Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsrp20

Transnitrosation from a stable thionitrate to an amine with concomitant formation of a sulfenic acid

Kei Goto[a], Shuhei Yoshikawa[a], Taku Ideue[a] & Shohei Sase[a]
[a] Department of Chemistry, Graduate School of Science and Engineering, Tokyo Institute of Technology, Tokyo, 152-8551, Japan
Published online: 14 May 2013.

To cite this article: Kei Goto, Shuhei Yoshikawa, Taku Ideue & Shohei Sase (2013) Transnitrosation from a stable thionitrate to an amine with concomitant formation of a sulfenic acid, Journal of Sulfur Chemistry, 34:6, 705-710, DOI: 10.1080/17415993.2013.794801

To link to this article: http://dx.doi.org/10.1080/17415993.2013.794801

Journal of Sulfur Chemistry, 2013
Vol. 34, No. 6, 705–710, http://dx.doi.org/10.1080/17415993.2013.794801

SHORT COMMUNICATION

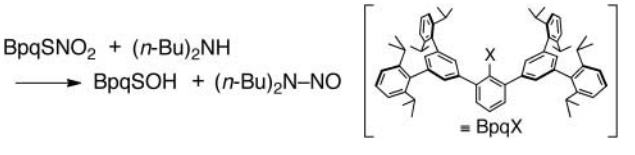
Transnitrosation from a stable thionitrate to an amine with concomitant formation of a sulfenic acid

Kei Goto*, Shuhei Yoshikawa, Taku Ideue and Shohei Sase

Department of Chemistry, Graduate School of Science and Engineering, Tokyo Institute of Technology, Tokyo 152-8551, Japan

(*Received 15 March 2013; final version received 8 April 2013*)

The reaction of a stable thionitrate bearing a bowl-shaped steric protection group with dibutylamine resulted in nitrosation of the amine with concomitant formation of a sulfenic acid, presenting the experimental evidence for the proposed mechanism of the reaction of thionitrates with amines.



Keywords: thionitrate; nitrosation; *N*-nitrosoamine; sulfenic acid; steric protection

1. Introduction

Thionitrates ($RSNO_2$) have been attracting increasing attention as key intermediates in the bioactivation of organic nitrates ($RONO_2$), such as nitroglycerin and isosorbide nitrates, which are known to exert a vasodilator effect through the transformation to nitric oxide (NO) (*1–4*). Many investigators have proposed that a cysteine residue (CysSH) in the active site of an enzyme mediates this bioactivation of $RONO_2$, and that a cysteine thionitrate ($CysSNO_2$) is formed as the initial intermediate, which produces NO through some chemical transformation. However, the mechanism for this biotransformation of organic nitrates to NO has not been elucidated yet. From such viewpoints, there has been a growing interest in chemical transformation processes from thionitrates to other nitrogen species. Although thionitrates are usually rather labile because of ready bimolecular decomposition, fundamental chemical properties of this species were intensively studied by Oae and Shinhama (*5*), Oae *et al.* (*6–8*), Kim and Kim (*9*) and Kim *et al.* (*10*). They examined the reaction of thionitrates with nitrogen nucleophiles, and reported that *t*-butyl thionitrate (*t*-$BuSNO_2$, **1**) serves as a diazotizing reagent of arylamines (*6–8*). As the plausible mechanism for the first stage of the diazotizing reaction, transnitrosation from a sulfenyl nitrite (RS-ONO) (*11*, *12*), a tautomeric form of a thionitrate, to an amine to produce the corresponding

*Corresponding author. Email: goto@chem.titech.ac.jp
Dedicated to the memory of Professor Alessandro Degl'Innocenti.

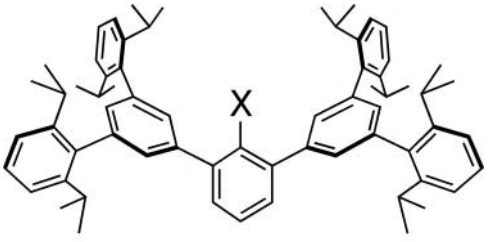
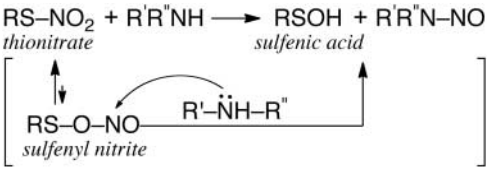


Figure 1. Stable thionitrate and sulfenic acid bearing a bowl-shaped substituent.

N-nitrosoamine and sulfenic acid (RSOH) was proposed (Scheme 1) (*7*). In the reported reactions (*6–8*), however, the formation of the sulfenic acid was not confirmed because of its instability (*13*). For the verification of the chemical process depicted in Scheme 1, a molecular system that can stabilize both thionitrate and resulting sulfenic acid is required. We have been investigating the stabilization of chalcogen-containing reactive species by taking advantage of bowl-shaped molecular cavities (*14–21*), and previously reported the synthesis and isolation of the stable thionitrate **2** (*18*) and sulfenic acid **3** (*20*) bearing a dendrimer-type steric protection group, a Bpq group (Figure 1). Here, we report the experimental demonstration of the nitrosation of an amine with a thionitrate accompanied by the formation of a sulfenic acid.



Scheme 1. Proposed mechanism for the reaction of a thionitrate with an amine.

2. Results and discussion

Thionitrate **2** bearing a Bpq group was synthesized according to the procedure we previously reported (*18*). Since the crystal structure of **2** was not determined, X-ray crystallographic analysis was performed with the single crystals of **2** obtained by recrystallization from chloroform/hexane (Figure 2). The selected bond lengths and angles are summarized in Table 1. In the literature, there have been only two examples of crystallographic analysis of thionitrates: the triarylmethyl-substituted thionitrate **4** (*16*) reported by us and the aromatic thionitrate **5** (*22*) reported by Itoh *et al*. (Figure 3). The S−N bond length of **2** is 1.7898(17) Å, which is similar to that of the aromatic derivative **5** and slightly longer than that of the aliphatic derivative **4** (Table 1).

The nitrosating ability of thionitrate **2** was examined by the reaction with a secondary amine. The treatment of a degassed $CDCl_3$ solution of thionitrate **2** with three equivalents of dibutylamine at room temperature resulted in the formation of the corresponding sulfenic acid **3** as the main product with concomitant formation of *N*-nitrosodibutylamine in 66% and 70% yields, respectively, as estimated by ^{1}H NMR spectroscopy (Scheme 2). In addition to sulfenic acid **3**, sulfenamide **6** was formed as the minor product in 26% yield. This is the first demonstration of the transformation of a thionitrate and an amine to the corresponding sulfenic acid and *N*-nitrosoamine. Usually, sulfenic

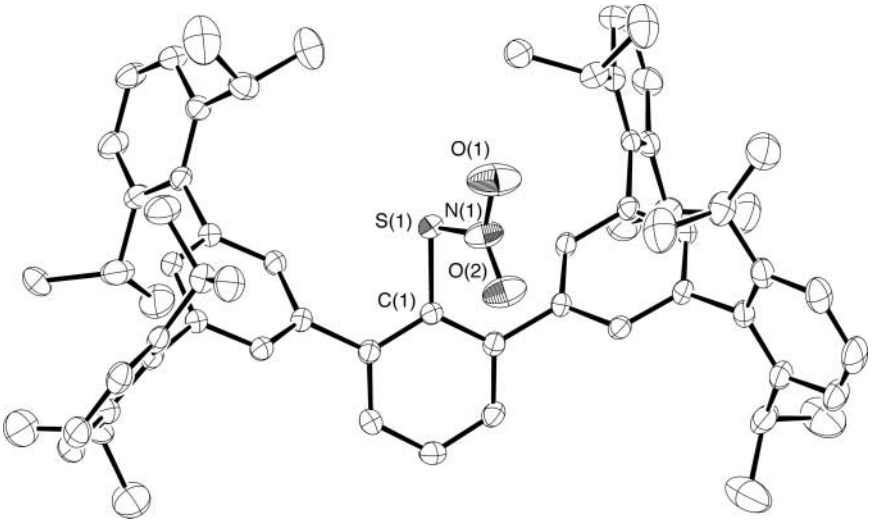


Figure 2. ORTEP drawing of **2** (50% probability). Hydrogen atoms and solvents are omitted for clarity.

Table 1. Selected bond lengths and angles for **2**, **4** and **5**.

	2	**4** (*16*)	**5** (*22*)
Bond lengths (Å)			
S(1)–N(1)	1.7898 (17)	1.746 (9)	1.795 (2)
N(1)–O(1)	1.213 (2)	1.239 (9)	1.228 (3)
N(1)–O(2)	1.2180 (19)	1.229 (9)	1.215 (3)
C(1)–S(1)	1.7651 (15)	1.789 (6)	1.764 (2)
Bond angles (°)			
S(1)–N(1)–O(1)	113.28 (13)	119.7 (9)	113.48 (18)
S(1)–N(1)–O(2)	120.25 (12)	114.1 (9)	121.19 (17)
O(1)–N(1)–O(2)	126.44 (17)	126.2 (11)	125.3 (2)
C(1)–S(1)–N(1)	100.47 (7)	107.9 (5)	99.75 (10)

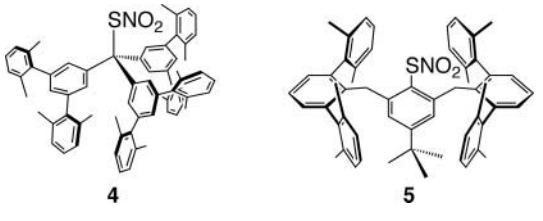
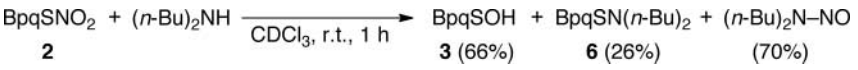


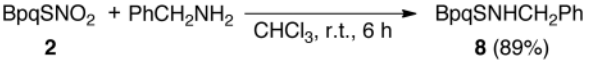
Figure 3. Crystallographically analyzed thionitrates.

acids are very unstable due to rapid bimolecular decomposition (*13*), and in the reported reactions utilizing thionitrate **1** only the corresponding thiosulfonate, *t*-BuSO_2S(*t*-Bu), was obtained (*6*–*8*). By utilizing the bowl-shaped substituent, which can stabilize both thionitrate and sulfenic acid, the elementary chemical process depicted in Scheme 1 was unambiguously demonstrated. During the reaction, the formation of the sulfenyl nitrite, BpqS-ONO (**7**), which is a tautomeric form of thionitrate **2**, was not detected. Theoretical reports predicted that sulfenyl nitrite forms (RS-ONO) would be much higher in energy than thionitrate forms (RS-NO_2) (*11*, *12*). The tautomeric form **7** is considered to be a transient species if generated.



Scheme 2. Reaction of thionitrate **2** with dibutylamine.

It was reported that thionitrate **1** reacts with octylamine to produce the corresponding sulfenamide, *t*-BuSNH(n-C_8H_{17}) (*7*). Similarly, the reaction of thionitrate **2** with benzylamine in $CDCl_3$ at room temperature afforded sulfenamide **8** (*17*) in 89% yield (Scheme 3), and no appreciable formation of any other products deriving from **2** and benzylamine was observed. These results indicate that substitution at the sulfur atom of thionitrates predominates in the reaction with primary alkylamines.



Scheme 3. Reaction of thionitrate **2** with benzylamine.

3. Conclusion

Nitrosation of an amine with a thionitrate accompanied by the formation of a sulfenic acid was demonstrated experimentally for the first time by taking advantage of a bowl-shaped molecular cavity. The present results would provide useful chemical information for the elucidation of the behavior of thionitrate intermediates in the bioactivation process of organic nitrates. Further investigations on the nitrosating ability of thionitrates are currently in progress.

4. Experimental

All synthetic experiments were performed under argon atmosphere. Chloroform and chloroform-*d* were distilled over CaH_2 prior to use. Reagents were purchased from commercial sources and used as received. ^{1}H NMR spectra were recorded on a JEOL JNM-AL400 or a JEOL LAMBDA-400, and the chemical shifts of ^{1}H are referenced to the residual proton signal of $CDCl_3$ (δ 7.25). ^{13}C NMR spectra were measured on a JEOL ECX-400, and the chemical shifts are referenced to the signal of $CDCl_3$ (δ 77.0). Mass spectra were obtained with a JEOL JMS-700 (FAB, matrix: *m*-nitrobenzyl alcohol).

4.1. *Reaction of thionitrate 2 with dibutylamine*

A solution of thionitrate **2** (9.6 mg, 10 μmol) in $CDCl_3$ (0.5 mL) was placed into a 5 mm o/d NMR tube and degassed via freeze-pump-thaw cycles. To the solution was added a degassed solution of dibutylamine in $CDCl_3$ (0.14 M, 0.22 mL, 31 μmol). The resulting solution was degassed again via freeze-pump-thaw cycles and sealed in the NMR tube. The reaction was monitored by ^{1}H NMR spectroscopy, and it was found that thionitrate **2** was totally consumed after 1 h at room temperature to afford sulfenic acid **3** (66%), sulfenamide **6** (26%), and *N*-nitrosodibutylamine (70%). All yields were estimated by ^{1}H NMR spectroscopy. Sulfenamide **6** of analytical purity was obtained by recrystallization from hexane. **6**: colorless solid, m.p. 239–240°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.69 (t, J = 7.0 Hz, 6H), 1.00–1.11 (m, 32H), 1.15 (d, J = 7.2 Hz, 24H), 2.36 (t, J = 6.0 Hz, 4H), 2.89 (sept, J = 7.2 Hz, 8H), 6.97 (t, J = 1.6 Hz, 2H), 7.20 (d, J = 7.6 Hz, 8H), 7.25 (d, J = 1.6 Hz, 4H), 7.28–7.35 (m, 4H), 7.36–7.41 (m, 3H); ^{13}C NMR (98.5 MHz, $CDCl_3$) δ 13.81

(q), 19.81 (t), 24.01 (q), 24.44 (q), 29.54 (t), 30.38 (d), 55.91 (t), 122.48 (d), 127.78 (d), 128.36 (d), 129.29 (d), 129.71 (d), 130.18 (d), 134.21 (s), 139.22 (s), 139.64 (s), 142.26 (s), 146.86 (s), 148.26 (s); LRMS (FAB, positive) m/z 1030 (M^+). Anal. Calcd for $C_{74}H_{95}NS$: C, 86.20; H, 9.50; N, 1.06; S, 3.26. Found: C, 86.24; H, 9.29; N, 1.36; S, 3.11.

4.2. *Reaction of thionitrate 2 with benzylamine*

To a solution of thionitrate **2** (13.9 mg, 14.7 μmol) in chloroform (1 mL) was added benzylamine (80 μL, 0.73 mmol), and the solution was stirred at room temperature for 6 h. After the removal of the solvent and excess of amine in vacuo, the resulting solid was washed with hexane to afford sulfenamide **8** (13.2 mg, 13.1 μmol, 89%) (*17*) as colorless crystals.

4.3. *X-ray crystallography*

Single crystals of **2**·0.5C_6H_{14} were grown in their chloroform/hexane solutions. The intensity data were collected at 120 K on a Rigaku/MSC Mercury CCD diffractometer with graphite-monochromated MoKα radiation ($\lambda = 0.71069$ Å). The structures were solved by the direct method and refined by full-matrix least squares on F^2 using SHELXL 97 (*23*). The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were idealized using the riding models. Crystallographic data for **2**·0.5C_6H_{14}: $C_{69}H_{84}NO_2$, $M = 991.43$, monoclinic, space group P-1, $a = 11.9733(9)$, $b = 15.5347(11)$, $c = 17.6554(13)$ Å, $\alpha = 71.621(4)°$, $\beta = 81.836(4)°$, $\gamma = 75.274(3)°$, $V = 3007.2(4)$ Å^3, $Z = 2$, $D_{calcd} = 1.095$ g cm^{-3}, 20,667 measured reflections, 10,354 independent, 719 parameters. $R_1 = 0.0474$ ($I > 2\sigma(I)$), $wR_2 = 0.1471$ (all data). Goodness-of-fit on $F^2 = 1.107$. Crystallographic data for the structure of **2**·0.5C_6H_{14} have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 926333.

Acknowledgements

This work was partly supported by Grants-in-Aid for The Global COE Program for Education and Research Center for Emergence of New Molecular Chemistry and for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References

(1) Fung, H.L. *Ann. Rev. Pharmacol. Toxicol.* **2004,** *44,* 67–85.
(2) Chen, Z.; Stamler, J. *Trends Cardiovasc. Med.* **2006,** *16,* 259–265.
(3) Mayer, B.; Beretta, M. *Br. J. Pharmacol.* **2008,** *155,* 170–184.
(4) Lang, B.S.; Gorren, A.C.F.; Oberdorfer, G.; Wenzl, M.V.; Furdui, C.M.; Poole, L.B.; Mayer, B.; Gruber, K. *J. Biol. Chem.* **2012,** *287,* 38124–38134.
(5) Oae, S.; Shinhama, K. *Org. Prep. Proced. Int.* **1983,** *15,* 165–198.
(6) Oae, S.; Shinhama, K.; Kim, Y.H. *Chem. Lett.* **1979,** *8,* 939–942.
(7) Oae, S.; Shinhama, K.; Kim, Y.H. *Bull. Chem. Soc. Jpn.* **1980,** *53,* 2023–2026.
(8) Oae, S.; Iida, K.; Shinhama, K.; Takata, T. *Bull. Chem. Soc. Jpn.* **1981,** *54,* 2374–2378.
(9) Kim, H.J.; Kim, Y.H. *Tetrahedron Lett.* **1987,** *28,* 1669–1670.
(10) Kim, Y.H.; Park, Y.J.; Kim, K. *Tetrahedron Lett.* **1989,** *30,* 2833–2836.
(11) Cameron, D.R.; Borrajo, A.M.P.; Bennett, B.M.; Thatcher, G.R.J. *Can. J. Chem.* **1995,** *73,* 1627–1638.
(12) Choi, Y.J.; Lee, Y.S. *Bull. Korean Chem. Soc.* **2004,** *25,* 1657–1660.
(13) Patai S., Ed. *The Chemistry of Sulphenic Acids and their Derivatives*; John Wiley & Sons: New York, 1990.
(14) Goto, K.; Kawashima, T. *J. Synth. Org. Chem., Jpn.* **2005,** *63,* 1157–1170.
(15) Goto, K.; Holler, M.; Okazaki, R. *J. Am. Chem. Soc.* **1997,** *119* , 1460–1461.
(16) Goto, K; Hino, Y.; Kawashima, T.; Kaminaga, M.; Yano, E.; Yamamoto, G.; Takagi, N.; Nagase, S. *Tetrahedron Lett.* **2000,** *41,* 8479–8483.
(17) Goto, K.; Yamamoto, G.; Tan, B.; Okazaki, R. *Tetrahedron Lett.* **2001,** *42,* 4875–4877.

(18) Goto, K.; Hino, Y.; Takahashi, Y.; Kawashima, T.; Yamamoto, G.; Takagi, N.; Nagase, S. *Chem. Lett.* **2001,** *30,* 1204–1205.
(19) Shimada, K.; Goto, K.; Kawashima, T.; Takagi, N.; Choe, Y.-K.; Nagase, S. *J. Am. Chem. Soc.* **2004,** *126,* 13238–13239.
(20) Goto, K.; Shimada, K.; Furukawa, S.; Miyasaka, S.; Takahashi, Y.; Kawashima, T. *Chem. Lett.* **2006,** *35,* 862–863.
(21) Goto, K.; Sonoda, D.; Shimada, K.; Sase, S.; Kawashima, T. *Angew. Chem., Int. Ed.* **2010,** *49,* 545–547.
(22) Itoh, M.; Takenaka, K.; Okazaki, R. *Nippon Joshi Daigaku Kiyo, Rigakubu* **2004,** *12,* 33–38.
(23) Sheldrick, G.M. *SHELXL-97. Computer Program for Crystal Structure Refinement*; University of Göttingen: Göttingen, Germany, 1997.