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The First Direct Oxidative Conversion of a Selenol to a Stable Selenenic Acid: Experimental Demonstration of Three Processes Included in the Catalytic Cycle of Glutathione Peroxidase

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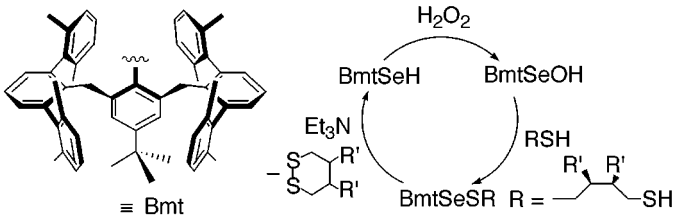
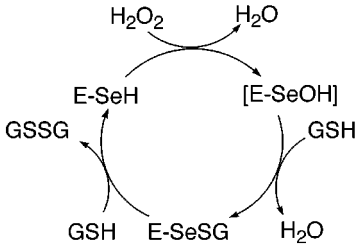
ABSTRACT



A stable selenenic acid was synthesized by direct oxidation of a selenol bearing a novel bowl-type substituent with H_2O_2, and its structure was established by X-ray crystallographic analysis. Selenenyl sulfides obtained by the reaction of the selenenic acid with 1,4-dithiols were reduced to the corresponding selenol by treatment with a tertiary amine, thus achieving the experimental demonstration of three processes included in the catalytic cycle of glutathione peroxidase.

Selenenic acids (RSeOH) have been well-recognized as important intermediates in organic[1] and biochemical[2] reactions of selenium compounds. In the catalytic cycle of glutathione peroxidase (GPx) shown in Scheme 1, a selenenic acid intermediate is considered to be formed by oxidation of a selenol with peroxides.[2] This process, which detoxifies the peroxides, has also been postulated to be included in the catalytic cycle of many synthetic GPx mimics.[3] However, the evidence for this process is very circumstantial; usually oxidation of a selenol rapidly affords the corresponding

Scheme 1



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diselenide as a result of ready reaction of the intermediary selenenic acid with a selenol. Furthermore, selenenic acids are notoriously unstable because they undergo very rapid self-condensation to form the corresponding selenoselenates. Although several selenenic acids have been observed so far,[3d,f,4−6] most of them were generated by selenoxide *syn* elimination, hydrolysis of selenenates, or oxidation of selenenyl sulfides and diselenides. Recently, we[5] and others[6] reported the isolation of stable selenenic acids, but they were also prepared by thermolysis of the corresponding butyl selenoxides. In this communication, we report the first direct oxidative conversion of a selenol to a stable selenenic acid and the experimental demonstration of three processes that are considered to compose the catalytic cycle of GPx by taking advantage of a novel bowl-type substituent **1** (denoted as Bmt)[7] developed by us (Figure 1).[8]

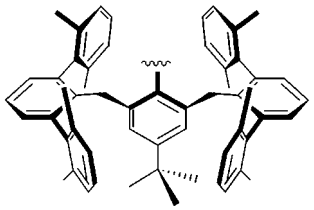

Figure 1. Novel bowl-type substituent.

We previously reported the synthesis of a stable sulfenic acid (RSOH) by direct oxidation of a thiol bearing the Bmt group.[7b] The bowl-shaped structure of the Bmt group was found to effectively prevent the disulfide formation as well as the self-condensation of the sulfenic acid. Similar steric effects are also expected for the selenium derivatives. Selenol **4** bearing a Bmt group was readily prepared by the reactions shown in Scheme 2. Lithiation of bromide **2** followed by

Scheme 2

treatment with elemental selenium afforded tetraselenide **3** as the main product, which was reduced to selenol **4** by $LiAlH_4$. When selenol **4** was treated with an equimolar amount of H_2O_2 in THF, selenenic acid **5** was obtained as a major product (Scheme 3). In this reaction, only a small

Scheme 3

amount of diselenide **6** was formed. Selenenic acid **5** was isolated by silica gel chromatography in 77% yield as stable pale yellow crystals.[9] The ^{1}H NMR spectrum ($CDCl_3$) of **5** showed the signal of the hydroxyl proton at δ 1.25 (readily exchangeable with D_2O), and in the ^{77}Se NMR ($CDCl_3$) a signal was observed at δ 1079. The structure of **5** was finally established by X-ray crystallographic analysis.[10] It was revealed that there are two discrete molecules of **5** and two hexane molecules in the unit cell. Figure 2 shows the ORTEP drawing of one fragment of these selenenic acids. The Se−O

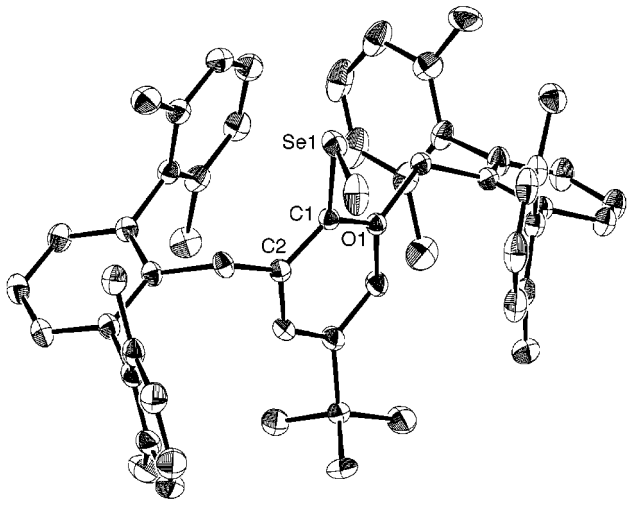

Figure 2. ORTEP drawing of BmtSeOH (**5**) with thermal ellipsoid plot (30% probability). Selected bond lengths (Å), bond angle (deg), and torsion angle (deg): Se(1)−O(1), 1.808(3); Se(1)−C(1), 1.914(3); O(1)−Se(1)−C(1), 96.80(12); O(1)−Se(1)−C(1)−C(2), 61.8(2).

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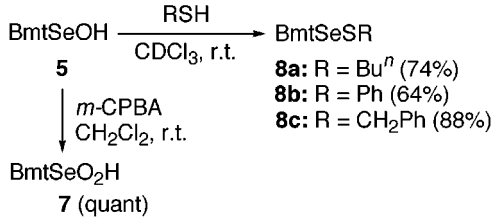
(8) A part of this work has been presented in the 8th International Conference on the Chemistry of Selenium and Tellurium, São Paulo, Brazil, Aug 6−11, 2000 (PS-59).

bond length of this fragment is 1.808(3) Å, clearly indicating the single-bond character of this bond. As for the other fragment, unfortunately, the disordering of the oxygen atom has made it difficult to discuss the detailed structural parameters of the SeOH moiety. In both fragments, two rigid *m*-terphenyl units surround the SeOH group like a brim of a bowl, thus preventing the self-condensation of the selenenic acid. During oxidation of selenol **4**, this bowl-shaped framework is considered to suppress the reaction of the initially formed selenenic acid **5** with the second molecule of **4** to yield diselenide **6**. Selenenic acid **5** showed remarkable stability, and no decomposition was observed even after heating at 80 °C for 1 d in toluene-d_8.

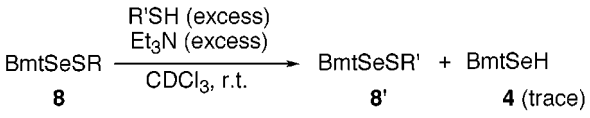
Selenenic acid **5** was further oxidized to seleninic acid **7** quantitatively by treatment with *m*-CPBA (Scheme 4). The

Scheme 4



reactions of **5** with several kinds of thiols proceeded at room temperature to afford the corresponding selenenyl sulfides **8a**−**c** (Scheme 4). Reduction of selenenyl sulfides **8a**−**c** to selenol **4** by treatment with a thiol was then examined. Treatment of **8a**−**c** with an excess amount of thiols in the presence of triethylamine, however, resulted in the thiol exchange on the selenium atom almost exclusively with the formation of a trace amount of selenol **4** (Scheme 5). These

Scheme 5

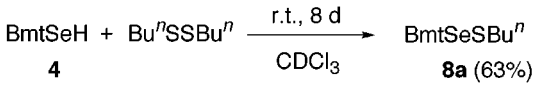


R	R'
Bu^n	Bu^n
Ph	Ph
Bu^n	Ph
CH_2Ph	CH_2Ph

results suggest that the equilibrium lies to the selenenyl sulfide and the thiol rather than the selenol and the disulfide.

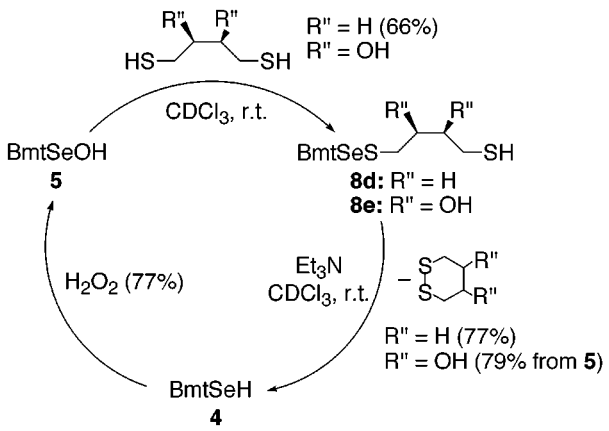
In fact, when the mixture of selenol **4** and dibutyl disulfide was allowed to stand in the presence of triethylamine for 8 d in $CDCl_3$, selenol **4** disappeared completely and selenenyl sulfide **8a** was obtained (Scheme 6). For enhancement of

Scheme 6



the selenol formation, 1,4-butanedithiol was employed, which affords a thermodynamically stable cyclic disulfide upon oxidation. Reaction of selenenic acid **5** with an excess of 1,4-butanedithiol afforded selenenyl sulfide **8d** (Scheme 7).

Scheme 7



When **8d** was treated with triethylamine, elimination of 1,2-dithiane took place and selenol **4** was obtained in a good yield. Use of dithiothreitol (DTT) as a 1,4-dithiol similarly reduced **5** to **4**. In the reaction of **5** with an excess of DTT, the quantitative formation of selenenyl sulfide **8e** was confirmed by ^{1}H NMR, which was further treated with triethylamine without isolation to give selenol **4**. These results are consistent with the report that the peroxidase activity of ebselen was improved when dithiols were used as a substrate instead of glutathione.[12]

In summary, the synthesis of a stable selenenic acid by direct oxidation of a selenol was achieved for the first time

(9) Data for **5**: pale yellow crystals, mp 198−202 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.25 (s, 1H), 1.94 (s, 24H), 3.82 (s, 4H), 6.55 (s, 2H), 6.79 (br, 8H), 6.94 (t, J = 7.5 Hz, 4H), 7.03 (d, J = 7.5 Hz, 4H), 7.32 (t, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0 (q), 31.0 (q), 34.6 (s), 37.2 (t), 123.9 (d), 126.5 (d), 126.8 (d), 127.1 (d), 129.0 (d), 136.4 (s), 138.5 (s), 138.8 (s), 141.0 (s), 141.6 (s), 143.6 (s), 150.8 (s); ^{77}Se NMR (95 MHz, $CDCl_3$, Me_2Se) δ 1079; IR (CH_2Cl_2) 3502 cm^{-1} (ν_{OH}); HRMS-(FAB) *m*/*z* obsd 826.3682, calcd for $C_{56}H_{58}OSe$ 826. 3653. Anal. Calcd for $C_{56}H_{58}OSe$: C, 81.43; H, 7.08; Se, 9.56. Found: C, 81.39; H, 7.08; Se, 9.14.

(10) Crystal data for **5**·C_6H_{14}: $C_{62}H_{72}OSe$, FW = 912.16, *triclinic*, space group P-1, a = 15.3560(6) Å, b = 18.9830(5) Å, c = 19.3350(8) Å, α = 87.445(2)°, β = 78.993(2)°, γ = 66.908(2)°, V = 5086.4(3) Å^3, Z = 4, D_{calcd} = 1.191 g/cm^3, μ = 7.79 cm^{-1}. The intensity data were collected at 150 K on a MAC Science DIP-2030 imaging plate area detector with Mo Kα radiation (λ = 0.71069 Å); 17779 independent reflections. The structure was solved by direct methods and refined by a full-matrix least-squares on F^2 using SHELXL 97.[11] $R1$ ($I > 2\sigma(I)$) = 0.0545, $wR2$ = 0.1552 (all data) for 1330 parameters.

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by taking advantage of a novel bowl-type substituent. The selenenic acid was reduced to the parent selenol via the selenenyl sulfides by the reaction with 1,4-dithiols and subsequent treatment with amine. These results present the conclusive experimental demonstration of the interconversion among the three species.

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Supporting Information Available: Experimental procedure for the preparation of **5**, physical and analytical data for **4**−**7** and **8a**,**d**, and crystallographic data for **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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