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Reactions of peroxynitrite with *N*,*N*-dimethyl-*p*-toluidine and 1,4-naphthoquinone. Evidence for heterolytic cleavage of a nitrogen–oxygen bond in peroxynitrous acid

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Abstract

Peroxynitrite ($ONOO^-$) has been found to react with the title amine **1** and quinone **5** to form *N*-nitrosoamine **2** and 2,3-epoxide **6**, respectively, in accord with the in situ generation of the nitrosonium and hydroperoxide ions as the respective reactive species. © 1999 Elsevier Science Ltd. All rights reserved.

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In recent years, peroxynitrite ($ONOO^-$) has been receiving considerable attention on account of its intriguing behavior in biological systems. It is generated from nitrogen oxide and a superoxide anion in vivo and affects biological functions. However, the reported reaction modes of this compound which include oxidation, nitration, nitrosation, and hydroxylation are limited at present. In the preceding paper, we have reported the kinetic feature of the reaction of peroxynitrite with substituted phenols.[1] We provide herein chemical evidences for the probable involvement of nitrosonium (NO^+) and hydroperoxide (HOO^-) ions as the reactive species, which should arise from an additional mode of decomposition of peroxynitrous acid, i.e., the heterolytic cleavage of the N–O single bond.

The in situ generation of NO^+ and HOO^- ions from peroxynitrite has been investigated using *N*,*N*-dimethyl-*p*-toluidine **1** and 1,4-naphthoquinone **5** as the respective chemical probes under three different conditions; neutral (**A**), acidified (**B**), and control (**C**). The progress of the reactions were monitored using ^1H NMR, and the product yields were estimated on the basis of integrated peak areas relative to the internal standard (*p*-dichlorobenzene). A stock solution of peroxynitrite was prepared as described previously. In method A, peroxynitrite (20 μmol) in D_2O (20–25 μl) was added to a solution of the given substrate (10 μmol) in CD_3CN (0.6 ml), while in method B, the same reaction was carried out in the presence of NaH_2PO_4 (20 μmol). In method C, solutions of peroxynitrite (20 μmol) in D_2O (20–25 μl) and of NaH_2PO_4 (20 μmol) in CD_3CN (0.2 ml), were mixed together and, after 10 min, the substrate (10 μmol) in CD_3CN (0.4 ml) was added to the resulting mixture. All reactions were run for 10 min at room temperature under air.

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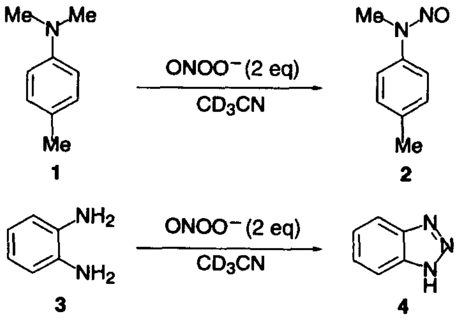
In methods A and B, *N,N*-dimethyl-*p*-toluidine **1** was transformed into an *N*-nitroso compound **2**, being accompanied by minor amounts of several unidentified products (Scheme 1). This type of oxidative dealkylation has often been observed under the conditions where the nitrosonium ion is generated in situ.[2] As additional evidence for the nitrosonium ion, 1,2-phenylenediamine **3** was converted into benzotriazole **4**.[3] Both substrates were recovered almost unchanged in method C, where the peroxynitrous acid had simply decomposed to lower oxides of nitrogen. The rate of decomposition of peroxynitrous acid was unaffected by the presence or absence of an added aromatic amine, i.e. zeroth order on the substrate; this strongly suggests that the products were formed in parallel with the decomposition of peroxynitrous acid. All observations are in accordance with the view that the nitrosonium ion is the actual reactive species responsible for the present transformations.

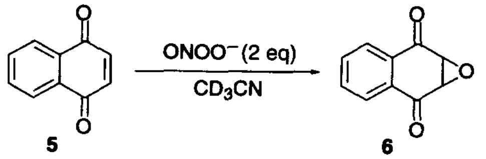


Method	Conversion (%)	Conversion yield (%)
A	~5	~20
B	27	26
C	~5	0

Method	Conversion (%)	Conversion yield (%)
A	51	33
B	53	26
C	~5	0

Scheme 1.

1,4-Quinones are subject to facile Michael-type addition of heteronucleophiles, such as the hydroperoxide ion.[4] Thus, in methods A and B, the reaction of peroxynitrite with 1,4-naphthoquinone **5** led to 2,3-epoxy-2,3-dihydro-1,4-naphthoquinone **6**, as expected (Scheme 2). Epoxide **6** was not produced in method C and hence the oxygenating species should have been generated concurrently with the decomposition of peroxynitrous acid. When a 1:1 mixture of amine **1** and quinone **5** was similarly treated, both **2** and **6** were formed, the latter being predominant.



Method	Conversion (%)	Conversion yield (%)
A	65	58
B	56	66
C	~5	0

Scheme 2.

In conclusion, all chemical evidences obtained are in favor of the polar mechanism proposed in the preceding paper, where the peroxynitrous acid undergoes heterolytic decomposition to NO^+ and HOO^- ions, the former dealkylating aromatic tertiary amine **1** via the electrophilic *N*-nitrosoation and the latter epoxidating quinone **5** to epoxide **6** via the nucleophilic 1,4-addition followed by ring closure.

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