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Effect of Oxygen on the Reaction of Secondary Amines with Nitric Oxide

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Secondary amines were allowed to react with nitric oxide in the presence of oxygen to afford *N*-nitrosamines in good yields. Detailed investigation revealed that the reaction proceeded by two pathways; the one involves the catalytic behavior of oxygen, and the other consumes a stoichiometrical amount of oxygen. Both pathways afforded the same nitroso adducts.

Key words nitric oxide; dinitrogen trioxide; nitrosation; *N*-nitrosamine

Nitric oxide (NO) is a molecule that has attracted much attention from the biological and physiological viewpoints because of its diverse bioactivity.[1] Compared to the extensive biological studies, little research has been performed with regard to its chemistry.[2] The reason for this is the sensitive and unreproducible reactivity of NO toward organic molecules. In particular, the reactivity of NO is disturbed by the presence of oxygen, and this adds complexity to the chemistry of NO.[3]

In the course of our study on the reaction of NO with amines, we were confronted by this complexity.[4] To clarify the reaction mechanism, the amount of oxygen in the reaction system was carefully controlled, and the influence of oxygen on the reaction of secondary amines with NO was thoroughly investigated. It was revealed that NO reacts with the amines in two different manners depending upon the substrate and reaction conditions. This paper describes these results.

There have been two previous reports on the reaction of NO with secondary amines. Drago reported that the secondary amines were allowed to react with NO under high pressure to give a 1 : 2 complex of amine and NO, so-called Drago's salts.[5] On the contrary, Challis *et al.* reported that NO did not react with secondary amines in the absence of O_2 in acetonitrile, and a trace amount of O_2 accelerated *N*-nitrosation, although the amount of O_2 used was not given in the paper.[6] Moreover, these two studies used different substrates and solvents, and therefore no data for direct comparison are available. Thus to settle the problem of O_2 participation, we used a catalytic amount of oxygen (0.1 eq) in the reaction of NO with *N*-methylaniline (**1a**) in various solvents (Chart 1 and Table 1). Under these conditions, a small amount of O_2 would be transformed to dinitrogen trioxide N_2O_3 according to the Eqs. 1 and 2.[7]

$$2NO+O_2 \rightarrow 2NO_2 \qquad (1)$$

$$NO_2+NO \rightleftarrows N_2O_3 \qquad (2)^{8)}$$

As shown in Table 1, the reaction was completed in nonpolar solvents within 24 h, and *N*-methyl-*N*-nitrosoaniline was obtained quantitatively in the presence of a catalytic amount of O_2 (Table 1, entries 1, 2, and 3).[10] As the polarity of the solvent increased, the yields became lower; in particular in acetone and H_2O the reaction stopped after about 40% of the starting material had been consumed. These results suggest that the catalytic effect of O_2 varies depending upon the polarity of the solvents. With acetone and H_2O, O_2 should be consumed stoichiometrically. That is, 0.1 eq of O_2 is converted to 0.2 eq of N_2O_3 in the presence of an excess amount of NO according to Eqs.1 and 2, and the N_2O_3 thus formed reacts with *N*-methylaniline to give the product and NO_2^-, which regenerates 0.5 eq of N_2O_3 *via* dimerization.

To study the substituent effects, various secondary amines were used as substrates in 1,2-dichloroethane solution[11] (Chart 2 and Table 2). When aromatic amines were used, the reaction was completed after 24 h (entries 1—3), but aliphatic amines afforded corresponding *N*-nitrosamines in less than 40% yield (entries 4—6). These results suggested that different reaction pathways were involved in these two

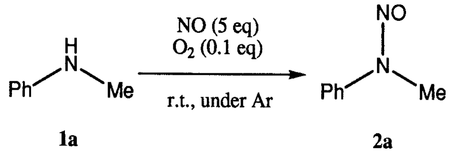

Chart 1

Table 1. Reaction of *N*-Methylaniline with NO in Various Solvents

Entry	Solvent[9]	Yield of **2a** (%)[b]		
		3 h	24 h	72 h
1	DCE[a]	44 (55)	100	—
2	Benzene	44 (55)	100	—
3	$CHCl_3$	38 (62)	100	—
4	THF	42 (54)	66 (33)	65 (33)
5	AcOEt	53 (47)	57 (40)	54 (40)
6	Acetone	33 (67)	41 (56)	41 (57)
7	MeOH	7 (85)	12 (76)	—
8	H_2O	17 (75)	42 (39)	34 (42)

a) DCE, 1,2-dichloroethane. *b*) Values in parentheses correspond to the recovery of **1a** (%).

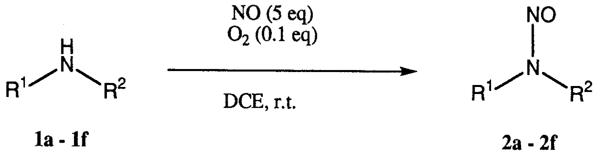

Chart 2

Table 2. Reaction of Secondary Amines with NO in the Presence of O_2

Entry	Substrate	R^1	R^2	Oxidation potential (*vs.* SCE)	Yield (%) of **2**	
					3 h	24 h
1	**1a**	Ph	Me	+1.10 V	44	100
2	**1b**	*p*-Cl–C_6H_4	Me	+1.20 V	47	100
3	**1c**	*p*-NO_2–C_6H_4	Me	+1.45 V	50	90
4	**1d**	$PhCH_2$	Me	+1.55 V	34	38
5	**1e**	$PhCH_2$	$PhCH_2$	+1.50 V	32	32
6	**1f**	$PhCH_2CH_2$	Me	+1.55 V	26	26

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$$\underset{(0.2\ \mathrm{mmol})}{\mathbf{1a}} + \underset{(0.2\ \mathrm{mmol})}{\overset{\text{one of}}{\mathbf{1b}\text{-}\mathbf{1f}}} \xrightarrow[\text{DCE, r.t., 5 h}]{\text{NO (0.2 mmol)}\ \ O_2\ (0.02\ \mathrm{mmol})} \mathbf{2a} + \mathbf{2b}\text{-}\mathbf{2f}$$

Chart 3

Table 3. Competitive Reaction of Amines with NO Using **1a** as a Reference Substrate

Entry	Substrate	Yield (%)	
		2a	**2b—f**
1	**1b**	50	23
2	**1c**	32	4
3	**1d**	2	24
4	**1e**	16	27
5	**1f**	5	35

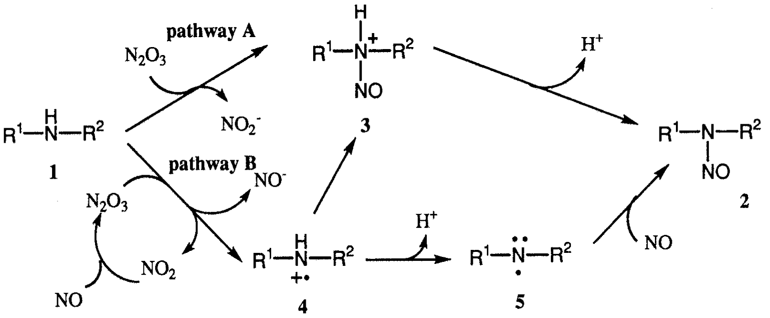

Chart 4

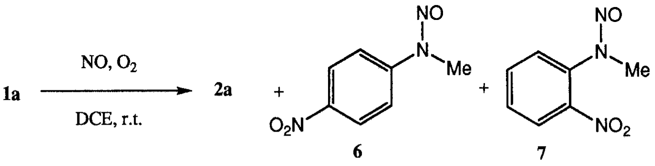

Chart 5

Table 4. Reaction of *N*-Methylaniline with NO and O_2 in DCE

Entry	NO (eq)	O_2 (eq)	Time (h)	Yield (%)		
				2a	**6**	**7**
1	5	0.1	24	100	0	0
2	5	1	0.5	95	5	0
3	5	2.5	0.5	44	38	18
4	5	5	0.5	17	52	29
5	NO_2 (5 eq)[15]		0.5	28	44	25
6	2	0.1	24	100	0	0
7	1	0.1	24	72	0	0
8	1	0.1	72	72	0	0

types of amines, although the detailed effects of substituents remained unclear. Thus competitive experiments were carried out using compound **1a** as a reference compound (Chart 3 and Table 3), and it was shown that aromatic amines had a tendency to give more products when the oxidation potential was lower (entries 1 and 2), but aliphatic amines were nitrosated faster than aromatic ones in spite of their higher oxidation potentials (entries 3—5).

Thus aromatic and aliphatic amines were revealed to react with NO (or N_2O_3) through different pathways. With aliphatic amines, the reaction proceeds by the attack of NO^+, which is stoichiometrically formed from N_2O_3, toward a lone pair of amines (Chart 4, pathway A). The pathway affords HNO_2, which reproduces N_2O_3 by dimerization. Thus pathway A consumes one equivalent of NO to form **2**. This ionic process should be dominant in polar solvents, which is in good accordance with the data shown in Table 1. On the other hand, aromatic amines have weaker basicity than aliphatic ones, and thus the reaction *via* pathway A might be slower than those of aliphatic ones. But these compounds have lower oxidation potentials, and one electron oxidation might be advantageous to alter the reaction process from pathway A to pathway B. On this occasion, N_2O_3 acts in a catalytic manner provided that N_2O_3 accepts one electron from the amine to form NO^- and NO_2.[12,13] If N_2O_3 decomposes to NO and NO_2^-, regeneration of N_2O_3 according to Eq. 2 woud not occur, and the catalytic behavior of O_2 would not be observed. This pathway consumes two equivalents of NO.[14]

The new observation mentioned above also reveals the importance of the amount of O_2 in regulating the reaction using NO. As an example, Table 4 shows the yield of **2a** with various amounts of NO and O_2 (Chart 5). In the presence of 5 eq of NO, the reaction rate becomes higher as the amount of O_2 is increased, but the ratio of side products **6** and **7** (nitration compounds of the aromatic ring moiety) becomes larger as more O_2 is added (Table 4, entries 3 and 4). Thus it is necessary to control the amount of O_2 to obtain *N*-nitroso compound in a high yield. That is, the amount of O_2 must be less than 1/4 that of NO so that nitrogen oxide thus formed is mainly N_2O_3 rather than NO_2. In the presence of 0.1 eq of O_2, the use of 2 eq of NO results in completion of the reaction, while the reaction stops at 72% yield with 1 eq of NO, accompanied by 28% recovery of the starting material. These results also suggest that *N*-nitrosation proceeds *via* two pathways shown in Chart 4.

In this paper, we describe the effect of oxygen on the reaction of secondary amines with NO. It was revealed that N_2O_3 formed in the presence of NO nitrosate aromatic secondary amines in a catalytic manner. Dinitrogen trioxide was suggested to have a redox property in organic reactions. Moreover, this phenomenon can readily be applied to the nitrosation process of an aromatic amine. Further application of oxygen-catalyzed nitrosation reactions is now under investigation.

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7) von Gratzel M., Taniguchi S., Henglein A., *Ber. Bunsenges. Phys. Chem.*, **74**, 488 (1970).

8) In organic solvents, the equilibrium constant of Eq. 2 is reported to be very high ($\approx 10^3$ to 10^5); Boughriet A., Wartel M., Fischer J. C., Auger Y., *J. Electroanal. Chem.*, **186**, 201 (1985).

9) The same solvent effect was investigated using *N*-benzyl-*N*-methylamine as a substrate, and some of the yields were 38% (in DCE), 16% (in AcOEt), and 28% (in acetone).

10) In a typical experiment, 0.2 mmol of substrate **1** was placed in a two-necked flask equipped with a septum rubber and three-way stopcock, one way of which was attached to an Ar balloon, and another joined to a pump. The flask was degassed *in vacuo* and filled with Ar gas. These operations were repeated five times. 1,2-Dichloroethane (10 ml) was added, the solution was bubbled with dry Ar gas for 20 min, and then the flask was sealed. NO gas was passed through a column of soda lime, measured at 22.4 ml using a Hamilton gas-tight syringe, and then added to the reaction vessel. Then 0.45 ml of oxygen gas was added and the reaction mixture was allowed to react for 24 h at room temperature. Then Ar was bubbled for degassing of excess NO and O_2, and product analysis was performed using HPLC or NMR.

11) 1,2-Dichloroethane has been the solvent of choice for reaction of NO with organic compounds, although the reason for this phenomenon remains unclear; Hata E., Yamada T., Mukaiyama T., *Bull. Chem. Soc. Jpn.*, **68**, 3629 (1995).

12) Reduction potentials of NO and NO_2 were measured in acidic aqueous solution to give the values of +0.712 and +1.065 V *vs* NHE, respectively; "Chemistry of the Elements," ed. by Greenwood N. N., Earnshaw A., Pergamon Press, Oxford, 1984.

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14) In addition to pathways A and B, there may be an another pathway that involves intermediary formation of a Drago's salt. Especially in the cases of primary amines, the latter pathway seems to become dominant using N_2O_3 in a catalytic manner.[4b)] The detailed mechanism will be reported in a subsequent paper.

15) When 2 eq of NO_2 was used, **6** and **7** were obtained in over 50% total yield, accompanied by a small amount of **1**.