

## 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.<sup>1)</sup> Compared to the extensive biological studies, little research has been performed with regard to its chemistry.<sup>2)</sup> 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.<sup>3)</sup>

In the course of our study on the reaction of NO with amines, we were confronted by this complexity.<sup>4)</sup> 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.<sup>5)</sup> On the contrary, Challis *et al.* reported that NO did not react with secondary amines in the absence of O<sub>2</sub> in acetonitrile, and a trace amount of O<sub>2</sub> accelerated *N*-nitrosation, although the amount of O<sub>2</sub> used was not given in the paper.<sup>6)</sup> 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<sub>2</sub> 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<sub>2</sub> would be transformed to dinitrogen trioxide N<sub>2</sub>O<sub>3</sub> according to the Eqs. 1 and 2.<sup>7)</sup>



As shown in Table 1, the reaction was completed in non-polar solvents within 24 h, and *N*-methyl-*N*-nitrosoaniline was obtained quantitatively in the presence of a catalytic

amount of O<sub>2</sub> (Table 1, entries 1, 2, and 3).<sup>10)</sup> As the polarity of the solvent increased, the yields became lower; in particular in acetone and H<sub>2</sub>O the reaction stopped after about 40% of the starting material had been consumed. These results suggest that the catalytic effect of O<sub>2</sub> varies depending upon the polarity of the solvents. With acetone and H<sub>2</sub>O, O<sub>2</sub> should be consumed stoichiometrically. That is, 0.1 eq of O<sub>2</sub> is converted to 0.2 eq of N<sub>2</sub>O<sub>3</sub> in the presence of an excess amount of NO according to Eqs. 1 and 2, and the N<sub>2</sub>O<sub>3</sub> thus formed reacts with *N*-methylaniline to give the product and NO<sub>2</sub><sup>-</sup>, which regenerates 0.5 eq of N<sub>2</sub>O<sub>3</sub> *via* dimerization.

To study the substituent effects, various secondary amines were used as substrates in 1,2-dichloroethane solution<sup>11)</sup> (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

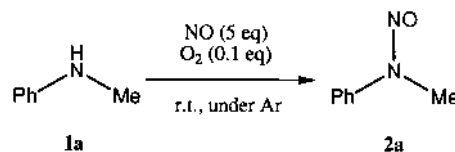


Chart 1

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

Entry	Solvent <sup>9)</sup>	Yield of <b>2a</b> (%) <sup>b)</sup>		
		3 h	24 h	72 h
1	DCE <sup>a)</sup>	44 (55)	100	—
2	Benzene	44 (55)	100	—
3	CHCl <sub>3</sub>	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 <sub>2</sub> O	17 (75)	42 (39)	34 (42)

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

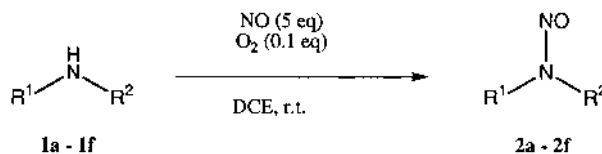


Chart 2

Table 2. Reaction of Secondary Amines with NO in the Presence of O<sub>2</sub>

Entry	Substrate	R <sup>1</sup>	R <sup>2</sup>	Oxidation potential (vs. SCE)	Yield (%) of <b>2</b>	
					3 h	24 h
1	<b>1a</b>	Ph	Me	+1.10 V	44	100
2	<b>1b</b>	<i>p</i> -Cl-C <sub>6</sub> H <sub>4</sub>	Me	+1.20 V	47	100
3	<b>1c</b>	<i>p</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	Me	+1.45 V	50	90
4	<b>1d</b>	PhCH <sub>2</sub>	Me	+1.55 V	34	38
5	<b>1e</b>	PhCH <sub>2</sub>	PhCH <sub>2</sub>	+1.50 V	32	32
6	<b>1f</b>	PhCH <sub>2</sub> CH <sub>2</sub>	Me	+1.55 V	26	26

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

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

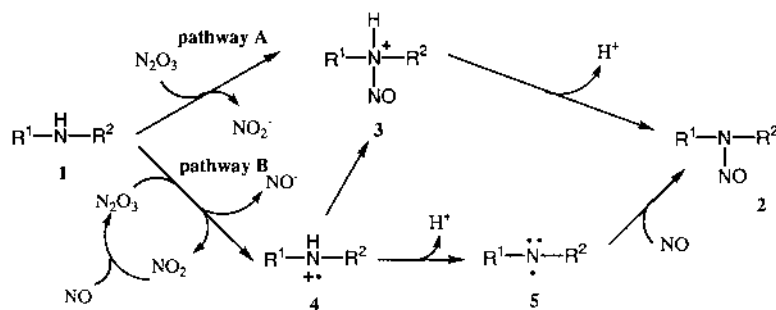
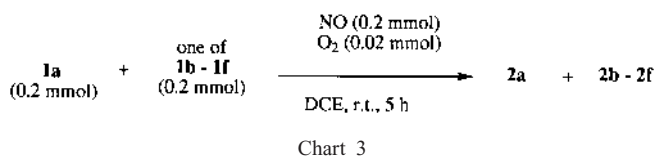


Chart 4

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 nitrated 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  $\text{N}_2\text{O}_3$ ) through different pathways. With aliphatic amines, the reaction proceeds by the attack of  $\text{NO}^+$ , which is stoichiometrically formed from  $\text{N}_2\text{O}_3$ , toward a lone pair of amines (Chart 4, pathway A). The pathway affords  $\text{HNO}_2$ , which reproduces  $\text{N}_2\text{O}_3$  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,  $\text{N}_2\text{O}_3$  acts in a catalytic manner provided that  $\text{N}_2\text{O}_3$  accepts one electron from the amine to form  $\text{NO}^-$  and  $\text{NO}_2^-$ .<sup>12,13</sup> If  $\text{N}_2\text{O}_3$  decomposes to NO and  $\text{NO}_2^-$ , regeneration of  $\text{N}_2\text{O}_3$  according to Eq. 2 would not occur, and the catalytic behavior of  $\text{O}_2$  would not be observed. This pathway consumes two equivalents of NO.<sup>14</sup>

The new observation mentioned above also reveals the importance of the amount of  $\text{O}_2$  in regulating the reaction using NO. As an example, Table 4 shows the yield of **2a** with various amounts of NO and  $\text{O}_2$  (Chart 5). In the presence of 5 eq of NO, the reaction rate becomes higher as the amount of  $\text{O}_2$  is increased, but the ratio of side products **6** and **7** (nitration compounds of the aromatic ring moiety) becomes larger as

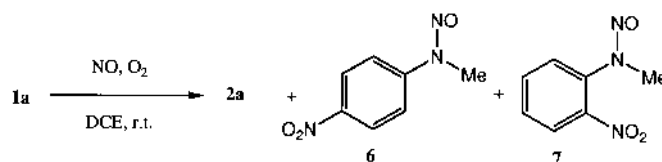


Chart 5

Table 4. Reaction of *N*-Methylaniline with NO and  $\text{O}_2$  in DCE

Entry	NO (eq)	$\text{O}_2$ (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	$\text{NO}_2$ (5 eq) <sup>15</sup>	0.5	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

more  $\text{O}_2$  is added (Table 4, entries 3 and 4). Thus it is necessary to control the amount of  $\text{O}_2$  to obtain *N*-nitroso compound in a high yield. That is, the amount of  $\text{O}_2$  must be less than 1/4 that of NO so that nitrogen oxide thus formed is mainly  $\text{N}_2\text{O}_3$  rather than  $\text{NO}_2$ . In the presence of 0.1 eq of  $\text{O}_2$ , 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  $\text{N}_2\text{O}_3$  formed in the presence of NO nitrosates aromatic secondary amines in a catalytic manner. Dinitrogen trioxide was sug-

gested 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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- 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<sub>2</sub>, 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<sub>2</sub> 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.
- 13) The electrochemical behaviour of N<sub>2</sub>O<sub>3</sub> solutions was reported to be the same as that exhibited by a NO<sub>2</sub>+NO mixture; Bontempelli G., Mazzochin G. A., Magno F., *J. Electroanal. Chem.*, **55**, 91 (1974).
- 14) In addition to pathways A and B, there may be 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<sub>2</sub>O<sub>3</sub> in a catalytic manner.<sup>4b)</sup> The detailed mechanism will be reported in a subsequent paper.
- 15) When 2 eq of NO<sub>2</sub> was used, **6** and **7** were obtained in over 50% total yield, accompanied by a small amount of **1**.