

Stable Sulfenyl Iodide Bearing a Primary Alkyl Steric Protection Group with a Cavity-shaped Framework

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A primary alkyl steric protection group bearing a cavity-shaped framework, a BpqCH₂ group, was developed. A sulfenyl iodide with the BpqCH₂ group was successfully synthesized and unambiguously characterized by X-ray crystallographic analysis. The sulfenyl iodide showed remarkable stability both in the solid state and in solution, demonstrating that the BpqCH₂ group is promising for kinetic stabilization of primary alkyl substituted reactive species.

In biological systems, thiol groups of cysteine residues play a crucial role in redox regulation and signaling.¹ While most of the cysteine thiols form inter- or intrachain disulfide bonds upon reaction with reactive oxygen (ROS) or nitrogen species (RNS), some thiol functionalities located within the cavities or clefts in proteins are sterically restrained from forming such disulfide linkages; instead, they produce highly reactive intermediates such as sulfenic acids (R–SOH),² *S*-nitrosothiols (R–SNO),³ and thionitrates (R–SNO₂)⁴ (Figures 1a and 1b), which undergo facile bimolecular decomposition in artificial systems. As chemical models for the reactive species derived from a –CH₂SH side chain of cysteine residues, compounds bearing a primary alkyl substituent are the most appropriate. However, it is a common idea that the synthesis of primary alkyl derivatives of such reactive species is difficult because the steric demands of primary alkyl groups are too small to protect the reactive species from bimolecular decomposition. For modeling the microenvironment depicted in Figure 1b, a new molecular design for steric protection with a primary alkyl group is necessary. We previously developed an aromatic steric protection group, a Bpq group,⁵ with a cavity-shaped framework. It is expected that by employing the Bpq group one could locate the –CH₂X (X = reactive functionality) moiety inside its large cavity, conferring sufficient kinetic stability upon the reactive species (Figure 1c). Here we report the development of an effective primary alkyl steric protection group based on the cavity-shaped framework and its application to kinetic stabilization of a sulfenyl iodide (R–SI), a sulfur-containing reactive species of biological importance.

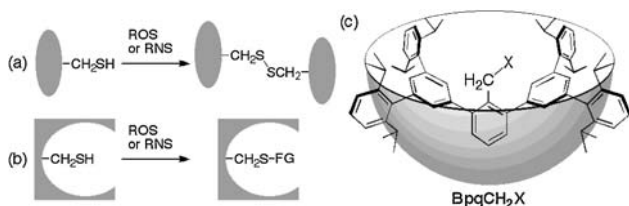
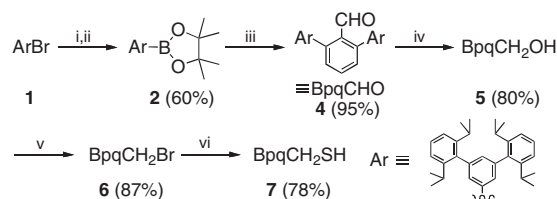


Figure 1. Schematic representations of (a) disulfide formation of cysteine residues in proteins, (b) cysteine residues in a sterically isolated environment affording sulfur-containing reactive species (FG = functional group such as OH, NO, and NO₂), and (c) a cavity-shaped molecule with a primary alkyl group.



Scheme 1. Reagents and conditions: (i) *n*-BuLi, THF, –78 °C, then (MeO)₃B; (ii) pinacol, toluene, 100 °C; (iii) 2,6-dibromobenzaldehyde (3) (0.5 mol amt.), Na₂CO₃, cat. Pd(PPh₃)₄, DME/EtOH/H₂O, reflux; (iv) LiAlH₄, THF, rt; (v) PBr₃, THF, 80 °C; (vi) thiourea, THF, reflux, then aq. NaOH, reflux.

A primary alkyl thiol with a cavity-shaped framework was synthesized through an array of prevalent transformations starting from terphenyl bromide **1** (Scheme 1). Thus, **1** was converted through a lithiation–boronation–esterification sequence into boronic ester **2**. The *m*-phenylene framework of the Bpq group was constructed efficiently via a Pd-catalyzed Suzuki–Miyaura coupling reaction of **2** and 2,6-dibromobenzaldehyde (**3**)⁶ to afford BpqCHO (**4**). Aldehyde **4** was converted to thiol **7** via alcohol **5** and bromide **6** by standard methods.

As a probe for the steric protection ability of the BpqCH₂ group, we targeted the stabilization of a primary alkyl substituted sulfenyl iodide. Sulfenyl iodides have attracted much interest in view of their important role as reaction intermediates in various types of modification of protein thiols.⁷ However, their lability due to ready disproportionation reaction to give disulfide and iodine hampers the detailed investigation.⁸ While we previously reported the synthesis of stable arenesulfenyl iodides, BmtSI (**8**)⁹ and BpqSI (**9**)^{5a} (Chart 1), isolation of a primary alkyl derivative is only limited to that bearing a poly(benzyl ether) dendron reported by Takaguchi et al.,¹⁰ and its crystal structure has not been determined.

The reaction of **7** with *N*-iodosuccinimide (NIS) in CCl₄ at room temperature successfully afforded the corresponding sulfenyl iodide **10** in 96% yield as red crystals (Scheme 2). Characterization of **10** was performed by NMR (¹H and ¹³C) and UV–vis spectroscopies and elemental analysis.¹¹ The UV–vis spectrum (CHCl₃) of **10** exhibited an absorption maximum at 464 nm, which is blue-shifted relative to that of its aromatic counterpart **9** (509 nm).^{5a} Finally, the molecular structure of **10** was established by X-ray crystallographic analysis.¹²

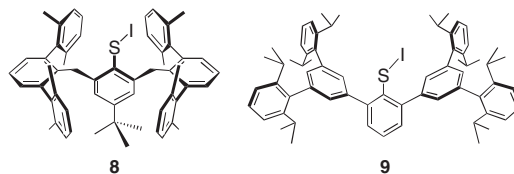
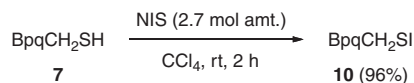


Chart 1.



Scheme 2.

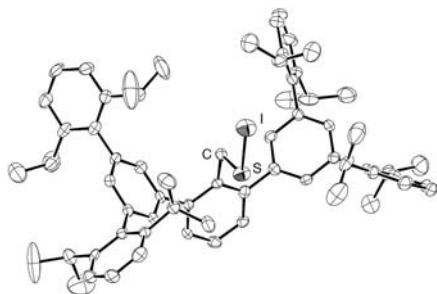
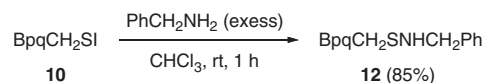


Figure 2. ORTEP drawing of **10** (50% probability). Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and bond angle (deg): S–I, 2.3743(17); C–S, 1.808(6); C–S–I; 101.62(18).

Figure 2 shows the crystal structure of **10** with selected bond lengths and angle. This is the first example of the crystallographic analysis of a primary alkyl substituted sulfenyl iodide. It is clearly shown that the cavity of the Bpq group is large enough to incorporate the entirety of the $-\text{CH}_2\text{SI}$ moiety. The sulfur atom is still located inside the cavity despite separation from the central benzene ring of the Bpq unit by a CH_2 group. The shortest intermolecular $\text{S}\cdots\text{I}$ and $\text{S}\cdots\text{S}$ distances (8.79 and 8.12 Å, respectively) are much longer than the sum of van der Waals radii of the corresponding atoms, showing that **10** is monomeric in the crystalline state. This is in sharp contrast to the crystal structure of Ph_3CSI (**11**),¹³ in which the molecules are linked via short $\text{S}\cdots\text{I}$ contacts of 3.210(4) Å, while similar to **8**⁹ and **9**^{5a} that have monomeric structures in the crystalline state. The S–I bond length of **10** (2.3743(17) Å) is comparable to those of **8** (2.386(4) Å) and **9** (2.316(4) Å), but nevertheless is shorter than that of **11** (2.406(4) Å) with oligomeric character.

As expected from the structural features, **10** is resistant to disproportionation and exhibited a high stability both in the solid state and in solution. In the solid state, **10** was decomposed in the range of 228.5–230.5 °C. Considering the reported fact that **11** with a bulky tertiary alkyl group is stable only below –70 °C in the solid state,¹⁴ the observed stability of **10** is remarkable. In solution, no decomposition was observed after heating a solution of **10** in toluene- d_8 at 80 °C for 9 days. These results clearly demonstrate that the steric protection due to the cavity-shaped framework is very effective for kinetic stabilization of primary alkyl substituted reactive species. Meanwhile, treatment of **10** with an excess amount of benzylamine in CHCl_3 at room temperature readily afforded sulfenamide **12** in a good yield (Scheme 3), which is in sharp contrast to the result reported by Takaguchi that the sulfenyl iodide bearing a poly(benzyl ether) dendron does not react with the same nucleophile. The facile reaction of **10** with benzylamine shows that the cavity-shaped substituent offers a space around the functional group large enough to allow the reaction with a relatively small reagent.

In summary, a potent primary alkyl steric protection group with a cavity-shaped framework, a Bpq CH_2 group, has been developed and successfully applied to the isolation and crystallographic analysis of a primary alkyl substituted sulfenyl iodide.



Scheme 3.

Investigation of stabilization of other sulfur-containing reactive species with the steric protection group is currently in progress.

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- 11 **10**: red crystals; Mp 228.5–230.5 °C (dec); ¹H NMR (500 MHz, CDCl_3): δ 1.12 (d, J = 6.8 Hz, 24H), 1.17 (d, J = 6.8 Hz, 24H), 2.87 (sept, J = 6.8 Hz, 8H), 4.37 (s, 2H), 7.06 (t, J = 1.5 Hz, 2H), 7.18–7.22 (m, 12H), 7.31–7.43 (m, 7H); ¹³C NMR (125 MHz, CDCl_3): δ 24.24 (q), 24.28 (q), 30.49 (d), 36.17 (t), 122.48 (d), 127.74 (d), 127.87 (d), 128.65 (d), 129.81 (d), 129.86 (d), 132.66 (s), 138.90 (s), 140.19 (s), 140.45 (s), 143.71 (s), 146.81 (s); UV–vis (CHCl_3) λ_{max} 464 nm (ϵ = 77). Anal. Calcd. for $\text{C}_{67}\text{H}_{79}\text{SI}$: C, 77.13; H, 7.63; S, 3.07%. Found: C, 76.92; H, 7.93; S, 3.09%.
- 12 Crystal data for **10**·hexane: $\text{C}_{67}\text{H}_{79}\text{SI} \cdot \text{C}_6\text{H}_{14}$, fw: 1129.43, crystal size: $0.45 \times 0.25 \times 0.15 \text{ mm}^3$, T = 120 K, monoclinic, $P2_1/n$, a = 11.399(4), b = 32.354(12), c = 18.332(7) Å, β = 105.0571(14)°, V = 6529(4) Å³, Z = 4, D_{calcd} = 1.149 g cm^{–3}, μ = 5.61 cm^{–1}, No. of indep reflns (parameters): 11433 (678), GOF = 1.177, $R_1(I > 2\sigma(I))$ = 0.0889, wR_2 (all data) = 0.2275. This crystallographic data have been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 752104. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).
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