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Long-Lasting Antioxidant Protection: A Regenerable BHA Analogue

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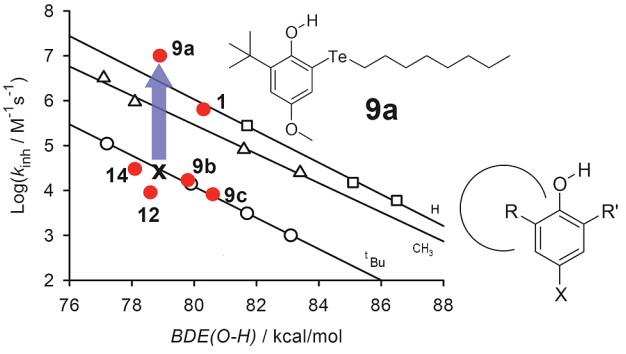
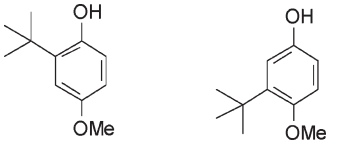


Introduction of an octyltelluro group *ortho* to the phenolic moiety in 3-*tert*-butyl-4-hydroxyanisole (BHA) was found to significantly improve the antioxidant characteristics of the material. In contrast to BHA and the corresponding *ortho*-substituted octylthio- (**9c**) and octylseleno (**9b**) derivatives, the organotellurium **9a** was regenerable when assayed for its capacity to inhibit azo-initiated peroxidation of linoleic acid in a chlorobenzene/water two-phase system containing *N*-acetylcysteine as a stoichiometric reducing agent, and peroxyl radicals were quenched more efficiently than with α-tocopherol. In the homogeneous phase, inhibition of styrene autoxidation occurred with a rate constant k_{inh} as large as 1×10^7 M^{-1} s^{-1} but with a low ($n = 0.4$) stoichiometric factor. Evans−Polanij plots of log (k_{inh}) versus BDE(O−H), which are usually linear for phenols with similar steric crowding reacting by H-atom transfer, revealed that compound **9a** was more than 2 orders of magnitude more reactive than expected. Although further mechanistic investigations are needed, it seems that the *ortho*-arrangement of an alkyltelluro group and hydroxyl should be considered a privileged structure for phenolic antioxidants.

Introduction

Butylated hydroxyanisole (BHA) has been used for more than 60 years[1] as a food additive (E320) to preserve products containing fats and oils[2] and as a stabilizer for cosmetics such as lipsticks and eye shadow. The commercially available antioxidant is prepared by alkylation (*tert*-butylation) of 4-hydroxyanisole and is obtained as a mixture of 3-*tert*-butyl-4-hydroxyanisole (**1**; > 85%) and 2-*tert*-butyl-4-hydroxyanisole (**2**; < 15%).[3]



1 **2**

As a mixture of phenolic compounds, BHA acts as a chain-breaking donating antioxidant.[4] It donates hydrogen atoms

(1) IARC monograph on the evaluation of the carcinogenic risks to humans. *Some Naturally Occurring and Synthetic Food Components, Furocoumarines and Ultraviolet Radiation*; Lyon, France, 1986; Vol. 40, p 123, ISBN 92832 1240 1.

(2) For example, the maximum level in frying oil is 200 mg/kg. European Parliament and Council Directive No 95/1/EC of 20 February, 1995 on food additives other than colors and sweeteners.

(3) Verhagen, H.; Schilderman, P. A. E. L.; Kleinjans, J. C. S. *Chem. Biol. Interactions* **1991**, *80*, 109–134.

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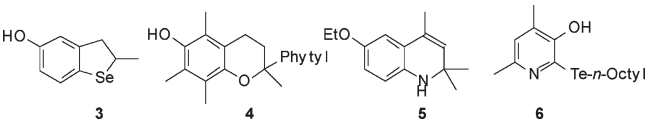
to peroxyl radicals at a rate much higher than chain propagation of lipid peroxidation. Since the resulting phenoxyl radical is well stabilized by resonance, it does not get involved in further hydrogen abstraction chemistry and peroxidation of the lipid is efficiently interrupted.

The effects of BHA in biological systems has been looked into in some detail.[5] At very high doses, forestomach squamous cell carcinomas was observed in rodents.[6] However, in humans there was no significant association with stomach cancer risk found for normal (ca. 100 μg/day) intake of BHA in the diet.[7] The present acceptable daily intake for BHA was set by the joint FAO/WHO expert committee to 0−0.5 mg/kg bodyweight.[5b] Largely, this value is rarely exceeded,[8] and there is no reason to believe that low-level intake of BHA should pose any cancer hazard.[9]

Antioxidants such as vitamins E and C cannot be biosynthesized in man. Because of their importance, it is not surprising that nature has evolved a mechanism for the regeneration of vitamin E in biological membranes in which it is the only antioxidant. It is thought that ascorbate is serving as the stoichiometric reducing agent by transferring a hydrogen atom to the tocopheroxyl radical before it is converted to nonradical products.[10]

We have for some time tried to design and synthesize regenerable antioxidants which could perform in a similar catalytic fashion in the presence of suitable stoichiometric reducing agents. Since −SH is arguably the most abundant reducing function available in biological systems, we focused on catalytic antioxidants regenerable by thiols. The primitive α-tocopherol analogue **3**, containing a dihydroselenophene moiety, performed in a truly catalytic fashion in a two-phase lipid peroxidation model containing *N*-acetylcysteine as a coreductant in the aqueous phase.[11] Although compound **3** did not quench peroxyl radicals as efficiently as α-tocopherol (**4**), it outperformed the natural antioxidant when it came to duration of protection. Peroxidation was inhibited as long as there remained some thiol in the aqueous phase. Ethoxyquin (**5**) was similarly reactive toward peroxyl radicals as α-tocopherol but considerably more regenerable.[12] Pyridinols such as telluride **6** showed still improved antioxidant characteristics. They were considerably more reactive than α-tocopherol ($k_{inh} = 1 \times 10^7$ M^{-1} s^{-1} as compared to $k_{inh} = 3 \times 10^6$ M^{-1} s^{-1} for α-tocopherol for quenching of peroxyl radicals), and regenerability was excellent in the two-phase system as well as under homogeneous phase conditions using a lipid-soluble thiol-reducing agent.[13]



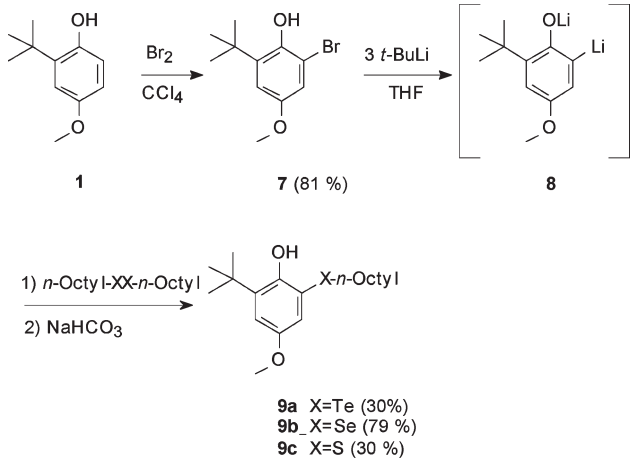
3 **4** **5** **6**

In search for novel regenerable antioxidants, it occurred to us that introduction of chalcogens into the BHA-scaffold may improve both the chain-breaking antioxidant capacity and regenerability of the compound. We have recently discussed the thermodynamic consequences of such a molecular arrangement on the phenolic O−H bond dissociation enthalpy.[14] In the following, we report on the synthesis and antioxidant characteristics of BHA-analogues carrying alkylthio, alkylseleno, and alkyltelluro substituents.

Results and Discussion

Synthesis. To introduce chalcogens *ortho* to the hydroxyl group in 3-*tert*-butyl-4-hydroxyanisole, 2-bromo-6-*tert*-butyl-4-methoxyphenol (**7**) was considered a suitable starting material. The bromoaromatic was prepared in 81% yield by bromination of **1** in carbon tetrachloride as previously described.[15] By treatment of phenol **7** with 3 equiv of *t*-BuLi in dry THF at −78 °C, a solution of the 2,*O*-dilithiated species **8** was formed in situ (Scheme 1).

SCHEME 1. Preparation of Compounds 9a−c



1 **7** (81 %) **8**

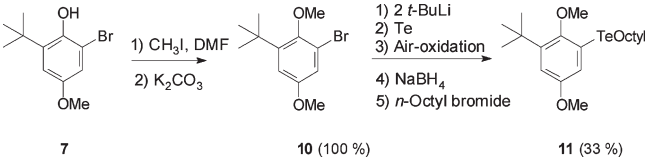
9a X=Te (30%)
9b X=Se (79 %)
9c X=S (30 %)

Addition of di-*n*-octyl ditelluride, diselenide, and disulfide, respectively, afforded the chalcogen containing BHA-analogues **9a**, **9b**, and **9c** after aqueous workup in yields ranging from 30 to 79% (Scheme 1). The yield's variability on changing the dichalcogen used in otherwise identical procedures was similarly recorded in our previous experience with this reaction; however, it did not seem to follow any clear trend. In order to study the antioxidative properties of a compound similar to BHA analogue **9a**, but lacking the

(4) Scott, G. In *Free Radicals: Chemistry, Pathology and Medicine*; Rice-Evans, C., Dormandy, T., Eds; Richelieu Press: London, 1988; p 103.
(5) (a) Joint FAO/WHO Expert Committee on Food Additives (JECFA) Monographs and Evaluations: Butylated Hydroxyanisole (BHA) (WHO Food Additives Series 15). (b) Joint FAO/WHO Expert Committee on Food Additives (JECFA) Monographs and Evaluations: Butylated Hydroxyanisole (BHA) (WHO Food Additives Series 18).
(6) Williams, G. M.; Iatropoulos, M. J.; Whysner, J. *Food Chem. Toxicol.* **1999**, *37*, 1027–1038.
(7) Botterweck, A. A. M.; Verhagen, H.; Goldbohm, R. A.; Kleinjans, J.; van den Brandt, P. A. *Food Chem. Toxicol.* **2000**, *38*, 599–605.
(8) Joint FAO/WHO Expert Committee on Food Additives (JECFA) Monographs and Evaluations: Butylated Hydroxyanisole (BHA) (WHO Food Additives Series 42, **1999**). ISBN-13 9789241660426.
(9) Soubra, L.; Sarkis, D.; Hilan, C.; Verger, Ph. *Reg. Toxicol. Pharmacol.* **2007**, *47*, 68–77.
(10) Halliwell, B.; Gutteridge, J. M. C. *Free radicals in biology and medicine*, 4th ed.; Oxford University Press: Oxford, 2007; p 168.
(11) (a) Kumar, S.; Johansson, H.; Engman, L.; Valgimigli, L.; Amorati, R.; Fumo, M. G.; Pedulli, G. F. *J. Org. Chem.* **2007**, *72*, 2583–2595. (b) Malmström, J.; Jonsson, M.; Cotgreave, I. A.; Hammarström, L.; Sjödin, M.; Engman, L. *J. Am. Chem. Soc.* **2001**, *123*, 3434–3440.
(12) Kumar, S.; Engman, L.; Valgimigli, L.; Amorati, R.; Fumo, M. G.; Pedulli, G. F. *J. Org. Chem.* **2007**, *72*, 6046–6055.
(13) (a) Kumar, S.; Johansson, H.; Kanda, T.; Engman, L.; Müller, T.; Jonsson, M.; Pedulli, G. F.; Petrucci, S.; Valgimigli, L. *Org. Lett.* **2008**, *10*, 4895–4898. (b) Kumar, S.; Johansson, H.; Kanda, T.; Engman, L.; Müller, T.; Bergenudd, H.; Jonsson, M.; Pedulli, G. F.; Amorati, R.; Valgimigli, L. *J. Org. Chem.* **2010**, *75*, 716–725.
(14) Amorati, R.; Pedulli, G. F.; Valgimigli, L.; Johansson, H.; Engman, L. *Org. Lett.* **2010**, *12*, 2326–2329.
(15) Tashiro, M.; Yoshiya, H. *Heterocycles* **1983**, *20*, 653–660.

capacity to act as a hydrogen atom donor, compound **7** was *O*-methylated before introduction of the octyltelluro group. The alkylation product **10** could only be obtained if methyl iodide was present when the base (K_2CO_3) was added (Scheme 2). Inversion of the order of addition caused a rapid degradation of the bromophenol. Further treatment of compound **10** with 2 equiv of *t*-BuLi and subsequent addition of finely ground elemental tellurium, followed by air oxidation, gave the corresponding ditelluride. This was then reduced with $NaBH_4$ and the tellurolate finally alkylated with *n*-octyl bromide to give compound **11** in 33% yield (Scheme 2).

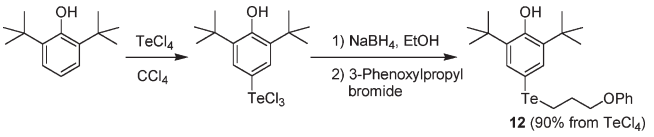
SCHEME 2. Preparation of Organotellurium Derivative 11



7 **10** (100 %) **11** (33 %)

In order to extend the investigation to include a phenol with a *p*-alkyltelluro group, we also prepared 3,5-di-*tert*-butyl-4-hydroxyphenyl 3-phenoxypropyl telluride (**12**). This compound was obtained in 90% overall yield from commercially available 2,6-di-*tert*-butylphenol by reaction with tellurium tetrachloride, sodium borohydride reduction of the resulting aryltellurium trichloride to a tellurolate, and alkylation with 3-phenoxypropyl bromide (Scheme 3).

SCHEME 3. Preparation of Compound 12



12 (90% from $TeCl_4$)

Inhibition Studies in the Two-Phase System. We have previously designed a two-phase system which allows the study of antioxidant regeneration by water-soluble coantioxidants during azo-initiated peroxidation of linoleic acid.[16] In the experimental setup, linoleic acid (L-H) and the antioxidant (40 μM) to be evaluated were stirred in chlorobenzene at 42 °C with an aqueous solution of *N*-acetylcysteine (NAC). 2,2′-Azobis(2,4-dimethylvaleronitrile) (AMVN) was used as an initiator in the organic phase, and the progress of peroxidation (formation of conjugated diene hydroperoxide) (eq 1) was monitored by HPLC. From the inhibited rate of peroxidation, R_{inh}, determined by least-squares methods from absorbance/time plots and the duration of the inhibited phase, T_{inh}, determined graphically as the cross-point for the inhibited and the uninhibited lines, comparison of antioxidant and catalyst efficiency could be done. As a reference control, α-tocopherol was used. Under the conditions used, it inhibited peroxidation with a R_{inh} of 24 ± 2 μM/h. It was not regenerable by NAC.

$$\text{L}-\text{H} \xrightarrow[\text{oxidant in chlorobenzene/}N\text{-acetylcycteine in H}_2\text{O}]{\text{AMVN, O}_2\text{, anti-}} \text{L}-\text{OOH} \quad (1)$$

(16) Vessman, K.; Ekström, M.; Berglund, M.; Andersson, C.-M.; Engman, L. *J. Org. Chem.* **1995**, *60*, 4461–4467.

In the two-phase system, 3-*tert*-butyl-4-hydroxyanisole **1** inhibited peroxidation for ca. 110 min whether or not *N*-acetylcysteine was present (Table 1). It was slightly inferior to α-tocopherol when it came to rate of inhibition (R_{inh} = 33 ± 5 μM/h in the presence of NAC). Introduction of bromine next to the hydroxyl (compound **7**) did not affect regenerability, but the inhibition capacity was much poorer (R_{inh} ca. 200 μM/h). The commercially available antioxidant 3,5-di-*tert*-butyl-4-hydroxyanisole **13** was also not regenerable in the two-phase system (T_{inh} = 112 ± 10 min). As compared with compound **1**, the additional *tert*-butyl group significantly lowered the antioxidant capacity (R_{inh} = 93 ± 6 μM/h). All chalcogen-containing BHA analogues **9** retarded peroxidation for 80 min in the absence of *N*-acetylcysteine, but they were all much poorer antioxidants than α-tocopherol (249 < R_{inh} < 295 μM/h). In the presence of thiol, the performance of the organoselenium compound **9b** and organosulfur compound **9c** was essentially unchanged, whereas organotellurium catalyst **9a** clearly outperformed α-tocopherol (Table 1 and Figure 1) both when it came to rate of inhibition (R_{inh} = 14 ± 2 μM/h) and inhibition time (T_{inh} = 365 ± 12 min). Since residual linoleic acid hydroperoxide present in commercial samples of the acid can rapidly oxidize organotelluriums, the retardation of peroxidation observed in the absence of thiol (R_{inh} = 252 and T_{inh} = 80 min) is likely to be due to the poor antioxidant activity of the corresponding telluroxide formed initially in the experiment. Compound **11**, the *O*-methylated telluride **9a**, did not inhibit peroxidation at all in the absence of thiol. NAC is obviously needed to keep the organotellurium compound in its reduced divalent state. Also, as hydrogen atom transfer (HAT) is impossible, the antioxidant activity (R_{inh} = 19 μM/h; T_{inh} = 90 min) presumably is due to electron transfer (ET) from tellurium to peroxyl radical. The resulting radical cation is then not efficiently regenerated by the thiol. Compound **12**, carrying an alkyltelluro group para to the phenolic moiety, turned out to be a good inhibitor (R_{inh} = 23 μM/h) of lipid peroxidation in the presence of NAC in the aqueous phase, but regenerability was poor (T_{inh} = 100 min).

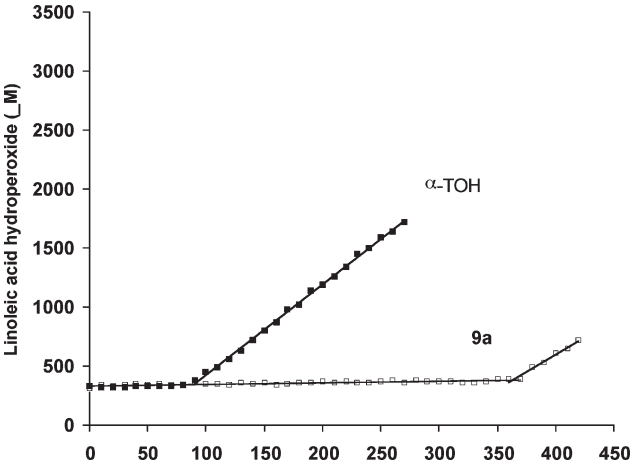
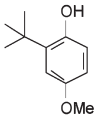
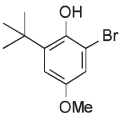
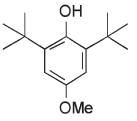
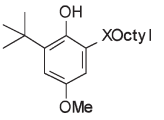
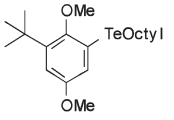
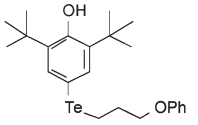


FIGURE 1. Peroxidation traces (linoleic acid hydroperoxide concentrations vs time) recorded using compound **9a** and α-tocopherol (40 μM) as antioxidants in the chlorobenzene layer in the presence of NAC (1 mM) in the aqueous phase.

TABLE 1. Inhibited Rates of Linoleic acid Peroxidation (R_{inh}) and Inhibition Times for Antioxidants and Reference Compounds Tested in the Two-Phase Model

			without *N*-acetyl-cysteine (1 mM) in the aqueous phase	
Antioxidant (40 μM)	R_{inh}[a] (μM/h)	T_{inh}[b] (min)	R_{inh}[a] (μM/h)	T_{inh}[b] (min)
				
1	33 ± 5	110 ± 0	37 ± 4	107 ± 6
				
7	202	100	196	100
				
13	112 ± 10	93 ±6	92 ± 13	93 ±6
				
9a X=Te	14 ± 2	365 ± 12	252	80
9b X=Se	252	80	249	80
9c X=S	278	80	295	80
				
11	19	90	664	0
				
12	23	100	614	0
α-Tocopherol	24 ± 2	90± 0	24 ± 2	87 ±7

[a]Average rate of peroxidation during the inhibited phase (uninhibited rate ca. 650 μM h^{-1}). Errors correspond to ± SD for triplicates. Where not indicated, errors are estimated as ±20% from available duplicates. [b]Average duration of the inhibited phase of peroxidation. Reactions were monitored for 400 min. Estimated errors are ±7%, unless differently indicated.

Inhibition Studies in the Homogeneous Phase. To achieve a deeper insight into the antioxidant activity of compound **9a** we investigated the homogeneous-phase autoxidation of styrene or cumene in chlorobenzene, initiated by thermal decomposition of 2,2′-azobisisobutyronitrile (AIBN) at 303 K and inhibited by **1**, **9a**−**c**, **11**, and **12** (eqs 2-7).[17]

$$\text{initiator} \xrightarrow{R_i} R^\bullet \quad (2)$$

$$R^\bullet + O_2 \rightarrow ROO^\bullet \quad (3)$$

$$ROO^\bullet + RH \xrightarrow{K_p} ROOH + R^\bullet \quad (4)$$

$$ROO^\bullet + ROO^\bullet \xrightarrow{2K_t} \text{nonradical products} \quad (5)$$

$$ROO^\bullet + ArOH \xrightarrow{k_{inh}} ROOH + ArO^\bullet \quad (6)$$

$$ROO^\bullet + ArO^\bullet \rightarrow \text{nonradical products} \quad (7)$$

(17) Burton, G. W.; Doba, T.; Gabe, E. J.; Hughes, L.; Lee, F. L.; Prasad, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 7053–7065.

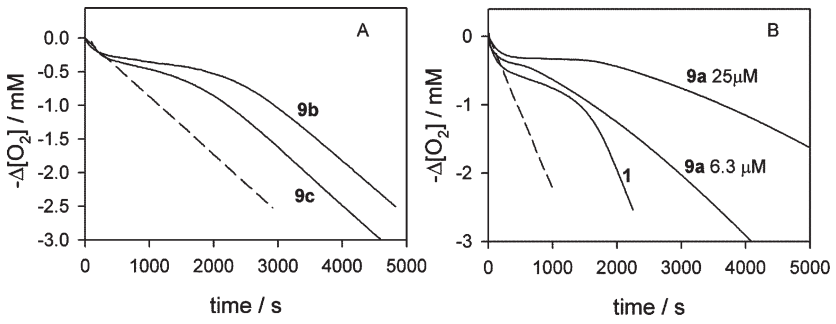
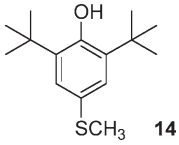


FIGURE 2. Typical oxygen uptake traces during homogeneous-phase autoxidation of cumene (7.1 M, panel A) or styrene (4.3 M, panel B) in chlorobenzene, initiated by AIBN (0.05 M) at 303 K, in the absence of inhibitors (dashed line) and inhibited by 6.3×10^{-6} M of **9a**−**c** or by 2.5×10^{-5} M of **9a**.

Compound **14**, was also included as its O−H bond dissociation enthalpy (BDE) had been studied in our previous works.[14,18]



14

Autoxidations were followed by measuring oxygen consumption (see Figure 2) by a custom-built differential oxygen-uptake apparatus that has been previously described in detail.[19] Rate constants for reaction of the title compounds with peroxyl radicals (k_{inh}), reported in Table 2, were obtained from the slopes during the inhibited periods.[19] The choice of oxidizable substrate was based on the reactivity of the antioxidant: less oxidizable cumene was first employed for all test compounds, and then the most effective antioxidants were further investigated in styrene, which due to the higher oxidizability ($k_p = 41\ M^{-1}\ s^{-1}$) allowed for chain reaction of length ≥8 even during the inhibited period.[17,19,20a] The number of peroxyl radicals trapped by each antioxidant molecule (n) is also reported in Table 2. For phenolic antioxidants, $n = 2$ is usually observed.[17,19] Homogeneous-phase autoxidations confirm the high reactivity of **9a** toward peroxyl radicals as compared with the other chalcogen-containing derivatives **9b** and **9c** or the reference BHA (**1**). Remarkably, compound **9a** is also more reactive than α-tocopherol, the most active natural lipophilic antioxidant,[17] commonly used as a benchmark for evaluating new inhibitors.[20]

However, in the homogeneous phase, the number of peroxyl radicals trapped by **9a** was quite low ($n = 0.4$), as was also observed for **12** and other Te-containing phenols.[13b] We previously explained these low n values by assuming that inhibition (eqs 6 and 7) is going on in competition with the reaction of the Te-alkyl moieties with peroxyl radicals to afford the corresponding telluroxides and alkoxyl radicals (RO•),[13b] which in turn propagate the oxidative chain. A previous investigation showed that telluroxide-containing phenols are so unreactive toward peroxyl radicals that their formation causes a dramatic decrease in the antioxidant activity (as was also observed in the two-phase system).[13b] From Figure 2, it is noteworthy that, at the end of the inhibited period using antioxidant **9a**, the rate of oxygen consumption is still retarded as compared with an uninhibited autoxidation under identical conditions. This effect, which depends on the concentration of **9a**, is related to residual antioxidant activity of the products formed after oxidation and/or detelluration of **9a**.[13b]

TABLE 2. Rate Constants k_{inh}, Stoichiometric Factors n, and Bond Dissociation Enthalpy (BDE) of the Phenolic OH Bond for the Investigated Compounds[a]

	k_{inh} ($M^{-1}\ s^{-1}$)	n	BDE[b] (kcal/mol)
1	$(6.4 \pm 0.5) \times 10^5$	1.8 ± 0.2	80.3
9a	$(1.0 \pm 0.3) \times 10^7$	0.4 ± 0.1	78.9
9b	$(1.7 \pm 0.2) \times 10^4$	2.1 ± 0.2	79.8
9c	$(8.2 \pm 0.4) \times 10^3$	1.9 ± 0.2	80.6
11	$< 1 \times 10^3$		
12	$(9 \pm 2) \times 10^3$	0.7 ± 0.2	78.6
14	$(3.0 \pm 0.2) \times 10^4$[c]	2.0 ± 0.2	78.1
α-tocopherol	3.2×10^6[d]	2[d]	77.1[e]

[a]Data are mean ± SD, each measurement in triplicate. [b]From ref 14. [c]From ref 18 [d]From ref 17. [e]From ref 21.

Rate constants measured in the present work can be discussed in light of linear Evans−Polanij relationships between log(k_{inh}) and BDE(O−H), as illustrated in Figure 3.[22,23] During H-atom transfer (HAT) from phenols to peroxyl radicals, the energy of activation is expected to be linearly dependent on the exothermicity of the reaction,[22] that is, inversely proportional to the phenolic BDE(O−H). Figure 3 clearly shows that such a correlation holds for series of phenols having the

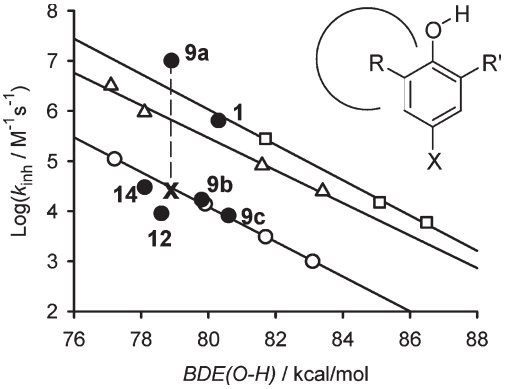


FIGURE 3. Evans−Polanij plot of log(k_{inh}) vs BDE(O−H) for investigated compounds (●) and some reference phenols:[23] (□) 4-X-C_6H_4OH; (△) 4-X-2,6-$Me_2C_6H_2OH$, (○) 4-X-2,6-t-Bu_2-C_6H_2OH.

(18) Amorati, R.; Fumo, M. G.; Menichetti, S.; Mugnaini, V.; Pedulli, G. F. *J. Org. Chem.* **2006**, *71*, 6325–6332.

(19) Amorati, R.; Pedulli, G. F.; Valgimigli, L.; Attanasi, O. A.; Filippone, P.; Fiorucci, C.; Saladino, R. *J. Chem. Soc., Perkin Trans. 2* **2001**, 2142–2146.

(20) (a) Valgimigli, L.; Brigati, G.; Pedulli, G. F.; DiLabio, G. A.; Mastragostino, M.; Arbizzani, C.; Pratt, D. A. *Chem.—Eur. J.* **2003**, *9*, 4997–5010. (b) Wijtmans, M.; Pratt, D. A.; Valgimigli, L.; DiLabio, G. A.; Pedulli, G. F.; Porter, N. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4370–4373.

same steric crowding around the OH group. Hence, different sets of substituents in the 2,6-positions belong to parallel correlations having different intercept on the *y*-axis.[23]

Compound **1** fits on the regression line for unhindered phenols, indicating that the OH group points away from the ortho *tert*-butyl group and thus there is no steric barrier to the approaching peroxyl radical.

Derivatives **9b** and **9c**, on the other hand, have much smaller k_{inh} values than **1**, despite their similar BDE(O−H). The BDE(O−H) values of **9b** and **9c** are the result of two opposing effects: the BDE-lowering electron donation from the chalcogen atoms and the BDE-rising effect due to formation of an intramolecular hydrogen bond between the reactive OH and the ortho substituents.[14] Since it is known that intramolecularly H-bonded phenolic groups are still reactive toward peroxyl radicals,[23,24] we envisage two possible reasons for the low k_{inh} values for **9b** and **9c** as compared to **1**. First, steric crowding of the ortho chalcogen groups is not negligible but similar to that of a methyl group (the van der Waals radii are 1.8, 1.9, 2.1, and ∼2 Å for S, Se, Te, and a methyl group respectively).[25] Second, stabilization of the incipient phenoxyl radical during the transition state of H-atom abstraction may be smaller than expected for geometrical reasons. It was previously noted, based on theoretical calculations, that in the phenols **9b** and **9c** the dihedral angle between the alkylchalcogeno substituents and the aromatic ring is approximately 90°, while the corresponding phenoxyl radicals have a planar geometry.[14] Therefore, it is conceivable that the planar conformation, necessary for full stabilization of the phenoxyl radical, is not attained during the TS, with a consequent increase in the barrier for hydrogen atom transfer.[26]

The high k_{inh} of **9a** is therefore surprising, as a k_{inh} of about 3×10^4 M^{-1} s^{-1} would be expected if **9a**−**c** were on the same Evans−Polanji plot (see the X in Figure 3). A possible explanation may be that this reaction is triggered by an electron transfer (ET) between **9a** and peroxyl radicals, followed by proton transfer (PT), that is, by an ET−PT mechanism.[27] To test this hypothesis, we performed the same measurements using a more polar solvent which should stabilize charged species. The rate constant k_{inh} for **9a** measured in MeCN was $(4 \pm 1) \times 10^6$ M^{-1} s^{-1}, is somewhat smaller than obtained in chlorobenzene, suggesting that ET plays a minor role in the reaction with peroxyl radicals. In line with this interpretation is also the observed poor inhibiting activity in chlorobenzene and MeCN of **11**, the methylated analogue of **9a**, which should behave as a similarly good electron donor. Interestingly, the enhanced reactivity toward peroxyl radicals is observed only when the Te-alkyl substituent is ortho-positioned with respect to the phenol (like in **9a**), while it disappears when the substituent is placed in the (conjugated) para position. Indeed, compound **12**, bearing the Te-alkyl group in the para position, did not show any enhanced antioxidant behavior with respect to the k_{inh} value expected from the Evans−Polanij correlation (Figure 3). Actually, compound **12**, even more so than analogous **14** bearing an S-alkyl substituent in the para position, has lower reactivity than that expected for its BDE(OH).[28]

We therefore feel that the good inhibitory activity of **9a** must be somehow related to the transfer of the phenoxylic H-atom, although the exact mechanism remains to be clarified.

Conclusions

Both in homogeneous and biphasic systems, the tellurium analogue **9a** of BHA showed an extraordinary reactivity toward peroxyl radicals which is due to the Te-alkyl group positioned ortho to the phenolic OH. In addition, compound **9a** showed excellent catalytic behavior when evaluated in a two-phase model for lipid peroxidation in the presence of stoichiometric amounts of *N*-acetylcysteine as a coantioxidant in the aqueous phase. Although the mechanisms for quenching of peroxyl radicals and for regeneration by thiol across a lipid aqueous interphase are presently not fully understood, it seems clear that the ortho arrangement of an alkyltelluro group and hydroxyl should be considered a privileged structure both for phenolic and isosteric pyridinolic[13] antioxidants.

Experimental Section

2-Bromo-6-*tert*-butyl-4-methoxyphenol (7). Compound **7** prepared as described showed NMR data in good agreement with literature.[15] Purification by column chromatography gave the title compound in 81% yield.

2-*tert*-Butyl-4-methoxy-6-(octyltelluro)phenol (9a). Compound **9a** was prepared according to the procedure for compound **9c** using di-*n*-octyl ditelluride instead of di-*n*-dioctyl disulfide: yield 30%; ^{1}H NMR δ 7.19 (d, J = 3.1 Hz, 1H), 6.92 (d, J = 3.1 Hz, 1H), 6.25 (s, 1H), 3.76 (s, 3H), 2.72 (t, J = 7.4 Hz, 2H), 1.71 (m, J = 7.4 Hz, 2H), 1.44−1.19 (several signals, 19H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR δ 152.7, 150.6, 135.6, 123.1, 117.2, 103.0, 56.0, 35.6, 32.0, 31.8, 31.7, 29.4, 29.3, 29.0, 22.8, 14.3, 10.4. Anal. Calcd for $C_{19}H_{32}O_2Te$: C, 54.33; H, 7.68. Found: C, 54.51; H, 7.74.

2-*tert*-Butyl-4-methoxy-6-(octylseleno)phenol (9b). Compound **9b** was prepared according to the procedure for compound **9c** using di-*n*-octyl diselenide instead of di-*n*-octyl disulfide: yield 79%; ^{1}H NMR δ 6.99 (d, J = 3.1 Hz, 1H), 6.89 (d, J = 3.1 Hz, 1H), 6.68 (s, 1H), 3.76 (s, 3H), 2.72 (t, J = 7.4 Hz, 2H), 1.63 (m, J = 7.4 Hz, 2H), 1.43−1.20 (several signals, 19 H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR δ 152.3, 149.5, 136.7, 118.2, 116.5, 116.5, 56.0, 35.4, 31.9, 30.4, 30.3, 29.7, 29.4, 29.3, 29.2, 22.8, 14.2. Anal. Calcd for $C_{19}H_{32}O_2Se$: C, 61.44; H, 8.68. Found: C, 61.37; H 8.70.

2-*tert*-Butyl-4-methoxy-6-octylthiophenol (9c). To 2-bromo-6-*tert*-butyl-4-methoxyphenol (0.3 g, 1.16 mmol) in THF (10 mL) under N_2 at −78 °C was added dropwise *t*-BuLi (2.1 mL 1.7 M solution in pentane; 3.6 mmol). After the mixture was stirred for

(21) (a) Lucarini, M.; Pedrielli, P.; Pedulli, G. F. *J. Org. Chem.* **1996**, *61*, 9259–9263. (b) Mulder, P.; Korth, H. G.; Pratt, D. A.; Di Labio, G. A.; Valgimigli, L.; Pedulli, G. F.; Ingold, K. U. *J. Phys. Chem. A* **2005**, *109*, 2647–2655.

(22) Foti, M.; Daquino, C.; Mackie, I. D.; DiLabio, G. A.; Ingold, K. U. *J. Org. Chem.* **2008**, *73*, 9270–9282.

(23) Amorati, R.; Menichetti, S.; Mileo, E.; Pedulli, G. F.; Viglianisi, C. *Chem.—Eur. J.* **2009**, *15*, 4402–4410.

(24) de Heer, M.; Korth, H.-G.; Mulder, P. *J. Org. Chem.* **1999**, *64*, 6969–6975.

(25) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441–451. Pauling, L.; Carpenter, D. C. *J. Am. Chem. Soc.* **1936**, *58*, 1274–1278.

(26) Amorati, R.; Catarzi, F.; Menichetti, S.; Pedulli, G. F.; Viglianisi, C. *J. Am. Chem. Soc.* **2008**, *130*, 237–244.

(27) Mayer, J. M. *Annu. Rev. Phys. Chem.* **2004**, *55*, 363–390.

(28) The fact that k_{inh} of both **12** and **14** is somewhat smaller than expected from BDE(O−H) values and the steric crowding around the OH group (see Figure 3) may derive from the fact that also in these compounds the optimal conformation of the alkylchalcogeno group in the parent phenol is different from that of the phenoxyl radical (90° and 0°, respectively)[14] and the planar conformation, necessary for the full stabilization of the phenoxyl radical, is not reached during the TS.[26]

60 min at −78 °C, di-*n*-octyl disulfide (1.04 g, 3.6 mmol) was added, and the reaction was stirred for an additional 2 h at room temperature. After the reaction mixture was poured into $NaHCO_3$ (5% aq), extracted with Et_2O, dried over Na_2SO_4, and concentrated in vacuo, the residue was purified by column chromatography using pentane/ethyl acetate (95/5) to give the title compound as a yellow oil in 30% yield: ^{1}H NMR δ 6.90 (s,1H), 6.89 (d, J = 3.0 Hz, 1H), 6.88 (d, J = 3.0 Hz, 1H), 3.76 (s, 3H), 2.69 (t, J = 7.3 Hz, 2H), 1.55 (m, J = 7.3 Hz, 2H), 1.44−1.18 (several signals, 19H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR δ 152.2, 150.0, 137.2, 119.7, 116.4, 116.3, 55.9, 37.2, 35.3, 31.9, 29.7, 29.4, 29.3, 29.2, 28.7, 22.8, 14.2. Anal. Calcd for $C_{19}H_{32}O_2S$: C, 70.32; H,9.94. Found: C, 70.58; H, 9.90.

2-Bromo-6-*tert*-butyl-1,4-dimethoxybenzene (10). To a solution of methyl iodide (0.5 mL, 8.03 mmol) in DMF (7.5 mL) was added 2-bromo-6-*tert*-butyl-4-methoxyphenol (0.80 g, 3.1 mmol) followed by K_2CO_3 (440 mg, 3.2 mmol), and the reaction was stirred under N_2 for 3 h and poured into water. After extraction with Et_2O, the organic phase was dried with Na_2SO_4, filtered, and evaporated in vacuo to give the title compound as a yellow oil in a quantitative yield: ^{1}H NMR δ 6.95 (d, J = 2.9 Hz, 1H), 6.84, (d, J = 2.9 Hz, 1H), 3.88 (s, 3H), 3.76 (s, 3H), 1.38 (s, 9H); ^{13}C NMR δ 155.4, 150.8, 145.9, 118.2, 115.5, 113.9, 61.7, 55.8, 35.8, 30.9; EI-MS 272.01/273.97 [M^+].

2-*tert*-Butyl-1,4-dimethoxy-6-(octyltelluro)benzene (11). To 2-bromo-6-*tert*-butyl-1,4-dimethoxybenzene (500 mg, 1.8 mmol) in THF (15 mL) was added dropwise *t*-BuLi (2.1 mL 1.7 M in pentane; 3.7 mmol) at −78 °C. The solution was stirred for 30 min at this temperature, and finely ground elemental tellurium (750 mg, 5.9 mmol) was added. The cooling bath was then removed and stirring continued for an additional 3 h at room temperature. The reaction was then poured onto crushed ice and kept in the open air overnight. After evaporation of the solvent in vacuo, the residue was dissolved in EtOH (10 mL) and filtered. To the solution of crude bis-(3-*tert*-butyl-2,5-dimethoxyphenyl)ditelluride under N_2, $NaBH_4$ (0.18 g, 5 mmol) was added in portions until the reaction mixture turned colorless. Octyl bromide (1.0 g, 5 mmol) was added and stirring continued for 1 h when the contents of the reaction flask was poured into brine and extracted with Et_2O (15 mL × 3). After drying over Na_2SO_4 and evaporation in vacuo, the product was purified by column chromatography using pentane/ethyl acetate (95/5) as an eluent. The title compound was obtained as a yellow oil (259 mg, 33%): ^{1}H NMR δ 6.90 (d, J = 3.0, 1H), 6.80 (d, J = 3.0, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 2.90 (t, J = 7.4, 2H), 1.82 (m, J = 7.4, 2H), 1.45−1.20 (several signals, 19H), 0.87 (t, J = 6.7, 3H); ^{13}C NMR δ 155.8, 154.8, 143.5, 118.3, 113.6, 110.7, 62.1, 55.7, 35.5, 32.2, 32.0, 31.6, 31.2, 29.3, 29.1, 22.8, 14.2, 7.8. Anal. Calcd for $C_{20}H_{34}O_2Te$: C, 55.34; H, 7.89. Found: C, 55.61; H, 7.80.

3,5-Di-*tert*-butyl-4-hydroxyphenyl 3-Phenoxypropyl Telluride (12). A solution of 2,6-di-*tert*-butylphenol (20.6 g, 100 mmol) in CCl_4 (20 mL) was slowly added to a slurry of finely crushed $TeCl_4$ (10.2 g, 38 mmol) in CCl_4 (10 mL) at 0 °C. The mixture was brought to room temperature and stirred for a further 2 h. The formed precipitate was then collected by filtration, washed with dichloromethane, and dried under vacuum to give the crude aryltellurium trichloride, 16.6 g (100%), which was used without further purification in the next step. Under inert atmosphere, solid sodium borohydride (large excess) was added portionwise to a solution of the aryltellurium trichloride (0.88 g, 2.0 mmol) in ethanol (10 mL) until the mixture remained colorless. Neat 3-phenoxypropyl bromide (0.52 g, 2.4 mmol) was then added, and the mixture stirred for 16 h. Water was added to the reaction, and the aqueous phase was extracted with diethyl ether, washed with brine, dried over $MgSO_4$, and evaporated to give crude product. This was subjected to column chromatography (pentane/ethyl acetate 8:2) to give 0.84 g (90%) of the pure title compound as beige crystals: mp 62−64 °C; ^{1}H NMR δ 7.57 (s, 2H), 7.27 (m, 2H), 6.94 (m, 1H), 6.87 (m, 2H), 5.25 (bs, 1H), 4.01 (t, J = 6.0 Hz, 2H), 3.00 (t, J = 7.4 Hz, 2H), 2.29 (m, 2H), 1.43 (s, 18H); ^{13}C NMR δ 159.0, 154.3, 137.2, 136.5, 129.6, 120.8, 114.7, 100.6, 68.9, 34.4, 31.6, 30.4, 4.5. Anal. Calcd for $C_{23}H_{32}O_2Te$: C, 59.02; H, 6.89. Found: C, 58.83; H, 6.86.

HPLC Peroxidation Assay. In the experimental setup, linoleic acid, and the antioxidant to be evaluated were vigorously stirred in chlorobenzene at 42 °C with an aqueous solution of *N*-acetylcysteine (NAC). 2,2′-Azobis(2,4-dimethylvaleronitrile) (AMVN) was added as an initiator in the organic phase and the progress of peroxidation monitored by HPLC (conjugated diene hydroperoxide formation). For comparison of catalyst efficiency, inhibition times (T_{inh}) and inhibited rates of peroxidation, R_{inh}, were determined by least-squares methods from absorbance/time plots as previously described.[11b,29]

Homogenous Phase Autoxidations. Kinetic measurements with peroxyl radicals were performed by studying the inhibited autoxidation of styrene or cumene in chlorobenzene or MeCN at 303 K, initiated by AIBN (0.05 M), in the presence of variable amounts ($(1-20) \times 10^{-6}$ M) of the investigated phenols and of 2,2,5,7,8-pentamethyl-6-chromanol (PMHC), a synthetic analogue of α-tocopherol, as reference antioxidants. The autoxidation was followed by monitoring the oxygen consumption in an oxygen uptake apparatus built in our laboratory and based on a differential pressure transducer, which have been previously described.[19] The rate of initiation R_i was measured in a preliminary set of experiments from the length of the inhibition period T_{inh}, using PMHC as a reference antioxidant: $R_i = 2[PMHC]/T_{inh}$. Integration of the oxygen consumption trace afforded the rate of reaction with peroxyl radicals k_{inh}, according to the equation $\Delta[O_2]_t = -k_p/k_{inh}\,[RH]\,\ln(1 - t/T_{inh})$. The k_p values of styrene and cumene at 303° are 41 and 0.32 $M^{-1}\ s^{-1}$, respectively.[19]

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Supporting Information Available: General experimental details and ^{1}H and ^{13}C NMR spectra of compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

(29) Shanks, D.; Amorati, R.; Fumo, M. G.; Pedulli, G. F.; Valgimigli, L.; Engman, L. *J. Org. Chem.* **2006**, *71*, 1033–1038.