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# Synthesis and crystal structure of a stable *S*-nitrosothiol bearing a novel steric protection group and of the corresponding *S*-nitrothiol

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## Abstract

The molecular structure of a stable *S*-nitrosothiol bearing a novel trityl-type steric protection group was established by X-ray crystallographic analysis together with that of the corresponding *S*-nitrothiol. It was found that the *S*-nitrosothiol exists as a mixture of the *syn* and *anti* isomers with respect to the C–S–N–O linkage in the crystalline state, in agreement with the theoretical calculation on $Ph_3CSNO$. © 2000 Elsevier Science Ltd. All rights reserved.

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*S*-Nitrosothiols (R–SNO) have been attracting increasing attention in view of their role in vivo as potential biocatalysts and reagents for the storage and transport of nitric oxide (NO).[1] Because of their inherent instability, however, only limited structural data on this species have been accumulated. The structures of only two *S*-nitrosothiols, *S*-nitrosoacetyl-D,L-penicillamine (SNAP)[2] and $Ph_3CSNO$,[3] have been crystallographically characterized so far, in both of which the C–S–N–O linkage was found to adopt only the *anti* conformation. On the other hand, the theoretical calculation on $CH_3SNO$ indicated that the *syn* isomer is slightly more stable than the *anti* isomer by ~0.07 kcal $mol^{-1}$.[3] Elucidation of the structural features of *S*-nitrosothiols is considered to be important for the understanding of the structure and reactivity of this species in proteins. *S*-Nitrothiols ($R–SNO_2$) have also been known to be a highly labile species, with the

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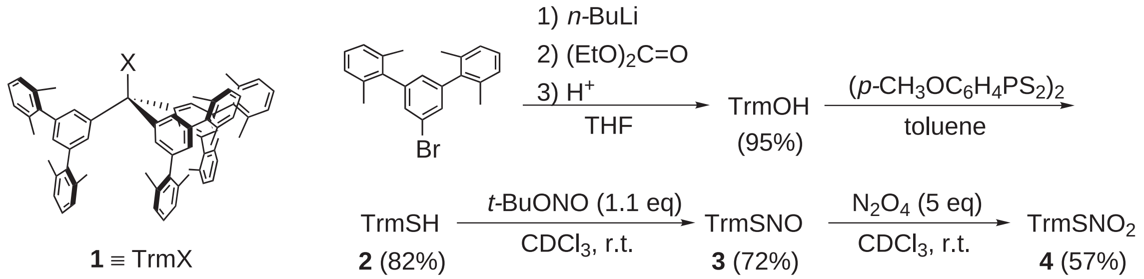
exception of those bearing a bulky alkyl substituent, and despite their synthetic and biological significance,[4] there has been no example of X-ray crystallographic analysis of an *S*-nitrothiol. We have been investigating the stabilization of a highly reactive organosulfur species by taking advantage of the bowl-shaped substituents.[5] In this communication, we report the synthesis and crystal structure of a stable *S*-nitrosothiol bearing a newly designed steric protection group and of the corresponding *S*-nitrothiol.

Although we have developed several types of bowl-shaped steric protection groups so far,[5] they are all aromatic substituents. As an aliphatic molecular bowl, we newly designed triarylmethyl derivative **1** (denoted as TrmX hereafter),[6] where the phenyl groups of $Ph_3CX$ are replaced by *m*-terphenyl-5′-yl groups so that it would form a dendrimer-type structure. The functionality X is incorporated in the shallow molecular cavity and its dimerization or self-condensation is expected to be effectively prevented. On the other hand, steric congestion in the vicinity of X is not increased as much in comparison with $Ph_3CX$ because there is no *ortho*-substituent on the aromatic rings connected to the central carbon atom. Thiol **2** was readily prepared by the procedure shown in Scheme 1. Treatment of **2** with *tert*-butyl nitrite (1.1 equiv.) in $CDCl_3$ afforded *S*-nitrosothiol **3** quantitatively, which was isolated as deep-green crystals by recrystallization from hexane in 72% yield (Scheme 1).[7] The UV–vis spectrum of **3** showed the characteristic bands at 346 nm (sh, $\varepsilon$ 611) and 602 nm ($\varepsilon$ 40). In the infrared spectra, the N–O stretching band was observed at 1522 $cm^{-1}$. *S*-Nitrosothiols have been known to undergo thermal decomposition via the bimolecular pathway.[1b] Upon heating at 80°C in $C_6D_6$, $Ph_3CSNO$ decomposed within 0.5 h. On the other hand, *S*-nitrosothiol **3** showed remarkable thermal stability, and its decomposition required 18 h under the same conditions. These results demonstrate that the bowl-shaped structure of the Trm group effectively suppresses the bimolecular decomposition of **3**.



Scheme 1.

It has been reported that oxidation of thiols bearing a *tert*-alkyl group with excess $N_2O_4$ affords the corresponding *S*-nitrothiols via the *S*-nitrosothiols.[8] Oxidation of *S*-nitrosothiol **3** with $N_2O_4$ gave the corresponding *S*-nitrothiol **4**, which was isolated as stable colorless crystals by silica gel chromatography in 57% yield.[9] On the other hand, the reaction of $Ph_3CSNO$ under the same conditions afforded a complex mixture and the formation of $Ph_3CSNO_2$, which is still an unknown compound, was not detected. In the infrared spectrum of *S*-nitrothiol **4**, bands at 1532 and 1290 $cm^{-1}$ were observed, which correspond to the asymmetric and symmetric stretching of $NO_2$, respectively.

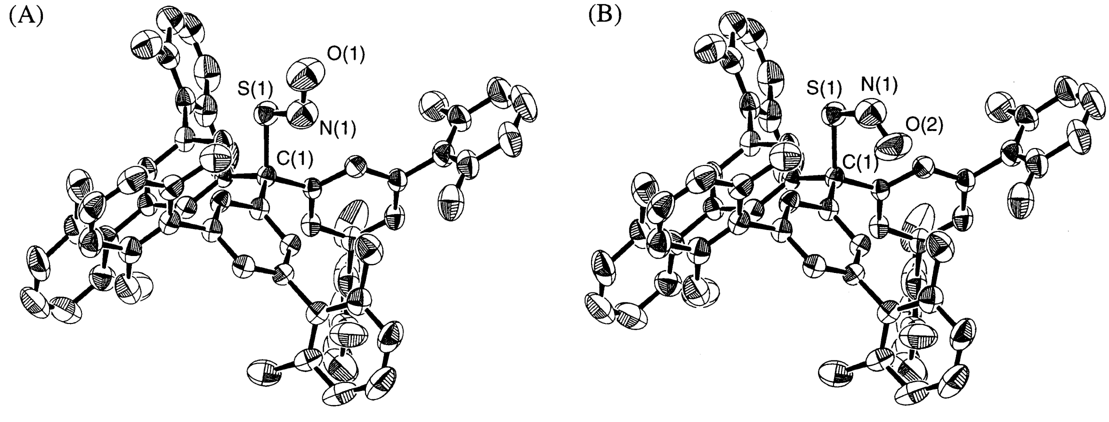


Fig. 1. Crystal structures of the *anti* (A) and *syn* (B) isomers of **3** (ORTEP drawing; thermal ellipsoids at 30% probability level). Selected bond lengths (Å), bond angles (°), and torsion angles (°): S(1)–N(1), 1.781(5); N(1)–O(1), 1.205(6); N(1)–O(2), 1.189(12); S(1)–C(1), 1.841(4); S(1)–N(1)–O(1), 111.4(6); S(1)–N(1)–O(2), 123.6(7); C(1)–S(1)–N(1), 104.2(3); C(1)–S(1)–N(1)–O(1), 179.6; C(1)–S(1)–N(1)–O(2), 7.3

The crystal structure of *S*-nitrosothiol **3** is shown in Fig. 1 with selected bond lengths, bond angles, and torsion angles.[10] It is noteworthy that **3** exists as a mixture of the *syn* and *anti* isomers with respect to the C–S–N–O linkage in the crystalline state, where the oxygen atom of the SNO group is disordered in the ratio of *anti*:*syn* = 0.67:0.33. After X-ray crystallographic analysis, the examined single crystal of **3** was checked by $^1$H NMR, and it was confirmed that the crystal did not contain *S*-nitrothiol **4**. The S–N bond length [1.781(5) Å] and N–O bond lengths [1.205(6) Å for the *anti* isomer and 1.189(12) Å for the *syn* isomer] are consistent with a sulfur–nitrogen single bond and a nitrogen–oxygen double bond. The rotational disorder of the SNO group of **3** is in sharp contrast with the crystal structure of $Ph_3CSNO$ recently reported by Bohle[3] as well as those of SNAP first reported by Field[2] and reexamined by Bohle,[3] in both of which only the *anti* isomers were observed. We carried out the theoretical calculation on $Ph_3CSNO$ with the density functional theory at the B3LYP/6-31G* level, using the Gaussian 98 program, and it was found that the *syn* isomer is 0.15 kcal mol$^{-1}$ more stable than the *anti* isomer, similar to the case of $CH_3SNO$. These results indicate that, among the three *S*-nitrosothiols crystallographically characterized so far, only the crystal structure of **3** bears similarity to the gas phase structure of RSNO with respect to the conformation of an SNO group. A major difference between **3** and $Ph_3CSNO$ is that the SNO group of **3** is embedded in the large cavity formed by the Trm group while that of $Ph_3CSNO$ is rather exposed to the bulk. The observation of both *syn* and *anti* isomers of **3** in the crystalline state could be explained in terms such as accommodation of the SNO group in the rigid and large cavity, which is considered to reduce the influence of the crystal packing force on its conformation. It is possible that in SNAP and $Ph_3CSNO$ the crystal packing forces lead to the solid-state preference for the *anti* conformation.

The structure of *S*-nitrothiol **4** was also established by X-ray crystallographic analysis (Fig. 2).[11] This is the first X-ray analysis of an *S*-nitrothiol. The S–N bond length [1.746(9) Å] is slightly shorter than that of **3**, which is still consistent with a sulfur–nitrogen single bond, while the N–O bond lengths [N(1)–O(1) 1.239(9), N(1)–O(2) 1.229(9) Å] are a little longer than that of **3**. The $SNO_2$ moiety has a completely planar geometry, the sum of the bond angles around the nitrogen atom being 360°.

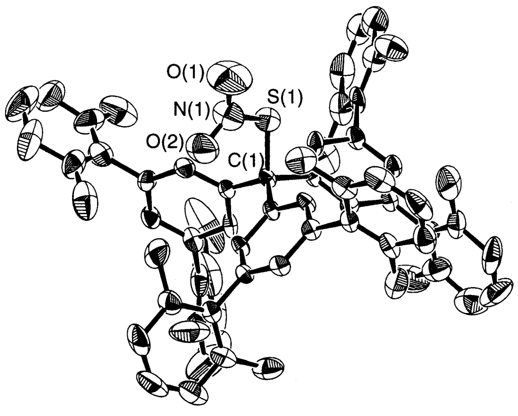


Fig. 2. Crystal structure of **4** (ORTEP drawing; thermal ellipsoids at 30% probability level). Selected bond lengths (Å), bond angles (°), and torsion angle (°): S(1)–N(1), 1.746(9); N(1)–O(1), 1.239(9); N(1)–O(2), 1.229(9); S(1)–C(1), 1.789(6); S(1)–N(1)–O(1), 119.7(9); S(1)–N(1)–O(2), 114.1(9); C(1)–S(1)–N(1), 107.9(5); C(1)–S(1)–N(1)–O(1), 171.7.

Further investigation on physical and chemical properties of **3** and **4** is currently in progress.

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## References

1. (a) Feldman, P. L.; Griffith, O. W.; Stuehr, D. J. *Chem. Eng. News* **1993**, *December 20*, 26; (b) For a review on the chemistry of *S*-nitrosothiols, see: Lyn, D.; Williams, H. *Acc. Chem. Res.* **1999**, *32*, 869–876.
2. (a) Field, L.; Dilts, R. V.; Ravichandran, R.; Lenhert, P. G.; Carnahan, G. E. *J. Chem. Soc., Chem. Commun.* **1978**, 249–250; (b) Carnahan, G. E.; Lenhert, P. G.; Ravichandran, R. *Acta Crystallogr.* **1978**, *B34*, 2645–2648.
3. Arulsamy, N.; Bohle, D. S.; Butt, J. A.; Irvine, G. J.; Jordan, P. A.; Sagan, E. *J. Am. Chem. Soc.* **1999**, *121*, 7115–7123.
4. (a) Kim, Y. H. *Phosphorus, Sulfur, and Silicon* **1993**, *74*, 249–260; (b) Artz, J. D.; Yang, K.; Lock, J.; Sanchez, C.; Bennett, B. M.; Thatcher, G. R. J. *Chem. Commun.* **1996**, 927–928.
5. (a) Goto, K.; Tokitoh, N.; Okazaki, R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1124–1126; (b) Saiki, T.; Goto, K.; Tokitoh, N.; Okazaki, R. *J. Org. Chem.* **1996**, *61*, 2924–2925; (c) Goto, K.; Holler, M.; Okazaki, R. *J. Am. Chem. Soc.* **1997**, *119*, 1460–1461; (d) Saiki, T.; Goto, K.; Okazaki, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2223–2224; (e) Goto, K.; Holler, M.; Okazaki, R. *Chem. Commun.* **1998**, 1915–1916; (f) Goto, K.; Okazaki, R. *Liebigs Ann./Recueil* **1997**, 2393–2407 (Microreview).
6. Trm denotes tris(2,2″,6,6″-tetramethyl-*m*-terphenyl-5′-yl)methyl.
7. **3**: mp 203°C (dec.); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.87 (s, 36H), 6.83 (br, 3H), 7.01–7.09 (m, 24H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 20.67, 127.14, 127.21, 129.00, 129.06, 135.65, 141.12, 141.40, 143.94; IR(KBr) 1522 cm$^{-1}$ ($\nu_{\text{n–o}}$); UV–vis (CHCl$_3$) $\lambda_{\text{max}}$ 346 nm (sh, $\varepsilon$=611), $\lambda_{\text{max}}$ 602 nm ($\varepsilon$=40); Calc. for $C_{67}H_{63}NOS$: C, 86.50; H, 6.83; N, 1.51; S, 3.45. Found: C, 86.28; H, 6.83; N, 1.51; S, 3.37%.
8. Oae, S.; Shinhama, K.; Fujimori, K.; Kim, Y. H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 775–784.

9. **4**: mp 244°C (dec.); $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 1.89 (s, 36H), 6.90 (br, 3H), 7.02–7.13 (m, 16H), 7.20 (d, $J=1.3$ Hz, 6H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 20.67, 127.14, 127.21, 129.00, 129.06, 135.65, 141.12, 141.40, 143.94; IR(KBr) 1532 cm$^{-1}$ (asym. $NO_2$), 1290 cm$^{-1}$ (sym. $NO_2$); Calc. for $C_{67}H_{63}NO_2S{\cdot}H_2O$: C, 83.45; H, 6.79; N, 1.45; S, 3.33. Found: C, 83.55; H, 6.64; N, 1.50; S, 2.98%.
10. Crystallographic data for **3**: $C_{67}H_{63}NOS$, $M=930.30$, monoclinic, $a=12.484(2)$, $b=23.290(3)$, $c=20.090(1)$ Å, $\beta=105.440(7)°$, $U=5630(1)$ Å$^3$, $T=296$ K, space group $P2_1/c$ (no. 14), $Z=4$, $D_{calc}=1.097$ g cm$^{-3}$, $\mu$(Mo–K$_\alpha$)= 0.990 cm$^{-1}$. The intensity data were collected at 296 K on a MAC Science DIP-2030 imaging plate area detector with Mo–K$_\alpha$ radiation ($\lambda=0.71069$ Å), and the structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 5143 observed reflections [$I>3.00\sigma(I)$] and 640 variable parameters with $R(R_w)=0.069(0.075)$.
11. Crystallographic data for **4**: $C_{67}H_{63}NO_2S$, $M=946.30$, monoclinic, $a=12.446(2)$, $b=23.327(3)$, $c=20.063(2)$ Å, $\beta=105.690(6)°$, $U=5608(1)$ Å$^3$, $T=296$ K, space group $P2_1/c$, $Z=4$, $D_{calc}=1.121$ g cm$^{-3}$, $\mu$(Mo–K$_\alpha$)=1.017 cm$^{-1}$. The intensity data were collected at 296 K on a MAC Science DIP-2030 imaging plate area detector with Mo–K$_\alpha$ radiation ($\lambda=0.71069$ Å), and the structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 3470 observed reflections [$I>3.00\sigma(I)$] and 640 variable parameters with $R(R_w)=0.085(0.076)$.