Reaction of Secondary and Tertiary Amines with Nitric Oxide in the Presence of Oxygen

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In order to clarify the role of oxygen in the reaction of amines with nitric oxide, secondary amines were allowed to react with nitric oxide in the presence of oxygen. Although *N*-nitrosamines were obtained as the main products in every case, the yields depended on the substituents and reaction solvents. Detailed investigation revealed that the reaction proceeded by at least two pathways: one involving oxygen as a catalyst, and the other consuming the stoichiometric amount of oxygen. Both paths afforded the same nitroso adducts. It was suggested that a third path, a catalytic process *via* Drago's salts was also possible. The same reaction was applied to a tertiary amine, and it was found that the oxygen was consumed stoichiometrically in this case.

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

In spite of its simple structure, nitric oxide (NO) has been found to play a variety of roles in biological systems, and extensive biological and chemical research has been carried out.[1] From a chemical viewpoint, NO itself has been found to exhibit low reactivity toward most organic molecules[2] with a few exceptions.[3] In the presence of oxygen, NO is converted to higher nitrogen oxides which have the ability to react with organic compounds in a variety of ways. Many of the reactions, however, are unproducible because the reaction of NO with O_2 gives a variety of nitrogen oxides[4] depending upon the ratio of the two gases, and the pressure, solvent, and reaction temperature used.

We have been studying the reaction of NO with amines and have been confronted by this difficulty.[5] In order to investigate the detailed reaction mechanism, the amount of oxygen in the reaction system has to be carefully controlled, and the effect of oxygen on the reaction of secondary and tertiary amines with NO was investigated. It was found that NO reacts with amines in at least two different ways depending upon the substrates and reaction conditions. This paper describes our results.[6]

Secondary amines were selected as substrates because they give *N*-nitrosamines as the sole products following reaction with nitrosating agents. There have been two studies which reported the reaction of NO with secondary amines. Drago showed that secondary amines reacted with NO under high pressure or at low temperature to give a 1:2 complex of amine and NO, the so-called Drago's salts.[7] In addition, Challis and Kyrtopoulos 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 reported.[8] Since these two studies adopted different substrates and solvents, it is impossible to draw firm conclusions. For the investigation of the detailed reaction mechanism of *N*-nitrosation with NO and O_2, catalytic amount of oxygen (0.1 eq) was used for the reaction of NO (5 eq) with *N*-methylaniline (**1a**) because, in the presence of excess NO, the small amount of O_2 should be converted to dinitrogen trioxide N_2O_3 according to Eqs 1 and 2,[9] and the reaction atmosphere must consist of a small amount of N_2O_3 and excess NO.

$$2NO + O_2 \rightarrow 2NO_2 \tag{1}$$

$$NO_2 + NO \rightleftarrows N_2O_3 \tag{2}^{[10]}$$

Under these conditions, the reactions of *N*-methylaniline in various solvents were investigated and the results are shown in Table 1. In the case of non-polar solvents, the reaction was completed within 24 h to afford the corresponding *N*-nitrosamine in almost quantitative yield despite the absence of a sufficient amount of O_2. With an increase in the polarity of the solvents, however, the yield became lower and, in acetone or H_2O solution, the reaction stopped after about 40% of the starting material had been consumed. This yield was thought to be obtained from the stoichiometry shown in Eq. 3, *i.e.* 0.1 eq of O_2 corresponds to 0.4 eq of product.

$$RR'NH + NO + 1/4 O_2 \rightarrow RR'NNO + 1/2 H_2O \tag{3}$$
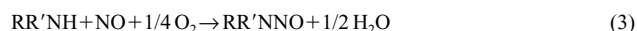
These results suggest that catalytic behavior of O_2 was observed in the case of non-polar solvents, whereas O_2 was consumed stoichiometrically in polar solvents.
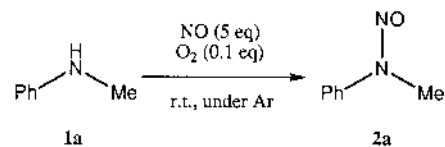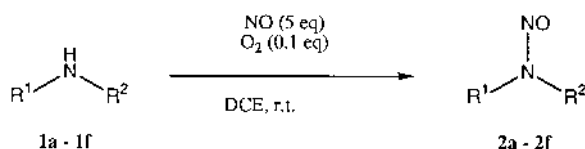

Chart 1

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

Entry	Solvent[9]	Yield of **2a** (%)[a]		
		3 h	24 h	72 h
1	DCE	44 (55)	100	—
2	Benzene	44 (55)	100	—
3	CHCl₃	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	H₂O	17 (75)	42 (39)	34 (42)

a) Values in parentheses correspond to the recovery of **1a** (%).

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In order to study the substituent effects, various secondary amines were used as substrates in 1,2-dichloroethane (DCE) solution[11] (Chart 2 and Table 2). In the case of aromatic amines, the reaction was completed after 24 h (entries 1—3), but aliphatic amines afforded the corresponding N-nitrosamines in less than 40 % yield (entries 4—6). The results also suggested that different reaction pathways were involved with these two types of amines. Thus, competition experiments were carried out to clarify the detailed substituent effects using compound **1a** as a reference (Chart 3 and Table 3), and aromatic amines tended to give more products when the oxidation potential was lower (entries 1, 2), while aliphatic amines were nitrosated faster than aromatic ones, in spite of their higher oxidation potential (entries 3—5). Thus, aromatic and aliphatic amines were found to react with NO (or N_2O_3) through different pathways. In the case of aliphatic amines, the reaction proceeds by attack of NO^+, which is sto-

ichiometrically formed from N_2O_3, on the amine lone pair (Chart 4, pathway A). This pathway affords HNO_2, which results in 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 agreement with the data shown in Table 1. On the other hand, aromatic amines are weaker bases than their aliphatic counterparts, thus reaction *via* pathway A will be slower than with aliphatic amines. However, these compounds have lower oxidation potentials, and one-electron oxidation might be advantageous, switching 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] There is an another possible pathway that must be considered in this reaction system, *i.e.* a process that involves a Drago's salt **8** as an intermediate (pathway C). When secondary amines were used as substrates, the total yields of the recovered starting materials and N-nitrosamines were almost quantitative in every case. Thus,
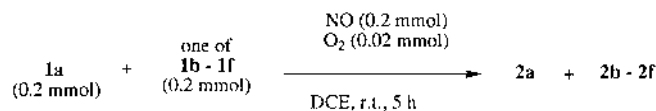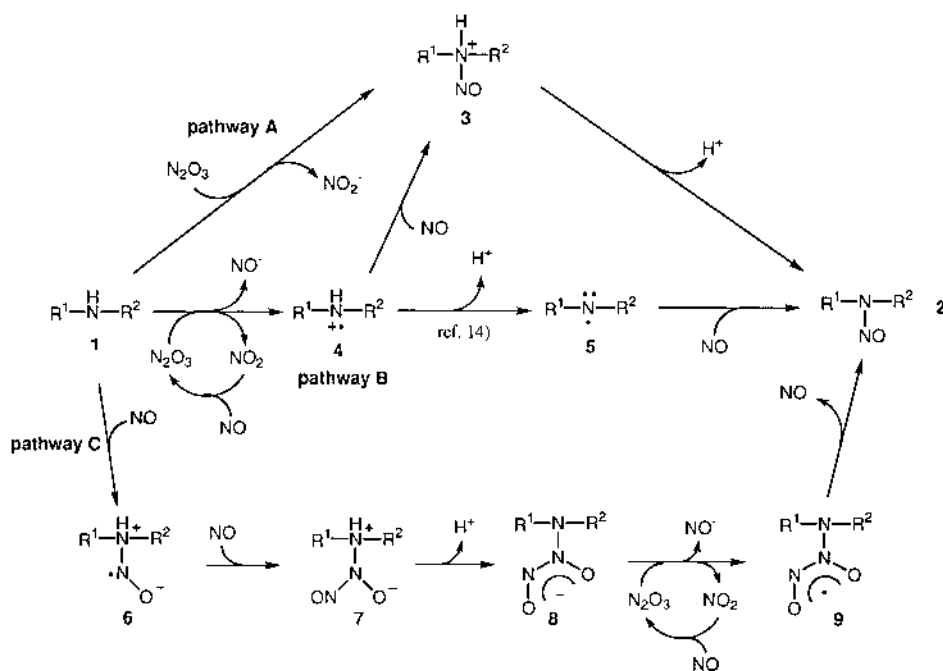

Chart 2

Chart 3

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

Entry	Substrate	R^1	R^2	Oxidation potential (*vs*. SCE)[a]	Yield (%) of **2** 3 h	Yield (%) of **2** 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

a) SCE: saturated calomel electrode.

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

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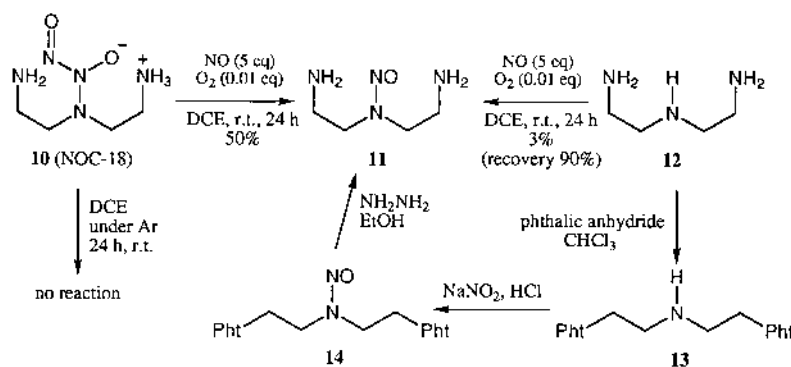
Chart 4

Chart 5

Chart 6

Chart 7

Table 4. Dealkylative Nitrosation of Tribenzylamine with NO and O₂

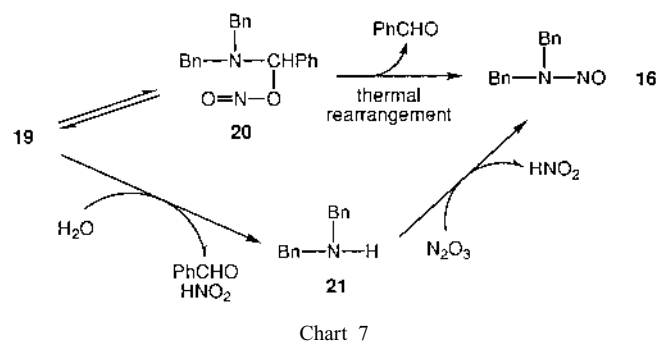| Entry	NO (eq)	O₂ (eq)	Time (h)	Yield (%)	
				16	**17**
1	5	0.01	2	8	7
2	5	0.1	2	25	18
3	5	0.1	18	27	16
4	5	0.5	2	90	53
5	5	1	2	95	66
6	5	5	2	53	43
7	NO₂ (5 eq)		2	66	42
8	2	0.5	5	84	54
9	2	0.5	18	81	43
10	1	0.5	18	67	44

Chart 8

the role of **8** as an intermediate was thought to be a minor one.[15] To investigate the possibility of pathway C being involved, a commercially available 1-hydroxy-2-oxo-3,3-bis(2-aminoethyl)-1-triazene[16] (**10**) was used as a substrate (Chart 5). When compound **10** was allowed to react with NO in the presence of a catalytic amount of O₂, N-nitroso derivative **11** was obtained in 50% yield. When **12** was subjected to the reaction under the same conditions, only a trace of **11** was detected. Therefore, this shows that **12** was not an intermediate in the reaction (**10**→**11**). From these results, it is suggested that compounds such as **8** could be transformed to N-nitroso derivatives **2** by NO plus catalytic O₂. The structure of **11** was confirmed by an alternative synthesis shown in Chart 5. The conversion from **10** to **11** uses a catalytic amount of O₂, and so pathway C in Chart 4 might be a substitute for pathway B. Next, a tertiary amine was adopted as a substrate for this system. Some papers have reported the reaction of tertiary amines with nitrosation reagents such as Ac₂O–HNO₃,[17] H₂O–HNO₂,[18] organic solvents–N₂O₄,[19] and organic solvents–alkyl nitrite.[20] These reports showed that the reaction products were dealkylated N-nitrosamines. In our reaction system, the same dealkylative nitrosation took place although it was necessary to heat the reaction medium in order to obtain reproducible results. The results using tribenzylamine as a substrate are shown in Chart 6 and Table 4.
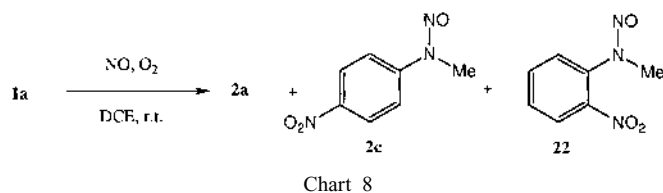
The reaction was found to proceed via a non-catalytic pathway which was shown by the data (entries 1–5). In addition, excess O₂ (entry 6) or the use of NO₂ (entry 7) reduced the yield of **16**, which suggested the most effective reagent was N₂O₃. In this case, the reaction is supposed to be initiated by the attack of NO⁺ (N₂O₃) on the lone pair of the amino nitrogen (corresponding to pathway A of Chart 4) to form a quaternary salt **18** (Chart 7), which eliminates HNO to form an iminium salt **19**. The process which involves a hydrolytic step (from **19** to **21**) does not seem to be a major one, because nitrosation of **21** has been reported to be slower than that of **15**. Thus, nitrite addition to **19** followed by thermal rearrangement might be a pathway to **16** (Chart 7).

The new observations related so far also show the importance of regulating the amount of O₂ in the reaction using NO. For example, Table 5 shows the yield of **2a** with various amounts of NO and O₂ (Chart 8). In the presence of 5 eq of NO, the reaction rate increased as the amount of O₂ increased, but the ratio of side products **2c** and **22** (nitration compounds of aromatic ring moiety) became greater follow-

Table 5. Reaction of *N*-Methylaniline with NO and O$_2$ in DCE

Entry	NO (eq)	O$_2$ (eq)	Time (h)	Yield (%)		
				2a	**2c**	**22**
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)[21]		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

ing increased addition of O$_2$ (Table 5, entries 3, 4). Thus, it was necessary to control the amount of O$_2$ to obtain the *N*-nitroso compound in high yield. So, the amount of O$_2$ must be less than 1/4 that of NO so that the nitrogen oxide formed is mainly N$_2$O$_3$, rather than NO$_2$.

In this paper, we described the effect of oxygen on the reaction of secondary amines with NO. It was found that N$_2$O$_3$ in the presence of NO nitrosates aromatic secondary amines in a catalytic manner. Dinitrogen trioxide was suggested to have redox properties in organic reactions. Therefore, *N*-nitrosation of secondary amines could proceed by at least two pathways, namely, A and B in Chart 4. In addition, the possibility that the process included a Drago's salt as an intermediate was suggested using a commercially available NONOate. The nitrosation of a tertiary amine was found to proceed through the stoichiometric consumption of O$_2$, which was analogous to path A for secondary amines. Moreover, the control of oxygen in the presence of NO was applied to the nitrosation process of an aromatic amine. Thus, this process affords an aprotic and non- or slightly acidic nitrosation method for organic compounds, and application of this method to other amino compounds is now in progress.

Experimental

Melting points were recorded on a Büchi 535 micro-melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were measured with JEOL GX400 and LA500 spectrometers using tetramethylsilane as an internal standard. Redox potentials were recorded on a Yanaco P-1100 polarographic analyzer.

Materials All chemicals were of analytical grade and were used as received. It was necessary, however, to freshly distill the reaction solvents to obtain reproducible results. Nitric oxide gas (99.9%) was purchased from Takachiho Chemical Company Ltd, and was passed through 10 M NaOH aqueous solution and a column of 4—8 mesh soda lime to remove NOx impurities.

General Procedure for the Reaction of Secondary Amines 1 with Nitric Oxide in the Presence of Oxygen In a typical experiment, 0.2 mmol substrate **1** was placed in a two-necked flask equipped with a rubber septum and a three-way stopcock, one outlet of which was attached to an Ar balloon, and another to a pump. The flask was degassed *in vacuo* and filled with Ar gas. These operations were repeated five times. DCE (10 ml) was added and the solution was bubbled with dry Ar gas for 20 min, then the flask was sealed. NO gas was passed through a column of soda lime and 22.4 ml was measured using a Hamilton gas-tight syringe, and added to the reaction vessel. Then, 0.45 ml oxygen was added and the reaction mixture was allowed to react for 24 h at room temperature. Then Ar was bubbled to degass excess NO and O$_2$, and analysis of the product was performed by NMR.

Synthesis of *N*-Nitrosamines as Standards *N*-Nitrosamines used as standards were synthesized using NaNO$_2$ and HCl in H$_2$O according to a reported procedure.[22]

N-Methyl-*N*-nitrosoaniline (**2a**): Colorless oil.[22] ^{1}H-NMR (CDCl$_3$) δ: 3.47 (3H, s), 7.37 (1H, t, *J*=7.3 Hz), 7.49 (2H, dd, *J*=7.7, 7.3 Hz), 7.55 (2H, d, *J*=7.7 Hz).

4-Chloro-*N*-methyl-*N*-nitrosoaniline (**2b**): Colorless oil.[23] ^{1}H-NMR (CDCl$_3$) δ: 3.44 (3H, s), 7.45 (2H, d, *J*=9.2 Hz), 7.50 (2H, d, *J*=9.2 Hz).

N-Methyl-4-nitro-*N*-nitrosoaniline (**2c**): Yellow needles from hexane–CH$_2$Cl$_2$; mp 100—101 °C (lit.[24] mp 101 °C). ^{1}H-NMR (CDCl$_3$) δ: 3.49 (3H, s), 7.77 (2H, d, *J*=9.4 Hz), 8.37 (2H, d, *J*=9.4 Hz).

N-Methyl-*N*-nitrosobenzylamine (**2d**): Colorless oil.[25] ^{1}H-NMR (CDCl$_3$) δ: 2.95 (3.69) (3H, s), 5.31 (4.81) (2H, s), 7.12—7.41 (5H, m). The NMR spectrum showed that there were two rotational isomers in a ratio of 3 : 1 due to restricted rotation of the N–N bond. The signals of the minor one are shown in parentheses.

N-Nitrosodibenzylamine (**2e**): Colorless needles from hexane–CH$_2$Cl$_2$; mp 55—56 °C (lit.[26] mp 58—59 °C). ^{1}H-NMR (CDCl$_3$) δ: 4.65 (2H, s), 5.19 (2H, s), 7.03—7.05 (2H, m), 7.22—7.25 (2H, m), 7.27—7.31 (3H, m), 7.35—7.39 (3H, m).

N-Methyl-*N*-nitroso-β-phenethylamine (**2f**): Colorless oil.[27] ^{1}H-NMR (CDCl$_3$) δ: 2.99 (3.57) (3H, s), 3.05 (2.80) (2H, t, *J*=7.3 Hz), 4.38 (3.79) (2H, t, *J*=7.3 Hz), 7.16—7.33 (5H, m). The NMR spectrum showed that there were two rotational isomers in a ratio of 2.6 : 1 due to restricted rotation of the N–N bond. The signals of the minor one are shown in parentheses.

Oxidation Potentials of Secondary Amines A secondary amine (0.08 mmol) was dissolved in 8 ml 0.1 M Bu$_4$NClO$_4$ in tetrahydrofuran (THF). The oxidation potentials were recorded after 5 min bubbling Ar using glassy carbon as the working electrode, platinum as the counter electrode, and SCE as the reference electrode, respectively.

Synthesis of Bis(2-aminoethyl)-*N*-nitrosamine Dihydrochloride (11) Bis(phthalimidylethyl)amine (**13**) was synthesized by the reaction of diethylenetriamine and phthaloyl anhydride in CHCl$_3$ according to a reported method.[28] Compound **13** (2 mmol) was suspended in 5 ml 1 N HCl, an aqueous solution (5 ml) of NaNO$_2$ (4 mmol) was added, and the mixture was stirred for 30 min at room temperature. Then, H$_2$O (10 ml) and CH$_2$Cl$_2$ (20 ml) were added, and the mixture was filtered to remove insoluble starting material. The organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$. The organic layers were combined, dried over MgSO$_4$, and evaporated to leave a residue, which was recrystalized from hexane–CHCl$_3$ to give bis(phthalimidylethyl)-*N*-nitrosamine (**14**) in 66% yield. Compound **14** (1 mmol) and hydrazine hydrate (2.1 mmol) were dissolved in EtOH, and the mixture was heated at reflux for 3 h. After removal of EtOH *in vacuo*, the residue was suspended in 1 N HCl (10 ml), and heated at 50 °C for 30 min. The precipitate formed (phthalhydrazide) was filtered, and the filtrate was evaporated to dryness. The solid thus obtained was washed with EtOH and acetone, and air-dried to give bis(2-aminoethyl)-*N*-nitrosamine dihydrochloride (**11**) in 54% yield.

Bis(phthalimidylethyl)amine (**13**): Colorless needles from CHCl$_3$; mp 180—181 °C (lit.[28] mp 180 °C). ^{1}H-NMR (CDCl$_3$) δ: 1.14 (1H, br), 2.95 (4H, t, *J*=6.1 Hz), 3.77 (4H, t, *J*=6.1 Hz), 7.65—7.69 (4H, m), 7.71—7.75 (4H, m).

Bis(phthalimidylethyl)-*N*-nitrosamine (**14**): Colorless needles from hexane–CHCl$_3$; mp 190—191 °C. *Anal.* Calcd for C$_{20}$H$_{16}$N$_4$O$_5$: C, 61.22; H, 4.11; N, 14.28. Found: C, 61.05; H, 3.87; N, 14.28. ^{1}H-NMR (CDCl$_3$) δ: 3.86 (2H, t, *J*=6.1 Hz), 3.97 (2H, t, *J*=6.1 Hz), 4.06 (2H, t, *J*=6.1 Hz), 4.47 (2H, t, *J*=6.1 Hz), 7.69—7.73 (4H, m), 7.79—7.84 (4H, m). ^{13}C-NMR (CDCl$_3$) δ: 34.19, 35.32, 41.05, 49.78, 123.48, 123.52, 131.69, 131.82, 134.17, 134.23, 167.82, 167.84.

Bis(2-aminoethyl)-*N*-nitrosamine Dihydrochloride (**11**): Colorless solid; mp 192 °C (dec.). *Anal.* Calcd for C$_4$H$_{14}$Cl$_2$N$_4$O: C, 23.43; H, 6.88; N, 27.32. Found: C, 23.71; H, 6.71; N, 27.24. ^{1}H-NMR (D$_2$O) δ: 3.10 (2H, t, *J*=6.1 Hz), 3.43 (2H, t, *J*=6.1 Hz), 3.91 (2H, t, *J*=6.1 Hz), 4.44 (2H, t, *J*=6.1 Hz). ^{13}C-NMR (D$_2$O) δ: 37.34, 37.89, 43.11, 50.58.

The Reaction of Compound 10 (NOC-18) with Nitric Oxide in the Presence of Oxygen Compound **10** (0.02 mmol) was suspended in DCE (1 ml), and the reaction vessel was flushed with Ar as previously described. NO (0.1 mmol) and O$_2$ (0.2 μmol) were introduced and the mixture was stirred for 24 h at room temperature. After the remaining NO was removed by bubbling with Ar, DCE was evaporated off. The residue was dissolved with D$_2$O, and this solution was used for ^{1}H-NMR measurements. The spectrum indicated that the sample consisted of a 1 : 1 mixture of compound **10** and the free base of **11**.

The Reaction of *N*-Methylaniline with NO in the Presence of Excess O$_2$ The reaction was carried out under the conditions previously described. The side products **2c** and **22** were identified by comparison of their spectral data with that of authentic samples.

N-Methyl-2-nitro-*N*-nitrosoaniline (**22**): Pale yellow oil.[29] ^{1}H-NMR (CDCl$_3$) δ: 3.42 (3H, s), 7.53 (1H, d, *J*=8.1 Hz), 7.63 (1H, dd, *J*=8.1, 7.2

Hz), 7.79 (1H, dd, $J=7.8$, 7.2 Hz), 8.09 (1H, d, $J=7.8$ Hz).

The Reaction of Tribenzylamine with NO in the Presence of Oxygen The reaction was carried out as previously described except that the reaction temperature was maintained at 50 °C. Product analysis was performed by NMR using mesitylene as an internal standard.

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13) The electrochemical behaviour of N_2O_3 solutions was reported to be the same as that exhibited by an NO_2+NO mixture; see, Bontempelli G., Mazzochin G. A., Magno F., *J. Electrochem. Chem.*, **55**, 91 (1974).
14) Although the ammoniumyl radical **4** has a general tendency to be deprotonated at its α-position, this is not a crucial process in our reaction, since diphenylamine, which does not have an α-proton, reacted in a catalytic manner. That is, *N*-nitrosodiphenylamine was obtained in 26% yield by the reaction with 20 eq of NO and 0.01 eq of O_2.
15) With aromatic primary amines, it was shown that consumption of the starting material did not correspond to the formation of products regardless of the fact that the final yields were almost quantitative. This observation suggests there might be a (meta)stable intermediate in the reaction system. We presume this is a Drago's salt; see, ref 5b.
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