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Remarkable Activity of a Novel Cyclic Seleninate Ester as a Glutathione Peroxidase Mimetic and Its Facile in Situ Generation from Allyl 3-Hydroxypropyl Selenide

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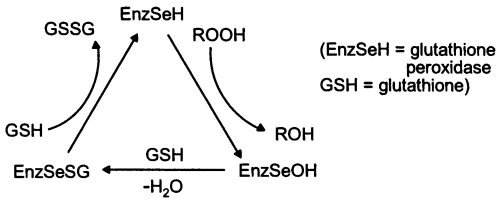
Peroxides and other reduced oxygen species are byproducts of aerobic metabolism that contribute to oxidative stress in living organisms.[1] This has been implicated in aging, as well as in a variety of disease states.[2] As a countermeasure, cells contain several types of antioxidants,[3] including glutathione peroxidase (GPx),[4] a selenium-containing enzyme that destroys peroxides through their catalytic reduction by the sacrificial thiol glutathione (GSH). Redox processes associated with selenocysteine residues in the enzyme are responsible for the catalytic activity. The catalytic cycle of GPx is shown in Scheme 1.[5]

A variety of small-molecule selenium compounds,[4a,6] including variously substituted diselenides[7] and N−Se heterocycles,[8] as well as other types of selenium compounds[9] and their tellurium analogues[9b,10] have been studied as potential mimetics of the enzyme. The cyclic selenenamide Ebselen (**1**) has been extensively investigated[11] and has undergone clinical trials as an antiinflammatory agent. However, **1** is a relatively inefficient catalyst for the oxidation of thiols to disulfides and causes only a relatively modest enhancement of the rates of such processes. Amino groups that are capable of interacting with the selenium atom are known to play a significant role in modulating the redox properties of selenium-based antioxidants.[7c,12] Several years ago, we reported[13] that the cyclic selenenamide **2** is capable of strongly accelerating the reduction of *tert*-butyl hydroperoxide (TBHP) with benzyl thiol (BnSH), which comprises a convenient model for the reduction of peroxides with GSH in biological systems. Mechanistic investigations revealed that **2** functioned as a procatalyst that was first converted to the corresponding selenenyl sulfide (BnSSeR), which served as the true catalyst in the oxidation via a cycle similar to that shown in Scheme 1.

Scheme 1



We now report that certain allyl selenides can be used to generate more active catalytic species in situ via [2,3]sigmatropic rearrangements of the corresponding allyl selenoxides,[14] which in turn are rapidly produced upon exposure of the selenides to TBHP. In particular, we discovered that allyl 3-hydroxypropyl selenide (**3**) had especially remarkable activity, as shown in Figure 1, where the formation of BnSSBn from the corresponding thiol in the presence of excess TBHP and 10 mol % of the catalyst is plotted against time (see Supporting Information for details). We include for comparison the results obtained under the same conditions for **1** and **2**, along with a control experiment with no catalyst. The selenocystine derivative **4** was also tested, but showed essentially no activity under these conditions. The half-lives of the oxidations ($t_{1/2}$, the time required for the 50% conversion of BnSH to BnSSBn) in the presence of **1**, **2**, and **3** were 42, 18, and 4.8 h, respectively, as compared to >300 h in the control experiment, or in the presence of **4**.

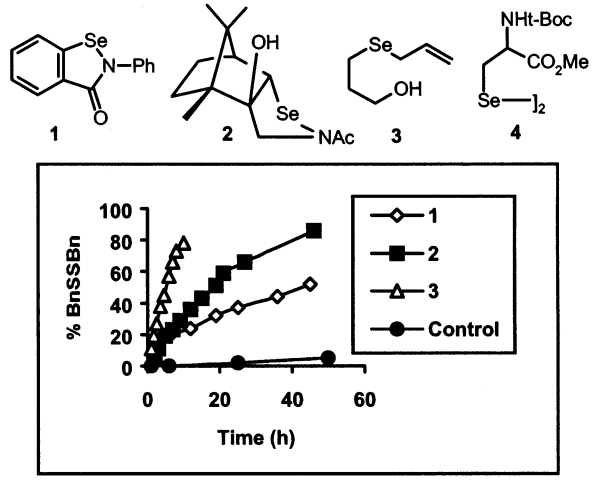


Figure 1. Rates of formation of BnSSBn from oxidation of BnSH (0.031 M) with 90% aqueous TBHP (0.043 M) in the presence of catalysts **1**−**3** (0.0031 M) in dichloromethane−methanol (95:5) at 18 °C.

Interestingly, the catalytic mechanism of **3** (Scheme 2) proved to be significantly different from that of GPx (Scheme 1). Thus, allyl selenide **3** undergoes rapid oxidation by TBHP (complete within 15 min at room temperature), presumably to selenoxide **5**, which undergoes immediate [2,3]sigmatropic rearrangement to the selenenate ester **6** (Scheme 2). Further oxidation to **8**, followed by cyclization, affords the cyclic seleninate ester **9**. In a control experiment in which **3** was oxidized with excess TBHP in the absence of the thiol, **9** was isolated in nearly quantitative yield and was fully characterized. Selenenate ester **6** was also generated in situ by oxidation of **3** with 1 mol of *m*-CPBA, but could not be isolated. A downfield shift of the allyl signals in the ^{1}H NMR spectrum (relative to **3**) was consistent with an *O*-allyl intermediate. Moreover, the absence of allyl alcohol and **9** in the reaction mixture at this stage indicates that **6** does not cyclize to **7**, followed by further oxidation to **9**, but instead undergoes oxidation to **8** prior to cyclization to **9**. The few known cyclic seleninates all contain other rings fused to the seleninate moiety, or other stabilizing

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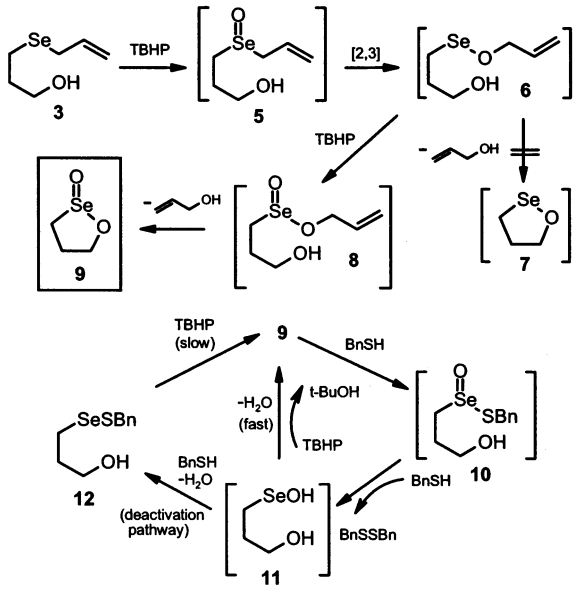
Scheme 2



substituents.[15] Thus, **9** is the first example of a simple unsubstituted monocyclic seleninate ester.

In the next stage of the catalytic cycle (Scheme 2), **9** reacts with BnSH to produce the thioseleninate **10**, followed by further thiolysis to afford the selenenic acid **11** and BnSSBn.[16] Oxidation and cyclization (or vice versa) of **11** then regenerates the cyclic seleninate **9**. Evidence for this mechanism is based on the following observations. First, authentic **9** displays even stronger activity compared to **3** itself in the oxidation of BnSH to BnSSBn with TBHP ($t_{1/2} = 2.5$ h). Moreover, when 10 mol % of **3** was employed as the catalyst and the oxidation was allowed to go to completion, **9** remained as the principal selenium-containing product, along with the selenenyl sulfide **12**. Thus, while **3** is rapidly consumed in the initial stages of the process, **9** is continuously regenerated. Selenenyl sulfide **12** was prepared independently and was also tested for catalytic activity in the model system. However, to our surprise, it displayed considerably lower activity ($t_{1/2} = 35$ h) and is therefore ruled out as a significant catalyst in Scheme 2. This is noteworthy in view of the fact that the corresponding selenenyl sulfides proved to be essential in the catalytic cycles of selenenamide **2**[13] and GPx (Scheme 1). In the present case, **12** is probably formed by the reaction of **11**[16] with BnSH. Indeed, in the absence of TBHP, cyclic seleninate **9** reacts rapidly with 3 mol of BnSH to afford **12** quantitatively. When authentic **12** was allowed to stand for prolonged periods with excess TBHP in the absence of the thiol, it slowly regenerated the cyclic seleninate **9**. Thus, in the present system, formation of **12** represents a deactivation pathway, in which catalytic activity is eventually restored by the slow oxidation of **12** back to **9**.

We also tested the 2-hydroxyethyl and 4-hydroxybutyl analogues of **3** in the BnSH−TBHP system and found half-lives of 7.7 and 9.8 h, respectively (relative to 4.8 h for **3**). In the case of the 4-hydroxybutyl analogue, the corresponding novel six-membered cyclic seleninate ester (1,2-oxaselenane *Se*-oxide) was also isolated and characterized. However, the significantly longer half-lives compared to that observed with **3** indicates that **3** has the optimum chain length and **9** has the optimum ring size for catalytic activity.

In summary, allyl selenide **3** is a stable, remarkably effective procatalyst that generates the unusual cyclic seleninate ester **9** by a series of oxidation and sigmatropic rearrangement steps upon reaction with TBHP. The novel heterocycle **9** is significantly more effective in catalyzing the reduction of TBHP than previously studied GPx mimetics such as **1** and **2**, or the selenocysteine analogue **4**. The relatively poor catalytic activity of selenenyl sulfide **12** in Scheme 2 is in striking contrast to the key role of the corresponding species in Scheme 1 and in the reduction of TBHP with BnSH mediated by **2**. These experiments also demonstrate that Se−O compounds can be even more effective than the more commonly studied Se−N derivatives in this regard.

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Supporting Information Available: Experimental procedures and NMR data for isolated compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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