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-nitrosoamines 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-nitrosoamine

Nitric oxide (NO) is a molecule that has attracted much attention from the biological and physiological viewpoints because of its diverse bioactivity.1)11 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 un reproducible 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 with 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 O2 in acetonitrile, and a trace amount of O2 accelerated N-nitrosation, although the amount of O2 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 O2 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 O2 would be transformed to dinitrogen trioxide N2O3 according to the Eqs. 1 and 2.7)

\[
2\text{NO} + \text{O}_2 \rightarrow 2\text{NO}_2 \quad (1)
\]

\[
\text{NO}_3^- + \text{NO} \rightarrow \text{N}_2\text{O}_3 \quad (2)^b
\]

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 O2 (Table 1, entries 1, 2, and 3).10) As the polarity of the solvent increased, the yields became lower; in particular in acetone and H2O the reaction stopped after about 40% of the starting material had been consumed. These results suggest that the catalytic effect of O2 varies depending upon the polarity of the solvents. With acetone and H2O, O2 should be consumed stoichiometrically. That is, 0.1 eq of O2 is converted to 0.2 eq of N2O3 in the presence of an excess amount of NO according to Eqs. 1 and 2, and the N2O3 thus formed reacts with N-methylaniline to give the product and NO2, which regenerates 0.5 eq of N2O3 via dimerization.

To study the substituent effects, various secondary amines were used as substrates in 1,2-dichloroethane solution (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

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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 N₂O₃) through different pathways. With aliphatic amines, the reaction proceeds by the attack of NO which is stoichiometrically formed from N₂O₃, toward a lone pair of amines (Chart 4, pathway A). The pathway affords HNO₂, which reproduces N₂O₃ 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, N₂O₃ acts in a catalytic manner provided that N₂O₃ accepts one electron from the amine to form NO⁻ and NO₂⁻. If N₂O₃ decomposes to NO and NO₂⁻, regeneration of N₂O₃ according to Eq. 2 would not occur, and the catalytic behavior of O₂ 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 O₂ in regulating the reaction using NO. As an example, Table 4 shows the yield of 2a with various amounts of NO and O₂ (Chart 5). In the presence of 5 eq of NO, the reaction rate becomes higher as the amount of O₂ is increased, but the ratio of side products 6 and 7 (nitration compounds of the aromatic ring moiety) becomes larger as more O₂ is added (Table 4, entries 3 and 4). Thus it is necessary to control the amount of O₂ to obtain N-nitroso compound in a high yield. That is, the amount of O₂ must be less than 1/4 that of NO so that nitrogen oxide thus formed is mainly N₂O₃ rather than NO₂. In the presence of 0.1 eq of O₂, 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-nitrosoation 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 N₂O₃ formed in the presence of NO nitrosate 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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References and Notes
8) In organic solvents, the equilibrium constant of Eq. 2 is reported to be very high (≈10^6 to 10^7); 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-methyl-amine 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 I 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 O₂, 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 NO₂ 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 N₂O₃ solutions was reported to be the same as that exhibited by a NO₂+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 N₂O₃ in a catalytic manner. ¹⁰ The detailed mechanism will be reported in a subsequent paper.
15) When 2 eq of NO₂ was used, 6 and 7 were obtained in over 50% total yield, accompanied by a small amount of 1.