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# GPx-Like Activity of Selenides and Selenoxides: Experimental Evidence for the Involvement of Hydroxy Perhydroxy Selenane as the Active Species

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Supporting Information

**ABSTRACT:** The reaction mechanism of the GPx-like oxidation of PhSH with $H_2O_2$ catalyzed by selenoxides proceeds via formation of the hydroxy perhydroxy selenane, which is a stronger oxidizing agent than selenoxide. A hydroxy perhydroxy selenane intermediate was observed by electrospray ionization mass spectrometry and $^{77}$Se NMR spectroscopy in reactions of selenoxide **8** with $H_2O_2$.The initial velocity of oxidation of PhSH by $H_2O_2$ with selenoxide **8** is 4 orders of magnitude higher than that of **8** without peroxide. Selenoxide **8** is not reduced to selenide **6** by PhSH in the presence of $H_2O_2$. While electronic substituent effects have minimal impact on the catalytic performance of selenoxides, chelating groups increase the rate of catalysis.

Glutathione peroxidase (GPx) is an important selenoenzyme found in humans that is responsible for the reduction of toxic peroxides at the expense of glutathione (GSH), an endogenous thiol.[1] The presence and action of peroxides is linked to a number of diseases, including Alzheimer's and Parkinson's diseases, in a process known as oxidative stress.[2]

The selenium(II)/(IV) redox cycle plays an important role in biological systems, especially in sulfide/disulfide redox chemistry.[3] Selenides have been studied as GPx mimetics, catalyzing the reduction of peroxides by a variety of thiols. One proposed catalytic cycle involves oxidation of selenides **1** to selenoxides **2** by peroxides, followed by the fast reduction of **2** to **1** by 2 equiv of thiol through the formation of thioselenurane **2′** (Scheme 1, cycle A).[4] In this catalytic cycle, the oxidation of selenides **1** to selenoxides **2**, presumably the working oxidant in the catalytic cycle, was assigned as the rate-determining step.[4e−g] The sluggish in situ formation of **2** accounts for its lower catalytic activity in comparison with the GPx mimetic ebselen.[5] Although a similar mechanism is well-established for telluride catalysts in the oxidation of thiols with $H_2O_2$,[6] it has been shown that in an aqueous environment, selenoxides **2** are in equilibrium with dihydroxy selenanes **3a** and, under acidic conditions, with hydroxyselenonium **3**.[6b,7] These species can add $H_2O_2$ reversibly to form hydroxy perhydroxy selenanes **4**, which are the active oxidizing agents and are much better than selenoxides **2** for the oxidation of a variety of substrates (Scheme 1, cycle B).[8]

Reduction of selenoxide **2** to selenide **1** by a thiol and the reaction of **2** with $H_2O_2$ to produce **4** are competing reactions (Scheme 1). Our previous findings suggested that selenoxides **2** may not be the active oxidants responsible for the GPx-like activity exhibited by organoselenides.[8] To probe the mechanism of action of selenides and selenoxides as GPx mimics, we examined ebselen **5**, selenides **6** and **7**, and selenoxides **8**−**12** (Chart 1) under both stoichiometric and catalytic loadings as promoters for the reduction of $H_2O_2$ using PhSH as the cofactor.

**Scheme 1. Oxidation Reactions Promoted by Peroxides Activated by Selenides 1 or Selenoxides 2**

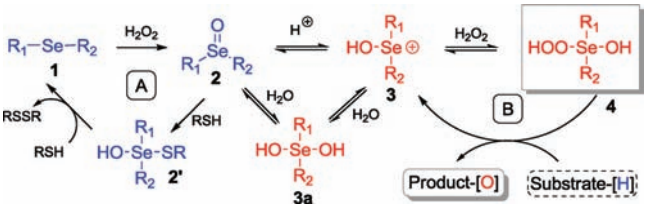
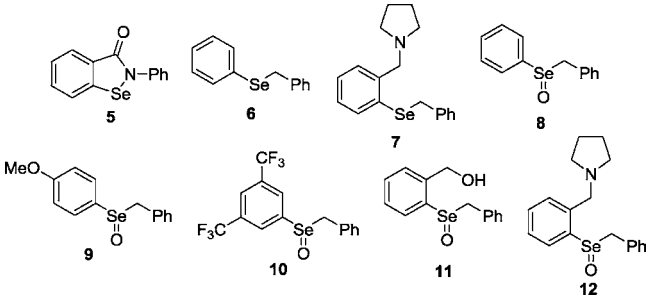



**Chart 1. Organoselenium Catalysts Employed in This Study**




The selenides used in our study were prepared by in situ reduction of the corresponding diselenides followed by reaction with benzyl bromide.[9] Selenoxides **8**−**12**, all lacking $\beta$-hydrogens to avoid undesired selenoxide syn elimination,[10] were prepared by oxidation of the parent selenides.[8d] In a first set of experiments, we carried out preparative reactions using

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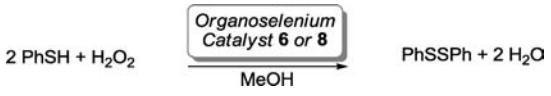
**Table 1. Preparative Reactions of Oxidation of PhSH with $H_2O_2$ Using Stoichiometric Amounts of 6 or 8**




| entry | cat | PhSH[a] | $H_2O_2$[a] | 6 or 8[a] | $v_0$ ($\mu$M min$^{-1}$)[b] |
|---|---|---|---|---|---|
| 1 | none | 1.0 | 0.5 | 0.0 | 0.53 ± 0.01 |
| 2 | 6 | 1.0 | 0.5 | 0.5 | 2.09 ± 0.002 |
| 3 | 8 | 1.0 | 0.0 | 0.5 | 2.02 ± 0.04 |
| 4[c] | 8 | 1.0 | 0.5 | 0.5 | (1.85 ± 0.007) × $10^4$ |
| 5 | none | 1.0 | 1.0 | 0.0 | 0.54 ± 0.01 |
| 6 | 6 | 1.0 | 1.0 | 0.5 | 7.11 ± 0.02 |
| 7[c] | 8 | 1.0 | 1.0 | 0.5 | (1.89 ± 0.006) × $10^4$ |

[a]Equivalents in MeOH at 276.8 ± 0.4 K. Final concentrations: PhSH = 0.5 mM; $H_2O_2$ = 0.25 or 0.5 mM; **6** or **8** = 0.25 mM. [b]Values of $v_0$ are averages ± standard deviations for three independent runs. [c]Reaction progress monitored in a stopped-flow apparatus.

stoichiometric amounts of benzyl phenyl selenide **6** or benzyl phenyl selenoxide **8** as activators of $H_2O_2$ in the oxidation of PhSH in MeOH. Formation of PhSSPh was monitored through the UV absorption increase at 305 nm.[11] Linear increases in absorbance ($k_0$) were observed in the initial stages of the reaction and converted to initial velocities ($v_0$) in units of $\mu$M min$^{-1}$ (Table 1).

Each equivalent of catalyst **6** or **8** would react with 1 equiv of $H_2O_2$ to produce the corresponding oxidizing agent. This species would then react with 2 equiv of PhSH. Surprisingly, the reaction rate for the oxidation of PhSH using selenide **6** and a stoichiometric amount of $H_2O_2$ was essentially identical to that observed for the reaction using selenoxide **8** in the absence of $H_2O_2$ and just 4-fold higher than that of the control reaction (entries 1−3). Selenoxide **8** and 1 equiv of $H_2O_2$ gave a $10^4$-fold increase in the rate of oxidation of PhSH to PhSSPh relative to the same reaction using **8** in the absence of $H_2O_2$ or with selenide **6** and $H_2O_2$ (entries 2−4). In a second set of experiments, the amount of $H_2O_2$ was increased to 2 equiv relative to the catalyst, and a 3-fold increase in initial velocity was observed with **6** relative to the reaction with 1 equiv of $H_2O_2$ (entries 2 and 6). Oxidation of **6** would be faster in higher concentrations of $H_2O_2$, producing selenoxide **8**, which reacts rapidly with $H_2O_2$ to deliver the active oxidizing agent in the reaction medium. The initial velocities of the control and selenoxide **8** reactions with different amounts of $H_2O_2$ were shown to be independent of the concentration of $H_2O_2$ (entries 1 vs 5 and 4 vs 7).

While selenoxides **2** are known to oxidize thiols to disulfides,[12] our results clearly indicate that the active oxidizing agent in the selenide/selenoxide assay as a GPx mimic (in which an excess of $H_2O_2$ is used) is not a selenoxide but is most likely hydroxyl perhydroxy selenane **4**, which appears to be a much better oxidizing agent than selenoxide. The presence of **4** during the catalytic cycle was established from the following series of experiments: (i) Products from the reaction between selenoxide **8** and 2 equiv of PhSH and $H_2O_2$ were isolated and analyzed by $^1$H NMR spectroscopy. Selenoxide **8** was recovered in 97% yield after 0.5 h of reaction [see the Supporting Information (SI)]. (ii) An aliquot of a 1:1 mixture of selenoxide **8** and $H_2O_2$ was analyzed by electrospray ionization mass spectrometry (ESI-MS) in negative ion mode. A peak at $m/z$ 297 for $C_{13}H_{13}O_3{}^{80}Se$ in an ion cluster with the isotopic distribution of Se was detected (Figure S1 in the SI). (iii) Selenide **6** ($^{77}$Se NMR: $\delta$ 375) was oxidized to selenoxide **8** ($^{77}$Se NMR: $\delta$ 885) with excess $H_2O_2$ (5 equiv) in MeOH-$d_4$. No other selenium species could be detected by $^{77}$Se NMR analysis, although in this environment, the equilibrium between selenoxide **2**, dihydroxy selenane **3a**, hydroxyselenonium **3**, and hydroxy perhydroxy selenane **4** is expected to form. When selenoxide **8** was treated with $H_2O_2$, the $^{77}$Se NMR spectrum showed two signals at $\delta$ 882 and 879. The intensity of the signal at $\delta$ 882 decreased with time relative to the selenoxide signal at $\delta$ 879 associated with gas evolution (presumably $O_2$), perhaps from decomposition of either $H_2O_2$ or **4** ($\delta$ 882), whose initial concentration would decrease with time and $H_2O_2$ concentration.[13] No benzeneseleninic acid ($PhSeO_2H$, $^{77}$Se NMR: $\delta$ 1218) was detected throughout the experiments, indicating that selenoxide **8** was robust under the conditions of reaction (see the SI). These data suggest that selenoxides **2** are not the functional oxidants for the GPx-like activity of selenides in the presence of $H_2O_2$ and that hydroxy perhydroxy selenane **4** is more likely the active oxidizing agent (Scheme 1, cycle B).

The performance of organoselenium compounds in a variety of oxidation reactions using peroxides, including their GPx-like activity,[14] has been shown to be substituent-dependent.[8,15] We next examined selenides **6** and **7** and selenoxides **8**−**12**, which incorporate electron-donating, electron-withdrawing, or chelating substituents, as catalysts (0.1 mol % relative to PhSH). Linear increases in absorbance were observed in the initial stages of the catalyzed reactions (Figure 1), and the results for

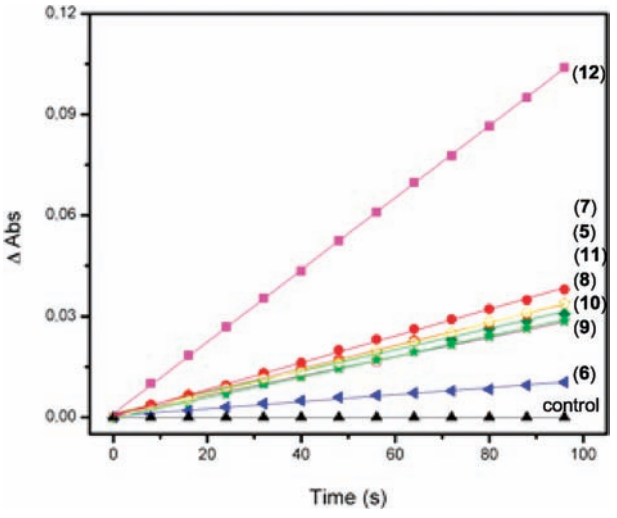



**Figure 1.** Initial rates of appearance of PhSSPh using catalytic loadings of organoselenium catalysts **5**−**12**.

the initial and relative reaction rates are listed in Table 2. All of the selenoxides screened showed some catalytic activity pro-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moting the oxidation of PhSH by $H_2O_2$ (Figure 1). For comparison purposes, ebselen **5** was selected as a standard compound and its relative activity assigned as 1.0 (Table 2, entry 1). The

**Table 2. GPx-like Activities of Organoselenium Catalysts 5−12**[a]

| entry | catalyst | $v_0$ ($\mu$M min$^{-1}$)[b] | $V_{rel}$ |
|---|---|---|---|
| 1 | **5** | 17.18 ± 0.17 | 1.00 |
| 2 | **6** | 5.08 ± 0.14 | 0.30 |
| 3 | **8** | 15.27 ± 0.30 | 0.89 |
| 4 | **9** | 13.92 ± 0.16 | 0.81 |
| 5 | **10** | 14.71 ± 0.13 | 0.86 |
| 6 | **11** | 16.50 ± 0.19 | 0.96 |
| 7 | **12** | 51.77 ± 0.18 | 3.01 |
| 8 | **7** | 19.29 ± 0.19 | 1.12 |

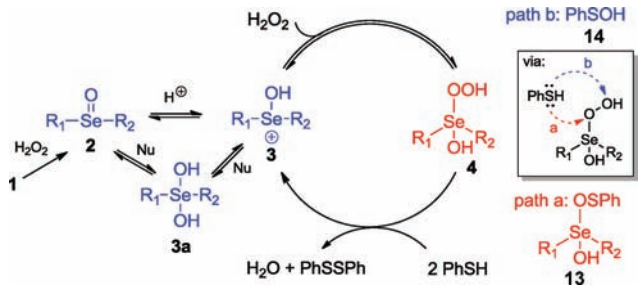
[a]Assay conditions: $H_2O_2$ (final concentration = 10.4 mM in MeOH), PhSH (final concentration = 10.0 mM in MeOH), and organoselenium catalyst **5−12** (final concentration = 10.0 $\mu$M in MeOH) at 276.8 ± 0.4 K. [b]Values of $v_0$ were corrected for the uncatalyzed background reaction and are averages ± standard deviations for three independent runs.

initial rate with selenoxide **8** was 3-fold higher than that observed for selenide **6** (entries 2 and 3). Although selenoxides **8−10** have aryl substituents with different electronic demands, their catalytic activities are essentially identical (entries 3−5). Compounds **8−10** were comparable to ebselen **5** as GPx mimics (entry 1).

Selenoxides **11** and **12** with chelating substituents had higher initial rates of reaction than selenoxides **8−10** (Table 2, entries 6 and 7). The X-ray crystal structure of **11** (see the SI for crystallographic details) revealed a Se···OH distance of 2.60 Å, which is much shorter than the sum of the van der Waals radii for O and Se (3.42 Å).[16] This noncovalent interaction would stabilize the corresponding hydroxyselenonium intermediate **3** prior to reaction with $H_2O_2$.[8d] While selenoxide **11** was comparable to ebselen **5** in reactivity (entry 6 vs 1), selenoxide **12** with a chelating amino group (entry 7) exhibited a 3-fold higher activity than **5**. Selenide 7 (entry 8) was a poorer catalyst than selenoxide **12** but did display catalytic activity comparable to that of ebselen **5**.

In light of the experimental evidence presented here, a more consistent catalytic cycle for the GPx-like activity of selenides and selenoxides is proposed in Scheme 2. Oxidation of selenide

**Scheme 2. Revised GPx Catalytic Cycle of Selenides and Selenoxides**




**1** with $H_2O_2$ generates selenoxide **2**, which is the true catalyst in these systems. In an aqueous solution, **2** adds water or an intramolecular nucleophile to produce the dihydroxy selenane **3a**. Both **2** and **3a** would be in equilibrium with hydroxyselenonium **3**.[17] Subsequently, **3** adds $H_2O_2$ reversibly to produce the final oxidizing agent, hydroxy perhydroxy selenane **4**. The final step is the reaction of **4** with 2 equiv of thiol to produce disulfide and regenerate the equilibrium among the selenium species **2**, **3a**, and **3** to restart the catalytic sequence.[18]

Once hydroxy perhydroxy selenane **4** is formed, two different pathways can be proposed for the oxidation of PhSH (Scheme 2). In path a, PhSH reacts with **4** to produce **13**, which reacts with another equivalent of PhSH to produce PhSSPh and **3a** to restart the catalytic cycle with $H_2O_2$. Alternatively, in path b, PhSH would attack the terminal oxygen of **4**, producing **3a** and PhSOH (**14**), which reacts with another equivalent of PhSH to produce PhSSPh. While both are plausible paths, the observed effect of substituents on the catalytic performance of selenoxides **8−10** favors path a. The attack of thiol in path a develops negative charge on the terminal oxygen of the −OOH group as $^-$OH is lost. In path b, the formation of **14** involves attack of the PhSH at the terminal oxygen and develops negative charge via the formation of Se−O$^-$. Charge development is further from Se in path a and would be less influenced by the electronic effects of the substituents attached to it. Moreover, the increased activity of selenoxide **12** bearing an amino chelating group can be explained by the increased stability of **3**. This nonbonded interaction with the electron lone pair of nitrogen results in a higher concentration of **3** and consequently a faster reaction with $H_2O_2$ to afford the active oxidizing agent, hydroxy perhydroxy selenane **4**.[19]

In summary, we have shown that the GPx-like catalytic activity of organoselenides does not follow a Se(II)/Se(IV) redox cycle. Kinetic evidence has revealed that in the presence of $H_2O_2$, selenoxides are converted to hydroxy perhydroxy selenanes **4**, which are kinetically better oxidizing agents than selenoxides **2**. The oxidation of PhSH by stoichiometric amounts of **4** is $10^4$-fold faster than that observed for selenoxide **2**. A catalytic cycle involving the interconversion of selenoxides **2** to hydroxy perhydroxy selenanes **4** followed by oxidation of PhSH to PhSSPh and regeneration of selenoxide **2** is more consistent with the kinetic, NMR, and MS data presented here. The performance of the selenoxide catalyst is little affected by electronic demands at the Se center, but selenoxides containing potential chelating groups, especially amino groups, appear to be better catalysts. Oxidation of PhSH with $H_2O_2$ is 3-fold faster with selenoxide **12** than with the GPx mimic ebselen **5**.

## ■ ASSOCIATED CONTENT

### Supporting Information

Details of catalyst preparation; kinetic studies; ESI-MS, $^{77}$Se NMR, and X-ray data for selenoxide **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The catalytic GPx-like cycles of selenides bearing specific functionalities (e.g., diamides, diols, or dicarboxylic acids) proceed by the formation of different active species (e.g., spirodiazoselenuranes, spirodioxoselenuranes, and cyclic seleninate esters, respectively). For more information about these catalysts and their GPx-like profiles, see: (a) Back, T. G.; Moussa, Z. *J. Am. Chem. Soc.* **2002**, *124*, 12104. (b) Back, T. G.; Moussa, Z. *J. Am. Chem. Soc.* **2003**, *125*, 13455. (c) Back, T. G.; Moussa, Z.; Parvez, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1268. (d) Back, T. G.; Kuzma, D.; Parvez, M. *J. Org. Chem.* **2005**, *70*, 9230. (e) Kuzma, D.; Parvez, M.; Back, T. G. *Org. Biomol. Chem.* **2007**, *5*, 3213. (f) Press, D. J.; Mercier, E. A.; Kuzma, D.; Back, T. G. *J. Org. Chem.* **2008**, *73*, 4252. (g) Sarma, B. K.; Manna, D.; Minoura, M.; Mugesh, G. *J. Am. Chem. Soc.* **2010**, *132*, 5364.

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