enhancement in the Ozone-Mediated Nitration of Some Aromatic Carbonyl Compounds with Nitrogen Dioxide

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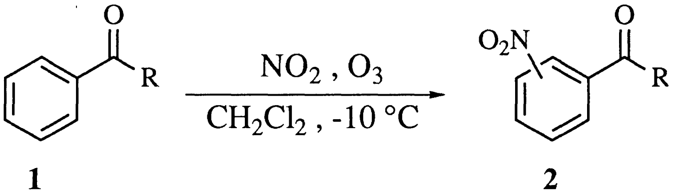
Alkyl aryl ketones react smoothly with nitrogen dioxide at low temperatures in the presence of ozone to give a mixture of *ortho* and *meta* nitration products (*o*/*m* = 1.1-3.8/1.0), the former becoming predominant with the increasing size of alkyl moiety.

The carbonyl-containing group attached to the aromatic ring withdraws electron through both the conjugative and inductive effects, giving rise to deactivation of all nuclear positions, especially of *ortho* and *para* positions. Thus, in the electrophilic substitution of aromatic carbonyl compounds, the *meta* orientation is generally predominant or in some cases almost exclusive.

Recently, we have observed that the lower oxides of nitrogen can be activated in the presence of ozone so that they substitute hydrogen as a nitro group in aromatic nucleus.1) When this non-acid nitration methodology was applied to aromatic ketones and aldehyde, some new features of the reaction become apparent, which we wish to communicate herein.

When an ozonized oxygen (O_3, 10 mmol/h) was bubbled slowly into a stirred solution of a ketone (**1b**-**1e**; 10 mmol) in dichloromethane (50 cm^3) containing an excess of nitrogen dioxide below 0 °C, the nitration occurred smoothly and selectively at *ortho* and *meta* positions and after usual work-up, the corresponding nitro compounds (**2b**-**2e**) were obtained as an isomeric mixture in nearly quantitative yield. The reaction was clean and no attack was observed on the alkyl side-chain.



Scheme 1.

In marked contrast to ordinary nitrations using mixed acid, which predominantly lead to *meta* substitutions (*meta* = 72-90%),2,3) the isomeric compositions of the nitroketones **2b**-**2e** obtained were always rich in the *ortho* isomer (Table 1). Under the similar conditions, but in the presence of methanesulfonic acid as a catalyst, benzaldehyde (**1a**) also gave a lower proportion of *meta* nitration product as compared with those from ordinary nitrations (*meta* = 84-91%).[2)] In the absence of the catalyst, extensive oxidation occurred concurrently to yield nitrobenzoic acids as the major product.

Table 1. Isomer Distributions and Yields of the Nitration Products from Compounds **1a**-**1h**[a)]

Entry	Substrate **1** R	G.l.c. yield %	Reaction time h	Isomer distribution[c)] % *ortho*	 *meta*	 *para*	*ortho*/*meta* Ratio
a	H[b)]	99	3	32	64	4	0.50
b	CH_3	99	4	52	48	0	1.08
b	CH_3[b)]	100	3	47	53	0	0.88
c	C_2H_5	100	6	55	40	5	1.38
d	$(CH_3)_2CH$	100	5	59	38	3	1.55
e	$(CH_3)_3C$	99	3	68	18	14	3.78
f	CH_2Cl	100	4	44	56	0	0.79
g	$CHCl_2$	100	6	17	83	0	0.20
h	CF_3[b)]	100	3	0	100	0	0

a)All reactions were carried out in dichloromethane (50 cm^3) at -10 °C, using a substrate (10 mmol). Ozone was fed continuously at a rate of 10 mmol/h.

b)Methanesulfonic acid (0.5 equiv.) was added as catalyst.

c)Product compositions were determined on a Shimadzu GC-14A gas chromatograph using a Shimadzu CBP1-M25-025 capillary column.

Interestingly, the ratio of the *ortho* isomer relative to two others increased with the increasing steric bulkiness of the alkyl moiety in **1**. Stepwise substitution of one, two or three halogen atoms into the acetyl group in **1b** resulted in a gradual change-over in orientation from predominantly *ortho-meta* to predominantly *meta* and finally to exclusively *meta*. ω,ω,ω-Trifluoroacetophenone (**1h**) was appreciably deactivated and the addition of methanesulfonic acid as catalyst was necessary for the reaction to proceed at convenient rate.

The relationship between the reaction time and product yield was examined for ketone **1b** by gas chromatography and the results revealed additional features of some interest. The reaction exhibited an induction period, beginning to start only after the amount of ozone introduced reached 1.0-1.5 mole equivalent to a substrate. Once started, the reaction proceeded at increasingly rapid rate and was complete very soon. Contrary to our expectation, the addition of a Lewis acid catalyst such as boron trifluoride etherate or titanium tetrachloride resulted only in the prolongation of the induction period. Methanesulfonic acid was found to be a good catalyst for the present nitration, while the initial addition of small amounts of nitric acid showed little accelerating effect. The isomer distribution varied considerably during the course of the reaction (Fig. 1). At the initiation stage the orientation was almost *meta*, but as the reaction proceeded, it rapidly changed to *ortho* and *meta*, reaching to a value of *o*/*m* around 1.1. Addition of a new portion of substrate to the reaction mixture at an intermediate stage (approximately 20% conversion) brought a sharp drop in the value of *ortho/meta* ratio from 1.0 to 0.35, but as the reaction was allowed to go on further, the value slowly regained to 0.5-0.6 (Fig. 2).

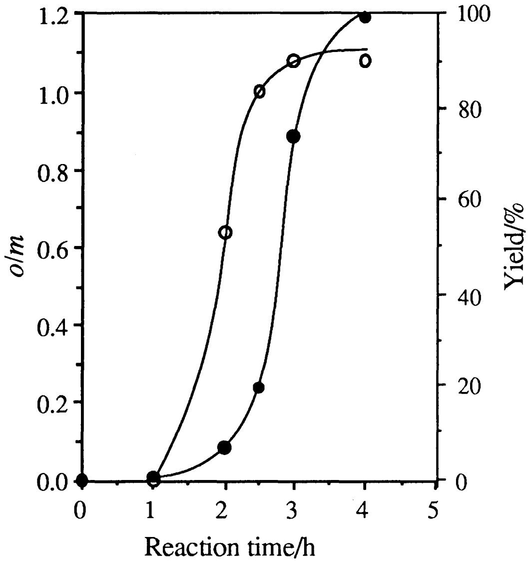


Fig. 1. Variations with reaction time of the yield and *ortho/meta* ratio of nitration product **2b**.[a]

[a] Solid and blanck circles denote the yield and *o/m* ratio, respectively. As for reaction conditions, see footnote a in Table 1.

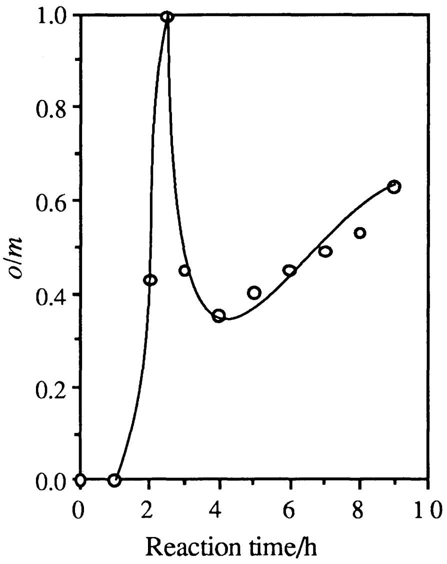
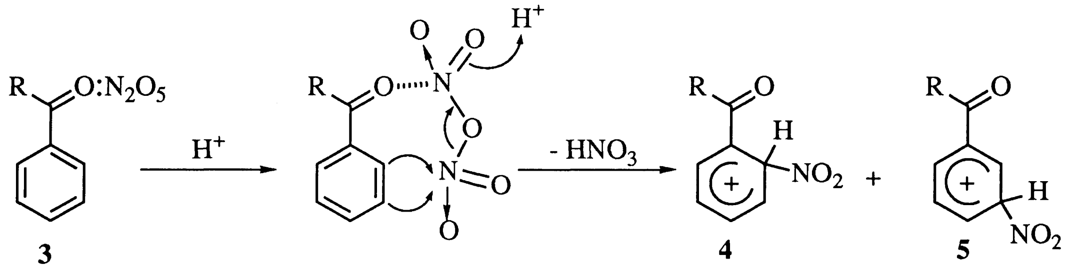


Fig. 2. Changes of the *ortho/meta* ratio of nitroketones **2b** caused by the addition of a new portion of substrate at an intermediate stage.[a]

[a] The reaction was began with 10 mmol of ketone **1b** and after 20% conversion, further 90 mmol of **1b** was added in one portion.

Dinitrogen pentoxide is the likely agent for the present nitration as this compound is rapidly formed from the interaction of nitrogen dioxide and ozone.4) Indeed, the action of a large excess of dinitrogen pentoxide on ketone **1b** led to a mixture of nitroketones **2b** of a similar isomeric composition (*o*:*m*:*p* = 52-56:48-44:0). In a recent paper,5) Moodie and coworker reported a rapid reversible formation of 4-(dinitratomethyl)nitrobenzene from 4-nitrobenzaldehyde and dinitrogen pentoxide in a concentrated nitric acid solution. That observation appeared to us to provide an attractive key to understand the puzzling feature of the ozone-mediated nitration of aromatic ketones, since the MM2 and MOPAC calculations carried out on a Sony Tektronix CAChe system6) predicted the electron-withdrawing property of the dinitratomethyl group as well as the predominant *ortho-meta* attack of electrophile on 1,1-dinitrato-1-phenylethane. However, the ^{13}C NMR inspection of a mixture of ketone **1b** and dinitrogen pentoxide in dichloromethane at -50 °C revealed no peak in the expected region of the spectra. The ^{13}C absorption due to the carbonyl group appeared at δ 201.7, appreciably downfield from the original place (δ 198.1), but absorptions of other carbon atoms remained almost unchanged, indicating the operation of a strong, but rather localized interaction between the carbonyl group and dinitrogen pentoxide.

These findings are suggestive of the formation of a Lewis acid-base complex (**3**). Then, the above-mentioned induction period may be attributed to the accumulation of this complex in the reaction system. During the course of this period, free ketone **1b** in equilibrium with the complex **3** (R = CH_3) reacts slowly with the nitronium ion derived from the ionic form of dinitrogen pentoxide, giving predominantly the *meta* isomer.[7] As the reaction proceeded, however, nitric acid formed would facilitate the heterolytic collapse of the complex **3**, leading to the usual intermediates (**4** and **5**) in *ortho* and *meta* nitration (Scheme 2). In view of the versatility of *o*-nitroketones as the precursor for a variety of heterocyclic compounds, the present finding is of considerable synthetic importance and the mechanism for the enhancement in *ortho* substitution needs to be clarified.



Scheme 2.

References

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2) J.W.Baker and W.G.Moffit, J. Chem. Soc., 1931, 314.
3) R.B.Moodie, J.R.Penton, and K.Schofield, J. Chem. Soc. B, 1969, 578.
4) For a review, see R.P.Wayne, I.Barnes, P.Briggs, J.P.Burrows, C.E.Canosa-Mas, J.Hjorth, G.Le Bras, C.K.Moortgat, D.Perner, G.Poulet, G.Restelli, and H.Sidebottom, Atomos. Environ., 25A, 1(1991).
5) R.B.Moodie and R.Willmer, J. Chem. Soc., Perkin Trans. 2, 1992, 229.
6) Sony Tektronix, Co. Ltd., Osaki, Shinagawa-ku, Tokyo 141, Japan.
7) A referee suggested an alternative possibility in which the complex **3** may act as a nitrating agent for free ketone **1b**, mainly leading to the *meta* substitution product.

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