Catalytic Antioxidant Activity of Diaryl Tellurides in a Two-Phase Lipid Peroxidation Model

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Diaryl tellurides, diaryl sulfides, ebselen, probucol, BHT, trolox, and vitamin E were assessed for their capacity to inhibit azo-initiated peroxidation of linoleic acid in a water/chlorobenzene two-phase system containing *N*-acetylcysteine as a thiol reducing agent in the aqueous phase. The progress of peroxidation in the organic layer was monitored by HPLC with UV detection, and the inhibited rate of peroxidation, R_{inh}, and the duration of the inhibited phase, T_{inh}, were determined. In catalytic amounts (40 μM), both phenolic and nonphenolic diaryl tellurides efficiently inhibited peroxidation in the chlorobenzene layer until the thiol reducing agent in the aqueous phase had been completely oxidized to the corresponding disulfide. Although efficient, trolox and vitamin E offered antioxidant protection only on a stoichiometric basis. BHT, probucol, and ebselen all showed poor antioxidant capacity under the conditions used. Some phenolic diaryl sulfides were moderately efficient inhibitors, with the antioxidant protection enduring for a considerable time without consumption of *N*-acetylcysteine in the aqueous phase. It is proposed that the diaryl tellurides act as hydrogen atom and/or electron donors toward peroxyl radicals. Further oxidation/hydrolysis probably provides tellurium(IV) dihydroxides, which can recycle to the active antioxidant through reduction by *N*-acetylcysteine at the water/chlorobenzene interphase.

Introduction

Antioxidants can act by interception at different levels in the oxidative degradation of organic materials. Chain-breaking donating and chain-breaking accepting antioxidants, which scavenge intermediate radicals, are usually consumed in this process, whereas preventive antioxidants such as metal complexing agents and UV absorbers are not. Peroxide decomposers, which are also preventive in their action, may (*e.g.* glutathione peroxidase enzymes) or may not (*e.g* phosphite esters) act in a catalytic fashion.[1,2] The tocopherols are potent, lipid-soluble, chain-breaking antioxidants in biological systems. It is now recognized that these species are the major peroxyl radical-trapping agents in human blood.[3] For efficient utilization of these precious compounds, nature has provided for their regeneration, most probably by vitamin C, at the lipid/water interphase. Such a regenerative mechanism has been corroborated by various *in vitro* experiments.[3,4]

Reactive oxygen metabolites have been implicated in the pathogenesis of many diseases[5,6] associated with oxidative stress, a situation that exhausts the endogenous antioxidant defense network. Therefore, the pharmacological concept of antioxidant treatment has emerged. It was recently emphasized that antioxidant drugs must be readily assimilated into the operating endogenous antioxidant screen.[5]

We have studied for some time the antioxidative properties of organotellurium compounds. It was recently demonstrated that diaryl ditellurides[7] and diaryl tellurides[8,9] act as catalytic peroxide decomposers in the presence of various thiols as stoichiometric reducing agents. The proposed mechanism for the diaryl telluride-catalyzed decomposition of hydrogen peroxide is shown in Figure 1. The ability of some of these compounds to inhibit stimulated peroxidation in rat hepatocytes[10,11] and rat liver microsomes[10,11] and of linoleic acid in methanol[12] suggested that this class of organotellurium compounds has the capacity to act also as chain-breaking antioxidants. We therefore developed a model that allows convenient assessment of such properties. In the following we report on the catalytic antioxidant action of diaryl tellurides in a water/chlorobenzene two-phase system for azo-initiated peroxidation of linoleic acid.

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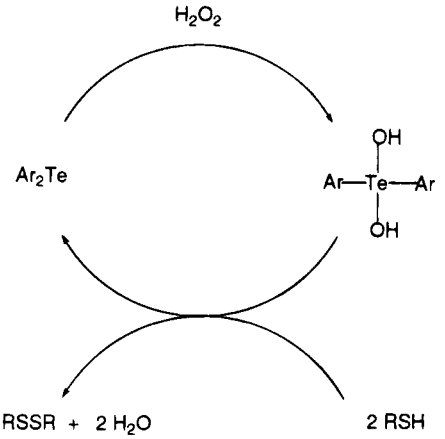


Figure 1. Proposed catalytic mechanism for the peroxide decomposing action of diaryl tellurides in the presence of thiols.

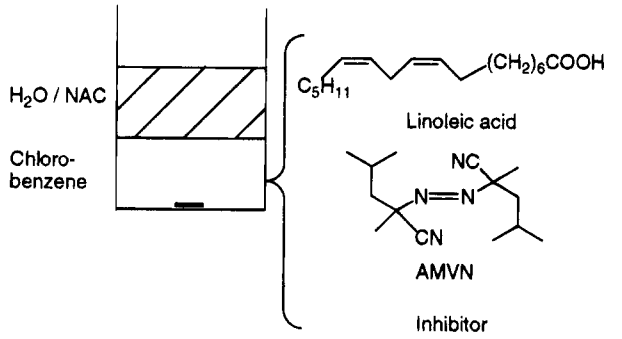
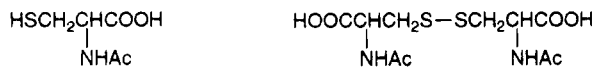


Figure 2. Lipid peroxidation two-phase system used for the assessment of antioxidant capacity.

Results

Azo-initiated peroxidation of linoleic acid or derivatives thereof has been frequently used for studying the antioxidant properties of synthetic and natural compounds in various organic solvents[13-15] or micellar systems.[16] Since diaryl tellurides are probably oxidized to the tetravalent state when they act as chain breakers (*vide infra*)[11,12] and these species are readily reduced by a variety of water-soluble reducing agents (thiols, ascorbate, sulfite, hydrazine etc.),[17] we decided to develop a two-phase peroxidation model[18] in which regeneration of the antioxidant could occur. In the procedure used (see Figure 2), linoleic acid and the antioxidant studied were vigorously stirred in chlorobenzene for 1 h at 42 °C with a solution containing *N*-acetylcysteine (NAC) as a thiol



NAC di-NAC

reducing agent. Then, 2,2′-azobis(2,4-dimethylvaleronitrile) (AMVN) was added to initiate peroxidation in the organic phase and the progress of peroxidation monitored by HPLC with UV detection of conjugated diene at 234 nm. For comparison of catalyst efficiency, the inhibited rate of peroxidation, R_{inh}, was determined by least-squares methods from absorbance/time plots during the first hour after addition of the initiator. The progress of peroxidation was then followed for another 3 h and the duration of the inhibited phase, T_{inh}, determined graphically as the cross-point for the inhibited and the uninhibited lines[16] (for typical peroxidation traces, see Figures 3–5). Under the standard experimental conditions used (inhibitor, 40 μM; NAC, 1 mM; linoleic acid, 34 mM; AMVN, 1.4 mM; temperature, 42 °C; stirring rate, 1500 rpm) the inhibited phase lasted for approximately 2 h for most of the diaryl tellurides tested. In a control experiment it was shown that the presence of NAC in the aqueous phase did not affect the uninhibited rate of peroxidation (1800–1900 μM/h) in the chlorobenzene layer. The R_{inh} values determined for various organotellurium compounds **1–7**, diaryl sulfides **8** and **9**, the organoselenium compound ebselen (**10**), probucol (**11**), BHT (**12**), trolox (**13**), and vitamin E (**14**) are shown in Table 1. It is clear from these values that some of the organotellurium compounds are as efficient inhibitors of lipid peroxidation as vitamin E and trolox and considerably more efficient than diaryl sulfides, BHT, probucol, and ebselen.

For some of the inhibitors studied (compounds **1b**, **3**, **7–9** and **14**), the concentration of NAC in the aqueous phase was monitored by HPLC during ordinary peroxidation conditions. A control experiment showed that some of the thiol was spontaneously oxidized to the corresponding disulfide (di-NAC) during the experiment. However, in the presence of compounds **1b**, **3**, and **7**, the oxidation of NAC to di-NAC was considerably faster. Furthermore, the inhibited phase of peroxidation lasted only until the thiol had been consumed in the aqueous phase. A typical peroxidation trace for a diaryl telluride-inhibited reaction is shown in Figure 3 (antioxidant **1b**). When the concentration of NAC in the aqueous layer was increased (4 mM) in this experiment, the inhibited phase of peroxidation was extended (>6 h). On the other hand, when a 0.1 mM NAC solution was used, peroxidation was hardly inhibited at all. Also, when the antioxidant concentration was reduced to 10 μM under the ordinary experimental conditions (NAC, 1 mM), the peroxidation rate was close to that recorded in the blank experiment.

When vitamin E was used as the antioxidant under the standard experimental conditions, the consumption of NAC during the course of the experiment corresponded only to the spontaneous oxidation and the inhibited phase of peroxidation lasted for 1.5 h (see Figure 4). Diaryl sulfide antioxidants **8** and **9** showed yet another behavior. The peroxidation was only moderately well inhibited, but the inhibitory action prevailed for all 4 h of the experiment. Also in this case, the consumption of NAC corresponded only to the spontaneous oxidation. A peroxidation trace for compound **8** is shown in Figure 5.

Discussion

Studies of the autoxidation of organic compounds and its inhibition by various synthetic and natural antioxidants have been performed in homogeneous solution, in micelles and liposomes, and in biological membrane preparations.[19] Far less work has been carried out in

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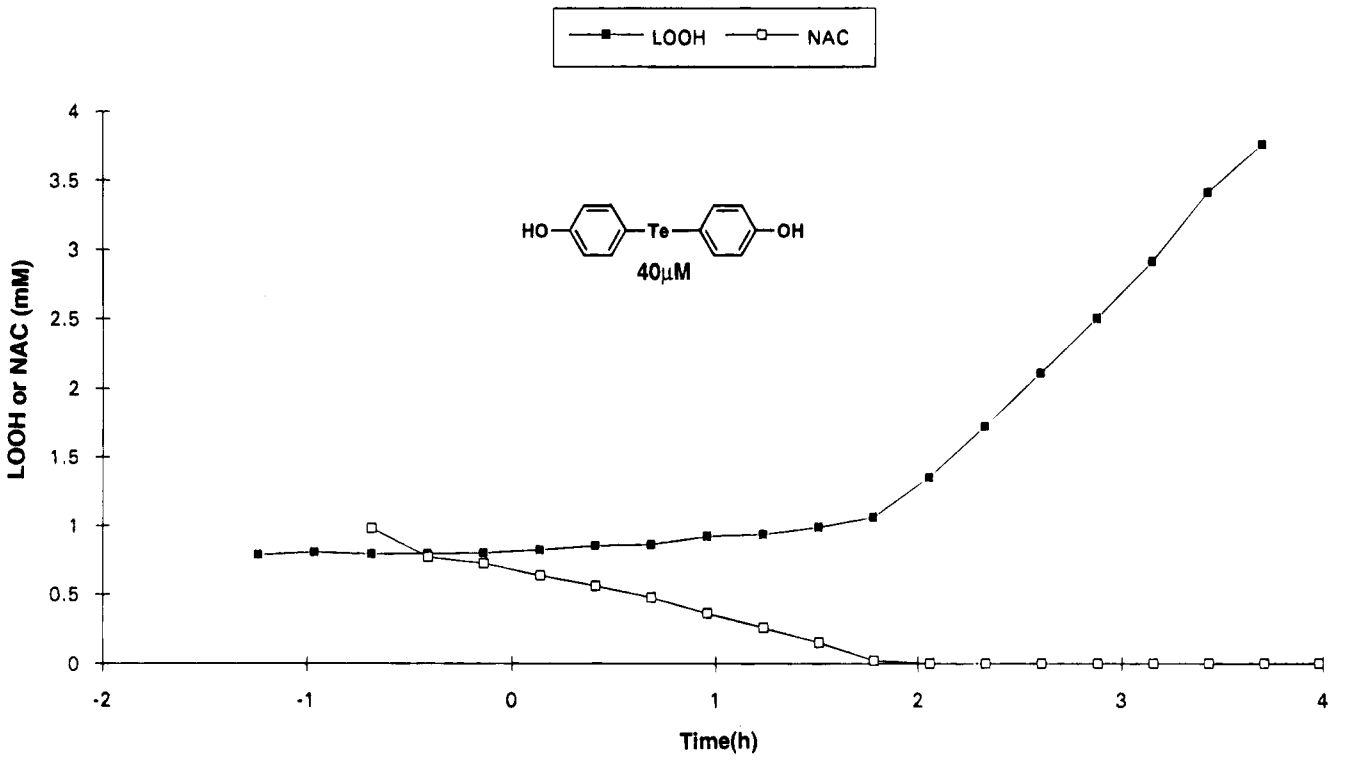

Figure 3. Concentration of conjugated diene (LOOH) and *N*-acetylcysteine (NAC) as a function of time using catalyst **1b** under the standard peroxidation conditions.

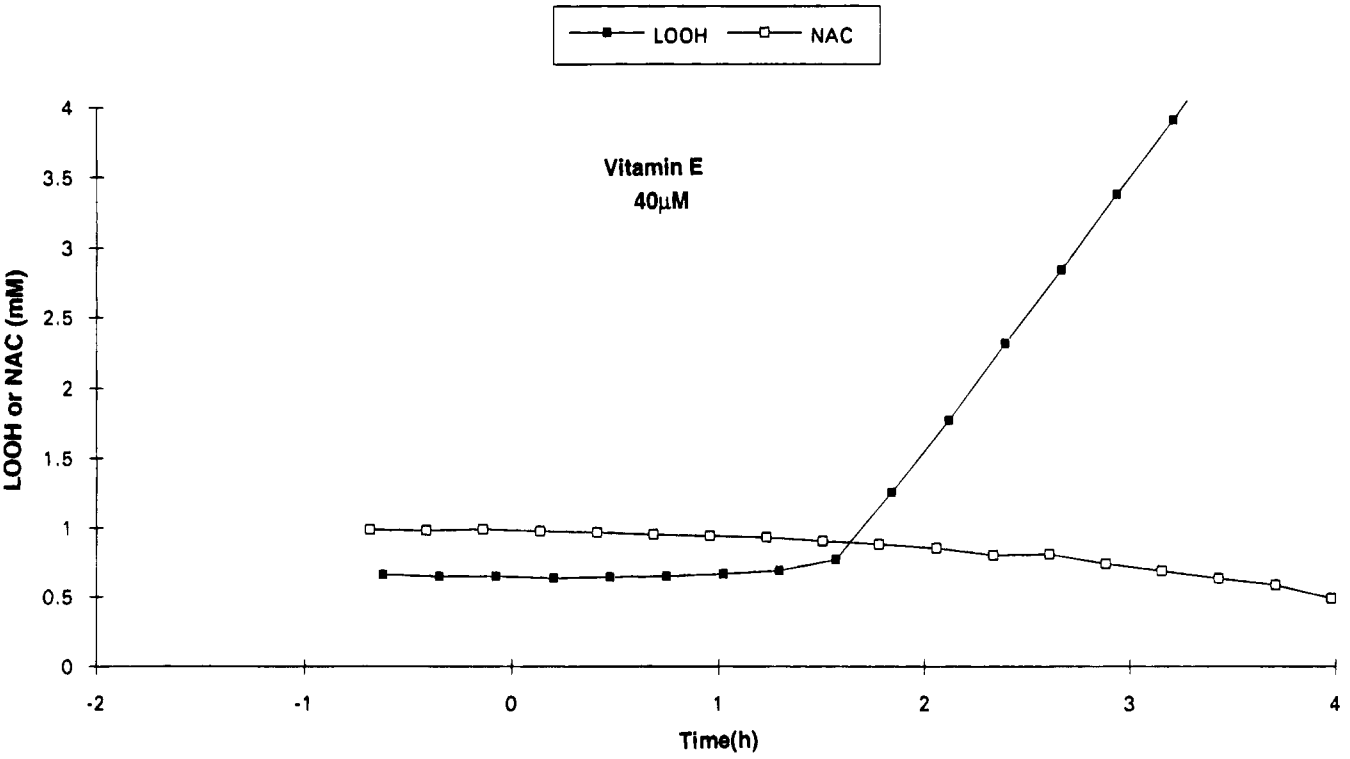

Figure 4. Concentration of conjugated diene (LOOH) and *N*-acetylcysteine (NAC) as a function of time using catalyst **14** under the standard peroxidation conditions.

pure bilayer systems, probably because equilibration between phases is not rapid enough to obtain quantitative kinetic data. The two-phase model described in the present work was designed to address the problem of regenerating a catalyst across a phase boundary. In such a study, it is necessary to separate the aqueous and oil-like phases to monitor the extent of peroxidation as well as the consumption of the regenerating species. Among the stoichiometric reducing agents considered, NAC was selected because of its high water solubility and ability to lower the pH of the aqueous phase (the pH of a 1 mM aqueous solution is ≈3.1). Attempts to buffer the solution at a higher pH resulted in too rapid spontaneous oxidation of the thiol. Except for compounds **1d** and **1e**, all antioxidants investigated can be assumed to be present predominantly in the chlorobenzene layer under the conditions of the assay. However, the similar R_{inh} and T_{inh} values for these and other organotellurium com-

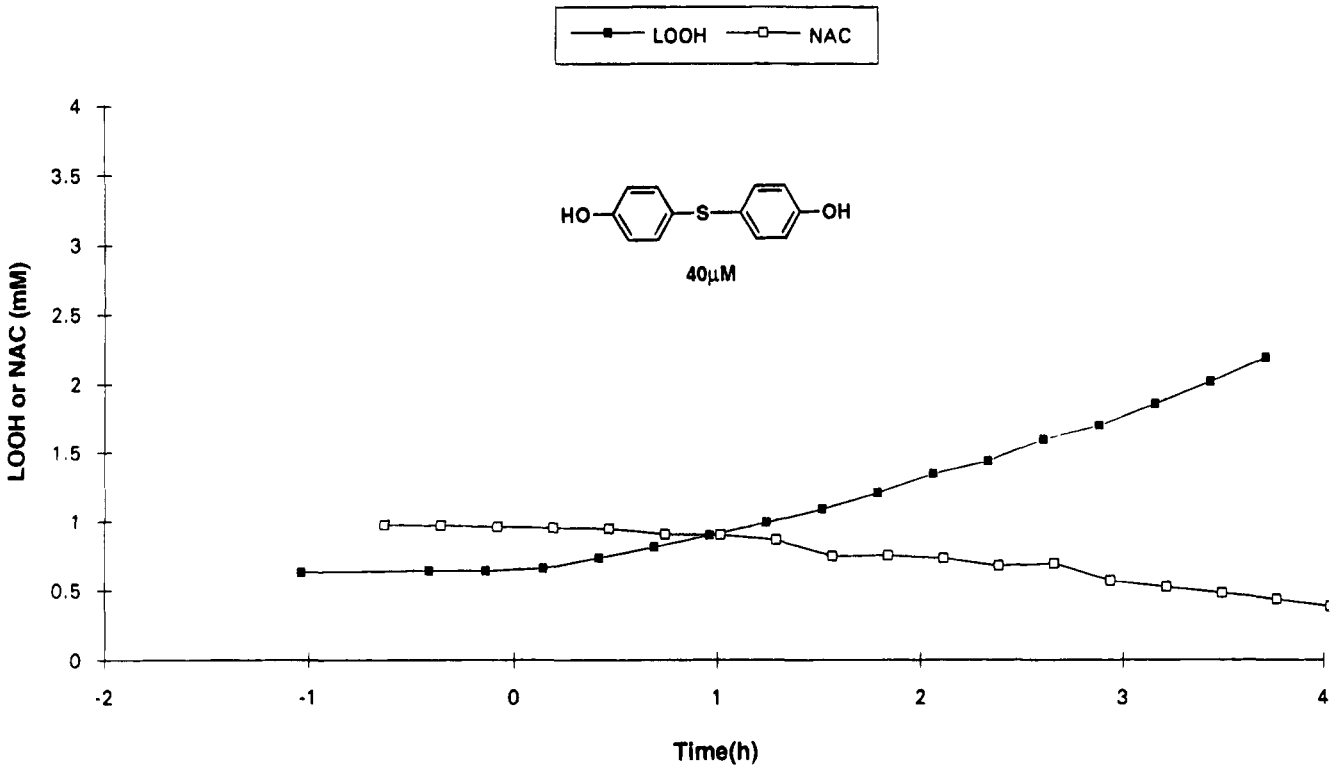

Figure 5. Concentration of conjugated diene (LOOH) and *N*-acetylcysteine (NAC) as a function of time using catalyst **8** under the standard peroxidation conditions.

pounds seem to indicate that equilibration between the two phases is not a restriction for antioxidant activity.

For the organotellurium antioxidants, the observed inhibited rates of peroxidation, R_{inh}, reflect both the intrinsic antioxidant capacity of the compounds and their regenerability. These two properties are not separable under the experimental conditions used. However, for the sterically unhindered 4,4′-disubstituted diaryl tellurides **1**, we believe that regeneration of the catalyst from its corresponding oxide occurs rapidly for all compounds and that the R_{inh} values reflect the capacity of these materials to scavenge lipid peroxyl radicals in chlorobenzene. It is noteworthy that the antioxidant efficiency increases as the oxidation potentials of the compounds decrease (the irreversible peak oxidation potentials, E_p, of compounds **1a**–**e** are 0.95, 0.80, 0.80, 0.56, and 0.50 V, respectively, as determined by cyclic voltammetry using an Ag/AgCl reference electrode; see Table 1). By assuming rapid catalyst regeneration, the superiority of phenolic 3,3′,5,5′-tetramethylated catalyst **2a** over its corresponding 3,3′,5,5′-tetra-*tert*-butylated derivative **2b** may also be explained by the lower oxidation potential of the former (E_p = 0.75 *vs* 1.12 V; Table 1). As compared with the corresponding unmethylated catalyst **1b**, we observed a slower consumption of NAC in the aqueous phase when the sterically hindered 2,2′,6,6′-tetramethylated phenolic inhibitor **3** was used. However, since the peak oxidation potential of the latter compound is higher by 0.20 V, we do not, even in this case, have to invoke the regeneration step to explain the difference in antioxidant activity.

Bis(2-hydroxyphenyl) telluride (**4**) was the most efficient inhibitor of lipid peroxidation in the series. This compound was also among the most readily oxidized of the phenolic organotellurium compounds (E_p = 0.70 V).

To modify the lipophilicity of the diaryl tellurides, one of the OH groups of the bisphenolic compound **1b** was tetradecylated and carboxymethylated, respectively, to give compounds **5a** and **5b**. Among these derivatives, the former was a slightly more efficient inhibitor than its precursor, whereas the latter, despite its low oxidation potential (E_p = 0.68 V), was considerably less efficient. At present, we have no rationalization for this observation. Substitution of one phenolic group for hydrogen in compound **1b** produced a less efficient antioxidant **6** with increased (by 0.13 V) oxidation potential.

Concerning the antioxidant mechanism, we believe that the organotellurium compounds act as reducing agents toward peroxyl radicals, thus being converted into tellurium(IV) dihydroxides. In keeping with this hypothesis, diaryl telluroxide **7** exhibited an R_{inh} value and a time of inhibition similar to those of telluride **1b**. All phenolic diaryl tellurides studied (compounds **1b** and **2**–**6**) can act both as hydrogen atom donors and as electron donors toward peroxyl radicals (see Scheme 1). However, since the radical cation formed in the latter case is known to readily lose a proton (the pK_a in water of the radical cation of compound **1b** is ≈2.5)[20] to give a resonance-stabilized phenoxyl radical, it is not meaningful to try to distinguish between the two modes of action. Further oxidation/hydrolysis of the phenoxyl radical then results in the formation of a thiol reducible tellurium(IV) dihydroxide. Considering the irreversible oxidation peaks in the cyclic voltammograms of these compounds,[21] it is unlikely that the phenoxyl radical would survive long enough to be reduced by thiol at the water/chlorobenzene interphase.

Compounds **1a**, **1c**, and **1e** can only reduce peroxyl radicals by electron transfer (Scheme 1). The radical cations so formed are also expected to be very reactive. After oxidation/hydrolysis or disproportionation/hydrolysis, thiol reducible tellurium(IV) dihydroxides would

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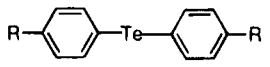
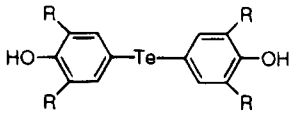
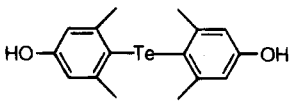
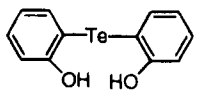
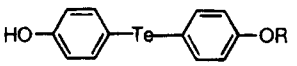
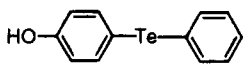
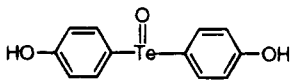
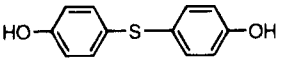
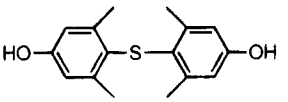
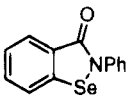
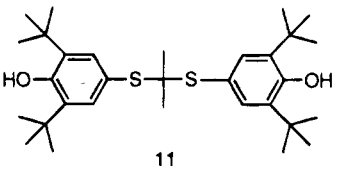
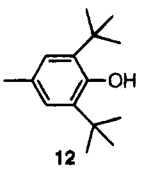
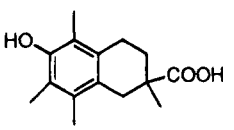
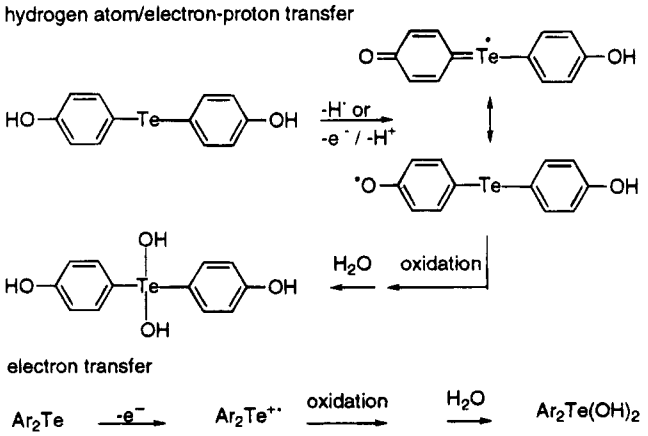
Table 1. Inhibited Rate of Peroxidation, R_{inh}, Oxidation Potential, E_p, and Time of Inhibition, T_{inh}, for Antioxidants Tested

antioxidant	R_{inh}(μM/h)[a]	E_p(V)[b]	T_{inh}(h)[c]
			
1 a R=H	760	0.95	1.8
b R=OH	110	0.80	1.8
c R=OMe	240	0.80	1.6
d R=NH_2	95	0.56	2.0
e R=NMe_2	51	0.50	2.6
			
2 a R=Me	75	0.75	2.0
b R=t-Bu	200	1.12	1.8
			
3	275	1.00	2.6
			
4	22	0.70	3.1
			
5 a R=$C_{14}H_{29}$	91	0.94	1.9
b R=CH_2COOH	330	0.68	1.7
			
6	165	0.93	2.3
			
7	66	-	2.0
			
8	290	1.37	>4.0
			
9	300	1.34	>4.0
			
10	1860	1.52	0
			
11	1045	1.16	1.8
			
12	810	1.48	1.0
			
13	67	-	1.5
Vitamin E (14)	36	0.84	1.5

[a] Rate of peroxidation during the inhibited phase (uninhibited rate ≈ 1800−1900 μM/h). [b] Irreversible peak oxidation potential *vs* Ag/AgCl. [c] Duration of the inhibited phase of peroxidation.

Scheme 1. Proposed Chain-Breaking Mechanisms for Diaryl Tellurides



result. Compound **1d** can probably act both as a hydrogen atom donor and as an electron donor. The deprotonation (NH_2 group) of the corresponding radical cation occurs in water at considerably higher pH (>10) than for compound **1b**.[20]

Diaryl tellurides are efficient catalysts not only for the thiol-mediated reduction of hydrogen peroxide (Figure 1)[8,9] but also for the reduction of a variety of organic hydroperoxides (*tert*-butylhydroperoxide,[8,9] cumene hydroperoxide,[8] and linoleic acid hydroperoxide[8]). This peroxide-decomposing effect should also be expressed in the bilayer system developed in the present work. In a separate experiment it was shown that linoleic acid hydroperoxide[22] rapidly oxidized telluride **1b** in chlorobenzene to telluroxide **7** and that this species was reduced to telluride upon treatment with an aqueous solution of NAC. Thus, hydroperoxides formed during the course of the peroxidation experiment or present as contaminants in the linoleic acid would be reduced to the corresponding alcohols. These processes would cause a

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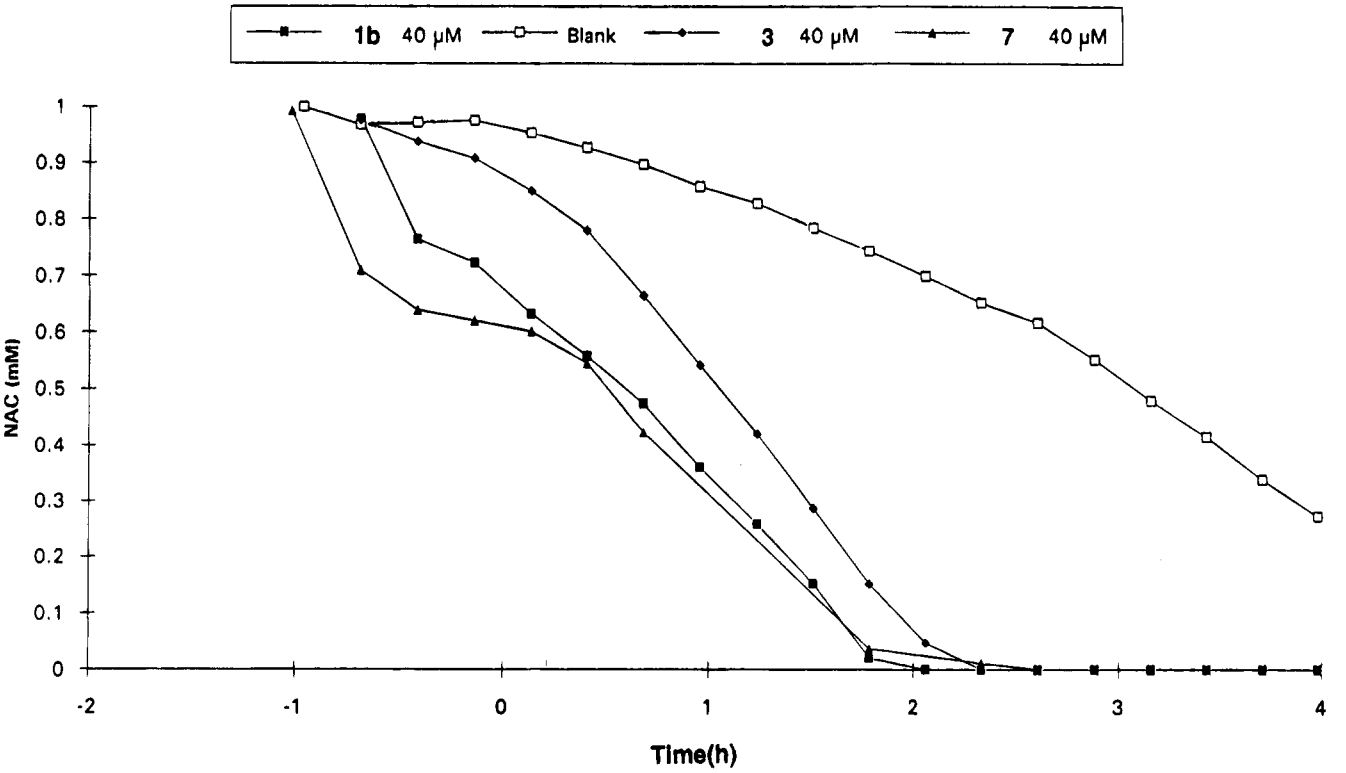

Figure 6. Concentration of *N*-acetylcysteine (NAC) as a function of time using catalysts **1b**, **3**, and **7** under the standard peroxidation conditions.

consumption of NAC in the aqueous phase. However, since the extinction coefficients for conjugated diene hydroperoxides and alcohols are similar,[23] the UV absorption will not be much affected. In Figure 6, the consumption of NAC during peroxidation experiments using compounds **1b**, **3**, and **7** are compared. For compound **7**, part of the rapid consumption of NAC during the equilibration phase (before addition of the initiator) is due to reduction of the tellurium(IV) compound to the divalent state. The remaining initial NAC consumption (*cf.* compound **1b**) is probably due to reduction of hydroperoxide impurities in the linoleic acid. As shown in Figure 6 (equilibration phase), telluride **3** is a poorer catalyst for hydroperoxide reduction than telluride **1b**. This is probably because the heteroatom in this compound is sterically hindered by the four *ortho* methyl groups.[9]

By assuming that the isomers of linoleic acid hydroperoxide formed are continuously reduced to the corresponding alcohols by NAC as shown in Figure 1, we can roughly estimate the duration of the inhibited phase of peroxidation in the telluride-inhibited reactions as follows. Vitamin E has a stoichiometric factor of 2.0.[19] Since it inhibits peroxidation for 1.5 h when present in a concentration of 40 μM, 53 μM/h of peroxyl radicals is generated. For their reduction to hydroperoxides (via electron transfer or hydrogen atom transfer from the organotellurium compound), 53 μM/h NAC will be consumed to regenerate the organotellurium compound. In addition, another 106 μM/h NAC will be consumed in the telluride-catalyzed reduction of the linoleic acid hydroperoxides formed. The spontaneous oxidation of NAC as determined from a blank experiment corresponds to approximately 170 μM/h. There is also a 250 μM consumption of NAC during the equilibration phase (due to hydroperoxide impurities). With these crude assumptions, a 1 mM solution of NAC would be consumed in 2.3 h. This is in reasonable agreement with the observed T_{inh} values in Table 1. Considering the relatively high NAC consumption during the equilibration phase of the experiments, the poor inhibition caused by telluride **1b** in the presence of a 0.1 mM NAC solution is rational.

The phenolic diaryl sulfides **8** and **9** do not consume thiol in the aqueous layer as they exert their antioxidative protection. Although only moderately efficiently, they inhibit peroxidation for longer times than any of the other antioxidants tested in the *absence* of any thiol reducing agent. At present, we have no suggestion for an antioxidant mechanism. However, the antioxidant mechanisms for similar compounds have been studied by Pospisil and co-workers.[24]

Ebselen has been reported to act both as a peroxide decomposer and as a chain-breaking agent.[25] In view of a recent investigation by Niki and co-workers[26] it is not surprising to find that the material is a very poor inhibitor in our model. As compared with the other phenolic antioxidants studied, probucol and BHT offered very poor protection against azo-initiated peroxidation under the conditions used.

The apparent intrinsic antioxidant capacities (*i.e* those in the absence of regenerating agents) in chlorobenzene of the diaryl tellurides investigated in this work are much poorer than those of vitamin E. However, this can be

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compensated for by an efficient regeneration of the catalyst as shown in Figure 1. Under the two-phase conditions used, it is possible to maintain a steady-state concentration of the organotellurium antioxidants high enough to essentially suppress peroxidation of the linoleic acid. Thus, by using relatively small quantities of the organotellurium compounds and larger amounts of a thiol reducing agent, it is possible to surpass vitamin E and other good antioxidants with respect to the duration of the antioxidant protection.

Experimental Section

Melting points were uncorrected. ^{1}H NMR spectra, obtained at 250 MHz, were recorded in solutions containing tetramethylsilane as the internal standard. Dimethyl sulfoxide was dried over molecular sieves. Tetrahydrofuran was freshly distilled from potassium/benzophenone. Linoleic acid (99%), 2,2′-azobis(2,4-dimethylvaleronitrile), chlorobenzene, octanesulfonic acid, bis(4-hydroxyphenyl) sulfide, probucol, BHT, trolox, and vitamin E were obtained from commercial sources. The organotellurium compounds **1a**,[27] **1b**,[17] **1c**,[28] **1d**,[29] **1e**,[29] **2a**,[9] **2b**,[9] **3**,[12] **4**,[9] **6**,[9] and **7**,[30] diaryl sulfide **9**,[31] and ebselen[32] were prepared according to literature methods.

4-Hydroxyphenyl 4-(Tetradecyloxy)phenyl Telluride (5a). Dimethyl sulfoxide (15 mL) was added to sodium hydride (0.051 g, 80%; 1.7 mmol) and bis(4-hydroxyphenyl) telluride (0.440 g, 1.4 mmol) under an atmosphere of dry nitrogen. When the evolution of hydrogen had ceased (≈10 min), tetradecyl bromide (0.386 g, 1.4 mmol) was added by syringe and the reaction mixture stirred at 90 °C for 2.5 h. After dilution with water (100 mL), extraction with methylene chloride (3 × 50 mL), drying ($MgSO_4$) of the organic phase, evaporation, and flash chromatography (SiO_2, CH_2Cl_2), 0.26 g (36%) of compound **5a**, mp 71–72 °C (hexanes), was isolated: ^{1}H NMR ($CDCl_3$) δ 0.68 (t, 3H), 1.20–1.50 (several peaks, 22H), 1.76 (m, 2H), 3.92 (t, 2H), 4.70 (s, 1H), 6.69 (d, 2H), 6.75 (d, 2H), 7.57 (d, 2H), 7.62 (d, 2H). Anal. Calcd for $C_{26}H_{38}O_2Te$: C, 61.21; H, 7.51. Found: C, 61.25; H, 7.39.

4-(Carboxymethoxy)phenyl 4-Hydroxyphenyl Telluride (5b). Sodium hydride (0.018 g, 80%; 0.60 mmol) and bis(4-hydroxyphenyl) telluride (0.16 g, 0.50 mmol) were placed under nitrogen in a flask equipped with a magnetic stirring bar and a reflux condenser. Dry tetrahydrofuran (15 mL) was then added by syringe and the reaction mixture stirred until the gas evolution had ceased (≈30 min). Methyl bromoacetate (0.153 g, 1.0 mmol) was then added and the reaction mixture heated at reflux for 24 h. After cooling, dilution with water (50 mL), extraction with methylene chloride (3 × 25 mL), drying ($MgSO_4$) of the organic phase, evaporation, and flash chromatography (SiO_2, CH_2Cl_2/MeOH = 99/1), 0.069 g (35%) of 4-(carbomethoxymethoxy)phenyl 4-hydroxyphenyl telluride was isolated: ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 4.61 (s, 2H), 5.57 (br s, 1H) 6.69 (d, 2H), 6.74 (d, 2H), 7.57 (d, 2H), 7.58 (d, 2H). When the above procedure was scaled-up five times, the yield was lower (21%).

4-(Carbomethoxymethoxy)phenyl 4-hydroxyphenyl telluride (0.45 g, 1.17 mmol) was dissolved in tetrahydrofuran (30 mL), and water (20 mL) containing lithium hydroxide monohydrate (0.24 g, 5.7 mmol) was added. The reaction mixture was then stirred for 20 h, poured into water (100 mL), and acidified with concd hydrochloric acid. After extraction with ether, drying ($MgSO_4$) of the organic phase, and evaporation, 0.39 g (90%) of compound **5b**, mp 120–128 °C (MeOH/H_2O), was obtained: ^{1}H NMR (DMSO-d_6) δ 4.65 (s, 2H), 6.68 (d, 2H), 6.80 (d, 2H), 7.51 (d, 2H), 7.53 (d, 2H), 9.67 (s, 1H). Anal. Calcd for $C_{14}H_{12}O_4Te$: C, 45.22; H, 3.25. Found: C, 45.06; H, 3.38.

Peroxidation Assay. An HPLC (Waters 600) equipped with an autoinjector (5 μL samples were withdrawn every 16.5 min) with a sample holder at 42.0 °C (Gilson 231 with thermostated sample rack), a UV detector (Kratos 757), and a Nelson 6000 chromatography data system was used for the peroxidation studies. In a typical experiment linoleic acid in chlorobenzene (7.5 mL, 36.2 mM) was stirred (1500 rpm) in a 20 mL thermostated reaction vessel. To this solution was added the inhibitor in 1-butanol (107 μL, 3.0 mM; 40 μM final concentration) by syringe followed by an aqueous thermostated solution of NAC (8.0 mL, 1.0 mM). Finally, a thermostated solution of AMVN in chlorobenzene (0.5 mL, 22.4 mM) was added. Samples were withdrawn (after interruption of the stirring and phase separation) from the lower chlorobenzene layer and injected onto a Waters Resolve Silica 90 Å column (5 μm, 3.9 × 150 mm) eluted with heptane/ethanol (95/5) at a flow rate of 1.0 mL/min. After sampling, stirring was immediately resumed, allowing for an overall 79% mixing time during an experiment. The formation of conjugated dienes (retention time 3.8–4.3 min) was monitored at 234 nm and the concentration determined by integration using an experimentally determined response factor. This was based on the amount of triphenylphosphine oxide formed in the reaction of linoleic acid hydroperoxides with excess triphenylphosphine.

Each of the three first additions of reactants to the reaction vessel was arranged to occur immediately before the automatic sampling. Then, after equilibration (three additional samplings), the initiator was added ($t = 0$ in Figures 3–6) followed by 15 more analyses during the next 4 h. The inhibited rate of peroxidation, R_{inh} (Table 1), was calculated by least-squares methods during the first hour (four injections) after addition of the initiator. In a blank experiment, in the absence of inhibitor, the uninhibited rate of peroxidation was 1800–1900 μM/h. T_{inh} values were determined graphically as the cross-point for the inhibited and the uninhibited lines.

For the determination of NAC/di-NAC in the aqueous phase during a peroxidation experiment, the above experimental procedure was repeated with the following modifications. Samples were withdrawn from the upper aqueous phase and injected onto a Supelcosil LC18 column (5 μm, 4.6 × 150 mm) eluted with methanol/octanesulfonic acid 15 mM + H_3PO_4 25 mM = 3/97 at a flow rate of 1.0 mL/min. The retention times for NAC and di-NAC, respectively, were 3.1 and 5.5 min. The progress of the reaction was monitored by UV at 220 nm. The concentration of NAC during the peroxidation experiment (see Figures 3–6) was determined by integration using an experimentally determined response factor.

Electrochemistry. The oxidation potentials, given as the peak potentials, E_p, in Table 1, were determined from cyclic voltammograms as previously described using an Ag/AgCl electrode as reference.[21]

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