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Antioxidant Profile of Ethoxyquin and Some of Its S, Se, and Te Analogues

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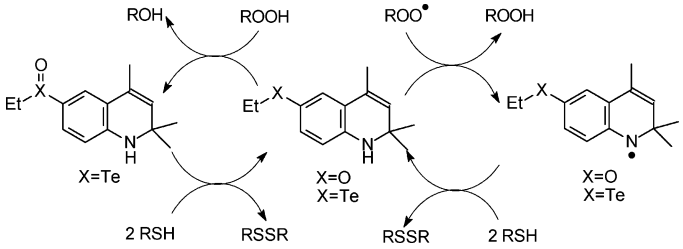

6-(Ethylthio)-, 6-(ethylseleno)-, and 6-(ethyltelluro)-2,2,4-trimethyl-1,2-dihydroquinoline—three heavier chalcogen analogues of ethoxyquin—were prepared by dilithiation of the corresponding 6-bromodihydroquinoline followed either by treatment with the corresponding diethyl dichalcogenide (sulfur derivative) or by insertion of selenium/tellurium into the carbon−lithium bond, oxidation to a diaryl dichalcogenide, borohydride reduction, and finally alkylation of the resulting areneselenolate/arenetellurolate. Ethoxyquin, its heavier chalcogen analogues, and the corresponding 6-PhS, 6-PhSe, and 6-PhTe derivatives were assayed for both their chain-breaking antioxidative capacity and their ability to catalyze reduction of hydrogen peroxide in the presence of a stoichiometric amount of a thiol reducing agent (thiol peroxidase activity). Ethoxyquin itself turned out to be the best inhibitor of azo-initiated peroxidation of linoleic acid in a water/chlorobenzene two-phase system. In the absence of *N*-acetylcysteine as a coantioxidant in the aqueous phase, it inhibited peroxidation as efficiently as α-tocopherol but with a more than 2-fold longer inhibition time. In the presence of 0.25 mM coantioxidant in the aqueous phase, the inhibition time was further increased by almost a factor of 2. This is probably due to thiol-mediated regeneration of the active antioxidant across the lipid−aqueous interphase. The ethyltelluro analogue **1d** of ethoxyquin was a similarly efficient quencher of peroxyl radicals compared to the parent in the two-phase system, but less regenerable. Ethoxyquin was found to inhibit azo-initiated oxidation of styrene in the homogeneous phase (chlorobenzene) almost as efficiently (k_{inh} = (2.0 ± 0.2) × 10^6 M^{-1} s^{-1}) as α-tocopherol with a stoichiometric factor n = 2.2 ± 0.1. At the end of the inhibition period, autoxidation was additionally retarded, probably by ethoxyquin nitroxide formed during the course of peroxidation. The N−H bond dissociation enthalpy of ethoxyquin (81.3 ± 0.3 kcal/mol) was determined by a radical equilibration method using 2,6-dimethoxyphenol and 2,6-di-*tert*-butyl-4-methylphenol as equilibration partners. Among the investigated compounds, only the tellurium analogues **1d** and, less efficiently, **1g** had a capacity to catalyze reduction of hydrogen peroxide in the presence of thiophenol. Therefore, analogue **1d** is the only antioxidant which is multifunctional (chain-breaking and preventive) in character and which can act in a truly catalytic fashion to decompose both peroxyl radicals and organic hydroperoxides in the presence of suitable thiol reducing agents.

Introduction

The dihydroquinoline ethoxyquin (**1a**) is readily available by condensation of 4-ethoxyaniline with two molecules of acetone.[1] Early on, it was used in the rubber industry as an antioxidant, antiozonant, an antifatigue agent.[2] More recently, it has been found to be the chain-breaking antioxidant of choice for

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(1) Knoevenagel, E. *Ber. Dtsch. Chem. Ges*. **1921**, *54B*, 181. de Koning, A. J.; Milkovitch, S. *Fat Sci. Technol*. **1991**, *93*, 378−382.

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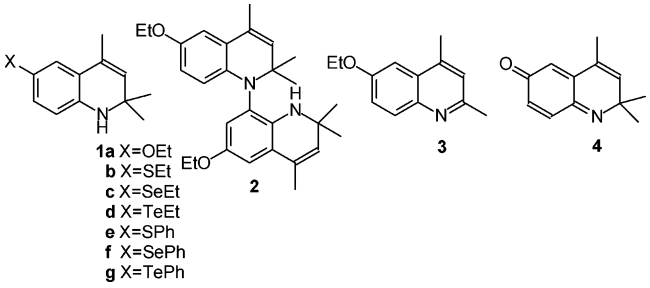
protection of polyunsaturated fatty acids in fishmeal and various animal feeds.[3,4] Its effects in biological systems have also been studied. In the rat, ethoxyquin has been found to act as a chemoprotector by increasing the levels of enzymes involved in detoxification of aflatoxin B_1-derived carcinogenic substances.[5] Similar but less pronounced effects were also seen in nonhuman primates.[6] Ethoxyquin has also been found to stimulate nuclear translocation of Nrf2 protein, and the subsequent increases in gene products that detoxify and eliminate cytotoxic metabolites are useful for treatment of diabetic retinopathy.[7] Among unfavorable side effects, one can mention an inhibitory effect on electron transport in the mitochondrial respiratory chain,[8] a hypothermal effect in rodents,[9] and apoptosis[10] and cytotoxicity and genotoxicity[11] in human lymphocytes. The toxicity of ethoxyquin is an area of ongoing debate. Many countries now have restrictions on the amounts of the antioxidant allowed. For example, the U.S. Food and Drug Administration allows ethoxyquin levels of up to 100 ppm in human-grade foods and up to 150 ppm in animal-grade foods.[12] Ethoxyquin acts primarily as a hydrogen atom donor toward peroxyl radicals. The major oxidation products of ethoxyquin[13−16] result from heterodimerization (compound **2**) or loss of methyl (quinoline **3**) or ethyl (quinoline quinone imine **4**) radicals from



the corresponding aminyl radical. The hyperfine splittings recorded in the EPR spectrum of the aminyl radical are indicative of extensive delocalization of the unpaired electron.[16] Some of the oxidation products also showed antioxidative capacity.[4] This may be the reason why ethoxyquin seems to possess such good antioxidant capacity. In a system where linoleic acid undergoes stimulated autoxidation in sodium dodecyl sulfate (SDS) micelles, ethoxyquin had a more than 5 times larger inhibition constant ($k_{inh} = 2 \times 10^5$ M^{-1} s^{-1}) than α-tocopherol (α-TOH; $k_{inh} = 3.7 \times 10^4$ M^{-1} s^{-1}) for quenching of peroxyl radicals.[17] As determined by stimulated oxidation of ethylbenzene, ethoxyquin is an efficient quencher of peroxyl radicals at temperatures <100 °C and a long-lasting inhibitor of β-carotene autoxidation.[18]

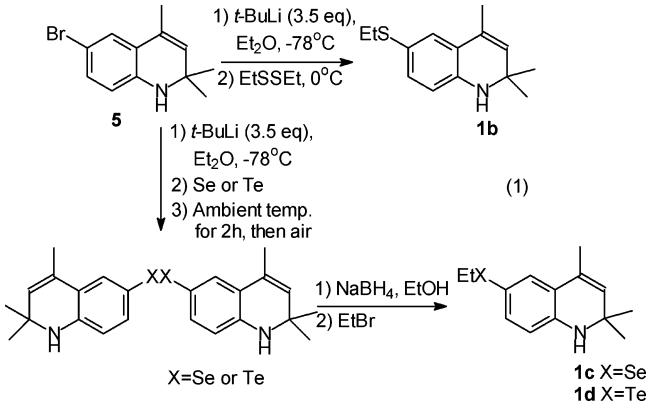
For a long time, we have been interested in the antioxidative properties of organochalcogen compounds. The glutathione peroxidases[19]—one of nature's most efficient hydroperoxide decomposers—have a selenocysteine residue at the active site. It is the facile redox cycling of this entity which brings about hydroperoxide reduction and glutathione oxidation to the corresponding disulfide. We have previously developed simple organochalcogen compounds that could mimic the properties of the glutathione peroxidases and catalyze the decomposition of hydroperoxides in the presence of suitable stoichiometric reducing agents.[20] Organochalcogens can also function as chain-breaking donating antioxidants. Interestingly, when assayed for their capacity to inhibit azo-initiated peroxidation of linoleic acid in a water/chlorobenzene two-phase system containing *N*-acetylcysteine (NAC) as a thiol reducing agent in the aqueous phase, some phenolic compounds were found to act in a catalytic fashion.[21−24] With the perspective to obtain catalytic, multifunctional (chain-breaking and hydroperoxide-decomposing) ethoxyquin antioxidants, we decided to synthesize analogues **1b**−**1d** carrying ethylthio, ethylseleno, and ethyltelluro groups in the 6-position and study their antioxidant profile in comparison with that of the corresponding phenylthio (**1e**), phenylseleno (**1f**), and phenyltelluro (**1g**) derivatives which we recently prepared.[25]

Results

Synthesis. 6-Bromo-2,2,4−trimethyl-1,2-dihydroquinoline (**5**) is readily available by condensation of 4-bromoaniline with 2

(2) (a) Braden, M.; Gent, A. N. *Rubber Chem. Technol.* **1962**, *35*, 200. (b) For a more recent example, see: Nishiyama, T.; Hashiguchi, Y.; Sakata, T.; Sakaguchi, T. *Polym. Degrad. Stab*. **2002**, *79*, 225−230.
(3) Spark, A. A. *J. Am. Oil Chem. Soc*. **1982**, *59*, 185−.
(4) (a) de Koning, A. J. *Int. J. Food Prop.* **2002**, *5*, 451−461. (b) Thorisson, S.; Gunstone, F.; Hardy, R. *J. Am. Oil Chem. Soc*. **1992**, *69*, 806−809.
(5) Ellis, E. M.; Judah, D. J.; Neal, G. E.; Hayes, J. D. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 10350−10354. Buetler, T. M.; Gallagher, E. P.; Wang, C.; Stahl, D. L.; Hayes, J. D.; Eaton, D. L. *Toxicol. Appl. Pharmacol*. **1995**, *135*, 45−57.
(6) Bammler, T. K.; Slone, D. H.; Eaton, D. L. *Toxicol. Sci*. **2000**, *54*, 30−41.
(7) U.S. Pat. Appl. 20050137146 and U.S. Pat. Appl. 20050137147, 2005.
(8) Reyes, J. L.; Hernández, M. E.; Meléndez, E.; Gómez-Lojero, C. *Biochem. Pharmcol.* **1995**, *49*, 283−289.
(9) Dorey, G.; Lockhart, B.; Lestage, P.; Casara, P. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 935−939.
(10) Blaszczyk, A.; Skolimowski, J. *Cell. Mol. Biol. Lett*. **2005**, *10*, 15−21.
(11) Blaszczyk, A.; Skolimowski, J. *Chem.-Biol. Interact.* **2006**, *162*, 70−80. Blaszczyk, A.; Skolimowski, J.; Materac, A. *Chem.-Biol. Interact.* **2006**, *162*, 268−273.
(12) See: http://www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=200621, Title 21, Parts 172 and 573, ethoxyquin.
(13) Taimr, L. *Angew. Macromol. Chem*. **1994**, *217*, 119−128.
(14) Thorisson, S.; Gunstone, F. D.; Hardy, R. *Chem. Phys. Lipids* **1992**, *60*, 263−271.
(15) He, P.; Ackman, R. G. *J. Agric. Food Chem*. **2000**, *48*, 3069−3071.
(16) Gunstone, F. D.; Mordi, R. C.; Thorisson, S.; Walton, J. C.; Jackson, R. A. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1955−1958.
(17) Pryor, W. A.; Strickland, T.; Church, D. F. *J. Am. Chem. Soc*. **1988**, *110*, 2224−2229.
(18) Kasaikina, O. T.; Kashkay, A. M.; Maximova, T. V. *Oxid. Commun.* **2000**, *23*, 383−391. See also: Sanhueza, J.; Nieto, S.; Valenzuela, A. *J. Am. Oil Chem. Soc*. **2000**, *77*, 933−936. Valenzuela, A.; Sanhueza, J.; Nieto, S. *J. Am. Oil Chem. Soc*. **2002**, *79*, 325−328.
(19) Spallholz, J. E.; Boylan, L. M. In *Peroxidases in Chemistry and Biology*; Everse, J., Everse, K. E., Grisham, M. B., Eds.; CRC Press: Boca Raton, FL, 1991; Vol. 1, Chapter 12; Sunde, R. A. In *Handbook of Nutritionally Essential Mineral Elements*; O'Dell, B., Sunde, R. A., Eds.; Marcel Dekker: New York, 1997; Chapter 18. Birringer, M.; Pilawa, S.; Flohé, L. *Nat. Prod. Rep*. **2002**, *19*, 693−718.
(20) (a) Engman, L.; Stern, D.; Cotgreave, I. A.; Andersson, C. M. *J. Am. Chem. Soc*. **1992**, *114*, 9737−9743. (b) Andersson, C.-M.; Hallberg, A.; Brattsand, R.; Cotgreave, I. A.; Engman, L.; Persson, J. *Bioorg. Med. Chem. Lett*. **1993**, *3*, 2553−2558. (c) Engman, L.; Stern, D.; Pelcman, M. Andersson, C-M. *J. Org. Chem*. **1994**, *59*, 1973−1979. (d) Kanda, T.; Engman, L.; Cotgreave, I. A.; Powis, G. *J. Org. Chem*. **1999**, *64*, 8161−8169. (e) McNaughton, M.; Engman, L.; Birmingham, A.; Powis, G., Cotgreave, I. A. *J. Med. Chem.* **2004**, *47*, 233−239.
(21) Vessman, K.; Ekström, M.; Berglund, M.; Andersson, C.-M., Engman L. *J. Org. Chem*. **1995**, *60*, 4461−4467.
(22) Malmström, J.; Jonsson, M.; Cotgreave, I. A.; Hammarström, L.; Sjödin, M.; Engman, L. *J. Am. Chem. Soc*. **2001**, *123*, 3434−3440.
(23) Shanks, D.; Amorati, R.; Fumo, M. G.; Pedulli, G. F.; Valgimigli, L.; Engman, L. *J. Org. Chem.* **2006**, *71*, 1033−1038.
(24) Kumar, S.; Johansson, H.; Engman, L.; Valgimigli, L.; Amorati, R.; Fumo, M. G.; Pedulli, G. F. *J. Org. Chem.* **2007**, *72*, 2583−2595.
(25) Kumar, S.; Engman, L. *J. Org. Chem*. **2006**, *71*, 5400−5403.

equiv of acetone.[26] Treatment of compound **5** with 3.5 equiv of *tert*-butyllithium at −78 °C in diethyl ether, followed by addition of diethyl disulfide to the resulting dilithium compound, afforded the sulfur analogue **1b** of ethoxyquin in 77% yield (eq 1). The selenium and tellurium analogues were best prepared



by insertion of the respective chalcogens into the carbon−lithium bond of the aryllithium, air oxidation of the resulting selenolate/tellurolate to diselenide/ditelluride, and, finally, borohydride reduction and alkylation with ethyl bromide (eq 1). The isolated yields of diselenide (59% crude), ditelluride (60%), **1c** (60%), and **1d** (70%) were fair.

Chain-Breaking Antioxidant Activity. Studies of the chain-breaking antioxidative activity of synthetic and natural compounds have been carried out under a variety of conditions including the homogeneous phase, micelles, and liposomes.[27] The rate of oxygen uptake, or the more sensitive rate of formation of conjugated diene hydroperoxide from a 1,4-diene,[28] has been commonly used for monitoring the inhibition of peroxidation of an organic substrate. Some time ago we described a two-phase variant of the latter model[21] which is suitable for the study of antioxidant regeneration by water-soluble coantioxidants. 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. 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, the inhibited rate of peroxidation, R_{inh}, was determined by least-squares methods from absorbance/time plots. The progress of peroxidation was followed for 320 min and the duration of the inhibited phase, T_{inh}, determined graphically as the cross-point for the inhibited and the uninhibited lines. We found that whether NAC (1 mM) was present in (T_{inh} = 90 min) or absent from (T_{inh} = 80 min) the aqueous phase, α-tocopherol (40 μM) inhibited peroxidation of linoleic acid for almost the same time in the lipid phase. Thus, it is not possible to regenerate α-tocopherol from the corresponding phenoxyl radical under these experimental conditions. On the other hand, certain 2,3-dihydrobenzo[*b*]selenophene-5-ols under similar conditions were found to inhibit peroxidation for more than 320 min in the two-phase system.[22,24] Since these antioxidants are effective for 50 min only in the absence of thiol, they are clearly acting in a catalytic fashion, being continuously regenerated by the *N*-acetylcysteine contained in the aqueous phase.

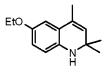
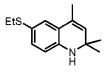
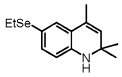
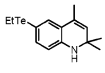
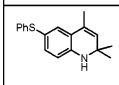
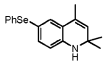
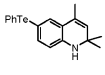
Inhibition studies with **1a** and the newly prepared derivatives **1b**−**1g** were initially performed in the two-phase system using the standard concentrations of antioxidant and coreductant given above. However, we were rather surprised to find that ethoxyquin in the presence of NAC inhibited peroxidation for such a long time (>350 min) that the inhibition time, T_{inh}, would not be a convenient means for comparing regenerability of these types of compounds. Therefore, the antioxidant concentration in the chlorobenzene layer was lowered to 20 μM and the thiol concentration to 0.25 mM. The inhibition time, T_{inh}, and the inhibited rate of peroxidation, R_{inh}, recorded under these conditions in the presence/absence of NAC in the aqueous phase are shown in Table 1 for compounds **1** and some reference compounds. When inhibition times are compared, it turns out that **1a** is superior to all of its derivatives both in the presence and in the absence of thiol in the aqueous phase. Under regeneration conditions it could inhibit peroxidation for 170 min, which is 20 min longer than recorded for the sulfur and selenium analogues **1b** and **1c**. All three phenyl derivatives **1e**−**1g** showed markedly shorter inhibition times ($120 < T_{inh} < 0$) than the corresponding ethyl derivatives **1b**−**1d**. It is also noteworthy that organotellurium compound **1g** did not inhibit peroxidation at all, whether thiol was present in or absent from the aqueous phase. In the absence of thiol in the aqueous phase, ethoxyquin inhibited peroxidation for 90 min. This is more than 2 times longer than recorded for α-tocopherol under similar conditions (40 min). Considering that each molecule of α-tocopherol is known to trap two peroxyl radicals (it has a stoichiometric factor of 2), each molecule of ethoxyquin can quench four to five peroxyl radicals. In the absence of NAC, sulfur and selenium analogues **1b** and **1c** of ethoxyquin both inhibited peroxidation for 50 min, whereas the rest of the compounds were active for short times only (0−30 min). The reason these compounds are effective for such short times could be rapid conversion to products which could no longer act as hydrogen atom or electron donors toward peroxyl radicals. The poor performance of compound **1d** under nonregenerating conditions is probably due to oxidation of tellurium to the corresponding telluroxide by residual hydroperoxide contained in the linoleic acid hydroperoxide and peroxyl radicals. In the presence of thiol in the aqueous phase, the active forms of the various antioxidants disappear more slowly because they are somehow regenerated at the aqueous−lipid interphase. If the two organotellurium antioxidants are excluded, the presence of thiol in the aqueous phase increases inhibition times for antioxidants **1** by a factor of 2−4. Since the oxidation of thiol to disulfide was not routinely monitored during the peroxidation experiments, we cannot be sure whether the inhibition time is restricted by the availability of thiol in the aqueous phase or by the efficiency of the regeneration process. In the evaluation of the most regenerable antioxidant **1a**, the aqueous phase was therefore sampled at intervals and the thiol concentration determined by reversed-phase HPLC. As shown in Figure 1, the concentration of NAC drops more or less linearly with time and can be extrapolated to reach zero after ca. 115 min. Thus, under these experimental conditions the coantioxidant is sparing ethoxyquin,

(26) Pooley, C. L. F.; Edwards, J. P.; Goldman, M. E.; Wang, M.-W.; Marschke, K. B.; Crombie, D. L.; Jones, T. K. *J. Med. Chem.* **1998**, *41*, 3461−3466.

(27) Pryor, W. A.; Cornicelli, J. A.; Devall, L. J.; Tait, B.; Trivedi, B. K.; Witiak, D. T.; Wu, M. *J. Org. Chem.* **1993**, *58*, 3521−3532 and references therein.

(28) Cosgrove, J. P.; Church, D. F.; Pryor, W. A. *Lipids* **1987**, *22*, 299. Braughler, J. M.; Pregenzer, J. F. *Free Radical Biol. Med.* **1989**, *7*, 125−130.

TABLE 1. Inhibition Times (T_{inh}) and Inhibited Rates of Peroxidation (R_{inh}) in the Two-Phase System for Antioxidants 1 and Reference Compounds in the Presence and Absence of *N*-Acetylcysteine and Initial Rates of Hydrogen Peroxide Reduction in the Presence of Thiophenol and Antioxidants 1 and Reference Compounds

Antioxidant	R_{inh}[a] ($\mu M \cdot h^{-1}$)	T_{inh}[b] (min)	Without NAC in aqueous phase		Thiol peroxidase activity[c] (μM min^{-1})
			R_{inh}[a] ($\mu M \cdot h^{-1}$)	T_{inh}[b] (min)	
 **1a**	27	170	20	90	0.34 (±0.06)
 **1b**	62	150	57	50	0.52 (±0.32)
 **1c**	74	150	70	50	1.26 (±0.33)
 **1d**	20	80	-	10	199.0(±9.0)
 **1e**	112	120	108	30	0.48 (±0.21)
 **1f**	109	60	-	20	0.53 (±0.34)
 **1g**	-	10	548	0	74.65(±4.19)
α-TOH	25	50	20	40	0.16 (±0.01)
PhSeSePh	-	-	-	-	0.59 (±0.21)

[a] Rate of peroxidation during the inhibited phase (uninhibited rate ca. 650 μM/h). [b] Duration of the inhibited phase of peroxidation. Reactions were monitored for ≤200 min. [c] Initial rate of hydrogen peroxide reduction in the presence of thiophenol and antioxidant.

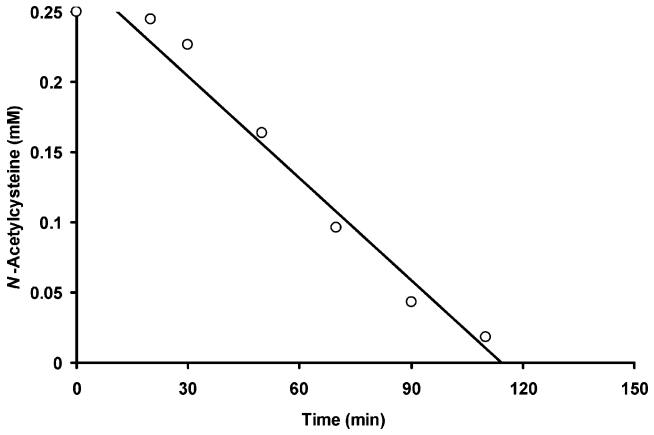


FIGURE 1. Concentration of *N*-acetylcysteine in the aqueous phase with time during a normal peroxidation experiment using antioxidant **1a** (20 μM).

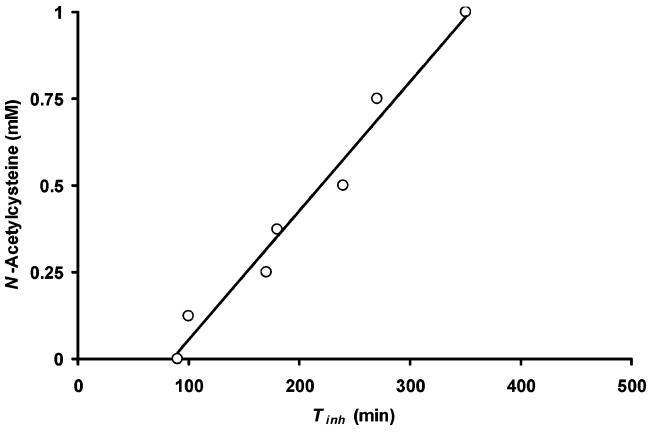


FIGURE 2. Inhibition time recorded with compound **1a** (20 μM) in the presence of various amounts of *N*-acetylcysteine (0, 0.125, 0.25, 0.375, 0.50, 0.75, and 1.00 mM) in the aqueous phase.

and when it is all consumed, residual ethoxyquin continues to inhibit peroxidation for another 55 min. Inhibition times were also recorded in the presence of other than the standard (0 or 0.25 mM) concentration of *N*-acetylcysteine (up to 1 mM). As shown in Figure 2, T_{inh} increases in a linear fashion from the limiting value of 90 to ca. 350 min in the presence of 1.0 mM coantioxidant. Compound **1d** when assayed under these conditions inhibited peroxidation for 260 min. Thus, it is less regenerable than the parent compound.

The relative antioxidant efficiencies of compounds investigated in the two-phase model are reflected by the inhibited rates of peroxidation, R_{inh}. The more effectively the antioxidant will quench peroxyl radicals, the lower will be the observed value of R_{inh}. It is noteworthy that most antioxidants investigated appear to be slightly more efficient when evaluated in the absence of NAC in the aqueous phase. This could be due to differences in pH (neutral in purely aqueous solution as compared with pH ca. 3.9 in a 0.25 mM aqueous solution of NAC) or ionic strength or due to different kinetic pathways of inhibition in the presence or absence of the coantioxidant. Similar differences were noted before.[22,24] Judging from the inhibited rates of peroxidation under regeneration conditions (Table 1), **1a** and its organotellurium analogue **1d** are as efficient quenchers of peroxyl radicals as α-tocopherol (all three with

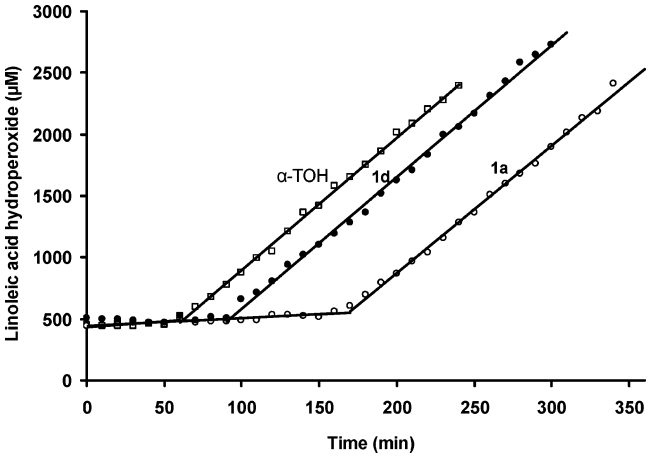


FIGURE 3. Peroxidation traces (linoleic acid hydroperoxide concentration vs time) recorded using a 20 μM concentration each of ethoxyquin (**1a**), tellurium analogue **1d**, and α-tocopherol as antioxidants in the chlorobenzene layer in the presence of NAC (0.25 mM) in the aqueous phase.

$R_{inh} = 20-25\ \mu$M/h), the two other ethyl derivatives **1b** and **1c** show a markedly lower quenching capacity ($R_{inh} = 60-80\ \mu$M/h), and the three phenyl derivatives **1e**−**1g** perform even worse ($R_{inh} > 109\ \mu$M/h). Overall, because of ready regeneration, both ethoxyquin and tellurium analogue **1d** clearly outperform α-tocopherol under regeneration conditions in the two-phase model (Figure 3).

Kinetic measurements with peroxyl radicals have been performed by studying the inhibited autoxidation of styrene at 303 K in chlorobenzene, initiated by AIBN, in the presence of **1a** using α-TOH as a reference antioxidant. The autoxidation was followed by monitoring the oxygen consumption in an oxygen uptake apparatus built in one of our laboratories and based on a Validyne DP15 differential pressure transducer, which has been previously described.[29] The observed kinetics are in accord with eqs 2−7.

$$\text{initiator} \xrightarrow{R_i} R^\bullet \tag{2}$$

$$R^\bullet + O_2 \rightarrow ROO^\bullet \tag{3}$$

$$ROO^\bullet + RH \xrightarrow{k_p} ROOH + R^\bullet \tag{4}$$

$$ROO^\bullet + ROO^\bullet \xrightarrow{2k_t} \text{products} \tag{5}$$

$$ROO^\bullet + AH \xrightarrow{k_{inh}} ROOH + A^\bullet \tag{6}$$

$$ROO^\bullet + A^\bullet \rightarrow \text{products} \tag{7}$$

Ethoxyquin showed a neat inhibition period T_{inh} in styrene, whose length provided the stoichiometric coefficient, i.e., the number of peroxyl radicals trapped by one molecule of antioxidant, $n = R_i T_{inh}/[AH]$, where R_i is the initiation rate, measeured in a preliminary set of experiments using α-tocopherol and [AH] is the initial concentration of antioxidant.

(29) 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.

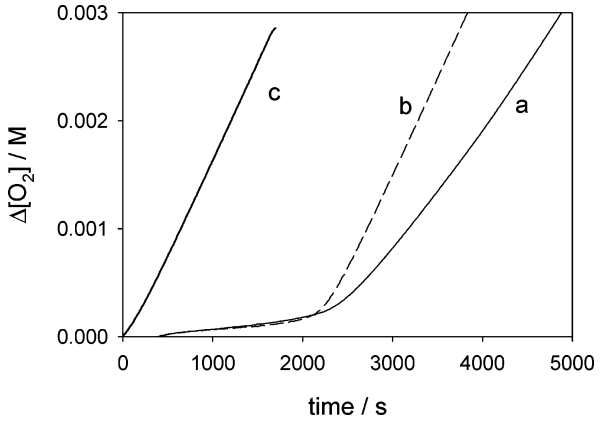


FIGURE 4. Autoxidation of styrene (4.3 M) initiated by AIBN (0.05 M) at 30 °C in chlorobenzene, without inhibitor (c) and in the presence of ethoxyquin (a) or α-TOH (b) (both 6.25×10^{-6} M).

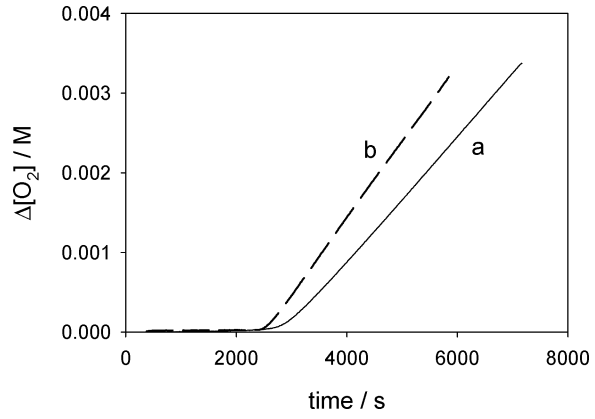


FIGURE 5. Autoxidation of cumene (7.1 M) initiated by AIBN (0.05 M) at 30 °C in the presence of ethoxyquin (a) or α-TOH (b) (both 6.25×10^{-6} M).

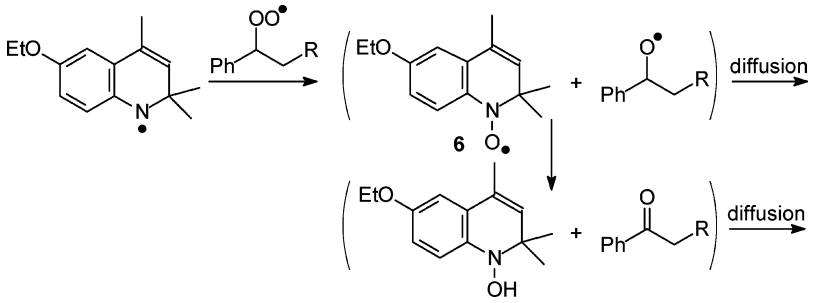
Integration of the oxygen consumption trace affords the rate of reaction with peroxyl radicals k_{inh}, provided k_p is known (eq 8).

$$\Delta[O_2]_t = (-k_p/k_{inh})[RH]\ \ln(1 - t/T_{inh}) \tag{8}$$

As can be seen from Figure 4, ethoxyquin behaves as a very effective chain-breaking antioxidant with a rate constant for trapping peroxyl radicals $k_{inh} = (2.0 \pm 0.2) \times 10^6\ M^{-1}\ s^{-1}$, i.e., just slightly lower than that of α-tocopherol ($3.2 \times 10^6\ M^{-1}\ s^{-1}$), and a stoichiometric factor $n = 2.2 \pm 0.1$. Unlike α-tocopherol and other effective phenolic chain-breaking antioxidants, after the inhibition period is over, the autoxidation of styrene was still "retarded" as can be seen from a comparison of traces a−c in Figure 4. To further investigate this unexpected additional antioxidant effect of ethoxyquin, we also performed autoxidation studies using cumene as the oxidizable substrate. The lower propagation rate constant k_p of cumene usually allows "weak" chain-breaking antioxidants to display neat inhibition periods in place of the retarding effect observed with highly oxidizable substrates such as styrene and methyl linoleate. A typical oxygen uptake trace recorded with ethoxyquin in cumene, compared to that recorded with α-tocopherol as the antioxidant, is shown in Figure 5.

As can be seen, qualitatively, the scenario is not much different from that observed in styrene. Actually, the retardation

SCHEME 1



of cumene autoxidation at the end of the inhibition period is even less important than observed in styrene. This clearly indicates that the residual retardation effect is not due to a chain-breaking antioxidant activity where peroxyl radicals are trapped by the antioxidant, but rather typical of species able to trap alkyl radicals. Stable nitroxides are known to act in a similar fashion.[30]

EPR Spectroscopy and the BDE_{N-H} of Ethoxyquin. When a deoxygenated benzene solution of a purified sample of ethoxyquin exposed to air was analyzed by EPR spectrometry, it provided a weak signal centered at $g = 2.0050$ (referenced to the DPPH radical at $g = 2.0036_4$[31]) and consisting of a broad 1:1:1 triplet ($a = 10.6$ G) of doublets ($a = 3.6$ G). The signal was attributed to trace impurities of the nitroxide radical **6** (see Scheme 1) by comparison with literature data.[16,32,33] Upon irradiation of the sample directly in the EPR cavity in the presence of 10% di-*tert*-butyl peroxide, an intense signal centered at $g = 2.0036$ rapidly grew, showing a hyperfine pattern ($a_N = 7.95$ G, $a_{6H} = 1.00$ G, $a_{1H} = 3.12$ G, $a_{3H} = 0.10$ G, $a_{1H} = 2.55$ G, $a_{2H} = 0.15$ G, $a_{1H} = 1.67$ G, $a_{1H} = 5.25$ G) which is consistent with the aminyl radical of ethoxyquin and was previously described by Walton and co-workers.[16] The BDE_{N-H} of ethoxyquin was measured by the radical equilibration technique using both 2,6-di-*tert*-butyl-4-methylphenol (BHT) and 2,6-dimethoxyphenol as reference compounds (the revised BDE_{O-H} values in benzene for these compounds are 79.9 and 82.06 kcal/mol, respectively[34]). In this method we measure the equilibrium constant, K_e, for the hydrogen atom transfer among one of the reference phenols (ArOH), ethoxyquin (EtOQ−H, **1a),** and the corresponding phenoxyl and aminyl radicals generated under continuous photolysis in deoxygenated benzene at room temperature (eq 9). In the calculation of K_e,

$$\mathrm{EtOQ{-}H + ArO^{\bullet} \leftrightarrows EtOQ^{\bullet} + ArOH} \qquad (9)$$

the initial concentrations of EtOQ-H and ArOH were used, while the relative radical concentrations were determined by means of EPR spectroscopy (Figure 6). The BDE_{N-H} for ethoxyquin was obtained assuming that the entropic term can be neglected[36] by means of eq 10 from K_e and the BDE value of the reference

$$\mathrm{BDE(EtOQ{-}H) \cong BDE(ArO{-}H) - \mathit{RT}\ln(\mathit{K}_e)} \qquad (10)$$

phenol. From these measurements, repeated under different light intensities to check the constancy of K_e, we obtained a BDE_{N-H} of 81.3 ± 0.3 kcal/mol for ethoxyquin reported in Table 2.

Hydroperoxide-Decomposing Antioxidant Activity. Organochalcogen compounds possess some unique properties which make them interesting as antioxidants. They are quite reactive toward hydrogen peroxide, organic hydroperoxides, and a variety of other two-electron-oxidizing agents such as peroxynitrite, hypochlorite, ozone, and singlet oxygen. In all these processes the chalcogen is oxidized to the tetravalent state. The nice feature about these hypervalent species is that they can be reduced to the divalent state under very mild conditions by reductants such as thiols and ascorbate. This redox cycling is especially facile for organoselenium and organotellurium compounds and allows for their use as catalysts for the decomposition of hydroperoxides. Thus, these materials are biomimetic in the sense that they can mimic the action of the selenium-containing glutathione peroxidase enzymes. There are several methods in use for the assessment of glutathione peroxidase-like activity of simple synthetic compounds (eq 11).[37] The only one using glutathione

$$\mathrm{2RSH + R'OOH \xrightarrow{catalyst} RSSR + R'OH + H_2O} \qquad (11)$$

as a substrate (eq 11; RSH = glutathione) is an enzymatic procedure where glutathione reductase and NADPH are present in the incubation (to reduce the disulfide RSSR formed) together with hydrogen peroxide (R′ = H) and the catalyst efficiency is monitored spectrophotometrically as the initial decrease in the absorbance of the cofactor. Problems with this system could arise if the catalyst has poor solubility in water. An NMR method was introduced by us some time ago where the time required to reduce the concentration of RSH (*N*-acetylcysteine, *tert*-butyl mercaptan, or 1-octyl mercaptan) in D_2O/CH_3OD by 50% was used as a measure of catalyst efficiency.[38] The time needed to aquire and process NMR data was sometimes a restriction when very potent catalysts were to be evaluated. In the method most commonly used today, the initial rate of reduction of hydrogen peroxide (v_0) is calculated by monitoring the formation of diphenyl disulfide from thiophenol (eq 11, R = phenyl, R′ = H) by UV spectroscopy at 305 nm.[39] Thus,

(30) Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4992−4996.
(31) Valgimigli, L.; Ingold, K. U.; Lusztyk, J. *J. Org. Chem.* **1996**, *61*, 7947−7950.
(32) Lin, J. S.; Olcott, H. S. *J. Agric. Food Chem.* **1975**, *23*, 798−800.
(33) Skaare, J. U.; Henriksen, T. *J. Sci. Food Agric*. **1975**, *26*, 1647−1654. Gunstone, F. D.; Mordi, R. C.; Thorisson, S.; Walton, J. C.; Jackson, R. A. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1955−1958.
(34) All the BDE values determined in benzene solution by means of the EPR radical equilibration technique, based on the BDE_{O-H} of 2,4,6-tri-*tert*-butylphenol, must be down-scaled by 1.1 kcal/mol due to the revision of the heat of formation of (*E*)-azobenzene.[35]
(35) Mulder, P.; Korth, H.-G.; Pratt, D. A.; DiLabio, G. A.; Valgimigli, L.; Pedulli, G. F.; Ingold, K. U. *J. Phys. Chem. A* **2005**, *109*, 2647−2655.
(36) Lucarini, M.; Pedrielli, P.; Pedulli, G. F.; Valgimigli, L.; Gigmes, D.; Tordo, P. *J. Am. Chem. Soc*. **1999**, *121*, 11546−11553.
(37) See: Mugesh, G.; Singh, H. B. *Chem. Soc. Rev*. **2000**, *29*, 347−357 and references therein.
(38) Engman, L.; Stern, D.; Cotgreave, I. A.; Andersson, C. M. *J. Am. Chem. Soc*. **1992**, *114*, 9737−9743.
(39) Iwaoka, M.; Tomoda, S. *J. Am. Chem. Soc*. **1994**, *116*, 2557−2561.

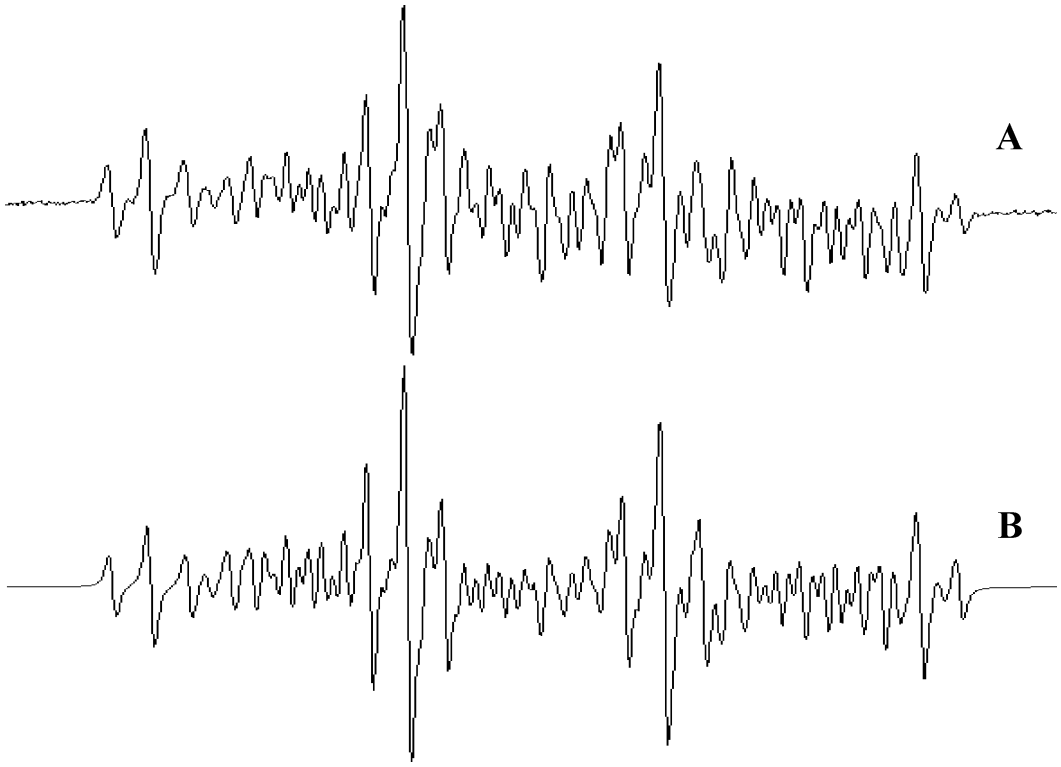


FIGURE 6. EPR spectrum obtained by UV irradiation of a mixture of ethoxyquin and BHT (50:1) in deoxygenated benzene containing 10% (v/v) di-*tert*-butyl peroxide at 298 K (A) and the computer simulation of the superimposition of the two radical species (aminyl and phenoxyl) equilibrating in the mixture (B).

TABLE 2. N−H Bond Dissociation Enthalpy (BDE_{N-H}) for Ethoxyquin Measured at 298 K in Benzene Containing 10% Di-*tert*-butyl Peroxide and Revised BDE_{O-H} of the Reference Phenols

compound	BDE (kcal mol^{-1})
ethoxyquin (**1a**)	81.3 ± 0.3
2,6-dimethoxyphenol	82.06 ± 0.2[a]
BHT	79.9 ± 0.1[a]

[a] Recalculated according to the revised BDE_{O-H} value for the reference phenol 2,4,6-tri-*tert*-butylphenol in benzene.[35]

what is measured here is thiol peroxidase activity rather than glutathione peroxidase activity. Shown in Table 1 are initial rates recorded for the reduction of hydrogen peroxide (3.75 mM) in methanol by thiophenol (1 mM) in the presence of compounds **1** (0.01 mM) as recorded by UV spectroscopy at 305 nm where the extinction coefficient of diphenyl disulfide ($\epsilon = 1.24 \times 10^3$ M^{-1} cm^{-1}) is much larger than that of thiophenol ($\epsilon = 9$ $M^{-1}cm^{-1}$). Among compounds **1**, the two organotelluriums **1d** and **1g** were the only compounds that showed any appreciable thiol peroxidase activity ($v_0 = 199$ and 75 μM min^{-1}, respectively). There are probably both steric and electronic reasons for the better activity of the former catalyst. An ethyl group is both smaller and more electron donating than a phenyl. Therefore, the chalcogen in compound **1d** is the better nucleophile in the reaction with hydrogen peroxide. The oxidation step is known to be rate determining in the redox cycling of diorganyl tellurides in the presence of oxidants and thiols.[20c] Diphenyl diselenide is commonly used as a benchmark when thiol peroxidase activities of synthetic compounds are compared. The initial rate of hydrogen peroxide reduction using this catalyst under our conditions was 0.59 μM min^{-1}. Thus, our organotellurium compounds are substantially more active. To the best of our knowledge, compound **1d** is the most efficient diorganyl telluride catalyst evaluated in the system used. Its activity is roughly one-third of that recorded for the most efficient diselenide catalyst studied under identical conditions.[40]

Discussion

Vitamin E is the most important lipophilic, chain-breaking antioxidant in man. It readily donates a hydrogen atom to peroxyl radicals and, due to the stability of the resulting phenoxyl radical, can quench a second peroxyl radical before it is converted into nonradical products. Our experiments in the absence of thiols, or under homogeneous phase conditions, showed that ethoxyquin inhibited lipid peroxidation almost as efficiently as α-tocopherol but with a longer than expected inhibition time. During ethoxyquin-inhibited autoxidation of styrene in the homogeneous phase, we found evidence for formation of an alkyl radical-trapping species during the course of peroxidation. This species is likely to be the nitroxide **6**, which, according to EPR spectroscopy (vide supra), is present in trace amounts even in samples of purified ethoxyquin.[41] Nitroxide **6** is probably formed from the reaction of ethoxyquin aminyl radical with alkylperoxyl radicals according to the

(40) Mugesh, G.; Panda, A.; Singh, H. B.; Punekar, N. S.; Butcher, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 839−850. See also: Zade, S. S; Singh, H. B.; Butcher, R. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 4513−4515. For an account on the thiol peroxidase activity of ditellurides see: Mugesh, G.; Panda, A.; Kumar, S.; Apte, S. D.; Singh, H. B.; Butcher, R. J. *Organometallics* **2002**, *21*, 884−892.

mechanism originally proposed by Ingold and co-workers[42] and reviewed by Howard[43] for secondary aromatic amines (Scheme 1).

The alkoxyl radical formed in this process can either escape the solvent cage and diffuse into solution where it could initiate new chains or react in-cage with the nitroxide to form the corresponding hydroxylamine that will possess good chain-breaking antioxidant activity. Clearly, the fine balancing of the chemistry depicted in Scheme 1 can account for the observed stoichiometric factors larger than 2 in the two-phase system and the residual retardation of styrene autoxidation when inhibited by ethoxyquin in the homogeneous phase. By numerical fitting of the oxygen uptake traces recorded during the inhibited autoxidation of styrene, particularly from the slope of the final "retardation" period, and calibration of the fitting against autoxidation experiments retarded by variable amounts of 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) in chlorobenzene, it was possible to estimate the amount of "effective" nitroxide **6** as 50% of the initial amount of ethoxyquin. Thus, half of the ethoxyquin used as an antioxidant under the experimental conditions employed was available to retard the autoxidation at the end of the inhibition period. This indicates that during styrene autoxidation in chlorobenzene roughly 50% of the aminyl radical traps a second peroxyl radical similarly to the phenoxyl radical, e.g., by addition into the aromatic ring, while the remaining 50% reacts with the peroxyl radical by way of oxygen transfer as shown in Scheme 1. This particular balancing would result in a stoichiometric factor of about 1.5 if all the nitroxide and the alkoxyl radical formed escaped the solvent cage. On the other hand, the stoichiomtric factor would increase to 2.5 if all nitroxide reacted in-cage with the alkoxyl radical to form the hydroxylamine, which is able to trap another peroxyl radical and re-form nitroxide **6** according to eq 12.

$$\mathrm{EtOQ{-}OH} + \mathrm{ROO^{\bullet}} \rightarrow \mathbf{6} + \mathrm{ROOH} \qquad (12)$$

Experimentally, we observe $n = 2.2$, clearly indicating that only a fraction of nitoxide **6** formed according to Scheme 1 escapes the solvent cage. The total amount of nitroxide formed either from escape from the cage or, subsequently, from reaction 12 would be available to retard the autoxidation at the end of the inhibition period by reacting with alkyl radicals in competition with molecular oxygen (reaction 3).

In addition to the large stoichiometric factor, the excellent antioxidant activity of ethoxyquin is due to its high reactivity toward peroxyl radicals, which in turn depends on the N−H bond dissociation enthalpy. As far as we know, only old calculated[2b] BDE_{N-H} data on ethoxyquin are available. Our radical equilibration EPR-measured value of 81.3 ± 0.3 kcal/mol is in accord with the observed high antioxidative capacity of the material. Considering that ethoxyquin quenches peroxyl radicals almost as efficiently as α-tocopherol ($BDE_{O-H} = 77.1$ ± 0.3 kcal/mol), the observed value may appear rather high. However, it should be noted that hydrogen atom transfer from the secondary amine is subject to much less steric hindrance than H atom transfer from α-tocopherol. Indeed, when the homolytic behavior of ethoxyquin with peroxyl radicals is compared to that of structurally related phenothiazines,[36] it becomes clear that kinetic and thermodynamic properties fall on the same linear free energy relationship (Figure 7).

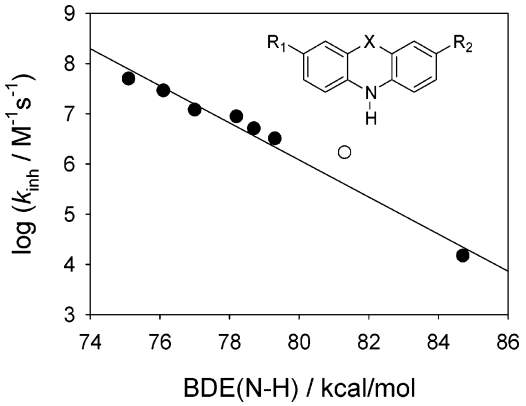


FIGURE 7. Relationship between the bond dissociation enthalpy of the N−H bond and the logarithm of the rate constant with peroxyl radicals for ethoxyquin (○) and structurally related phenothiazines (●).

Ethoxyquin and some of its chalcogen analogues are efficiently regenerated by thiol in the two-phase system for lipid peroxidation. This process resembles the regeneration of α-tocopherol by ascorbate which is thought to occur at the lipid−aqueous interphase in biomembranes. Ethoxyquin primarily serves as a hydrogen atom donor toward peroxyl radicals to generate an aminyl radical. The simplest process for regeneration of the parent antioxidant would involve hydrogen atom transfer from thiol contained in the aqueous phase. However, this mechanism is likely to be operative only if the bond dissociation enthalpy of the thiol is lower than or at least comparable to that of the N−H bond of ethoxyquin and the rate of H atom transfer is sufficiently high.[44] Although we have not been able to find a useful BDE_{S-H} value for *N*-acetylcysteine, it seems reasonable to assume that it would be in the range of 85−90 kcal/mol. The predicted value for cysteine in proteins is 87.8 ± 2.4 kcal/mol.[45] Thus, *N*-acetylcysteine is not likely to act as a regenerating agent by donation of a thiol-derived hydrogen atom to the aminyl radical of ethoxyquin. If direct hydrogen atom transfer is a thermodynamically unfavorable process, regeneration of ethoxyquin by thiol in water or in a two-phase system may still be possible if it occurs in a stepwise fashion by transfer of an electron and a proton. We previously came to the qualitative conclusion that this mechanism could be operative in the regeneration of certain phenolic organoselenium antioxidants in the two-phase system.[24] The lack of relevant thermochemical data on ethoxyquin precludes a more quantitative treatment of the issue. We cannot exclude the possibility that one or several of the many oxidation products of ethoxyquin could somehow be involved in the regeneration process. Authentic samples of dimer **2** and quinone imine **4** showed such poor regenerability ($T_{inh} < 20$ min) when tested with thiol under the standard conditions in the two-phase system that they are not likely to be relevant.

(41) Unfortunately, following literature procedures,[14,32,41a−c] we were unable to prepare a pure sample of nitroxide **6**. (a) Wu, T.; Lin, J. S.; Olcott, H. S. *J. Agric. Food Chem.* **1976**, *24*, 1255. (b) Bharucha, K. R.; Cross, C. K.; Rubin, L. J. *J. Agric. Food Chem.* **1987**, *35*, 915−917. (c) Taimr, L.; Prusikova, M.; Pospisil, J. *Angew. Macromol. Chem.* **1991**, *190*, 53−65.

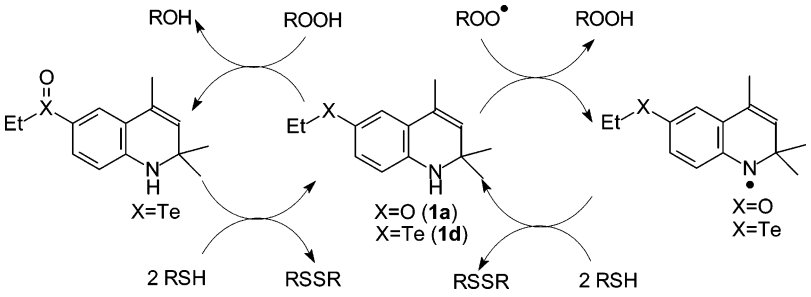
(42) Adamich, K.; Dunn, M.; Ingold, K. U. *Can. J. Chem.* **1969**, *47*, 257.

(43) Howard, J. A. Homogeneous liquid-phase autoxidations. In *Free Radicals*; Kochi, J. K., Ed.; Wiley-Interscience: New York, 1973; Vol. II pp 3−63.

(44) Amorati, R.; Ferroni, F.; Pedulli, G. F.; Valgimigli, L. *J. Org. Chem.* **2003**, *68*, 9654−9658.

(45) Rauk, A.; Yu, D.; Armstrong, D. A. *J. Am. Chem. Soc.* **1998**, *120*, 8848−8855.

SCHEME 2



In contrast to the regenerable organoselenium antioxidants mentioned above, ethoxyquin and its chalcogen analogues carry a basic nitrogen. Depending on the protonation state, the antioxidant, as well as the corresponding aminyl radical, would be more soluble in the hydrophilic (protonated form) or the lipophilic (deprotonated form) layer of the two-phase system. According to Malkin, Pirogov, and co-workers[46] the pK_a of protonated ethoxyquin and the corresponding aminyl radical is 3.7 and 4.6, respectively. Thus, substantial amounts of both the antioxidant and the corresponding aminyl radical would be present in the aqueous phase (pH 3.9 in a 0.25 mM aqueous solution of NAC) during the course of a peroxidation experiment. In fact, regeneration of ethoxyquin by thiol may occur in the aqueous phase rather than at the lipid−aqueous interphase. The hydrochloride salt of ethoxyquin was also rather efficient as an antioxidant. Under the standard conditions in the two-phase system it inhibited peroxidation for 150 and 60 min, respectively, in the presence and absence of the coantioxidant.

The reason compound **1d** is not as regenerable as ethoxyquin at low thiol concentrations is probably decomposition under the conditions of the assay. Probably, the antioxidant or some of its oxidation products are continuously transformed into inactive components before regeneration occurs. For example, one mode of decomposition could involve cleavage of the weak tellurium−carbon bond in the ethyltelluro moiety of the aminyl radical with formation of a tellurium analogue of compound **4**. Considering the excellent hydroperoxide-decomposing ability of ethoxyquin derivative **1d**, we rank this compound as the potentially most useful analogue prepared. This is the only antioxidant which is chain-breaking and hydroperoxide-decomposing in character and which can act in a truly catalytic fashion in the presence of suitable thiol reducing agents. Its "antioxidant profile" is outlined in Scheme 2 in comparison with that of ethoxyquin itself. The catalytic cycle to the right shows peroxyl radical quenching by way of hydrogen atom transfer and regeneration by thiol reduction of the corresponding aminyl radical. Due to its more robust structure, ethoxyquin outperforms its chalcogen analogues in this function. The catalytic cycle to the left shows hydroperoxide reduction by way of two-electron oxidation of the chalcogen and regeneration by thiol-mediated reduction of the corresponding telluroxide. Due to its higher nucleophilicity, tellurium analogue **1d** clearly outperforms all the other chalcogen analogues in this function.

We feel multifunctional, catalytic antioxidants such as compound **1d** could find many applications. Antioxidants are added today to a large variety of man-made and natural products to extend their service life (foods, polymers, oils, and lubricants). All these antioxidants exert their protection only on a stoichiometric basis. Therefore, although the concentrations are low, the total amounts of antioxidants that our bodies and the surrounding environment have to cope with are substantial. From a toxicological and environmental point of view, it would be much better if one could cut down on the amount of antioxidant used and make it act in a catalytic fashion together with readily available nontoxic regenerating agents. The compounds and concepts described above would seem ideal for development of such "green" antioxidant systems.

(46) Malkin, Ya. N.; Pirogov, N. O.; Kopytina, M. V.; Nosova, V. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1984**, 1866−1868.

Experimental Section

Ethyl 2,2,4-Trimethyl-1,2-dihydroquinolin-6-yl Sulfide (1b). To a solution of bromide **5** (504 mg, 2.00 mmol) in dry Et_2O (30 mL) was added *t*-BuLi (4.9 mL of a 1.42 M solution in pentane, 7.0 mmol) under nitrogen at −78 °C. Then the reaction mixture was brought to 0 °C and stirred for an additional 2 h. The colorless mixture was cooled again to −78 °C and diethyl disulfide (854 mg, 7.00 mmol) added dropwise. After removal of the cooling bath, the reaction mixture was stirred at ambient temperature for 2 h before addition of water. After separation and extraction of the aqueous phase with diethyl ether (2 × 25 mL), the combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and evaporated. Chromatography on silica gel (pentane/EtOAc, 97:3) afforded the title compound as a light yellow liquid (360 mg, 77%): ^{1}H NMR δ 7.17 (d, J = 2.1 Hz, 1H), 7.10 (dd, J = 2.1, 8.1 Hz, 1H), 6.36 (d, J = 8.1 Hz, 1H), 5.31 (s, 1H), 3.78 (br s, 1H), 2.77 (q, J = 7.3 Hz, 2 H), 1.98 (s, 3H), 1.27 (s, 6H), 1.23 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 143.9, 133.6, 128.9, 128.7, 128.0, 121.8, 121.0, 113.2, 52.0, 31.2, 30.9, 18.6, 14.8. Anal. Calcd for $C_{14}H_{19}NS$: C, 72.05; H, 8.21. Found: C, 72.01; H, 8.32.

Bis(2,2,4-Trimethyl-1,2-dihydroquinolin-6-yl) Ditelluride. To a solution of bromide **5** (504 mg, 2.00 mmol) in dry Et_2O (20 mL), under nitrogen, was added *t*-BuLi (4.9 mL of a 1.42 M solution in pentane, 7 mmol) at −78 °C. The cooling bath was then removed and the reaction mixture stirred at 0 °C for 45 min, at which time elemental tellurium (256 mg, 2.00 mmol) was added in one portion. Stirring was continued at ambient temperature for 1 h. The resulting brown heterogeneous mixture was poured into a beaker containing crushed ice and kept overnight in the open air. After extraction of the aqueous phase with diethyl ether (3 × 25 mL), the combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and evaporated. Chromatography on silica gel (pentane/EtOAc, 92:8) afforded the red title compound (360 mg, 60%) as a solid: mp 108−109 °C; ^{1}H NMR δ 7.42−7.39 (several peaks, 4H), 6.24 (d, J = 8.1 Hz, 2H), 5.29 (s, 2H), 3.77 (s, 2H), 1.92 (s, 6H), 1.28 (s, 12 H); ^{13}C NMR δ 144.0, 140.4, 135.6, 128.5, 128.1, 122.3, 113.8, 93.0, 52.2, 31.6, 18.7.

Ethyl 2,2,4-Trimethyl-1,2-dihydroquinolin-6-yl Telluride (1d). To a stirred solution of bis(2,2,4-trimethyl-1,2-dihydroquinolin-6-yl) ditelluride (150 mg, 0.250 mmol) in EtOH (15 mL) was added $NaBH_4$ (39 mg, 1.0 mmol) in one portion at 0 °C under N_2. After addition, the reaction mixture was brought to ambient temperature and stirred for an additional 30 min. Ethyl bromide (0.07 mL, 1.0

mmol) was added to the cooled (0 °C) reaction mixture and stirring continued for 1 h. After addition of brine, extraction with Et_2O, drying of the organic phase over Na_2SO_4, filtration, evaporation, and chromatographic purification on silica (pentane/EtOAc, 95:5), the title compound, 115 mg, 70%, was obtained as a yellow oil: ^{1}H NMR δ 7.47 (d, J = 1.8 Hz, 1H), 7.40 (dd, J = 1.7, 8.0 Hz, 1H), 6.29 (d, J = 8.0 Hz, 1H), 5.31 (s, 1H), 3.73 (br s, 1H), 2.76 (q, J = 7.6 Hz, 2H), 1.98 (1H, s), 1.60 (t, J = 7.6 Hz, 3H), 1.28 (6H, s); ^{13}C NMR δ 143.4, 140.8, 136.0, 128.6, 128.1, 122.5, 113.8, 95.4, 52.1, 31.5, 18.7, 17.4, 0.8. Anal. Calcd for $C_{14}H_{19}NTe$: C, 51.13; H, 5.82. Found: C, 51.19; H, 5.92.

Kinetic Measurements. Rate constants for the reaction of the antioxidants with peroxyl radicals have been measured by following the autoxidation of styrene (4.3 M) in chlorobenzene at 303 K using as the initiator AIBN (5×10^{-2} M). The antioxidant concentration was 6.25×10^{-6} to 5.0×10^{-5} M. The autoxidation of cumene (7.1 M) in chlorobenzene at 303 K was followed using AIBN (5×10^{-2} M) as the initiator and antioxidant at a concentration of 6.25×10^{-6} M.

EPR and Thermochemical Measurements. Deoxygenated benzene solutions containing ethoxyquin (0.01−0.001 M) and di-*tert*-butyl peroxide (10%, v/v) were sealed under nitrogen in a suprasil quartz EPR tube. The sample was inserted at room temperature in the cavity of an EPR spectrometer and photolyzed with unfiltered light from a 500 W high-pressure mercury lamp. The temperature was controlled with a standard variable-temperature accessory and was monitored before and after each run with a copper−constantan thermocouple. The EPR spectra were recorded on a spectrometer equipped with a microwave frequency counter for the determination of the g factors, which were corrected with respect to that of DPPH radical ($g = 2.0036_4$). When using mixtures of BHT or 2,6-dimethoxyphenol with compound **1a**, the molar ratio of the two equilibrating radicals was obtained from the EPR spectra and used to determine the equilibrium constant, K_e. Spectra were recorded a few seconds after irradiation was started to avoid significant consumption of the antioxidants during the course of the experiment. Relative radical concentrations were determined by comparison of the digitized experimental spectra with computer-simulated ones as previously described.[47]

Assay for Thiol Peroxidase Activity. Thiol peroxidase activity was determined essentially as described by Tomoda.[39] Initial rates recorded for the reduction of hydrogen peroxide (3.75 mM) in methanol by thiophenol (1 mM) at 25 °C in the presence of catalyst (0.01 mM) were recorded by monitoring the UV absorption of diphenyl disulfide at 305 nm. Initial rates were measured at least six times and calculated for the first 60 s of reaction. The rate of disulfide formation was corrected for the slow spontaneous thiol oxidation by subtracting the rate of disulfide formation in a control experiment run without added catalyst.

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

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