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Chain-Breaking Antioxidants

Chain-Breaking Phenolic 2,3-Dihydrobenzo[b]selenophene Antioxidants – Proximity Effects and Regeneration Studies

Vijay P. Singh,*[a,b] Jiajie Yan,[b] Jia-fei Poon,[b] Paul J. Gates,[c] Ray J. Butcher[d] and Lars Engman*[b]

Abstract: Phenolic 2,3-dihydrobenzo[b]selenophene antioxidants carrying the OH-group ortho (**9**), meta (**10**, **11**) and para (**8**) to the Se were prepared by seleno-Claisen rearrangement/intramolecular hydroselenation. Meta-isomer (**11**) was studied by X-ray crystallography. The radical-trapping activity and regenerability of compounds **8-11** were evaluated using a two-phase system where linoleic acid was undergoing peroxidation in the lipid phase while regeneration of the antioxidant by co-antioxidants (N-acetylcysteine, glutathione, dithiothreitol, ascorbic acid, tris(carboxyethyl)phosphine hydrochloride) was ongoing in the aqueous layer. Compound **9** quenched peroxyl radicals more efficiently than α-tocopherol. It also provided the most long-lasting antioxidant protection. With thiol co-antioxidants it could inhibit peroxidation for more than five-fold longer than the natural product. Regeneration was more efficient when the aqueous phase pH was slightly acidic. Since calculated O-H bond dissociation energies for **8-11** were substantially larger than for α-tocopherol, an antioxidant mechanism involving O-atom transfer from peroxyl to selenium was proposed. The resulting phenolic selenoxide/alkoxyl radical would then exchange a hydrogen atom in a solvent cage before antioxidant regeneration at the aqueous lipid interphase.

Introduction

Although novel findings concerning the uptake, transport, metabolism and function as a regulator of transduction and gene expression continue to appear in the literature,[1] the role of α-tocopherol (**1**) as the most important lipophilic chain-breaking antioxidant in man is undisputed.[2] The stoichiometric number for α-tocopherol is two. This means that it can quench two peroxyl radicals before it is converted into non-radical products. Since the compound cannot be biosynthesized, regeneration would seem imperative. In biological membranes, this is thought to occur at the aqueous-lipid interphase by formal donation of a hydrogen atom from water soluble ascorbate (AscH⁻) to the tocopheroxyl radical (α-TO˙), the primary product in the quenching process (Figure 1).[3,4]
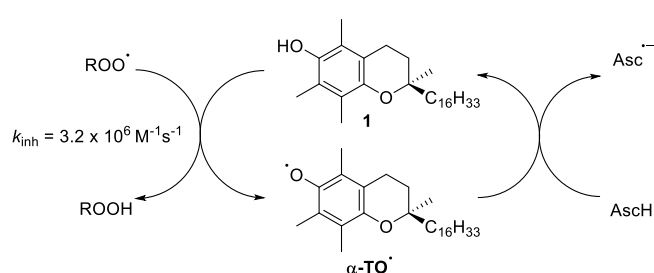

Figure 1. Regeneration of α-tocopherol by ascorbate at the aqueous lipid interphase in a membrane

Since α-tocopherol is regenerable and highly reactive it has presently the status of a benchmark in the search for novel synthetic chain-breaking antioxidants. Indeed, newly prepared compounds such as pyrimidinols[5] and alkyltellurophenols[6] can outperform α-tocopherol when it comes to reactivity. Some of these compounds are regenerable in simple model systems, but, so far, none has proven regenerable in vivo.

Traditionally, the key to improve the reactivity of phenolic antioxidants has been to introduce substituents that could

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stabilize the developing phenoxyl radical.[7] Obviously, the chromane oxygen in α-tocopherol has such a function (Figure 1).[8] This oxygen has been replaced by other chalcogens (S, Se) on the basis that the heavier chalcogens would also stabilize the developing phenoxyl radical.[9] However, both the racemic sulfur (**2a**; $k_{inh} = 1.3 \times 10^6$ M^{-1}s^{-1})[10] and selenium (**2b**; $k_{inh} = 1.2 \times 10^6$ M^{-1}s^{-1})[11] analogues turned out to be slightly less reactive than the parent. This was also true for the 4-thiachromanol derivative **3** ($k_{inh} = 1.3 \times 10^6$ M^{-1}s^{-1}).[12] Annulation of a thiophene to tocopherol turned out to be more rewarding. Compound **4** ($k_{inh} = 9.8 \times 10^6$ M^{-1}s^{-1}) quenched peroxyl radicals three times faster than **1**.[13] Non-covalent S···O interactions in the phenoxyl radical corresponding to **4** was proposed to account for the rate-acceleration.

2a X = S
2b X = Se

3

4

5

6
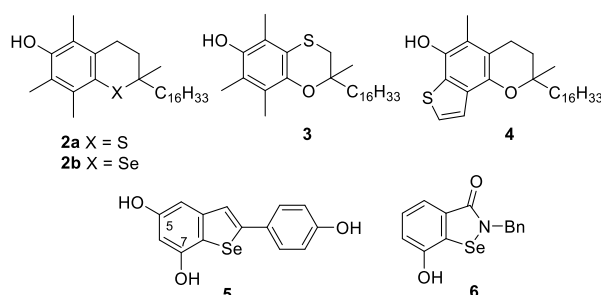
In resveratrol-derived polyphenolic benzo[*b*]selenophene antioxidant **5**, the heteroatom caused a considerable weakening of the O-H bond in both positions 5 and 7.[14] As compared to the parent, a five-fold increase in reactivity was observed ($k_{inh} = 8.8 \times 10^5$ M^{-1}s^{-1}). Likewise, the close arrangement of Se and OH in ebselenol **6** imposes a chain-breaking activity on this compound in addition to its glutathione peroxidase (GPx)-like activity.[15]

Some time ago, we found that 2,3-dihydrobenzo[*b*]-selenophene-5-ol (**7**)[16] and the more readily available 2-methyl analogue **8** were highly regenerable chain-breaking antioxidants in the presence of *N*-acetylcysteine (NAC) as a co-antioxidant.[17] However, none of them ($k_{inh} = 3.8 \times 10^5$ M^{-1}s^{-1} for **8**) could quench lipid peroxyl radicals as efficiently as α-tocopherol. In the light of the results with compounds **4**-**6** it occurred to us that the placement of the phenolic group in position 5 may not be optimal.
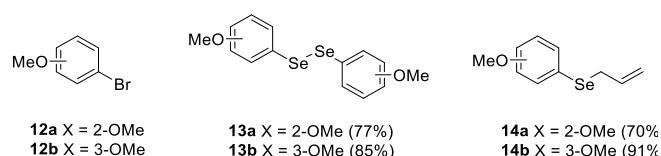

7

8

9

10

11
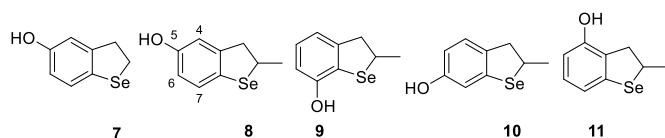
Described in the following is the synthesis of the novel benzo[*b*]dihydroselenophenes **9**-**11**, carrying the phenolic group in positions 7, 6, and 4, respectively, and an evaluation of their reactivity and regenerability in comparison with **8**.

Results and Discussion

Synthesis: The desired phenolic hydroxydihydrobenzo-selenophenes **9**-**11** were synthesized, with slight modifications, according to a previously reported procedure.[17] Key to the preparation was a seleno-Claisen rearrangement[18] of allyl aryl selenides. The diaryl diselenides **13a**-**b**[19] were prepared in good

yields as precursors thereof from bromoanisoles **12a**-**b** by conversion to Grignard reagents, insertion of elemental selenium into the carbon-magnesium bond and final air-oxidation of the resulting magnesium areneselenolates. Sodium borohydride (NaBH$_4$) reduction of the diaryl diselenides **13a**-**b**, followed by the addition of allyl bromide, returned the corresponding allylic selenides **14a**-**b** in 70% and 91% yield, respectively.

12a X = 2-OMe
12b X = 3-OMe

13a X = 2-OMe (77%)
13b X = 3-OMe (85%)

**14a** X = 2-OMe (70%)
14b X = 3-OMe (91%)

Heating of **14a** for 3 h in quinoline at 230 °C in a microwave reactor afforded 2,3-dihydrobenzoselenophene **15a** as a result of a Claisen rearrangement followed by an intramolecular hydroselenation (Scheme 1). Unfortunately, the desired **15a** was formed as the minor product (25%) in the reaction in addition to diselenide **13a** (50%). Since the two compounds almost co-elute when chromatographed, a mixture enriched in **15a** was taken to the next step (vide infra).
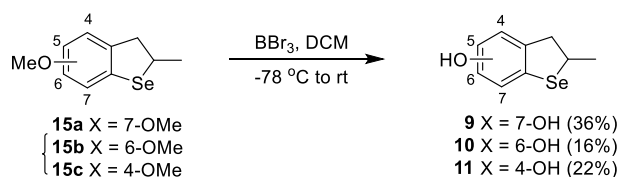

14a

15a (25%)
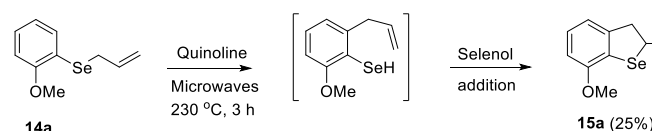
Scheme 1. Seleno-Claisen rearrangement for the preparation of **15a**

In a similar fashion, allylic selenide **14b** was heated in the microwave cavity. In this case, both of the two possible rearrangement products **15b** and **15c** were formed (Scheme 2). The yield was 40% and again the corresponding diselenide, **13b** was formed as the major product (50% yield) in the reaction. As revealed by ^{77}Se-NMR spectroscopy, **15b** and **15c** were formed in equal amounts (see the Supporting Information for ^{77}Se-NMR spectrum).

14b

15b

15c
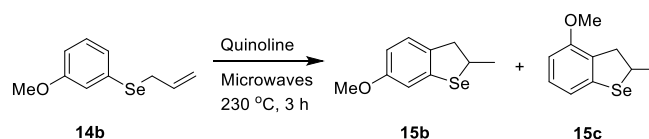
Scheme 2. Formation of **15b** and **15c** in the microwave-assisted reaction of selenide **14b**

All our attempts to purify the two compounds by column chromatography were unsuccessful. Therefore, the mixture was subjected to BBr$_3$-induced *O*-demethylation in DCM at -78 °C (Scheme 3).

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Scheme 3. Synthesis of hydroxydihydrobenzoselenophenes **9-11**

Figure 3. Packing diagram of **11** showing intermolecular hydrogen-bondin Se···H between the Se atom and the OH of a neighbouring molecule

Although the isolated yields were not impressive, we were pleased to find that compounds **10** and **11** were separable by silica gel column chromatography using DCM as an eluent. Compounds **9** (prepared by demethylation of **15a**) **10** and **11** were fully characterized by ^{1}H-, ^{13}C- and ^{77}Se- NMR spectroscopy and the identity of **11** was confirmed by X-ray crystallography.

Structure: The structure of dihydrobenzoselenophene **11** was determined by X-ray crystallography (Figure 2). Square-shaped colorless crystals of **11** suitable for X-ray crystallographic analysis were obtained by slow evaporation of a CH_2Cl_2-solution at room temperature. The coordination geometry around the Se atom is V-shaped with the bond angle C1—Se—C8 = 88.12(9)°. The bond lengths of the C1—Se and Se—C8 covalent bonds are 1.909(2) and 1.980(2) Å, respectively.

Inhibition studies in a two-phase lipid peroxidation system Dihydrobenzoselenophenes **8-11** were evaluated for the capacity to inhibit azo-initiated peroxidation of linoleic acid in a stirred two-phase chlorobenzene/water system open to the atmosphere. In the lipid layer, linoleic acid was stimulated by an azo-initiator (AMVN; azo-bis-dimethylvaleronitrile) to undergo oxidation. The lipid-soluble antioxidant could be regenerated by a water-soluble co-antioxidant contained in the upper phase (Figure 4).[21] The progress of peroxidation was monitored by sampling o the organic phase and analysis by HPLC with UV detection o conjugated diene at 234 nm.
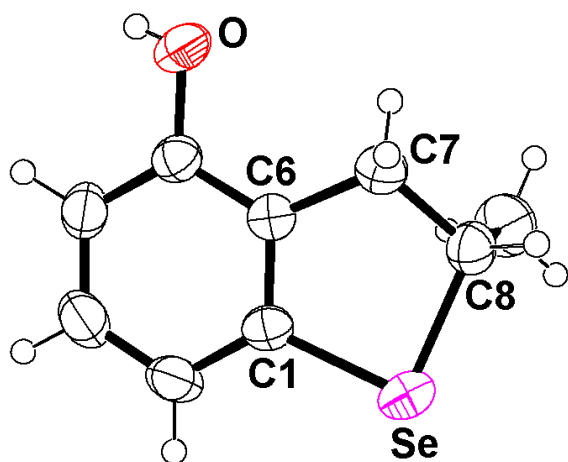

Figure 2. ORTEP diagram of **11**. Thermal ellipsoids are set at 50% probability. Significant bond lengths [Å] Se—C1 1.909(2); Se—C8 1.980(2), and angles [°] C1—Se1—C8 88.12(9)
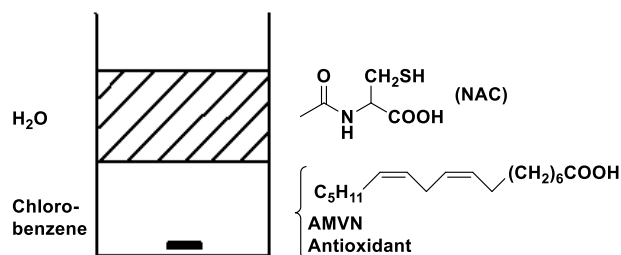
Figure 4. Two-phase system used for studying regeneration of antioxidants

The packing diagram of **11** clearly reveals an intermolecular hydrogen bonding interaction (Se···H 2.795 Å) between the Se atom and the H atom of a phenolic group in a neighbouring molecule (Figure 3). The distance is significantly shorter than the sum of the van der Waals radii of the Se and H atoms (3.10 Å).[20]
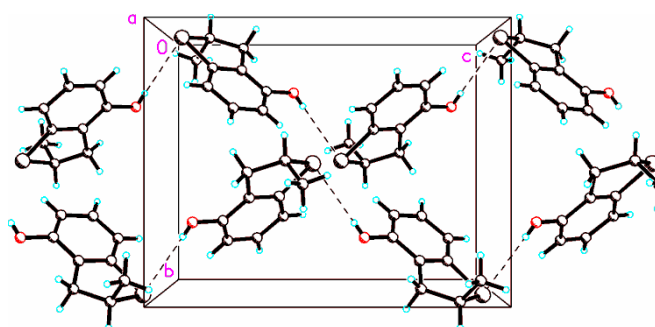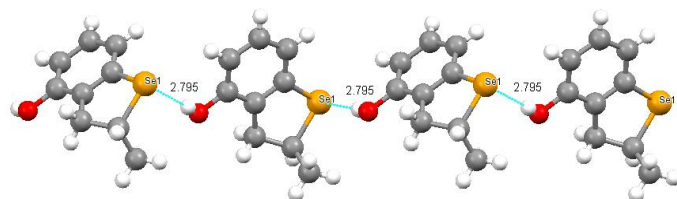
α-Tocopherol was used as a reference. In the absence of any co-antioxidant, it inhibited peroxidation efficiently with an inhibited rate of peroxidation R_{inh} = 28 µM/h. The inhibition time recorded (T_{inh}) was 109 minutes. Then the rate of conjugated diene formation suddenly increased to a value corresponding to uninhibited peroxidation (R_{uninh} = 544 µM/h; Table 1, Figure 5). R_{inh} and T_{inh} for α-tocopherol (40 µM) were also recorded in the presence of the following aqueous-phase co-antioxidants: *N-*

acetylcysteine (NAC), glutathione (GSH), dithiothreitol (DTT), L-ascorbic acid (AscOH) and tris(2-carboxyethyl)phosphine hydrochloride (TCEP). However, in none of these experiments did the values differ much from those recorded in the above control experiment with pure water (Table 1). Thus, α-tocopherol is not regenerable under the conditions of our assay. In contrast, T_{inh} for dihydrobenzoselenophenes **8**-**11** was always extended in the presence of these co-antioxidants. The four organoseleniums represent compounds where the OH is oriented both ortho (**9**), meta (**10** and **11**) and para (**8**) to selenium. The R_{inh} and T_{inh} data presented in Table 1 clearly indicate that the two meta-substituted compounds are outperformed by the ortho/para-substituted ones.

Compound **11** was the least regenerable compound. With none of the five co-antioxidants did T_{inh} exceed 200 min. Compound **10** offered a slightly better protection. In the presence of ascorbic acid, T_{inh} was 301 min. Inhibited rates of peroxidation with **10** and **11** were higher than recorded with α-tocopherol. They are therefore intrinsically poorer radical-trapping agents than the natural product. Compound **9** showed the lowest R_{inh}-value (9 μM/h with GSH or no co-antioxidant) of all the antioxidants studied. Also, it was the most regenerable one. With the thiol co-antioxidants GSH and DTT, compound **9** inhibited peroxidation for 546 and 588 min, respectively. Compound **8** also offered both long-lasting and efficient antioxidant protection. For example, with aqueous-phase NAC, T_{inh} was notably longer (504 min) than recorded with **9** (420 min). In most other experiments, T_{inh}-values for **8** were shorter and R_{inh}-values were larger than recorded with **9** (Table 1, see page 9).
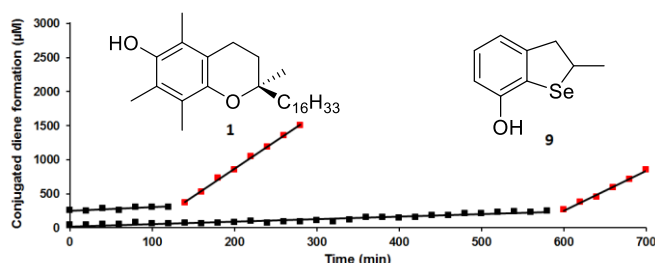

Figure 5. Conjugated diene concentration vs time recorded with dihydroselenophene **9** and α-tocopherol **1** (40 μM) as antioxidants in the chlorobenzene layer and DTT (0.5 mM) in the aqueous phase

Curious about what was going on in the aqueous phase during a normal peroxidation experiment, thiol consumption was followed according to a recently described procedure.[22] By using NAC as a co-antioxidant, the aqueous layer was sampled every 30 min and the remaining thiol was allowed to react with bis-4-pyridyl disulfide. The amount of pyridine-4-thiol formed by thiol exchange was then determined spectrophotometrically at 324 nm and used as a measure of the NAC concentration. As shown in Table 2, NAC-consumption is low (33 μM/h) when α-tocopherol is used and in the same range as in the control experiment without any lipid-phase antioxidant. This is because NAC reacts only slowly with linoleic acid hydroperoxide formed. In the presence of **8**-**11**, NAC is consumed at a considerably faster rate (120-158 μM/h). This is because the organoselenium compounds are oxidized by

hydroperoxide to the corresponding selenoxides and these are readily reduced by thiol with disulfide formation. That NAC-consumption was slower with **8** than with **9** is in line with the longer T_{inh} recorded with the former. It is also noteworthy that the aqueous-phase thiol is all consumed at the end of the inhibited phase of peroxidation. Thus, the availability of thiol seems to be limiting for the duration of the antioxidant protection (T_{inh}) for compounds **8** and **9**. This is not the case with compounds **10** and **11**. The reason may be that these compounds react only slowly and incompletely with linoleic acid hydroperoxide. In order to find out about the capacity of these compounds to catalyze the reduction of hydroperoxides in the presence of thiols (GPx-like activity) the initial rates (v_0) for the reduction of H_2O_2 by PhSH in the presence of dihydrobenzoselenophenes **8**-**11** were determined in methanol by monitoring the formation of diphenyl disulfide (PhSSPh) by UV spectroscopy at 305 nm for the initial 10 seconds of reaction.

Table 2. NAC-consumption in the aqueous phase during peroxidation inhibited by antioxidants, GPx-like activity as determined by the thiophenol assay and calculated O-H bond dissociation energies (BDE_{O-H}) of **1** and **8**-**11**.

	antioxidants				
	8	**9**	**10**	**11**	**1**
Consumption of NAC (μM/h)[a]	120 ± 7	139 ± 4	158 ± 3	133 ± 1	33 ± 4
GPx-like activity (μM/min)[b]	1.1 ± 0.4	2.7 ± 0.8	0.3 ± 0.1	inactive	----
Calculated BDE_{O-H} (kcal/mol)	82.1 81.6[c]	83.9	85.3	86.0	77.1[c]

[a]Consumption of NAC with linoleic acid + AMVN in the lipid phase and with pure chlorobenzene were 37 ± 8 μM/h and 27 ± 5 μM/h, respectively. Errors correspond to ± SD for triplicates. [b]Initial rates of PhSSPh formation were corrected for the spontaneous oxidation of PhSH induced by H_2O_2 (v_0 = 0.7 0.2 μM/min). Errors correspond to ± SD for triplicates. [c]Experimental value from ref 17.

Compound **9** was found to be the best catalyst, three times more reactive than diphenyl diselenide (0.9 ± 0.2 μM/min) used as reference. Compound **8** was slightly more active than the reference compound. Compound **10** turned out to be a very poor GPx-mimic while **11** was essentially inactive. This is because these compounds react only very slowly in the rate-determining oxidation step of the GPx-mechanism.

The fact that regeneration of our antioxidants has to occur across an aqueous-lipid interphase (Figure 4) is a complicating factor. For example, the protonation state of the co-antioxidant (which is pH-dependent) could affect the local concentration of the compound at the interphase. The increased antioxidant reactivity of ascorbic acid in liposomes as compared to ascorbate has been rationalized in terms of a higher local concentration of the uncharged species.[23] Four out of five of our co-antioxidants are weak acids with similar pKa-values: 2.99 (TCEP), 3.24 (NAC), 3.53 (GSH) and 4.04 (AscOH). The 1.0 mM or 0.5 mM aqueous solutions of co-antioxidant used in the two-phase model are

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therefore all slightly acidic with similar but not identical pH (pH ca. 3.3 for 1.0 mM NAC). One of them (NAC) was also tested with antioxidant **9** at lower (pH = 2) and higher (pH = 5 and 7) pH. As shown in Table 3, the R_{inh}-values did not vary much. However, T_{inh} dropped markedly at pH = 5 and more so at pH = 7. This may be because deprotonation reduces the local concentration of the thiol at the aqueous-lipid interphase. A 0.5 mM aqueous solution of DTT is only slightly acidic (pH ca. 6.3). Judging from the long inhibition times recorded with compounds **8** and **9**, it therefore seems to be the co-antioxidant of choice if regeneration at physiological pH is required.

Table 3. Inhibited rates of peroxidation (R_{inh}) and inhibition times (T_{inh}) for antioxidant **9** with NAC as a co-antioxidant at pH = 2, 5 and 7.					
antioxidant **9**					
pH 2		pH 5		pH 7	
R_{inh}[a] (μM/h)	T_{inh}[b] (min)	R_{inh}[a] (μM/h)	T_{inh}[b] (min)	R_{inh}[a] (μM/h)	T_{inh}[b] (min)
19 ± 1	415 ± 6	17 ± 1	340 ± 9	14 ± 1	251 ±7

[a]Rate of peroxidation during the inhibited phase (uninhibited rate ca. 544 μM/h). [b]Duration of the inhibited phase of peroxidation. Reactions were monitored for 700 min. Errors correspond to ± SD for triplicates

Mechanistic Considerations: α-Tocopherol quenches peroxyl radicals by formal donation of a hydrogen atom to peroxyl radicals. The bimolecular rate constant for this process is high because the O-H bond dissociation energy, BDE_{O-H}, is low (77.1 kcal/mol). The strength of the O-H bond in compounds **8-11** was calculated in the gas phase at the M062X/aug-ccpVDZ level of theory as the energy difference between the optimized geometry of the molecule and the corresponding phenoxyl radical plus hydrogen atom.[13] The geometry of **11** was in good agreement with the X-ray structure (for example, the calculated bond lengths C1—Se (1.910 Å) and Se—C8 (1.985 Å) and the angle C1—Se—C8 (87.03°) were close to the experimental values shown in Figure 2). As shown in Table 2, phenolic compound **8**, carrying a para-Se substituent, has the weakest O-H bond (82.1 kcal/mol). Compound **9** with an ortho-arrangement of OH and Se has a ca. 2 kcal/mol stronger O-H bond while the BDE_{O-Hs} of meta-compounds **10** and **11** are still larger by ca. 1 and 2 kcal/mol, respectively. The relative strength of the O-H bonds in **8-11** is in accord with the substituent effects of selenium in phenols reported some time ago.[9] In meta-compounds **10** and **11** resonance stabilization of the phenoxyl radical is not possible. That **9** has a stronger O-H bond than **8** is likely due to the better radical stabilization offered by a para- as compared to an ortho-Se. It is clear from the optimized geometry of **9** that the O–H bond is pointing towards selenium in the most stable conformer to allow hydrogen bonding to the heteroatom. Also, we could not see any σ-hole in the phenoxyl radical corresponding to **9** which could be indicative of a non-covalent Se···O interaction. Why then is dihydrobenzoselenophene **9** a better radical-trapping agent than α-tocopherol? Since the O-H bond is 5 kcal/mol stronger (77.1 kcal/mol for the natural product) a direct hydrogen transfer

mechanism does not seem likely to be operative. We instead propose a mechanism similar to the one suggested for the action of alkyltelluro phenols (Scheme 4).[24] The first step would involve O-atom transfer from peroxyl radical (ROO·) to the selenium. In fact, the ortho-disposed OH-group may hydrogen bond to the peroxyl radical and facilitates this process. This would also explain the poorer quenching capacity of **8** where the OH is further away. The alkoxyl radical (RO·) and the phenolic selenoxide generated would then exchange a hydrogen atom in a solvent cage. At this point, the reactive peroxyl radical has been reduced to form a alcohol and a phenoxyl radical/selenoxide – a process which likely to be thermodynamically favoured. What follows next regeneration of the antioxidant. Reduction of selenoxide t selenide is a facile process and mild reducing agents such a thiols,[25] ascorbate[26] and phosphines[27] are known to bring abou such transformations. Reduction of phenoxyl radicals to pheno by the same reducing agents has less precedence in th literature. We speculate that one-electron reduction across a lipi aqueous interphase is occurring.
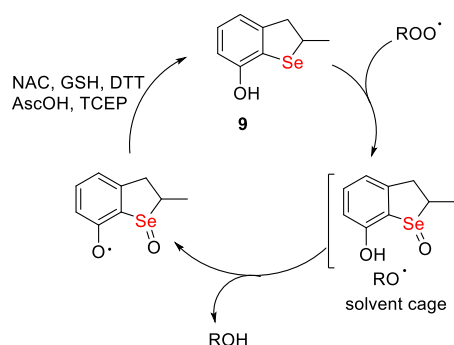
Scheme 4. Proposed catalytic cycle for quenching of peroxyl radicals dihydrobenzoselenophene **9**

Conclusion

We found already some ten years ago that 2,3 dihydrobenzoselenophene **8**, carrying an OH-group para t selenium, was a highly regenerable, chain-breaking antioxidan In the present work we have prepared three novel isomeri compounds **9-11** where the hydroxyl group is closer (ortho c meta) to the large heteroatom. When it comes to BDE_{O-H}, none c the novel compounds could match **8**. Nevertheless, ortho compound **9** turned out to be the most reactive radical-trappin agent in the series. It also provided the longest protection against lipid peroxidation in the presence of various aqueous-phase co-antioxidants. Furthermore, it showed the best GPx activity of all the organoseleniums. In fact, only very few selenium antioxidants are multifunctional in the sense that they can act both chain-breaking and peroxide decomposing.[15, 29] Initially, we were largely ignorant about the mechanism responsible for quenching of peroxyl radicals by **8**. In light of the results presented in this paper, conventional H-atom transfer from phenol to the peroxyl radical does not seem to be an important reaction with compounds **9-11**. Rather, an O-atom transfer mechanism, similar to the one

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proposed for alkyltelluro phenols, is likely to be operative. The close (ortho) arrangement of OH and Se has many advantages. Hydrogen bonding brings peroxyl radicals close to the hetero atom. Once oxygen transfer is complete, the resulting alkoxyl radical can abstract a hydrogen atom from the nearby phenolic moiety, before it diffuses out of the solvent cage. Whenever the alkoxyl radical escapes, new chain-reactions are started and some of the co-antioxidant is wasted in the reduction of selenoxide to selenide. The fact that the OH-bond is weaker in **8** than in **9** apparently does not compensate for the disadvantages caused by the distant arrangement of OH and Se.

Our initial experiments with compound **8** involved only NAC as an aqueous-phase co-antioxidant. We have now demonstrated that other mild reducing agents such as GSH, DTT, AscOH and TCEP can also regenerate our antioxidants across an aqueous-lipid interphase. Since some of these co-antioxidants are present in humans in substantial concentrations (GSH), our antioxidants may well turn out to be regenerable also in biological systems. More information concerning the regeneration process would be needed, though. We have demonstrated that antioxidant recycling with NAC is pH-dependent. Since "communication" between the lipid- and aqueous phases is important, antioxidant lipophilicity may also turn out to have a great effect on regenerability.

Experimental Section

Experimental Details. 3-Bromoanisole was purchased and used as such. ^{1}H and ^{13}C NMR spectra for all compounds prepared were recorded on 400 MHz ([1]H: 399.97 MHz; [13]C: 100.6 MHz) spectrometers, using the residual solvent peaks of CDCl$_3$ ([1]H: δ = 7.26 ppm; [13]C: δ = 77.0 ppm), as an indirect reference to TMS (δ = 0 ppm). ^{77}Se NMR spectra were recorded on 400 MHz ([77]Se: 76 MHz) spectrometers with Ph$_2$Se$_2$ (δ = 460 ppm) as an indirect reference to Me$_2$Se (δ = 0 ppm). Flash column chromatography was performed using silica gel (0.04-0.06 mm). Melting points are uncorrected. The high resolution mass spectra (HRMS) were obtained using a time of flight (TOF) instrument equipped with electron ionization (EI) operating in the positive ion mode. Tetrahydrofuran (THF) was dried in a solvent purification system by passing it through an activated alumina column before use.

Preparation of 2-bromoanisole (12a).[29] To a solution of 2-bromophenol (4.00 g, 2.50 mL, 23.12 mmol) in DMF (15 mL) was added K$_2$CO$_3$ (3.20 g, 23.12 mmol) and iodomethane (1.44 mL, 3.28 g, 23.12 mmol) at room temperature under inert atmosphere. Additionally, the reaction was stirred for overnight at the same temperature. The reaction mixture was poured into water (30 mL) and extracted with diethyl ether. The separated organic layers were combined, dried over anhydrous Na$_2$SO$_4$, and evaporated under reduced pressure. The crude was chromatographed on silica gel using 2% diethyl ether/n-pentane as eluent to afford the title compound as a colourless liquid. Yield: 3.69 g (85%). The ^{1}H and ^{13}C NMR spectra were in good agreement with literature and have been included in the Supporting Information.

Bis(2-methoxyphenyl) diselenide (13a).[19] A solution of **12a** (1.50 g, 8.02 mmol) in anhydrous THF (20 mL) was added dropwise with stirring to Mg turnings (0.192 mg, 8.02 mmol) activated with iodine at room temperature under an inert atmosphere. The reaction mixture was stirred until all magnesium had dissolved. Selenium powder (0.633 g, 8.02 mmol) was then added to the Grignard reagent formed. The mixture was further stirred at room temperature for 4 h and the resulting solution of magnesium areneselenolate was poured into water and kept open to air oxidation for approximately 1 h. The residue was extracted with diethyl ether. The separated organic layers were dried over anhydrous MgSO$_4$ and evaporated under reduced pressure to give yellow oil. The crude was chromatographed on silica gel using 2% diethyl ether/n-pentane as eluent to afford the title compound as a yellow crystalline solid. Yield: 1.15 g (77%); mp 84-86 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.91 (s, 6H), 6.81-6.90 (several peaks, 4H), 7.23 (t, J = 8.0 Hz, 2H), 7.56 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 56.1, 110.4, 118.9, 122.1, 128.3, 130.8, 157.0; ^{77}Se NMR

(76 MHz, CDCl$_3$): δ 333; HRMS (TOF MS EI[+]) m/z calcd for C$_{14}$H$_{14}$O$_2$Se$_2$ [M][+]: 373.9324; found: 373.9326.

Bis(3-methoxyphenyl) diselenide (13b).[19] Diselenide **13b** prepared from **12b** according to the procedure described for diselenide **13a** was obtained as a yellow liquid. Yield: 1.27 g (85%); ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.78 (s, 6H), 6.79 (d, J = 7.2 Hz, 2H), 7.18-7.21 (several peaks, 6H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 55.4, 114.0, 116.7, 123.7, 130.1, 132.0, 160.0; ^{77}Se NMR (76 MHz, CDCl$_3$): δ 465; HRMS (TOF MS EI[+]) m/z calcd for C$_{14}$H$_{14}$O$_2$Se$_2$ [M][+]: 373.9324; found: 373.9322.

Allyl 2-methoxyphenyl selenide (14a). Diselenide **13a** (1.12 g, 3.0 mmol) was dissolved in ethanol (20 mL) and kept at 0 °C under nitrogen while NaBH$_4$ (0.228 g, 6.0 mmol) was added. The mixture was then warmed to room temperature and stirred for another 30 min before addition of allyl bromide (0.726 g, 0.52 mL, 6.0 mmol). Stirring was continued for an additional 1 h at room temperature before work-up including addition of water and extraction with diethyl ether. The combined organic layers were dried over MgSO$_4$, and evaporated. Purification by chromatography using 2% diethyl ether/n-pentane as an eluent afforded the pure title compound as a colorless liquid. Yield: 0.96 g (70%); ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.45 (d, J = 7.6 Hz, 2H), 3.88 (s, 3H), 4.96-5.92 (several peaks, 2H), 5.96 (m, 1H), 6.86 (d, J = 7.2 Hz, 1H), 6.89 (m, 1H), 7.24 (m, 1H), 7.38 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 28.2, 55.9, 110.6, 117.2, 119.6, 121.5, 128.2, 132.3, 134.5, 158.1; ^{77}Se NMR (76 MHz, CDCl$_3$): δ 261; HRMS (TOF MS ES[+]) m/z calcd for C$_{10}$H$_{12}$OSe [M+H][+]: 228.0053; found: 228.0059.

Allyl 3-methoxyphenyl selenide (14b). Selenide **14b** synthesized from diselenide **13b** (1.40 g, 3.76 mmol), NaBH$_4$ (0.280 g, 7.52 mmol) and allyl bromide (0.65 mL, 7.52 mmol) according to the procedure described for the preparation of selenide **14a** was obtained as a colorless liquid. Yield: 1.55 g (91%); ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.54 (d, J = 7.6 Hz, 2H), 3.80 (s, 3H), 4.96-5.05 (several peaks, 2H), 5.96 (m, 1H), 6.79 (m, 1H), 7.05-7.09 (several peaks, 2H), 7.18 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 30.7, 55.4, 113.1, 117.1, 118.5, 125.4, 129.9, 131.2, 134.6, 159.8; ^{77}Se NMR (76 MHz, CDCl$_3$): 334; HRMS (TOF MS EI[+]) m/z calcd for C$_{10}$H$_{12}$OSe [M][+]: 228.0053; found 228.0054.

2-Methoxy-2-methyl-2,3-dihydrobenzo[b]selenophene (15a). Selenide **14a** (1.80 g, 7.92 mmol) was dissolved in quinoline (10 mL) and transferred to a microwave glass tube (20 mL). The sealed vial was heated in a microwave reactor for 3 h at 230 °C. The dark black reaction mixture was then poured into a 4M HCl solution and extracted with diethyl ether. The combined organic layers were dried over Na$_2$SO$_4$, evaporate and the residue purified by chromatography using 2% ether/n-pentane as an eluent to afford the almost pure title compound as a yellow liquid. Yield: 0.450 g (25%). For the identity of **15a**, the HRMS was recorded. HRMS (TOF MS EI+) m/z calcd for C$_{10}$H$_{12}$OSe [M][+]: 228.0053; found 228.0055.

2-Methyl-2,3-dihydrobenzo[b]selenophene-6-ol (10) and 2-methyl-2,3-dihydrobenzo[b]-selenophene-4-ol (11). Selenide **14b** (1.50 g, 6.60 mmol) was subjected to the conditions for microwave-induced rearrangement described for **15a**. Column chromatography afforded 600 mg (40%) of an inseparable mixture of **15b** and **15c** as a yellow liquid. This was dissolved in dry dichloromethane (10 mL) and BBr$_3$ (2.97 mL, 2.97 mmol) was added at -78 °C under an inert atmosphere. After stirring for 3 h at this temperature, the reaction was left at room temperature for overnight. Following addition of more dichloromethane and washing with brine, the separated organic layer was dried over anhydrous MgSO$_4$. The solvent was then removed under reduced pressure and the residue was purified by column chromatography using DCM as an eluent to afford the two title compounds. Compound **10** was isolated as a colorless liquid which solidified in the freezer. Yield: 120 mg (22%); mp 89-91 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.58 (d, J = 6.4 Hz, 3H), 2.97 (dd, J = 6.8, 15.2 Hz, 1H), 3.37 (dd, J = 6.8, 15.2 Hz, 1H), 4.16 (m, 1H), 4.62 (s, 1H), 6.53 (dd, J = 5.6, 2.4 Hz, 1H), 6.80 (d, J = 2.4 Hz, 1H), 7.00 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 22.8, 42.4, 46.4, 112.1, 113.2, 125.7, 135.0, 138.7, 155.0; ^{77}Se NMR (76 MHz, CDCl$_3$): δ 439; HRMS (TOF MS EI[+]) m/z calcd for C$_9$H$_{10}$OSe [M][+]: 213.9897; found: 213.9893.

Compound **11** was a white solid. Yield: 90 mg (16%); mp 99-102 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.61 (d, J = 6.8 Hz, 3H), 3.04 (dd, J = 6.4, 15.6 Hz, 1H), 3.43 (dd, J = 7.2, 15.6 Hz, 1H), 4.20 (m, 1H), 4.64 (s, 1H), 6.51 (d, J = 7.6 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 6.99 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz,

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CDCl₃): δ 23.2, 41.1, 42.6, 112.1, 118.8, 128.4, 128.8, 139.3, 152.4; ^{77}Se NMR (76 MHz, CDCl₃): δ 441; HRMS (TOF MS EI⁺) *m/z* calcd for $C_9H_{10}OSe$ [*M*]⁺: 213.9897; found: 213.9896.

2-Methyl-2,3-dihydrobenzo[*b*]selenophene-7-ol (9). 15a (450 mg, 1.98 mmol) was subjected to the conditions for *O*-demethylation as described for the preparation of compounds **10** and **11**. Purification by column chromatography using DCM as an eluent afforded the title compound as a colorless liquid which solidified in the freezer. Yield: 0.15 g (36%); mp 68-70 °C; ^{1}H NMR (400 MHz, CDCl₃): δ 1.59 (d, *J* = 6.8 Hz, 3H), 3.10 (dd, *J* = 6.0, 15.2 Hz, 1H), 3.46 (dd, *J* = 6.8, 15.2 Hz, 1H), 4.20 (m, 1H), 4.55 (s, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.98 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl₃): δ 22.8, 42.4, 47.8, 113.7, 118.2, 126.1, 126.7, 144.9, 152.6; ^{77}Se NMR (76 MHz, CDCl₃): δ 385; HRMS (TOF MS EI⁺) m/z calcd for $C_9H_{10}OSe$ [*M*+H]⁺: 213.9897; found: 213.9904.

2-Methyl-2,3-dihydrobenzo[b]selenophene-5-ol (8).[17] Dihydroselenophene **8** was prepared as reported in literature. The ^{1}H and ^{13}C NMR spectra were in good agreement with literature and have been included in the Supporting Information.

X-ray Crystallographic Analysis. X-ray crystallographic studies of **11** were carried out using graphite-monochromatized Mo Kα radiation (λ = 0.7107 Å). The structure was solved by direct methods (SHELXS-2016) and refined by a full-matrix least-squares procedure on F^2 for all reflections using SHELXL-2016 software.[30] Hydrogen atoms were localized by geometrical means. A riding model was chosen for refinement. The isotropic thermal parameters of hydrogen atoms were fixed at 1.5 times and 1.2 times U(eq) of the corresponding carbon atoms for sp³ C-H and sp² C-H bonds, respectively. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as supplementary publications. CCDC 1538259 (for compound **11**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the CCDC via www.ccdc.cam.ac.uk/data_request/cif

Crystal data for 11. $C_9H_{10}OSe$, Mr = 213.13, orthorhombic, space group *P b c a*, a = 12.8266(9) Å, b = 10.2338(7) Å, c = 12.9340(9) Å, α = β = γ = 90°, V = 1697.8(2) Å³, λ = 0.71073 Å, Z = 8, T = 296(2) K, ρ_{calcd} = 1.668 Mg/m³, GOF = 1.022, R1 = 0.0262, wR2 = 0.0557 [I>2σ (I)]; R1 = 0.0441, wR2 = 0.0611 (all data). Of the 15941 reflections that were collected, 2104 were unique (R_{int} = 0.0332).

HPLC Peroxidation Assay: The experimental setup for recording inhibition times (T_{inh}) and inhibited rates of peroxidation (R_{inh}) during azo-initiated peroxidation of linoleic acid in a two-phase system were recently described.[21] Fresh linoleic acid was used as purchased. Values reported in Tables 1 and 3 for reactions performed in the presence of NAC are means ± SD based on triplicates. As R_{inh}- and T_{inh}-values show slight variations depending on the amount of linoleic acid hydroperoxide which is always present in commercial samples as an impurity, and increases upon storage. In the pH-variation experiments HCl or NaOH were added to the NAC-solution until a pH-meter indicated pH = 2, 5 and 7. Buffer solutions were tried but they always caused serious problems in the HPLC analysis of conjugated diene.

NAC Consumption Assay: The concentration of NAC in the aqueous phase of the two-phase model system during ongoing peroxidation was determined by using the assay of Means,[31] with slight modifications. After every 30 min during the first 3 hours of peroxidation, 20 μL of the aqueous phase was withdrawn by syringe and injected into a UV cuvette. Then, 1 mL of a 0.25 M solution of Aldrithiol-4 in water/DMF (49:1) was added. The concentration of pyridin-4-thiol was determined spectrophotometrically at 324 nm in comparison with a standard curve. The rate of NAC-consumption was calculated by least-square methods from time/concentration plots. Values reported in Table 2 are means ± SD based on triplicates.

Thiol Peroxidase Acivity: The GPx-like activities of dihydrobenzoselenophenes **8-11** were assessed by UV-spectroscopy at 305 nm as the rate of formation of diphenyl disulfide (PhSSPh) following the protocol by Tomoda[32] with slight modifications. The test mixture contained PhSH (1 mM) and catalyst (0.01 mM) at 21 °C and the reaction was initiated by addition of H_2O_2 (3.75 mM) in methanol. The initial reduction rates calculated from the first

10 seconds of reaction by using 1.24 mM⁻¹cm⁻¹ as the extinction coefficient for PhSSPh. Values reported in Table 2 are means ± SD based on triplicates.

Computational Details. Computational studies of compounds **8-11** were performed by using the Gaussian 09 suite of quantum chemical programs.[33] The geometry optimizations were carried out at the M062X/aug-cc-pVDZ level of theory and the frequencies were also calculated at the same level of theory. Calculations were performed by using Gaussian09/d.01 suite of programs.

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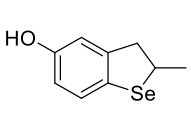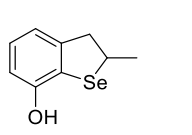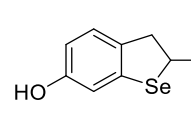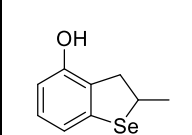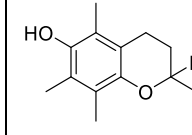
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Table 1. Inhibited rates of peroxidation (R_{inh}) and inhibition times (T_{inh}) for conjugated diene formation in the presence of antioxidants **1** and **8-11** (40 μM) and various co-antioxidants: NAC (1 mM), GSH (1 mM), DTT (0.5 mM), AscOH (0.5 mM), and TCEP (0.5 mM) in two-phase model system.
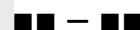
Co-antioxidants[a]	Antioxidants (40 μM)									
	8		**9**		**10**		**11**		**1**	
	R_{inh}[b] (μM/h)	T_{inh}[c] (min)	R_{inh}[b] (μM/h)	T_{inh}[c] (min)	R_{inh}[b] (μM/h)	T_{inh}[c] (min)	R_{inh}[b] (μM/h)	T_{inh}[c] (min)	R_{inh}[b] (μM/h)	T_{inh}[c] (min)
NAC (509)	35 ± 5	504 ± 7	15 ± 1	420 ± 9	42 ± 3	253 ± 5	28 ± 3	143 ± 5	25 ± 1	97 ± 5
GSH (539)	14 ± 4	252 ± 1	9 ± 1	546 ± 9	33 ± 2	242 ± 8	35 ± 1	129 ± 3	27 ± 3	116 ± 5
DTT (526)	23 ± 1	529 ± 2	19 ± 3	588 ± 8	55 ± 3	156 ± 3	31 ± 4	187 ± 4	25 ± 3	125 ± 4
AscOH (490)	18 ± 2	181 ± 8	23 ± 3	332 ± 8	27 ± 2	301 ± 9	29 ± 2	192 ± 9	19 ± 3	115 ± 8
TCEP (478)	34 ± 3	469 ± 4	22 ± 3	480 ± 8	26 ± 1	266 ± 4	29 ± 2	172 ± 7	21 ± 2	123 ± 7
No co-antioxidant (544)	19 ± 2	113 ± 7	9 ± 1	83 ± 2	46 ± 2	127 ± 4	38 ± 2	104 ± 3	28 ± 2	109 ± 2

[a]The control values in brackets are uninhibited rates in μM/h of linoleic acid peroxidation obtained with the respective co-antioxidants contained in the aqueous phase (no antioxidant in the chlorobenzene). [b]Rate of peroxidation during the inhibited phase. [c]Duration of the inhibited phase of peroxidation. Reactions were monitored for 700 min. Errors correspond to ± SD for triplicates.

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Phenolic dihydrobenzoselenophene antioxidant **9**, carrying the OH-group *ortho* to the Se atom quenches lipid peroxyl radicals more efficiently than α-tocopherol and is readily regenerable by aqueous-phase co-antioxidants such as *N*-acetylcysteine, glutathione, dithiothreitol, ascorbic acid, and tris(carboxyethyl)phosphine hydrochloride.
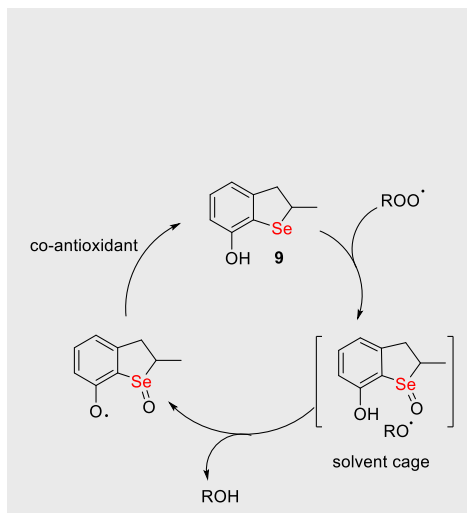
Antioxidants

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