Synthesis, Structure, and Reactions of the First Stable Aromatic *S*-Nitrosothiol Bearing a Novel Dendrimer-Type Steric Protection Group

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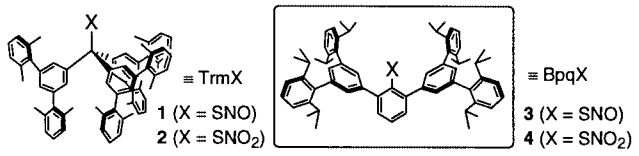
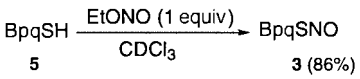
(Received August 9, 2001; CL-010769)

A stable aromatic *S*-nitrosothiol was synthesized by taking advantage of a novel dendrimer-type steric protection group, and its structure was determined by X-ray crystallographic analysis. Its reactions including oxidation to a stable *S*-nitrothiol are described.

S-Nitrosothiols (R–SNO) have been attracting increasing attention in view of their role as potential biocatalysts and reagents for the storage and transport of nitric oxide (NO).[1] However, because of their inherent instability, only limited physical and structural data have been accumulated. As for aliphatic *S*-nitrosothiols, there have been several compounds isolated and structurally characterized so far,[2–5] including compound **1** bearing a bowl-shaped triarylmethyl group (denoted as Trm), which we reported recently.[5] On the other hand, aromatic *S*-nitrosothiols are much less stable than aliphatic derivatives and there has been no example of isolation of an aromatic *S*-nitrosothiol. Usually, they accumulate only transiently and rapidly decompose to the corresponding disulfides and NO.[6,7] *S*-Nitrothiols (R–SNO_2) have also been recognized as important species from the viewpoints of their physiological activity and synthetic utility.[1a,8] However, they have also been known as highly labile species except for the compounds bearing a bulky alkyl substituent such as *t*-BuSNO_2[1a] and TrmSNO_2 (**2**);[5] there has been no example of an aromatic *S*-nitrothiol which is stable at room temperature. Recently we have developed a novel aromatic steric protection group bearing a dendrimer-type framework (denoted as Bpq).[9] In this communication, we report the synthesis, structure, and reactions of the first stable aromatic *S*-nitrosothiol **3** and the corresponding *S*-nitrothiol **4** bearing the Bpq group.[10,11]



Treatment of thiol **5** with an equimolar amount of ethyl nitrite in $CDCl_3$ afforded *S*-nitrosothiol **3** quantitatively, which was isolated as brownish green crystals by recrystallization from hexane in 86% yield (Scheme 1).[12] This is the first isolation of an aromatic *S*-nitrosothiol.[11] The UV–vis spectrum of **3** showed the absorptions at 345 nm (sh, ε 488) and 557 nm (ε 11), which are characteristic of the S–N=O group. In the IR spectrum, the N–O stretching band was observed at 1548 cm^{-1}.



Scheme 1.

The conformation of the S–N=O group of *S*-nitrosothiols is one of the current topics, and several theoretical and experimental studies on this subject have recently been reported.[3–5] Until very recently, there had been only two examples of the crystallographic analysis of *S*-nitrosothiols, *S*-nitroso-D,L-penicillamine[2] and Ph_3CSNO,[3] in both of which the C–S–N–O linkage adopts only the anti conformation. We recently reported that TrmSNO (**1**) exists as a mixture of the syn and anti isomers in the crystalline state.[5] This result was in good agreement with the theoretical calculation on Ph_3CSNO (B3LYP/6-31G*), where the syn isomer was found to be slightly more stable by 0.15 kcal mol^{-1} than the anti isomer. *S*-Nitrosocaptopril bearing a primary alkyl group was reported to adopt exclusively the syn conformation.[4] As for an aromatic *S*-nitrosothiol, there has been no information about its structure. X-ray crystallographic analysis established the structure of *S*-nitrosothiol **3** (Figure 1).[13] In the crystalline state, there was a rotational disorder of the N–O moiety around the C–S bond in the ratio of 0.55:0.45. Owing to this disorder, unfortunately, it is difficult to discuss the detailed structural parameters of the SNO moiety at present.[14] It is noteworthy, however, that in both cases the C–S–N–O linkage adopts only the syn conformation. In order to examine whether this result is due to the intrinsic property of an aromatic *S*-nitrosothiol or due to the steric bulkiness of the Bpq group, theoretical calculations on PhSNO were carried out with the density functional theory at the B3LYP/6-31G* level, using the Gaussian 98 program. It was found that the syn isomer is more stable than the anti isomer by 0.66 kcal mol^{-1}.[15] This energy difference is much larger than that of Ph_3CSNO (0.15 kcal mol^{-1}).[8] In view of these calculations, it is considered to be reasonable that only the syn isomer was observed in the crystalline state of **3** whereas **1** was observed as a mixture of the syn and anti isomers. The conformations of the SNO groups of **1** and **3** in the crystalline state do not seem to be affected by the steric bulkiness of the substituents.

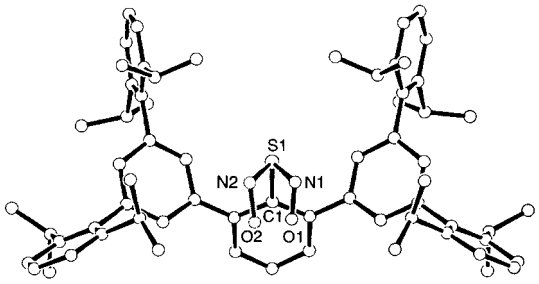
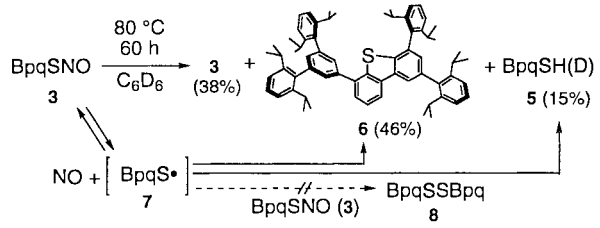


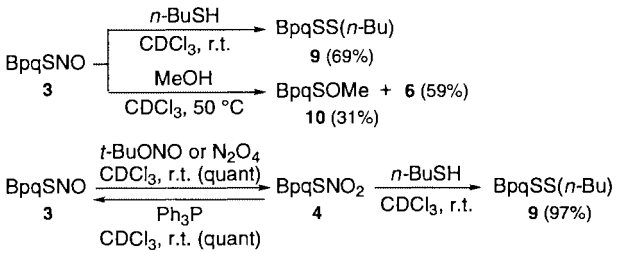
Figure 1. Crystal structure of **3**. The disorder ratio of N(1)–O(1) to N(2)–O(2) is 0.55:0.45. Hydrogen atoms and the solvent molecules are omitted for clarity.

Usually, aromatic *S*-nitrosothiols undergo rapid decomposition to the corresponding disulfide and NO. It was reported that the half-life times of ArSNO (Ar = phenyl, *p*-methoxyphenyl, *p*-nitrophenyl, 3,5-di-*t*-butyl-4-hydroxyphenyl) are 7–14 min in dichloromethane (85 mM) at room temperature.[7] In sharp contrast with these compounds, *S*-nitrosothiol **3** showed remarkable thermal stability. It was found that, even after heating in C_6D_6 at 80 °C for 60 h, 38% of **3** remained unchanged. The rest of **3** was converted to the dibenzothiophene derivative **6** (46%) and thiol **5** (15%), which are considered to be formed via thiyl radical **7** (Scheme 2). In this reaction, the formation of the symmetrical disulfide **8** was not detected. The mechanism of thermolysis of *S*-nitrosothiols in hydrocarbon solvents is usually considered to involve the bimolecular reaction of an initially formed thiyl radical with the second molecule of *S*-nitrosothiol.[1e] The present results suggest that the Bpq group effectively suppressed the reaction of thiyl radical **7** with the second molecule of *S*-nitrosothiol **3**, which enabled the very slow reaction to **6** and **5** to take place.



Scheme 2.

In spite of such high thermal stability, **3** reacted with several reagents (Scheme 3). The reaction of **3** with 1-butanethiol afforded the unsymmetrical disulfide **9**. When **3** was treated with excess methanol, methyl sulfenate **10** was obtained along with **6**. Oxidation of **3** with an excess amount of *t*-butyl nitrite or N_2O_4 afforded the corresponding *S*-nitrothiol **4** quantitatively. Considering the fact that the aliphatic *S*-nitrosothiol **1** does not react with *t*-butyl nitrite, aromatic *S*-nitrosothiols are considered to be more readily subject to oxidation than aliphatic derivatives. It was reported that *p*-X-$C_6H_4SNO_2$ (X = Cl, Br, CH_3) are isolable at low temperature, but they were found to decompose readily at room temperature. On the other hand, *S*-nitrothiol **4** was isolated as stable pale yellow crystals, the decomposition point of which is 173 °C.[16] *S*-Nitrothiol **4** reacted with 1-butanethiol to give the unsymmetrical disulfide **9** similarly to *S*-nitrosothiol **3**. Reduction of **4** with an equimolar amount of triphenylphosphine afforded **3** quantitatively, presenting a new method for generation of an *S*-nitrosothiol. These results indicate that the Bpq group effectively stabilizes the *S*-nitrosothiol and *S*-nitrothiol without diminution of their intrinsic reactivities towards appropriate molecules.



Scheme 3.

Further investigations on the reactivity of **3** and **4** are currently in progress.

This work was partly supported by Grants-in-Aid for Scientific Research (Nos. 12042220 and 12440204 (K.G.)) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We also thank Tosoh Finechem Corporation, for a generous gift of alkyllithiums.

Dedicated to Prof. Hideki Sakurai on the occasion of his 70th birthday.

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11 Okazaki et al. also reported the synthesis of a stable aromatic *S*-nitrosothiol. See the following paper. M. Ito, K. Takenaka, and R. Okazaki, *19th International Symposium on the Organic Chemistry of Sulfur*, Sheffield, June 2000; Abstr., No. PP35.

12 **3**: brownish green crystals; mp 156 °C (dec); ^{1}H NMR($CDCl_3$, 500 MHz) δ 1.06 (d, *J* = 6.7 Hz, 24H), 1.17 (d, *J* = 6.7 Hz, 24H), 2.71 (m, 8H), 6.95–6.97 (m, 6H), 7.18–7.46 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.0 (q), 24.2 (q), 30.4 (d), 122.4 (d), 126.5 (d), 127.9 (d), 128.5 (d), 129.9 (d), 130.0 (d), 131.5 (s), 138.8 (s), 139.8 (s), 139.9 (s), 145.7 (s), 146.8 (s). UV/Vis ($CHCl_3$) λ_{max} 345 (ε 488, sh), 557 (11) nm. IR (KBr) 1548 cm^{-1} (ν(N=O)). Found; C, 82.81; H, 8.08; N, 1.46; S, 3.32; Cl, 1.82%. Calcd for $C_{66}H_{77}NOS\cdot0.2CHCl_3$: C, 83.15; H, 8.14; N, 1.46; S, 3.35; Cl, 2.22%.

13 Crystallographic data for **3**: $C_{66}H_{67}NOS\cdot0.2C_6H_{14}$, M_r = 939.57, *monoclinic*, space group $P2_1/n$, *a* = 19.379(3), *b* = 9.328(3), *c* = 36.128(9) Å, β = 101.46(1)°, *U* = 6400(3) Å^3, *Z* = 4, D_c = 0.994 g cm^{-3}, *T* = 296 K, μ(Mo Kα) = 0.883 cm^{-1}, $R(R_w)$ = 0.084(0.081).

14 The preliminary results for the bond lengths (Å), bond angles (deg), and torsion angle (deg) around the major fragment of the SNO group: S(1)–N(1), 1.85(3); N(1)–O(1), 1.23(3); C(1)–S(1), 1.803(10); S(1)–N(1)–O(1), 103.0(25); C(1)–S(1)–N(1), 109.4(10); C(1)–S(1)–N(1)–O(1), –21.3(28).

15 The calculated bond lengths (Å), bond angles (deg), and torsion angle (deg) are as follows. For the syn isomer; S–N, 1.927; N–O, 1.176; C–S, 1.773; S–N–O, 115.973; C–S–N, 101.602; C–S–N–O, –2.00. For the anti isomer; S–N, 1.909; N–O, 1.179; C–S, 1.778; S–N–O, 114.808; C–S–N, 96.435; C–S–N–O, –178.24.

16 **4**: pale yellow crystals; mp 173 °C (dec); ^{1}H NMR($CDCl_3$, 500 MHz) δ 1.05–1.25 (br, 48H), 2.68–2.81 (br, 8H), 7.03 (t, *J* = 1.5 Hz, 2H), 7.11 (d, *J* = 4.0 Hz, 4H), 7.17–7.20 (m, 8H), 7.30–7.34 (m, 4H), 7.65–7.67 (m, 2H), 7.76–7.79 (m, 1H). ^{13}C NMR($CDCl_3$, 125 MHz) δ 23.8 (q, br), 24.1 (q, br), 24.2 (q), 30.4 (d), 30.5 (d), 122.4 (d), 127.9 (d), 128.8 (d), 130.2 (d), 130.5 (d), 134.4 (d), 138.6 (s), 139.3 (s), 140.3 (s), 146.8 (s), 149.3 (s). UV/Vis ($CHCl_3$) λ_{max} 349 (ε 200, sh) nm. IR (KBr) 1543 (ν(NO_2) asym), 1288 cm^{-1} (ν(NO_2) sym). Found; C, 82.09; H, 8.17; N, 1.11; S, 3.15%. Calcd for $C_{66}H_{77}NO_2S\cdot H_2O$: C, 82.03; H, 8.24; N, 1.45; S, 3.32%.