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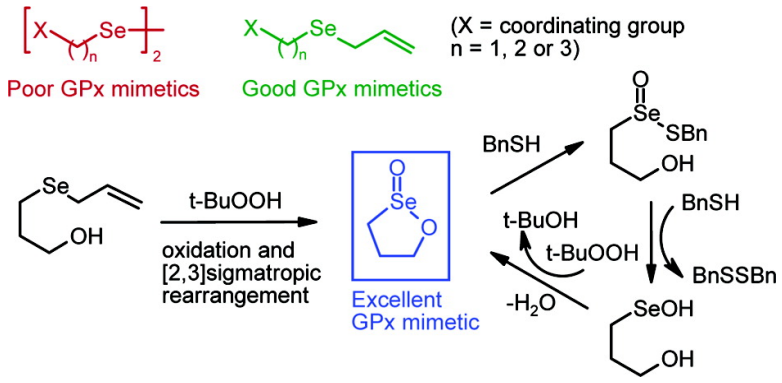

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Diselenides and Allyl Selenides as Glutathione Peroxidase Mimetics. Remarkable Activity of Cyclic Seleninates Produced in Situ by the Oxidation of Allyl ω-Hydroxyalkyl Selenides

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Abstract: A series of aliphatic diselenides and selenides containing coordinating substituents was tested for glutathione peroxidase (GPx)-like catalytic activity in a model system in which the reduction of *tert*-butyl hydroperoxide with benzyl thiol to afford dibenzyl disulfide and *tert*-butyl alcohol was performed under standard conditions and monitored by HPLC. Although the diselenides showed generally poor catalytic activity, allyl selenides proved more effective. In particular, allyl 3-hydroxypropyl selenide (**25**) rapidly generated 1,2-oxaselenolane *Se*-oxide (**31**) in situ by a series of oxidation and [2,3]sigmatropic rearrangement steps. The remarkably active cyclic seleninate **31** proved to be the true catalyst, reacting with the thiol via a postulated mechanism in which the thioseleninate **32** is first produced, followed by further thiolysis to selenenic acid **33** and oxidation-dehydration to regenerate **31**. In contrast to catalysis with GPx, formation of the corresponding selenenyl sulfide **34** comprises a competing deactivation pathway in the catalytic cycle of **31**, as a separate experiment revealed that authentic **34** was a much less effective catalyst than **31**. 1,2-Oxaselenane *Se*-oxide (**37**), the six-membered homologue of **31**, was formed similarly from allyl 4-hydroxybutyl selenide (**26**), but proved a less effective catyalyst than **31**. Compounds **31** and **37** are the first examples of unsubstituted monocyclic seleninate esters.

Introduction

Peroxides and other reduced oxygen species are byproducts of aerobic metabolism that cause oxidative stress in living organisms.[1] The formation of peroxides leads to the generation of reactive radical species that cause damage to various types of biologically important molecules and ultimately to cells. Consequently, oxidative stress has been implicated in a variety of degenerative processes and disease states, including inflammation, mutagenesis and cancer, atherosclerosis, Alzheimer's disease, and possibly the aging process itself.[2] Endogenous antioxidants, as well as antioxidants obtained in the diet, mitigate the damage caused by peroxides and related species.[1,3] Among the former, glutathione peroxidase (GPx) is a selenium-containing enzyme that protects cells by the catalytic reduction of peroxides with the thiol glutathione (GSH).[4] The enzyme has a tetrameric structure, in which each subunit contains a selenocysteine residue.[5] The redox chemistry associated with the selenocysteine selenol moieties is responsible for the catalytic properties of GPx, and the catalytic cycle is shown in Scheme 1.[6] Thus, the selenol (EnzSeH) is first oxidized by the peroxide to the corresponding selenenic acid (EnzSeOH), which reacts with GSH to afford a selenenyl sulfide intermediate (EnzSeSG). The latter undergoes further reaction with GSH, thereby regenerating the original selenol and producing oxidized glutathione (GSSG) as a byproduct. Overall, GSH functions as a sacrificial stoichiometric reducing agent in this process. At high peroxide concentrations, the corresponding seleninic acid ($EnzSeO_2H$) may also be involved in the catalytic cycle.

Because of the biological importance of this process, several attempts to emulate the behavior of the enzyme with certain types of small-molecule selenium compounds have been reported.[7] These include variously substituted diaryl selenides and diselenides,[8] N-Se heterocycles,[8c,9] the artificial selenoenzyme selenosubtilisin,[10] selenopeptides,[11] and other types of selenium compounds[12] and their tellurium analogues.[12b,13] Amino groups

(1) (a) *Oxidative Stress*; Sies, H., Ed; Academic Press: London, 1985. (b) *Free Radicals and Oxidative Stress: Environment, Drugs and Food Additives*; Rice-Evans, C., Halliwell, B., Lunt, G. G., Eds.; Portland Press: London, 1995.
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(3) *Oxidative Processes and Antioxidants*; Paoletti, R., Samuelsson, B., Catapano, A. L., Poli, A., Rinetti, M., Eds.; Raven Press: New York, 1994.
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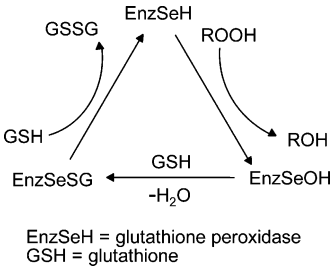
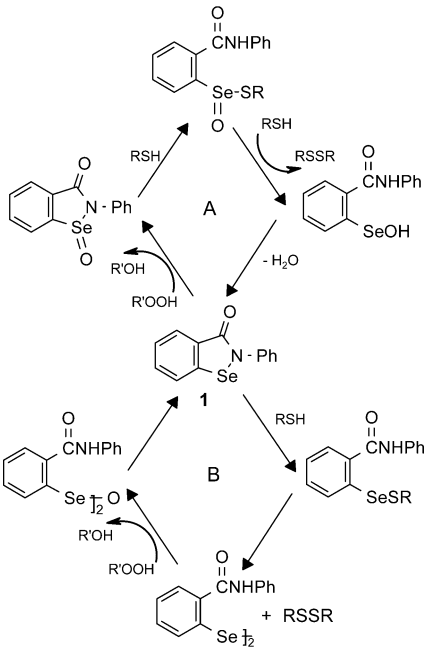
Scheme 1



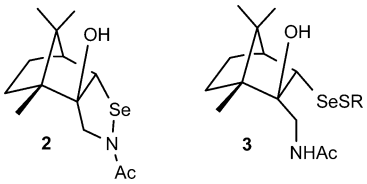
that are capable of coordinating with the selenium atom appear to play a significant role in modulating the antioxidant properties of both GPx and its synthetic mimetics.[8d,9b,14] A similar function of hydroxyl substituents in diaryl diselenides has been adumbrated.[8f] Ebselen (**1**) is a cyclic selenenamide that has been extensively studied as an antioxidant and GPx mimetic,[15] and has been the subject of clinical trials to evaluate its antiinflammatory properties.[16] Ebselen functions via different mechanisms from that shown in Scheme 1 for GPx, that vary with thiol and peroxide concentration (Scheme 2).[17] Thus, at high peroxide concentrations, catalytic cycle A is followed, where the initial step consists of the oxidation of the selenium atom. On the other hand, path B dominates at high thiol concentrations, leading to the corresponding selenenyl sulfide intermediate via the initial thiolysis of **1**. Variations of the processes shown in Scheme 2 have also been proposed.[13b,17] However, regardless of the mechanism, **1** displays relatively poor catalytic activity, and so the discovery of other, more active GPx mimetics continues to be a major objective for researchers in this field.

Several years ago, we reported that the camphor-based selenenamide **2** displays strong catalytic activity in a model peroxide/thiol system.[18] Mechanistic investigations revealed that **2** is a procatalyst that reacts rapidly with the thiol to produce the corresponding selenenyl sulfide **3**, which then functions as the true catalyst in the reduction of the peroxide via a cycle

Scheme 2



similar to that in Scheme 1. In view of the high catalytic activity of **2** and the relative paucity of earlier studies of aliphatic selenium compounds as GPx mimetics,[19] we embarked on an investigation of other simple diselenides and selenides containing potential coordinating groups to investigate structure−activity effects upon their catalytic behavior.[20]



Results and Discussion

To compare the catalytic activity of a series of potential GPx mimetics, we required an assay that could be used under a standard set of conditions as a model of the GPx-GSH system. For this purpose, we chose readily available *tert*-butyl hydroperoxide (TBHP) and benzyl thiol (BnSH) as the oxidant and stoichiometric reductant, respectively. The oxidation of the thiol to its disulfide (BnSSBn) could then be conveniently monitored by HPLC (UV detection). Moreover, the choice of BnSH as the thiol provided the opportunity to identify possible intermediates via ^{1}H NMR spectroscopy because of the distinctive methylene signals of the thiol and its congeners. The reactions were thus performed with BnSH (0.031 M), excess TBHP (0.043 M), and 10 mol % (0.0031 M) of the catalyst in dichloromethane−methanol (95:5) under homogeneous conditions in a water bath maintained at 18 °C. Under these conditions, a control reaction performed in the absence of a selenium-containing catalyst had a half-life ($t_{1/2}$; the time required for the 50% conversion of BnSH to BnSSBn) of >300 h. The $t_{1/2}$ values determined in this model system thus comprise a

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(16) For potential medicinal applications of Ebselen, see: Fong, M. C.; Schiesser, C. H. *Tetrahedron Lett.* **1995**, *36*, 7329 and references therein.
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(18) Back, T. G.; Dyck, B. P. *J. Am. Chem. Soc.* **1997**, *119*, 2079.
(19) Whereas aryl selenides and especially diselenides have been studied extensively (see ref 8), there appears to be no reported structure−activity data on aliphatic selenides and diselenides.
(20) Preliminary communication: Back, T. G.; Moussa, Z. *J. Am. Chem. Soc.* **2002**, *124*, 12104.

Table 1. Relative Catalytic Activity of Ebselen **1**, Selenenamide **2**, and Diselenides **4**−**16** in the BnSH−TBHP System[a]

	Catalyst			$t_{1/2}$ (h)
Control (No catalyst)				>300
1	Ebselen			42
2				18
	$[X\text{-}(CH_2)_n\text{-}Se]_2$			
	X		n	
4	HO_2C		1	73
5	HO_2C		2	121
6	HO_2C		3	90
7	MeO_2C		1	90
8	HO		2	89
9	HO		3	90
10	HO		4	82
11	NH_2		2	45
12	NH_2		3	33
13	PhC(=O)NH		3	119
14	MeOC(=O)NH		3	170
15	AcNH		3	6.0
16	NHt-Boc MeO_2C	Se	2	ca. 300

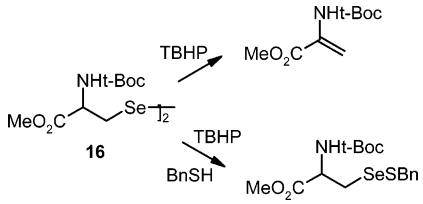
[a] Reactions were performed with BnSH (0.031 M), TBHP (0.043 M), and the catalyst (0.031 M) in CH_2Cl_2−MeOH (95:5) at 18 °C.

convenient means for comparing the activity of various compounds as potential GPx mimetics.

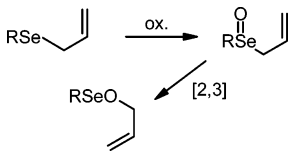
The $t_{1/2}$ values measured in this manner for a series of diselenides **4**−**16** are shown in Table 1. Full plots of the yields of the disulfide versus time in the presence of various catalysts are presented in the Supporting Information. The half-lives obtained similarly for Ebselen (**1**) and selenenamide **2** are included for comparison, along with the control reaction. The diselenides were readily obtained by the treatment of the corresponding alkyl halides with Na_2Se_2.[21] Diselenides containing free carboxylic acid side chains showed very little catalytic activity, regardless of the chain length (compounds **4**−**6**). The methyl ester analogue **7** proved even less effective than the free acid **4**. Similarly, bis(ω-hydroxyalkyl) diselenides **8**−**10** were only weakly active. However, significantly improved results were observed with the 2-aminoethyl and 3-aminopropyl derivatives **11** (selenocystamine) and **12**, which produced half-lives ($t_{1/2}$ = 45 and 33 h, respectively) comparable to that measured with Ebselen (**1**; $t_{1/2}$ = 42 h), but longer than that observed with selenenamide **2** ($t_{1/2}$ = 18 h). The benzamide and methyl carbamate derivatives **13** and **14** were considerably less active than the parent amine **12**, while, surprisingly, the corresponding acetamide **15** proved remarkably effective in catalyzing the model reaction, affording the shortest half-life ($t_{1/2}$ = 6 h) of all of the above compounds. Unfortunately, the latter compound was difficult to prepare in a pure state, prompting us to search for other types of selenium-based catalysts. Finally, the selenocystine derivative **16** displayed essentially no catalytic activity in the model system.

Closer examination of selenocystine **16** showed that it was converted into the corresponding dehydroalanine derivative

Scheme 3



Scheme 4



essentially quantitatively (NMR analysis) when treated with TBHP in $CDCl_3$ for 50 h in the absence of thiol (Scheme 3), indicating that a selenoxide elimination had taken place. When **16** was subjected to a similar oxidation in the presence of BnSH, it produced only a small amount of the dehydroalanine derivative, while the major product was the corresponding selenenyl sulfide, isolated in 44% yield (Scheme 3). Thus, while selenenyl sulfides have been identified as key intermediates in the relatively efficient catalytic cycles of GPx (Scheme 1) and selenenamide **2**, the selenenyl sulfide derived from **16** is evidently much less efficacious in this regard. Similarly, carboxylic acid **5** afforded acrylic acid quantitatively when oxidized in the absence of thiol, whereas in the presence of BnSH, the major product, which could not be completely purified, was again tentatively identified as the corresponding selenenyl sulfide.

Previous studies[8e] have shown that diaryl selenides are essentially devoid of catalytic activity, even when amino substituents capable of coordinating with the selenium atom are present. However, we observed that alkyl selenides react more rapidly with TBHP than the corresponding alkyl diselenides. Moreover, selenoxides derived from the oxidation of allyl selenides are known to undergo very rapid [2,3]sigmatropic rearrangements to afford selenenic esters (Scheme 4).[22] We therefore reasoned that an allyl selenide might offer the advantage of a relatively rapid initial oxidation step that would be followed by the even faster in situ formation of a highly thiophilic selenenic ester species, thereby providing rapid entry into the catalytic manifold. Furthermore, coordinating groups could be accommodated on the alkyl substituent of the selenide, possibly further enhancing the catalytic activity.

The desired selenides **17**−**26** were obtained by reduction of the corresponding ω-functionalized dialkyl diselenides with sodium borohydride, followed by reaction with allyl bromide (Scheme 5). They were then subjected to the same model assay system that was used for evaluating the diselenides in Table 1, and the corresponding $t_{1/2}$ values were measured. The results are compiled in Table 2. Full plots of the yields of the disulfide versus time in the presence of various catalysts are again presented in the Supporting Information. In general, it was noted that the allyl selenides are considerably more active catalysts

(21) Klayman, D. L.; Griffin, T. S. *J. Am. Chem. Soc.* **1973**, *95*, 197.

(22) (a) Nishibayashi, Y.; Uemura, S. In *Organoselenium Chemistry − A Practical Approach*; Back, T. G., Ed.; Oxford University Press: Oxford, 1999; Chapter 11. (b) Nishibayashi, Y.; Uemura, S. In *Topics in Current Chemistry: Organoselenium Chemistry*; Wirth, T., Ed.; Springer-Verlag: Berlin, 2000; Vol. 208, pp 201−233.

Scheme 5

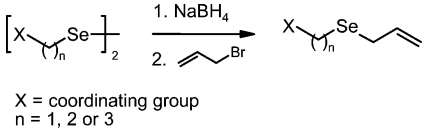


Table 2. Relative Catalytic Activity of Allyl Selenides **17**−**26** in the BnSH−TBHP System[a]

	catalyst X–$(CH_2)_n$–$SeCH_2CH{=}CH_2$		
no.	X	*n*	$t_{1/2}$ (h)
17	MeO_2C	1	28
18	MeO_2C	2	23
19	AcNH	2	29
20	AcNH	3	7.7
21	PhC(=O)NH	3	5.6
22	MeOC(=O)NH	3	9.2
23	CF_3C(=O)NH	3	6.9
24	HO	2	7.7
25	HO	3	4.8
26	HO	4	9.8

[a] Reactions were performed with BnSH (0.031 M), TBHP (0.043 M), and the catalyst (0.031 M) in CH_2Cl_2−MeOH (95:5) at 18 °C.

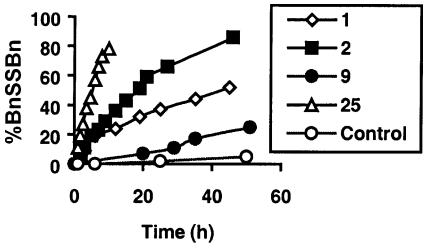
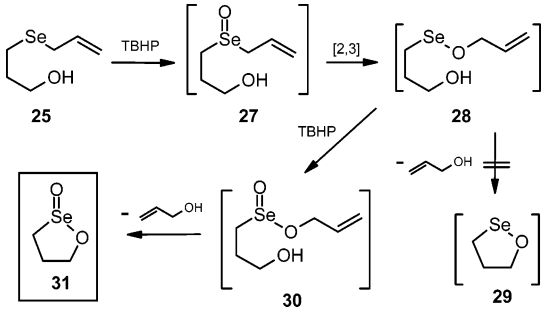


Figure 1. Rates of formation of BnSSBn from oxidation of BnSH (0.031 M) with 90% aqueous TBHP (0.043 M) in the presence of catalysts **1**, **2**, **9**, and **25** (0.0031 M) in CH_2Cl_2−MeOH (95:5) at 18 °C.

(shorter half-lives in the model system) than the corresponding diselenides in Table 1. Only in the case of the acetamido derivatives **15** and **20** was the diselenide slightly more active than its allyl selenide counterpart ($t_{1/2}$ = 6.0 and 7.7 h, respectively). It is evident that all of the allyl selenides in Table 2 displayed greater activity than Ebselen ($t_{1/2}$ = 42 h) and all except **17**−**19** afforded shorter half-lives than selenenamide **2** ($t_{1/2}$ = 18 h). Alkyl allyl selenides containing free carboxylic acid groups proved extremely malodorous and were not studied further. In contrast, allyl amidopropyl selenides **20**−**23** all produced much shorter $t_{1/2}$ values (in the range 5.6−9.2 h) than **17**−**19**. The improved behavior of **20**−**23** was perhaps predictable in view of the numerous studies indicating the importance of coordinating nitrogen substituents in enhancing the catalytic activity of diaryl diselenides[8] and related selenium compounds.[9] On the other hand, the similar use of hydroxyl groups as coordinating substituents in GPx mimetics has been little studied, except for a recent investigation of hydroxyl-containing diaryl diselenides by Wirth.[8f] Thus, we were surprised to observe that the ω-hydroxyalkyl allyl selenides **24**−**26** all displayed remarkably short half-lives in the model assay, with the 3-hydroxypropyl derivative **25** affording the greatest catalytic activity ($t_{1/2}$ = 4.8 h) of all of the compounds studied in Tables 1 and 2. This is illustrated in Figure 1, where a plot of the % yield of BnSSBn versus time is shown for the standard assay conditions performed in the presence of 10 mol % of **1**, **2**, **9**, **25**, and no catalyst (control).

The unexpectedly high activity of allyl selenide **25** as compared to the corresponding bis(3-hydroxypropyl) diselenide

Scheme 6



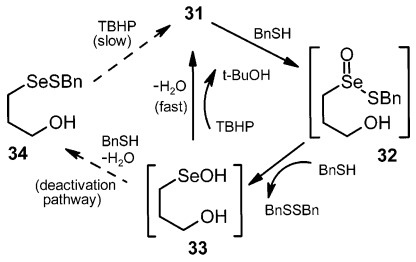
(**9**) prompted a further investigation into the mechanisms by which these two compounds catalyze the model reaction of TBHP with BnSH. As expected, the selenide **25** was inert toward BnSH in the absence of an oxidant. However, we observed that the oxidation of selenide **25** with excess TBHP in deuteriochloroform in the absence of BnSH was complete in less than 15 min when monitored by ^{1}H NMR spectroscopy. The corresponding selenoxide **27** was not detected in the oxidation of selenide **25**, presumably because of its even more rapid [2,3]-sigmatropic rearrangement to the selenenic ester **28** (Scheme 6). The latter product was too unstable to isolate, but when generated from **25** and 1 equiv of *m*-CPBA, a downfield shift of the allyl signals in the ^{1}H NMR spectrum (relative to those in **25**) was consistent with the rearrangement of an *Se*-allyl to an *O*-allyl species. When **25** was oxidized with excess TBHP, it afforded the cyclic seleninate ester **31**, which was isolated in nearly quantitative yield. Because neither **31** nor allyl alcohol was detected when selenide **25** was oxidized with 1 equiv of *m*-CPBA, we conclude that the cyclization does not take place directly from selenenate ester **28** to produce **29**, but instead requires further oxidation to the corresponding seleninate ester **30**, prior to spontaneous cyclization to 1,2-oxaselenolane *Se*-oxide (**31**) (Scheme 6). The novel cyclic seleninate ester **31** proved to be a stable product that was fully characterized (see Experimental Section). Only a few cyclic seleninates have been reported to date,[23] all of which contain stabilizing substituents or other rings fused to the cyclic seleninate moiety. It therefore appears that **31** is the first example of a simple unsubstituted monocyclic seleninate ester.

The above experiments established that allyl selenide **25** is rapidly oxidized to the cyclic seleninate **31** in the presence of excess TBHP. In the next stage of the catalytic cycle, in the presence of BnSH, we postulate that **31** reacts with the thiol to produce the thioseleninate **32**, followed by further thiolysis[24] to afford the selenenic acid **33**[25] and BnSSBn. The latter intermediate then undergoes oxidation to the corresponding seleninic acid, followed by cyclization (or vice versa), to regenerate **31** as shown in Scheme 7. The following evidence supports this mechanism. First, we subjected authentic cyclic seleninate **31** to the usual assay conditions with TBHP and BnSH, and observed a half-life ($t_{1/2}$ = 2.5 h) that was even shorter than the one measured with selenide **25**. Second, **31** was

(23) For fused-ring and substituted 1,2-oxaselenolane *Se*-oxides, see: (a) Rabelo, J.; van Es, T. *Carbohydr. Res.* **1974**, *32*, 175. (b) Kawashima, T.; Ohno, F.; Okazaki, R. *J. Am. Chem. Soc.* **1993**, *115*, 10434. (c) Lindgren, B. *Chem. Scr.* **1980**, *16*, 24. A Δ^4-1,2-oxaselenane *Se*-oxide ring system is also known: (d) Mock, W. L.; McCausland, J. H. *Tetrahedron Lett.* **1968**, 391.

(24) (a) Kice, J. L.; Lee, T. W. S. *J. Am. Chem. Soc.* **1978**, *100*, 5094. (b) Kice, J. L.; Purkiss, D. W. *J. Org. Chem.* **1987**, *52*, 3448.

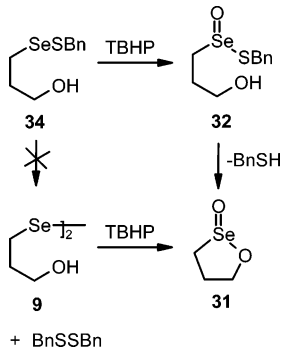
Scheme 7



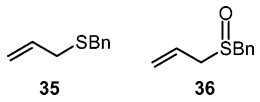
inert toward methanol and TBHP in the absence of the thiol, thus ruling out ring-opening of **31** by the solvent or by TBHP to produce the corresponding methyl ester or *tert*-butyl perester, respectively, as the first step of the catalytic cycle. Furthermore, when either allyl selenide **25** or cyclic seleninate ester **31** was used in the assay and the reaction was allowed to go to completion, **31** was the principal selenium-containing product, along with a smaller amount of the selenenyl sulfide **34**. Thus, while **25** is rapidly consumed in the early stages of the reaction, **31** is continuously regenerated.

The key role of selenenyl sulfides in the catalytic cycles both of GPx (see Scheme 1) and of synthetic mimetics such as Ebselen (see Scheme 2) prompted further study of the byproduct **34**. An authentic sample of selenenyl sulfide **34** was prepared (vide infra) and assayed in the usual model system. Surprisingly, **34** displayed $t_{1/2} = 35$ h, ca. 14 times longer than that measured with the cyclic seleninate **31** ($t_{1/2} = 2.5$ h). This effectively rules out any significant role of **34** in the catalytic cycle shown in Scheme 7 and indicates that its formation comprises a deactivation pathway in the cycle. It will be recalled that selenocystine **16** also produced a relatively inert selenenyl sulfide intermediate under the conditions of Table 1 (Scheme 3). This is noteworthy in view of the key role that selenenyl sulfides are reported to play in the catalytic cycles of other selenium-based antioxidants. When **31** was treated with an excess of BnSH in the absence of an oxidant, it was rapidly converted into the selenenyl sulfide. This reaction thus provides a convenient source of authentic **34**. Moreover, it is consistent with the mechanism in Scheme 7, where the absence of an oxidant would preclude the recycling of intermediate **33** back to **31** and result in the accumulation of **34**. We also observed that the oxidation of an authentic sample of selenenyl sulfide **34** with excess TBHP in the absence of BnSH slowly regenerated **31** along with BnSSBn. Thus, even when the deactivation pathway in Scheme 7 is followed, catalytic activity is gradually restored by the slow oxidation of **34** back to **31**. This process presumably proceeds via the oxidation of **34** to thioseleninate **32**, resulting in re-entry into the main catalytic cycle of Scheme 7. When the oxidation of **34** is carried out in the absence of the thiol, formation of **31** probably ensues from the slow cyclization of **32**, followed by catalytic oxidation of the byproduct BnSH to the corresponding disulfide (Scheme 8). An alternative mechanism for the oxidation of **34** to **31** is disproportionation of **34** into the corresponding diselenide **9** and BnSSBn (Scheme 8), followed by oxidation of **9**, as in the case of the diselenide shown in path B of the Ebselen catalytic cycle in Scheme 2. However, we were unable to detect the formation of **9** during the reduction of TBHP with BnSH in the presence of catalytic amounts of either **31** or **34**. Because the low reactivity of the diselenide under these conditions would presumably result in its accumulation, its absence suggests that disproportionation of the selenenyl sulfide is not a major pathway in the regeneration of **31** from **34**.[26]

Scheme 8



When the reaction of BnSH with excess TBHP in the presence of 10 mol % of **25** was performed in the usual manner and volatile material was removed in vacuo, we also detected the presence of small amounts (ca. 3% based on BnSH and 30% based on **25**) of allyl benzyl sulfide (**35**), in addition to the products noted above. Longer reaction times resulted in the further oxidation of **35** to the corresponding sulfoxide **36**, which was isolated. The formation of sulfide **35** can be rationalized by the nucleophilic substitution reaction (possibly S_Ni) of BnSH with **27**, **28**, or **30** to afford **35** and the selenenic acid **33**, or its corresponding seleninic acid, respectively. Because of side reactions leading to the relatively inert selenenyl sulfide **34** and, to a lesser extent, the byproducts **35** and **36**, the formation of BnSSBn is not quantitative, even after the complete consumption of BnSH. Significant amounts of sulfide **35** and sulfoxide **36** were also produced when allyl selenides **17** and **18** were employed as the catalyst.



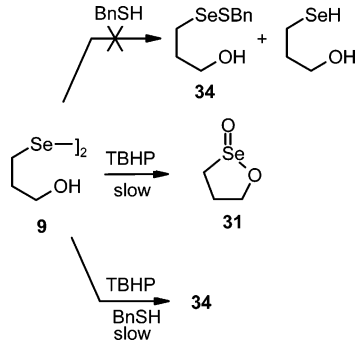
In view of the disparity in catalytic activity between selenide **25** and its diselenide counterpart **9**, we further investigated the role of the latter in catalyzing the oxidation of BnSH with TBHP. Several mechanisms have been proposed for the catalytic activity of diaryl diselenides.[7b,8] In principle, either of two initial processes can convert the diselenide into intermediates that are part of the redox cycle shown in Scheme 1 for GPx. First, oxidation of the diselenide could produce an unstable selenenic acid[25] (or anhydride), which could react further as in Scheme 1. Alternatively, entry into the catalytic cycle could occur from the reaction of the diselenide with the thiol prior to oxidation, thus affording the corresponding selenol and selenenyl sulfide, species that also propagate the catalytic cycle in Scheme 1.

When diselenide **9** was treated with an equimolar amount of BnSH in the absence of TBHP in deuteriochloroform, NMR

(25) In general, selenenic acids are too unstable to isolate. However, a highly hindered, isolable selenenic acid was recently reported, whose generation from the corresponding selenol and subsequent reactions with a dithiol were analogous to those in Scheme 1. See: (a) Goto, K.; Nagahama, M.; Mizushima, T.; Shimada, K.; Kawashima, T.; Okazaki, R. *Org. Lett.* **2001**, *3*, 3569. For other reports of the characterization of selenenic acids and related compounds, see: (b) Reich, H. J.; Jasperse, C. P. *J. Org. Chem.* **1988**, *53*, 2389. (c) Reich, H. J.; Willis, W. W., Jr.; Wollowitz, S. *Tetrahedron Lett.* **1982**, *23*, 3319.

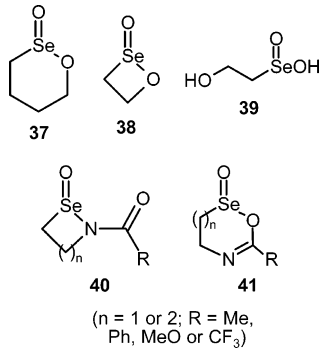
(26) Gradual disproportionation of **34** to BnSSBn and diselenide **9** does, however, occur when **34** is stored under ambient conditions.

Scheme 9



spectroscopy showed no formation of the selenenyl sulfide **34** even after 1 week at room temperature. This rules out the thiol−selenol exchange process shown in Scheme 9 as the initial step in the catalytic cycle of **9**. The reaction of **9** with excess TBHP and no thiol was monitored similarly. As compared to the rapid oxidation of selenide **25** (complete in <15 min; vide supra) under similar conditions, the oxidation of **9** was considerably slower, and even after 5 h, ca. 20% of the unreacted diselenide persisted in the reaction mixture. During this time, the diselenide was gradually transformed into the cyclic seleninate **31**. Moreover, when 10 mol % of the diselenide **9** was treated simultaneously with BnSH and excess TBHP in deuteriochloroform, a very slow oxidation of the thiol to BnSSBn was observed, requiring ca. 3 days to go to 50% completion under these conditions. We also observed that in the latter experiment, **9** was unexpectedly converted into the relatively inactive selenenyl sulfide **34** instead of the strongly catalytic seleninate ester **31** that had been formed in the absence of the thiol (Scheme 9). It therefore appears that the poor catalytic activity of diselenide **9**, as compared to that of the selenide **25**, can be attributed to the slow initial oxidation of **9**, as well as to its subsequent conversion into the relatively inactive selenenyl sulfide **34** instead of the cyclic seleninate ester **31** that is produced from selenide **25**.[27]

We also considered the possibility that the novel cyclic seleninate esters **37** and **38** might be implicated in the catalytic cycles involving allyl 4-hydroxybutyl and 2-hydroxyethyl selenides (**26** and **24**, respectively). When selenide **26** was oxidized with excess TBHP, **37** was obtained as expected, while the similar oxidation of **24** afforded the corresponding ω-hydroxyseleninic acid **39**.[28] Presumably, the strain in the oxaselenetane ring prevents the facile cyclization of **39** to **38**. The lower catalytic activities of **24** and **26** as compared to that of **25** indicate that the 3-hydroxypropyl derivative **25** has the optimum chain length and the cyclic seleninate **31** has the optimum ring size for catalytic activity. Attempts to isolate analogous cyclic seleninamides **40** or their isomers **41** from the oxidation of allyl amidoalkyl selenides **19**−**23** were unsuccessful, but it is reasonable to suppose that the corresponding cyclic intermediates play a similar role in the manifestation of catalytic activity in amido-substituted allyl selenides.



Conclusions

We have found that aliphatic diselenides, with the exception of the acetamido derivative **15**, are generally poor catalysts for the oxidation of BnSH with TBHP, as determined by the relatively long half-lives of these oxidations. On the other hand, allyl selenides **17**−**26** proved considerably more effective in this regard, with the 3-hydroxypropyl derivative **25** displaying exceptional activity. We have established that selenide **25** serves as a procatalyst by undergoing a series of rapid oxidation and [2,3]sigmatropic rearrangement steps, ultimately leading to the novel cyclic seleninate ester **31** (Scheme 6). The latter was implicated as the true catalyst in the process, functioning via the pathway shown in Scheme 7. The corresponding 2-hydroxyethyl and 4-hydroxybutyl analogues **24** and **26** function similarly, by generating the seleninic acid **39** and cyclic seleninate **37**, respectively, upon oxidation with TBHP. However, the longer half-lives obtained with the latter derivatives indicate that the 3-hydroxypropyl analogue **25** has the optimum chain length and the corresponding cyclic seleninate **31** has the optimum ring size for catalytic activity. The cyclic seleninates **31** and **37** are novel compounds that were isolated and fully characterized. They represent the first reported examples of unsubstituted cyclic seleninate esters. In contrast to the catalytic cycle of GPx and many of its other mimetics, the corresponding selenenyl sulfide **34** does not play a significant role in the catalytic cycle of **31**. Indeed, the formation of **34** represents a competing deactivation pathway in this process.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for financial support.

Supporting Information Available: Experimental procedures, NMR data for new compounds, and kinetic plots for the oxidations of BnSH with TBHP in the presence of diselenide and allyl selenide catalysts (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) The plots corresponding to several of the diselenides listed in Table 1 (most notably, see **10** and **13** in Figure 6, **14** in Figure 7, and **16** in Figure 8 in the Supporting Information) indicate an induction period, during which the oxidation of BnSH to BnSSBn is very slow. This is consistent with the slow initial oxidation of the diselenide, eventually resulting in the formation of catalytic selenium species. In at least some cases, the latter are relatively poor catalysts (e.g., the selenenyl sulfide derivatives of **9** or **16**), resulting in relatively slow reaction rates even in the later stages of the process. Compound **16** gives a slightly slower oxidation rate in the initial stages than was observed in the control reaction for reasons that are not clear.

(28) A reviewer has pointed out the interesting possibility that the diastereotopic methylene hydrogens in the ^{1}H NMR spectrum of seleninic ester **39** in CD_3OD (see Supporting Information, p 53) could be the result of spontaneous in situ formation of its CD_3 ester, because the acid itself would be expected to undergo rapid epimerization of the chiral Se atom through proton exchange that would render each pair of methylene protons equivalent. We note, however, that the ^{13}C NMR spectrum (see Supporting Information, p 54) does not show a signal attributable to the CD_3 ester moiety, although it could conceivably be obscured by the solvent signal. Moreover, the ^{1}H NMR spectrum obtained in D_2O (see Supporting Information, p 56), where ester formation is precluded, still shows methylene signals that are more complex than is expected under conditions of rapid proton exchange. Thus, while a more detailed NMR study of this compound is warranted, the structure **39** is in accord with its ^{13}C, ^{77}Se NMR, IR, MS, and analytical data (see Supporting Information, pp 11−12 and 54−55).