Formation of a Stable Sulfenic Acid by Hydrolysis of a Thionitrate and a Sulfenyl Bromide

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Alkaline hydrolysis of a thionitrate and a sulfenyl bromide bearing a bowl-type steric protection group produced a stable sulfenic acid. This provides a conclusive demonstration of these elementary processes. It was shown that a very efficient steric protection group is necessary to prevent the condensation of the sulfenate anion generated during the hydrolysis.

Cysteine residues located in clefts within proteins are sterically restrained from forming inter- or intramolecular disulfide bonds. Reactive intermediates, such as sulfenic acids (RSOH) and *S*-nitrosothiols (RSNO), generated by the reactions of such cysteine residues with reactive oxygen and nitrogen species play a crucial role in redox regulation. Thionitrates ($RSNO_2$) have been proposed as important intermediates in biotransformations such as the metabolism process from organic nitrates ($RONO_2$) to nitric oxide (NO).[1] In biological studies, hydrolysis of thionitrates is usually assumed to produce sulfenic acids and nitrite (NO_2^-) by nucleophilic substitution at the sulfur atom (eq 1).[2] However, no chemical evidence has been available for this process because of the intrinsic instability of both $RSNO_2$ substrates and RSOH products; these species readily undergo bimolecular reaction to give products containing a sulfur–sulfur bond such as thiosulfinates (RS(O)–SR). Sulfenic acids have also been recognized as the products of hydrolysis of sulfenyl halides (RSX) (eq 2).[3] In all reported reactions, however, the initially formed sulfenic acids or sulfenate anions readily undergo condensation, and have never been obtained as the final products. We have developed a novel bowl-shaped substituent (denoted as Bpq, Chart 1) for modeling sterically isolated microenvironments in proteins, and have applied it to the stabilization of various reactive species including a thionitrate.[4] Here, we report the first synthesis of a stable sulfenic acid by hydrolysis of the corresponding thionitrate and sulfenyl bromide.

$$RSNO_2 + H_2O \rightarrow [RSOH] + NO_2^- + H^+ \quad (1)$$

$$RSX + H_2O \rightarrow [RSOH] + X^- + H^+ \quad (X = \text{halogen}) \quad (2)$$

It was reported that *t*-butyl thionitrate (*t*-$BuSNO_2$) decomposes rapidly in neutral aqueous solution to yield di-*t*-butyl thiosulfinate (*t*-BuS(O)–S(*t*-Bu)) and di-*t*-butyl thiosulfonate (*t*-$BuSO_2$–S(*t*-Bu)).[5] Steric protection due to the Bpq group is expected to prevent the formation of such products containing a sulfur–sulfur bond. Thionitrate **1** bearing a Bpq group was synthesized according to our previous report.[4b] When **1** was treated with aqueous acetic acid in $CDCl_3$, or with aqueous THF, at

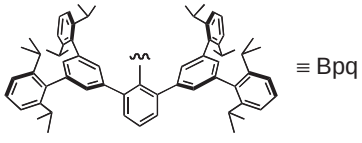
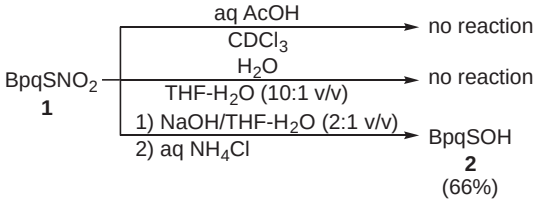


Chart 1.



Scheme 1.

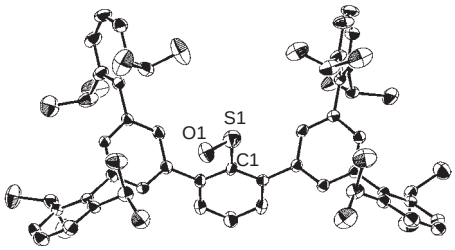


Figure 1. ORTEP drawing of **2** (50% probability). Hydrogen atoms and the minor component of the OH moiety are omitted for clarity.

room temperature for 4 h, no reaction took place (Scheme 1). It was found that hydrolysis of **1** proceeds under alkaline conditions. Treatment of **1** with sodium hydroxide in THF/water (2:1 v/v) at room temperature for 10 min afforded sulfenic acid **2** after quenching with aqueous NH_4Cl, and **2** was isolated by silica-gel chromatography in 66% yield.[6] X-ray crystallographic analysis established the structure of **2** (Figure 1),[7] where the SOH functionality is incorporated in the cleft formed by two *m*-terphenyl-5′-yl groups. In the crystalline state, there was rotational disorder of the OH moiety around the C–S bond in the ratio of 0.52:0.48. Owing to this disorder, it is difficult to discuss the detailed structural parameters of the SOH moiety at present.[8]

We previously reported the synthesis of the stable sulfenic acid **4** carrying another bowl-type substituent (denoted as Bmt),[9] and the synthesis of the corresponding thionitrate **3** was reported by Okazaki et al.[10] The reactivity of **3** was examined for comparison. Unexpectedly, alkaline hydrolysis of thionitrate **3** under the same conditions as those for **1** afforded a complex mixture, and the formation of sulfenic acid **4** was not detected (Scheme 2). Considering the high stability of sulfenic acid **4** toward heat and water,[9] it is suggested that the species generated in alkaline hydrolysis, that is, the sulfenate anion, is more reactive than the sulfenic acid, and that even the steric protection due to the bulky Bmt group is not sufficient for stabilization of the anionic species.[11] These results indicate that a very effective steric protection group like Bpq is necessary for the formation of a sulfenic acid by alkaline hydrolysis of a thionitrate.

Although many mechanistic studies have been performed on the hydrolysis of sulfenyl chlorides and bromides,[12] there has been no reported example of the isolation of a sulfenic acid as

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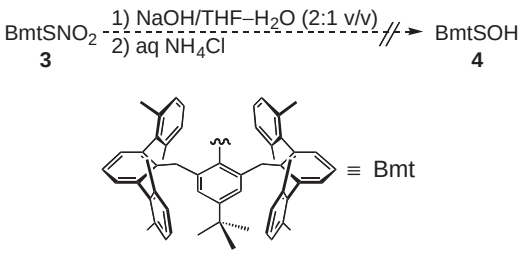
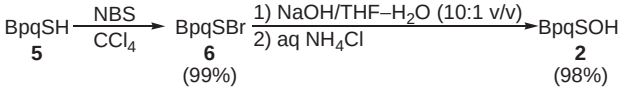


Scheme 2.



Scheme 3.

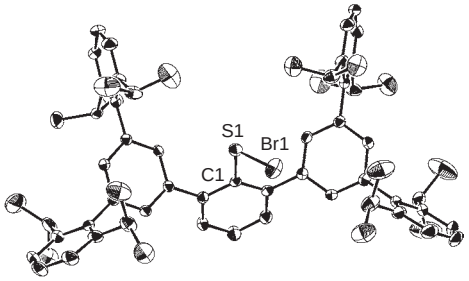


Figure 2. ORTEP drawing of **6** (50% probability). There is rotational disorder of the Br atom around the C–S bond in the ratio of 0.75:0.25. Hydrogen atoms and the minor component of the Br atom are omitted for clarity. Selected bond lengths (Å) and angles (deg): Br(1)–S(1), 2.1251(12); S(1)–C(1), 1.779(4); Br(1)–S(1)–C(1), 105.90(10).

the product. It has even been reported that the relatively stable anthraquinonesulfenic acid could not be obtained from hydrolysis of the corresponding sulfenyl bromide.[12a] The reaction of sulfenyl bromide **6** bearing the Bpq group was then examined. Sulfenyl bromide **6** was readily prepared by reaction of thiol **5** with *N*-bromosuccinimide (NBS) (Scheme 3).[13] The structure of **6** was determined by X-ray crystallographic analysis (Figure 2).[7] The S–Br bond length (2.1251(12) Å) is close to that of Ph_3CSBr (2.169 Å).[14] When **6** was treated with sodium hydroxide in THF/water (10:1 v/v) for 10 min, quantitative formation of sulfenic acid **2** was observed after quenching with aqueous NH_4Cl, and **2** was isolated in 98% yield. The reaction of the sulfenate anion with the starting material **6**, as well as the condensation of the sulfenate anion and sulfenic acid **2**, is considered to be effectively prevented by the Bpq group.

In summary, we have demonstrated that a stable sulfenic acid can be obtained by alkaline hydrolysis of a thionitrate and a sulfenyl bromide. These results corroborate the possible formation of cysteine sulfenic acids by similar transformation in the clefts of proteins.

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6 **2**: Colorless crystals; mp 159–161 °C (dec); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.07 (d, $J = 6.9$ Hz, 24H), 1.15 (d, $J = 6.8$ Hz, 24H), 2.76 (sept, $J = 6.8$ Hz, 8H), 2.81 (s, 1H), 7.05 (t, $J = 1.5$ Hz, 2H), 7.19 (d, $J = 7.7$ Hz, 8H), 7.28 (d, $J = 1.5$ Hz, 4H), 7.32 (t, $J = 7.7$ Hz, 4H), 7.42–7.44 (m, 3H). HRMS (FAB$^+$) m/z 918.5739, calcd for $C_{66}H_{78}OS$ 918.5773.

7 Crystallographic data for $\mathbf{2}\cdot C_6H_6\cdot 4/9C_6H_{14}$: M_r 1034.48, orthorhombic, space group *Pbca*, $a = 9.271(2)$, $b = 36.733(9)$, $c = 37.388(9)$ Å, $U = 12733(5)$ Å^3, $Z = 8$, $D_{calcd} = 1.079$ g cm^{-3}, $T = 120$ K, $R_1 = 0.0856$ ($I > 2\sigma(I)$), $wR_2 = 0.2164$ (all data). $\mathbf{6}\cdot(1/2 + 4/9)C_6H_{14}$: M_r 1063.25, monoclinic, space group $P2_1/n$, $a = 19.518(6)$, $b = 9.330(3)$, $c = 35.779(11)$ Å, $\beta = 103.2321(11)°$, $U = 6342(3)$ Å^3, $Z = 4$, $D_{calcd} = 1.113$ g cm^{-3}, $T = 120$ K, $R_1 = 0.0844$ ($I > 2\sigma(I)$), $wR_2 = 0.2229$ (all data). Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication Nos. CCDC 609614 and 609615.

8 The preliminary results for the bond lengths (Å) and angle (deg): O(1)–S(1), 1.559(6); S(1)–C(1), 1.779 (4); O(1)–S(1)–C(1), 106.8(3).

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13 **6**: Red-brown crystals; mp 276–277 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (d, $J = 6.8$ Hz, 24H), 1.12 (d, $J = 6.8$ Hz, 24H), 2.88 (sept, $J = 6.8$ Hz, 8H), 7.03 (t, $J = 1.5$ Hz, 2H), 7.17 (d, $J = 7.7$ Hz, 8H), 7.26 (d, $J = 1.5$ Hz, 4H), 7.31 (t, $J = 7.7$ Hz, 4H), 7.45–7.55 (m, 3H). Found: C, 80.52; H, 8.05%. Calcd for $C_{66}H_{77}BrS$: C, 80.70; H, 7.90%.

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