Synthesis, Structure, and Reactivities of a Stable Primary-alkyl-substituted Sulfenic Acid

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A primary-alkyl-substituted sulfenic acid was synthesized and isolated by taking advantage of a cavity-shaped steric protection group and characterized by X-ray crystallographic analysis. The reactivities of the sulfenic acid toward various reagents were investigated, and it was demonstrated experimentally and theoretically that the addition of a sulfenic acid to a simple alkene to produce the corresponding sulfoxide is thermodynamically more favorable than the reverse reaction, i.e. syn- β -elimination of a sulfoxide.

Sulfenic acids (RSOH) have been recognized as important intermediates not only in organosulfur chemistry but also in biological systems.^{1,2} They are the reversibly oxidized form of cysteine thiols, which play crucial roles as a catalytic center in enzymes and as a sensor of oxidative stress in enzymes and transcriptional regulators.² However, much of our knowledge of the chemistry of sulfenic acids has been obtained in quite an indirect and speculative manner because they are notoriously unstable in artificial systems because of very rapid self-condensation, leading to the corresponding thiosulfinates (RSS(O)R) (Scheme 1).¹

For the synthesis of stable sulfenic acids, kinetic stabilization using bulky substituents has been successfully employed, and isolation of tertiary-alkyl derivatives³ as well as aromatic derivatives⁴ has been achieved by taking advantage of appropriate steric protection groups. However, there has been no example of the isolation of a primary-alkyl-substituted sulfenic acid although it is the most relevant as chemical models of sulfenic acids derived from cysteine residues in protein.² As for thermodynamically stabilized sulfenic acids, some solutionstable sulfenic acids stabilized by strong electron-withdrawing effects of perfluoroalkyl (RCF2CF2) groups have been reported recently although they have not been isolated.⁵ Here, we report the synthesis and isolation of a stable primary-alkyl-substituted sulfenic acid by taking advantage of a cavity-shaped steric protection group. We also demonstrated that addition reactions of sulfenic acids to simple alkenes are thermodynamically more favorable processes than the reverse reactions, i.e. syn- β elimination of sulfoxides.

Recently, we have developed a primary-alkyl steric protection group, a BpqCH₂ group (Chart 1), with a cavity-shaped framework and applied it to the stabilization of primary-alkylsubstituted derivatives of a sulfenyl iodide (X = SI)^{6a} and a selenenic acid (X = SeOH),^{6b} both of which are usually known



Scheme 1. Facile self-condensation of a sulfenic acid to form a thiosulfinate.



Chart 1. Structure of $BpqCH_2X$.

 $\begin{array}{cccc} BpqCH_2Br \xrightarrow{i} BpqCH_2S-t-Bu \xrightarrow{ii} BpqCH_2S(O)-t-Bu \xrightarrow{iii} BpqCH_2SOH \\ 1 & 2 (81\%) & 3 (89\%) & 4 (99\%) \end{array}$

Scheme 2. Synthesis of sulfenic acid 4. Reagents and conditions; (i) *t*-BuSH, NaH, THF, rt; (ii) *m*CPBA, CH_2Cl_2 , 0 °C; (iii) solid state, 180 °C, in vacuo.



Figure 1. ORTEP drawing of **4** (50% probability). Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and bond angle (degree) for **4**: C–S, 1.813(4); S–O, 1.631(4); C–S–O, 100.96(18).

to undergo facile bimolecular decomposition. It is expected that the peripheral steric protection effect due to this substituent will also efficiently suppress the self-condensation of a sulfenic acid. As the precursor of a sulfenic acid bearing the BpqCH₂ group, *t*-butyl sulfoxide **3** was prepared according to Scheme 2. Thermolysis of **3** in the solid state at 180 °C in vacuo afforded the desired sulfenic acid **4** almost quantitatively, which was isolated as colorless crystals in 99% yield. This is the first example of the isolation of a primary-alkyl-substituted sulfenic acid.

The ¹H NMR (C₆D₆) spectrum of **4** showed the signal of SO*H* at $\delta = 2.02$. It is readily exchangeable with D₂O. The IR spectrum (CHCl₃) showed a sharp O–H stretching absorption at 3398 cm⁻¹ indicating that **4** has the sulfenyl form (R–S–O–H) rather than the sulfoxide form (R–S(O)–H) in solution. The structure of **4** was finally established by X-ray crystallographic analysis (Figure 1).⁷ The CH₂–S–O–H moiety is incorporated within the cavity and effectively protected by the peripheral moiety of the substituent. The S–O bond length of **4** (1.631(4) Å) is comparable to those of the kinetically stabilized sulfenic acids reported so far.^{3c,4c} Furthermore, the bond length is significantly longer than those of sulfoxides,⁸ showing that **4** has the sulfenyl



Scheme 3. Reactions of sulfenic acid 4 with 1-butanethiol and benzylamine. All yields were estimated by ${}^{1}HNMR$ by using a $(TMS)_{2}CH_{2}$ as an internal standard.

Scheme 4. Syn- β -elimination of sulfoxides and addition of sulfenic acids to alkenes.

form even in the crystalline state. The shortest intermolecular S…S distance (7.76 Å) is much longer than the sum of van der Waals radii of the sulfur atoms, showing that **4** is monomeric in the crystalline state.

Sulfenic acid **4** showed remarkable thermal stability both in the solid state and in solution. In the solid state, it decomposed at high temperature (220.5–222.0 °C). In benzene- d_6 , no decomposition of **4** was observed after heating at 80 °C in a sealed tube for 7 d. This indicates that the peripheral steric protection provided by the BpqCH₂ group is efficient enough to prevent a sulfenic acid inside the cavity from undergoing selfcondensation.⁹

The reactions of sulfenic acids with thiols and amines have been postulated to be important from a biological point of view.² We previously reported the reactions of stable sulfenic acids bearing an aromatic substituent with these reagents.^{4a,4c} The primary-alkyl derivative **4** was also found to react with 1-butanethiol and benzylamine to produce the corresponding disulfide **5** and sulfenamide **6**, respectively, in high yields (Scheme 3).

The synthesis of alkenes by syn- β -elimination of sulfoxides^{1,10} has been employed as an important synthetic method, and the reaction generally proceeds on heating to generate sulfenic acids concomitantly (Scheme 4).

On the other hand, examples of the reverse reaction, i.e. addition of sulfenic acids to alkenes, have been rather limited. While there have been several reports on the reactions of transiently generated sulfenic acids with a large excess of alkenes,^{1,11} addition of isolated sulfenic acids to alkenes has not been investigated except for the reaction with a strained cyclic alkene.¹² Reactions of **4** with simple alkenes as well as an alkene conjugated with an activating group were then examined. It was reported that the transiently generated sulfenic acid was trapped by simple alkenes to afford the corresponding Markovnikov adducts.^{11d} Treatment of 4 with 1-hexene (4 equiv) at 60 °C in CDCl₃ afforded sulfoxide 7a, a Markovnikov adduct, in a high vield of 95% (Table 1, Entry 1). The reaction of 4 with styrene also produced the Markovnikov adduct 7b in 94% yield (Entry 2). In the reaction of 4 with methyl acrylate, an activated alkene, the Michael-type addition proceeded promptly to produce the corresponding sulfoxide 8c quantitatively (Entry 3), which is consistent with the previous reports on the reaction of sulfenic acids generated in situ with an acrylate.^{11a,11c,11e}

Table 1. Reaction of 4 with alkenes



Entry	Alkene	Conditions	7 (Yield/%) ^a	8 (Yield/%) ^a
1	$\mathbf{R'} = n$ -Bu	60 °C, 64 h	7a, 95	8a, ND ^b
2	R' = Ph	60 °C, 21 h	7b, 94	8b , ND ^b
3	$R' = CO_2Me$	rt, <1 h	7c , ND ^b	8c, 99

 aEstimated by $^1H\,NMR$ using $(TMS)_2CH_2$ as an internal standard. bNot detected.



Figure 2. Energy profiles of the reaction of MeSOH with propene to give sulfoxides at B3LYP/6-31G(d) level.

While β-elimination of sulfenic acids from sulfoxides is usually carried out under heating, the present results suggest that the addition of sulfenic acids to alkenes is thermodynamically more favorable than the elimination. To elucidate the energy profile and regioselectivity of the addition of a sulfenic acid to a simple alkene, DFT calculations on the reaction of MeSOH with propene were performed (Figure 2). The calculation showed that the addition of MeSOH to propene is more exothermic than the reverse reaction, i.e. the β -elimination from the sulfoxides. In terms of the regioselectivity, the formation of the Markovnikov adduct A was found to be more favorable than the anti-Markovnikov adduct B. These calculations are consistent with the experimental results, corroborating that, in the reaction of sulfenic acid and alkenes, the addition reaction is thermodynamically more favorable than the reverse elimination process. It is reasonably explained that, in the usual alkene syntheses by thermal syn-β-elimination of sulfoxides (Scheme 4, forward reaction), the resulting sulfenic acids are so labile that they readily undergo irreversible decomposition to leave the alkenes as products. By using sulfenic acid 4 with high thermal stability, which can be subject to prolonged heating conditions (Table 1, Entries 1 and 2), the reverse process of Scheme 4 was demonstrated unequivocally.

Table 2.	Reaction	of 4	with	alkynes
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	BpqCH ₂ –SOH 4	R1R (4 equiv) CDCl ₃	2		² −CH₂Bpq
Entry	Alkyne		Cond	itions	9 (Yield/%) ^a
1	$R^1 = H, R^2$	= <i>n</i> -Bu	rt, 72	h	9 a, 77
2	$R^1 = CO_2M$	e, $R^2 = H$	rt, <1	h	9b , 93

^aEstimated by ¹H NMR using (TMS)₂CH₂ as an internal standard.

rt, $<5 \min$

9c, 96

3

 R^1 , $R^2 = CO_2Me$

We also investigated the reactions of sulfenic acid 4 with alkynes. It has been reported that sulfenic acids generated in situ react with alkynes to produce vinyl sulfoxides as adducts with different regioselectivities. The reactions with activated alkynes such as methyl propiolate to give the corresponding Michaeltype adducts have often been utilized for trapping of transient sulfenic acids.^{1,11a,11c,11e} It was reported that the addition follows Markovnikov's rule in the reactions with simple alkynes.^{1,11c,13} When 4 was treated with 1-hexyne, the corresponding vinyl sulfoxide 9 with the Markovnikov orientation was obtained in 77% yield (Table 2, Entry 1). This reaction proceeded even at room temperature in contrast with the reaction of 4 with 1hexene, which required heating conditions, indicating that the reactivity of a sulfenic acid toward a simple alkyne is somewhat higher than that to a simple alkene. The reaction of 4 with methyl propiolate produced the Michael-type addition product **9b** in high yield within an hour (Entry 2). Treatment of **4** with dimethyl acetylenedicarboxylate also gave the corresponding vinyl sulfoxide 9c in excellent yield (Entry 3).

In summary, we have succeeded in the synthesis and isolation of a primary-alkyl-substituted sulfenic acid. Remarkable thermal stability of the sulfenic acid was achieved by utilizing a cavity-shaped substituent, which enabled us to study the reactivities of otherwise labile species toward various reagents. The addition of sulfenic acids to unsaturated C-C bonds has been investigated both experimentally and theoretically, and it was shown that the addition of a sulfenic acid to a simple alkene is intrinsically exothermic, although the reverse process, i.e. thermolysis of sulfoxides, has been widely utilized in organic syntheses. Further investigations on the reactivities of the sulfenic acid toward various reagents are currently in progress.

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Supporting Information is available electronically on J-STAGE.

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- 7 Crystallographic data for $4 \cdot MeCN \cdot c \cdot C_5H_{11}OMe: C_{67}H_{80}OS \cdot$ $C_2H_3N \cdot C_6H_{12}O$, fw: 1074.58, crystal size: $0.22 \times 0.07 \times$ 0.07 mm^3 , T = 123 K, monoclinic, $P2_1/n$, a = 19.646(5), b =9.293(2), c = 36.951(9) Å, $\beta = 104.358(4)^{\circ}$, V = 6535(3) Å³, Z = 4, $D_{calcd} 1.092 \text{ g cm}^{-3}$, $m = 0.094 \text{ mm}^{-1}$, No. of indep refins (parameters): 9526 (796), GOF = 1.019, $R_1(I > 2\sigma(I)) =$ $0.0742, wR_2$ (all data) = 0.1828.
- 8 S-O distances and C-S-O angles of sulfoxides: 1.47-1.53 Å, 103.5-108.9°; Cambridge Structural database, ConQuest version 1.16, the 2014 release.
- 9 In the case of the selenium analogue, BpqCH₂SeOH, heating at $60 \,^{\circ}\text{C}$ in benzene- d_6 for 230 h resulted in dehydrative decomposition. See ref 6b.
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