Synthesis, Structure, and Reactions of a Sulfenic Acid Bearing a Novel Bowl-Type Substituent: The First Synthesis of a Stable Sulfenic Acid by Direct Oxidation of a Thiol

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Sulfenic acids are generally assumed to be transient intermediates in the oxidation of thiols to both disulfides and sulfinic acids (Scheme 1),[1] and redox reactions between thiols and sulfenic acids are of great importance from a biological point of view.[2] It has been suggested that oxidation of cysteinyl side chains of papain and glyceraldehyde-3-phosphate dehydrogenase (GPD) yields stable active-site sulfenic acid derivatives, which can be reduced to the native forms.[2a] Sulfenic acid derivatives have also been suggested to play important roles in redox regulation in some enzymatic reactions.[2b,c] However, under nonenzymatic conditions, the evidence for the redox processes in Scheme 1 is entirely circumstantial due to the instability of sulfenic acids. Although a trapping experiment of a transient sulfenic acid in the oxidation of 2-methyl-2-propanethiol was reported,[3] there has been no example of even the observation of the intermediary sulfenic acid in direct oxidation of a thiol.[4,5] As for the redox reactions of sulfenic acids to thiols and to sulfinic acids, only those of transient species have been reported so far, where the sulfenic acids were neither actually isolated nor detected.[3,5,7] In this communication, we describe the first synthesis of a stable sulfenic acid by direct oxidation of a thiol along with its structure and reactions, which provide the conclusive demonstration of redox reactions of a sulfenic acid.

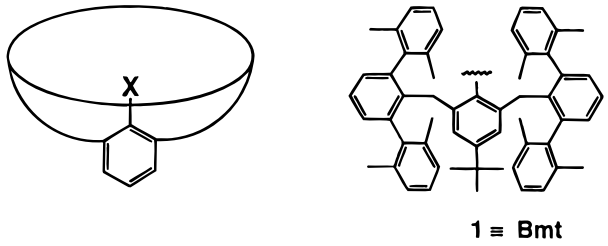
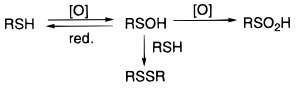


Figure 1. Schematic drawing of a *reaction bowl.*

Scheme 1



We previously reported that the bowl-shaped cyclophane framework, which we refer to as a *"reaction bowl"* (Figure 1), is quite effective for stabilization of the reactive species such as sulfenic acids.[8] Recently, we have developed a novel bowl-type substituent **1** (denoted as Bmt[9] hereafter) with a rigid and more inert framework and synthesized thiol **2** bearing this substituent.[10] For the investigation on the intrinsic properties of a sulfenic acid, the all-carbon framework of the Bmt group is considered to be favorable compared with the compounds where the properties of the SOH functionality are perturbed by the effects of the heteroatoms such as the intramolecular hydrogen bonding effects.[1b] If iodosobenzene (**3**), a mild oxidant which converts thiols to disulfides,[11] is used in the oxidation of **2**, it is expected that formation of the symmetrical disulfide is sterically prevented and the sulfenic acid is obtained as the final product. Treatment of **2** with 1.1 equiv of **3** in $CHCl_3$ at room temperature afforded sulfenic acid **4**,[12] which was isolated as a crystalline solid in 41% yield by silica gel chromatography (Scheme 2).[13,14] The same compound **4** was also obtained by pyrolysis of butyl sulfoxide **5**[15] at 225 °C under no solvent conditions (67%). The reaction of **4** with methyl propiolate in CH_2Cl_2 at room temperature afforded an adduct **6** in 58% yield. Sulfenic acid **4** is stable at room temperature in air for more than several weeks. The ^{1}H NMR ($CDCl_3$) spectrum showed the signal of the hydroxyl proton at $\delta = 1.36$ (readily exchangeable with D_2O), indicating that it is shielded by the xylyl rings of the *m*-terphenyl units similarly to the

(1) For leading references on the chemistry of sulfenic acids, see: (a) Hogg, D. R. In *The Chemistry of Sulfenic Acids and Their Derivatives*; Patai, S., Ed.; John Wiley & Sons: New York, 1990; pp 361−402. (b) Davis, F. A.; Jenkins, L. A.; Billmers, R. L. *J. Org. Chem.* **1986**, *51*, 1033−1040. (c) Kice, J. L. *Adv. Phys. Org. Chem.* **1980**, *17*, 65−181.

(2) For leading references on the biological reactions of sulfenic acids, see: (a) Allison, W. S. *Acc. Chem. Res.* **1976**, *9*, 293−299. (b) Claiborne, A.; Ross, R. P.; Parsonage, D. *Trends Biochem. Sci.* **1992**, *17*, 183−186. (c) Claiborne, A.; Miller, H.; Parsonage, D.; Ross, R. P. *FASEB J.* **1993**, *7*, 1483−1490. The natural formation of sulfenic acids when onion and garlic are cut has also been reported: (d) Block, E.; Gillies, J. Z.; Gillies, C. W.; Bazzi, A. A.; Putman, D.; Revelle, L. K.; Wang, D.; Zhang, X. *J. Am. Chem. Soc.* **1996**, *118*, 7492−7501, and references therein.

(3) Davis, F. A.; Billmers, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 7016−7018.

(4) For the synthesis of stable sulfenic acids by other methods, see: (a) Fries, K. *Chem. Ber.* **1912**, *45*, 2965−2973. (b) Bruice, T. C.; Markiw, R. T. *J. Am. Chem. Soc.* **1957**, *79*, 3150−3153. (c) Jenny, W. *Helv. Chim. Acta* **1958**, *41*, 326−331. (d) Pal, B. C.; Uziel, M.; Doherty, D. G.; Cohn, W. E. *J. Am. Chem. Soc.* **1969**, *91*, 3634−3638. (e) Kato, K. *Acta Crystallogr., Sect. B.* **1972**, *28*, 55−59. (f) Chou, T. S.; Burgtorf, J. R.; Ellis, A. L.; Lammert, S. R.; Kukolja, S. P. *J. Am. Chem. Soc.* **1974**, *96*, 1609−1610. (g) Bachi, M. D.; Gross, A. *J. Org. Chem.* **1982**, *47*, 897−898. (h) Heckel, A.; Pfleiderer, W. *Tetrahedron Lett.* **1983**, *24*, 5047−5050. (i) Nakamura, N. *J. Am. Chem. Soc.* **1983**, *105*, 7172−7173. (j) Yoshimura, T.; Tsukurimichi, E.; Yamazaki, S.; Soga, S.; Shimasaki, C.; Hasegawa, K. *J. Chem. Soc., Chem. Commun.* **1992**, 1337−1338. (k) Tripolt, R.; Belaj, F.; Nachbaur, E. *Z. Naturforsch., Sect. B.* **1993**, *48*, 1212−1222. (l) Machiguchi, T.; Hasegawa, T.; Otani, H. *J. Am. Chem. Soc.* **1994**, *116*, 407−408.

(5) As for the reactions of silver salts, the oxidation of silver 1,3,6-trimethyllumazine-7-thiolate to the corresponding silver sulfenate with 1 equiv of hydrogen peroxide and the reduction of the latter to the former with sodium borohydride have been reported without description of the conditions and the yield.[4h] The oxidation of 1,3,6-trimethyllumazine-7-sulfenic acid to the corresponding sulfinic acid with hydrogen peroxide has also been reported,[4h] although this sulfenic acid reportedly shows behavior atypical of sulfenic acids such as disproportionation to the thiol and the sulfinic acid under acidic conditions. Recently the synthesis of thiophenetriptycene-8-sulfenic acid by oxidation of the corresponding sodium thiolate with mCPBA has been reported.[6]

(6) Komiya, K.; Ishii, A.; Nakayama, J. In *Abstracts of the 70th Spring Annual Meeting of the Chemical Society of Japan*; the Chemical Society of Japan, Tokyo, 1996: Vol. 2, p 1244 (3H5 31).

(7) For examples of reduction of a transient sulfenic acid to a thiol, see: (a) Cooper, R. D. G.; José, F. L. *J. Am. Chem. Soc.* **1970**, *92*, 2575−2576. (b) Hatfield, L. D.; Fisher, J.; José, F. L.; Cooper, R. D. G. *Tetrahedron Lett.* **1970**, 4897−4900.

(8) (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.

(9) Bmt denotes 4-*tert*-butyl-2,6-bis[(2,2″,6,6″-tetramethyl-*m*-terphenyl-2′-yl)methyl]phenyl.

(10) Goto, K.; Holler, M.; Okazaki, R. *Tetrahedron Lett.* **1996**, *37*, 3141−3144.

(11) Takaya, T.; Enyo, H.; Imoto, E. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1032.

(12) Monitoring of the reaction in $CDCl_3$ by ^{1}H NMR indicated the formation of **4** at the expense of **2**, no intermediate being confirmed.

(13) **4** (4-*tert*-butyl-2,6-bis[(2,2″,6,6″-tetramethyl-*m*-terphenyl-2′-yl)-methyl]benzenesulfenic acid): colorless crystals, mp 145−146 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (s, 9H, $C(CH_3)$), 1.36 (s, 1H, OH), 1.94 (s, 24H, CH_3), 3.73 (s, 4H, CH_2), 6.53 (s, 2H), 6.87 (d, J = 7.5 Hz, 8H), 6.93 (t, J = 7.5 Hz, 4H), 7.02 (d, J = 7.5 Hz, 4H), 7.31 (t, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0 (q), 31.0 (q), 34.0 (t), 34.6 (s), 124.0 (d), 126.4 (d), 126.6 (d), 127.1 (d), 129.0 (d), 136.4 (s), 136.9 (s), 138.3 (s), 141.0 (s), 141.6 (s), 143.3 (s), 150.6 (s); ν_{OH} (CH_2Cl_2) 3460 cm^{-1}; HRMS (FAB) *m/z* 778.4239, calcd for $C_{56}H_{58}OS$ 778.4208. Anal. Calcd for $C_{56}H_{58}OS\cdot H_2O$: C, 84.38; H, 7.59; S, 4.02. Found: C, 84.55; H, 7.87; S, 3.52.

(14) Physical and analytical data of **4**−**6** and **8**−**10** are described in the Supporting Information.

(15) Sulfoxide **5** was prepared by oxidation of the corresponding butyl sulfide[10] with mCPBA in 87% yield.

S0002-7863(96)02994-0 CCC: $14.00

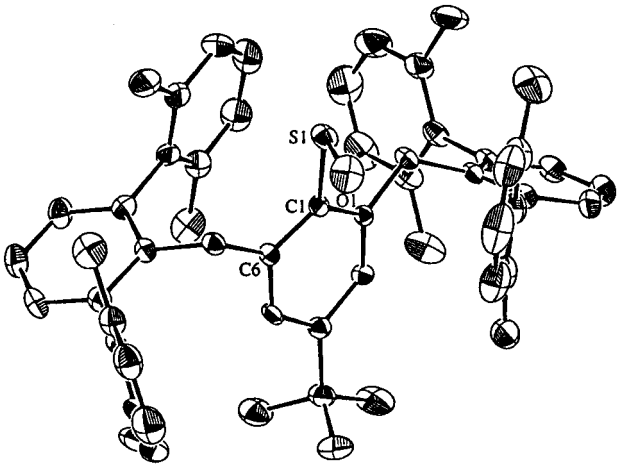
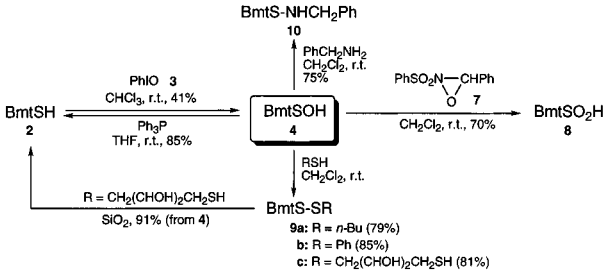
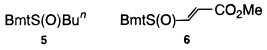


Figure 2. ORTEP drawing of BmtSOH (**4**) with thermal ellipsoid plot (30% probability). Selected bond lengths (Å), bond angles (deg), and torsion angle (deg): S(1)−O(1), 1.679(5); S(1)−C(1), 1.770(5); O(1)−S(1)−C(1), 100.3(3); O(1)−S(1)−C(1)−C(6), 67.1(5).

Scheme 2



mercapto proton of **2** [δ(SH) = 1.13].[10] In the IR spectrum (CH_2Cl_2) **4** showed a strong OH stretching absorption at 3460 cm^{-1}, while the bands attributable to the S−H or S═O stretching vibration were not observed,[16] indicating that **4** has the sulfenyl form (R−S−O−H) rather than the sulfoxide form (R−S(H)═O).



The molecular structure of **4** was established by X-ray crystallographic analysis (Figure 2).[17] The S−O bond length [1.679(5) Å] of the SOH group is distinctly longer than that of sulfoxides,[18] indicating that this compound takes the sulfenyl form also in the crystalline state.[19] Although there have been some examples of the X-ray analysis of sulfenic acids,[4e,k,6,8b] all of those compounds have nitrogen, sulfur, or oxygen atoms in the vicinity of the SOH group[20] and their S−O bond lengths fall between 1.58−1.63 Å. The present one is significantly longer than any of them and slightly longer than that of methanesulfenic acid [1.658(2) Å] determined by microwave spectroscopy,[21] showing the structural features of an arenesulfenic acid unaffected by heteroatoms. As clearly shown in Figure 2, **4** has a bowl-shaped structure, where two rigid *m*-terphenyl units surround the SOH group like a brim of a bowl. It has been suggested that a major factor of the stabilization of sulfenic acids in enzymes is the geometry of their active sites with a functional group embedded in the cavity and isolated from other reactive groups.[2c] Also in compound **4**, the sulfenic acid functionality is incorporated in the molecular cavity, thus being effectively protected from the self-condensation leading to the corresponding thiosulfinate. During the oxidation of thiol **2**, this bowl-shaped framework is considered to prevent the initially formed sulfenic acid **4** from reacting with a second molecule of **2** to yield the symmetrical disulfide. These results demonstrate that a sulfenic acid can be synthesized by direct oxidation of a thiol if it is generated in an appropriate environment.

The reactions of sulfenic acid **4** with a reductant or an oxidant presented the conclusive demonstration of redox processes from sulfenic acids to thiols and to sulfinic acids. Trivalent phosphorus reagents have been suggested to reduce a transient sulfenic acid.[7,22] Treatment of **4** with triphenylphosphine afforded thiol **2** in a good yield of 85%. It has been reported that the oxidation of 2-methyl-2-propanethiol with 2-(benzenesulfonyl)-3-phenyloxaziridine (**7**) rapidly affords the corresponding sulfinic acids and that the intermediary sulfenic acid can be trapped as an adduct with methyl propiolate.[3] Oxidation of sulfenic acid **4** with an equimolar amount of **7** in CH_2Cl_2 afforded sulfinic acid **8** in 70% yield (Scheme 2).

It has been reported that the acylphosphatase activity of the oxidized form of GPD is inactivated by various nucleophiles such as thiols and amines, which suggests the reaction of the active-site sulfenic acid with these reagents.[2a] In the previous paper, we reported the reaction of a sulfenic acid bearing a bicyclic cyclophane skeleton with a thiol to afford the corresponding disulfide.[8a] The reactions of sulfenic acid **4** with an excess of 1-butanethiol or thiophenol afforded the unsymmetrical disulfides **9a**,**b**, respectively, in good yields (Scheme 2). Dithiothreitol (DTT) reduced sulfenic acid **4** to thiol **2** via disulfide **9c**. The reaction of **4** with DTT in CH_2Cl_2 at room temperature first gave **9c**, which was converted to **2** on silica gel in a total yield of 90%.[23] Treatment of sulfenic acid **4** with an excess of benzylamine in CH_2Cl_2 afforded sulfenamide **10** in 75% yield. These reactions of **4** with nucleophiles demonstrate that a sulfenic acid exhibits the electrophilic reactivity, even under basic conditions.

In summary, a stable sulfenic acid bearing a novel *reaction-bowl*-type substituent was synthesized by direct oxidation of a thiol, and its structure and unique reactivities were revealed. By taking advantage of this new type of reaction environment, all the processes in Scheme 1 have been demonstrated conclusively. Further investigations on the mechanistic aspects of these reactions as well as applications of the Bmt group to the stabilization of other reactive species are currently in progress.

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Supporting Information Available: Physical and analytical data of products **4**−**6** and **8**−**10** and the IR spectra of **2** and **4** and crystallographic data with complete tables of bond lengths, angles, and thermal and positional parameters for **4** (39 pages). See any current masthead page for ordering and Internet access instructions.

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(16) Thiol **2** showed the SH absorption at 2542 cm^{-1}. For the IR charts of **2** and **4**, see the Supporting Information.

(17) Crystallographic data for **4**·CH_2Cl_2: $C_{57}H_{60}OSCl_2$, FW = 864.07, *triclinic*, space group *P*1, a = 12.715(7) Å, b = 18.47(2) Å, c = 11.590(8) Å, α = 104.47(6)°, β = 99.84(5)°, γ = 103.81(6)°, V = 2481(3) $Å^3$, Z = 2, D_{calcd} = 1.157 g/cm^3, μ = 2.10 cm^{-1}, R (R_w) = 0.064 (0.077). Full details of the crystallographic structure analysis are described in the Supporting Information.

(18) S−O distance of sulfoxides (103 examples in the Cambridge Structural Database): 1.444−1.584 Å.

(19) For a discussion about the structure of sulfenic acids, see ref 2d and the following paper: Lacombe, S.; Loudet, M.; Banchereau, E.; Simon, M.; Pfister-Guillouzo, G. *J. Am. Chem. Soc.* **1996**, *118*, 1131−1138 (and references therein).

(20) The X-ray structure of 9-triptycenesulfenic acid has been determined, although not published: Nakamura, N. Private communication.

(21) Penn, R. E.; Block, E.; Revelle, L. K. *J. Am. Chem. Soc.* **1978**, *100*, 3622−3623.

(22) Trialkyl phosphites have often been used as a sulfenic acid trap in olefin formation by thermolysis of sulfoxides. For example: Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887−4902.

(23) The intermediary disulfide **9c** was isolable by gel permeation liquid chromatography (81%).