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DIARYL TELLURIDES AS INHIBITORS OF LIPID PEROXIDATION IN BIOLOGICAL AND CHEMICAL SYSTEMS

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Diaryl tellurides carrying electron-donating substituents in the *para* positions were found to efficiently inhibit peroxidation of rat hepatocytes, rat liver microsomes and a chlorobenzene solution of phosphatidylcholine. The most active compound in the microsomal assay, bis(4-dimethylaminophenyl) telluride, showed an IC_{50}-value of 30 nM. This compound also caused a dose-dependent delay of the onset of the linear phase of microsomal peroxidation stimulated by iron/ADP/ascorbate. The peak oxidation potentials of the diaryl tellurides (0.50-1.14 V in MeCN) correlated linearly with the IC_{50}-values in this assay, with a point of inflection around 0.85 V. In the hepatocyte system, all compounds showed similar protective activity. It is proposed that diaryl tellurides exert an antioxidative effect by deactivating both peroxides and peroxyl radicals under the formation of telluroxides. These oxides may regenerate the active divalent organotellurides upon exposure to a suitable reducing agent.

KEY WORDS: Lipid peroxidation, microsomes, hepatocytes, diaryl tellurides, antioxidants.

INTRODUCTION

It is now well established that most cell types undergoing aerobic metabolism produce reduced metabolites of oxygen which possess considerable chemical reactivity.[1] These reactive oxygen metabolites (ROMS) include the superoxide anion radical, hydrogen peroxide and the hydroxyl radical.[2] Apart from possessing intrinsic reactivity themselves, ROMs can also induce the formation of secondary oxidative metabolites of tissue macromolecules such as the lipid hydroperoxides produced during

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lipid peroxidation.[3] As a consequence of this "oxidative stress", most tissues rely on an intricate network of antioxidant principles designed to hold the existence of ROMs in equilibrium.[4] Under certain circumstances oxidants may also be produced in extremely high concentrations locally in the tissues during specialised physiological reactions, such as the acute inflammation reaction,[5] and during pathophysiological processes, such as those occurring during the reperfusion of ischemic tissue.[6] During such episodes, the endogenous antioxidants are placed under an increased burden and may become compromised, allowing uncontrolled oxidation of biological molecules and subsequent cell damage.[4] It is thus of considerable medicinal interest to develop suitable xenobiotic antioxidant molecules which may protect, or augment the activity of endogenous antioxidants. Such molecules might find application in the treatment of a variety of human disease states involving increased tissue-specific "oxidative stress".

The redox activity of the active site selenocysteine in a variety of glutathione-dependent peroxidases,[7] such as soluble glutathione peroxidase (GSH-px) and phospholipid hydroperoxide glutathione peroxidase (PLGSH-px), allows these enzymes to efficiently catalyse the reduction of both hydrogen peroxide and organic hydroperoxides, including lipid hydroperoxides. Several attempts have been made to synthesise low molecular weight antioxidant compounds which utilize the redox activity of selenium.[8-12] One of the best studied GSH-px mimetics is Ebselen (2-phenyl-benzisoselenazol-3(2H)-one). This compound has been ascribed radical scavenging, as well as GSH-px-like activities.[8] More recent reports, however, suggest that the latter property is the more relevant in biological systems.[13] We recently reported that diaryl selenides possess antioxidant capacity in biological systems undergoing lipid peroxidation.[11] In this paper we report that the substitution of selenium by tellurium in a series of diarylchalcogenides results in a pronounced increase in antioxidant capacity. The compounds investigated are, to our knowledge, among the most potent inhibitors of lipid peroxidation described in the literature to date.

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MATERIALS AND METHODS

Compounds

The diaryl tellurides used in this study were synthesised according to published procedures.[14] Bis(4-aminophenyl) selenide,[15] bis(4-dimethylaminophenyl) selenide,[16] bis(4-methoxyphenyl) selenide,[17] and bis(4-methoxyphenyl) telluroxide,[18] were also prepared according to literature procedures. Bis(4-methoxyphenyl) selenoxide was purchased from TCI, Japan. Ebselen was a gift from A Nattermann GmbH, Köln, Germany. The peak oxidation potentials were determined by standard cyclic voltammetry in acetonitrile, using tetraethylammonium perchlorate as the electrolyte.[14] Azoisobutyronitrile (AIBN) was purchased in >99% purity from Riedel de Haën. Chlorobenzene (>99%) was from Aldrich, and phosphatidyl choline (PC), type *III*-s from Soybean (99% pure), was purchased from Sigma, St Louis, MO, USA. All other materials and chemicals for the preparation of hepatocytes and liver microsomes, as well as for the analysis of lipid peroxidation products, were as referenced and obtained from local suppliers in the highest grade available.

Preparation of Biological Materials

All biological material was prepared from male Sprague-Dawley rats (200 g) which were fed a standard diet and water *ad libitum*. Hepatocytes were isolated by

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collagenase perfusion of the liver as described by Moldéus *et al.*[19] Liver microsomes were prepared by homogenisation of the liver in sucrose (250 mM) at 4°C, followed by differential density centrifugation, as described previously.[11]

Peroxidation Assays

Lipid peroxidation was initiated in incubations of purified rat liver microsomes (1 mg/ml in 50 mM phosphate buffer, pH 7.4) by coincubation with Fe^{2+} (1 μM), ADP (200 μM) and ascorbate (50 μm) at 37°C. Reactions were initiated by the addition of the ascorbate. Where appropriate, the test substances (**1–16**) were pre-incubated with the microsomes for 5 minutes at 37°C before the addition of the stimulus. Aliquots (0.5 mL) were removed after 30 minutes for the assessment of thiobarbituric acid-reactive substances (TBARS).[20]

The effect of some of the compounds on the peroxidation of microsomes was determined as a function of time. Such incubations were constructed and analysed as above.

Similarly, peroxidation was initiated in suspensions of hepatocytes (10^6/ml) in Krebs buffer (pH 7.4) supplemented with HEPES (10 mM) by the addition of t-butylhydroperoxide (tBH, 1 mM). Samples were removed after 30 and 60 minutes for the determination of TBARS.

Peroxidation of purified PC in chlorobenzene was stimulated using the initiator AIBN as follows. Crude PC was dissolved in $CHCl_3$ and extracted three times with acetone to remove complicating substances (e.g. vitamin E). The lipid layer was then evaporated under N_2 and dissolved to a stock solution (2 mg/mL) in chlorobenzene. Reactions were constructed with nine parts PC to one part AIBN (16.3 mg/ml in chlorobenzene) and peroxidation conducted over 30 minutes at 37°C. Reactions were terminated by the addition of butylated hydroxytoluene (10 mM) and assayed for TBARS.

Statistical Appraisals

Inhibition curves were constructed for each of the test substances with a minimum of 10 concentrations and the concentration of compound inhibiting the control peroxidation by 50% (IC_{50}) determined by regression analysis. Where applicable, plots of redox potential versus IC_{50} were constructed for the compounds and regression coefficients of line-fit calculated using the Sigma Plot software.

NMR Experiments

Competitive experiment To a CD_3OD solution (0.7 ml) containing compound **17a** (0.0043 g, 0.0139 mmol) and compound **17b** (0.0050 g, 0.0139 mmol), benzyl thiol (3.3 μl), 0.0281 mmol) was added by syringe. The ^{1}**H NMR** spectrum recorded 3 min after addition showed that compounds **18** and **4** were present in a 5/95 ratio in addition to compounds **17a**, **17b** and dibenzyl disulfide. A control experiment showed that telluroxide **17b** was incapable of oxidising selenide **18** under the conditions used. On the other hand, it was observed that selenoxide **17a** slowly oxidised telluride **4** to its oxide **17b** (11% conversion after 4.5 min; 29% conversion after 12 min). This reaction has not been compensated for in the competitive experiment.

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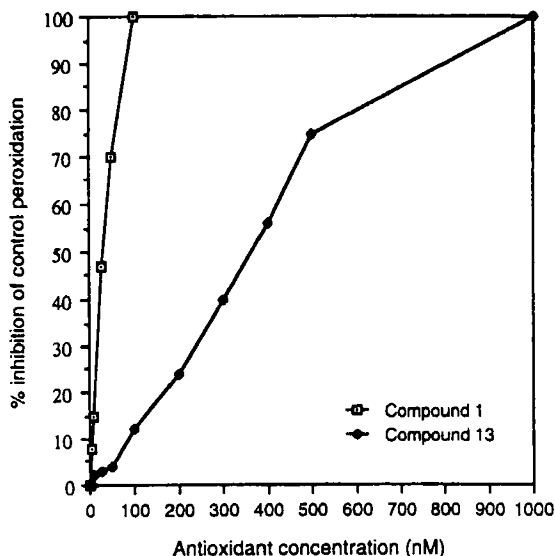

FIGURE 1 The concentration-dependency of the antioxidant activity of diaryl tellurides **1** and **13** in a microsomal preparation undergoing lipid peroxidation. The data were obtained from microsomes incubated with ADP-Fe^{2+}-ascorbate and assayed for the production TBARs after a fixed 30 minute period, as described in Materials and Methods.

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Oxidation of compounds **4** *and* **18** To a CD_3OD solution of compound **4** (0.0080 g, 0.0223 mmol) was added by syringe t-butylhydroperoxide (70% in H_2O; 5.0 μl, 0.0365 mmol). The ^{1}**H NMR** spectrum recorded 8 min after addition showed that telluride **4** was completely oxidised to its oxide **17b**. When selenide **18** was similarly treated, less than 5% of the compound was oxidised within 1 h. The conversion after 20 days was 87%.

RESULTS

The table shows the results of a comparison of the peak oxidation potentials of symmetrically substituted diaryl tellurides (**1–13**) with their effects on lipid peroxidation in liver microsomes and rat hepatocytes, as well as peroxidation of purified phosphatidylcholine (PC) in chlorobenzene. All of the diaryl tellurides tested possessed more potent antioxidant capacity (IC_{50} < 0.5 μM) in the microsome system than did two of the most active diaryl selenides from a previous report[11] (**14,16**) or did Ebselen (**15**, IC_{50} = 3 μM). It will be noted that this rank order was determined by comparing data at one fixed time during the peroxidation. Seven of the compounds (**1–7**) inhibited 50% or more of the peroxidation at 100 nM or lower in the microsomal incubations. Bis(4-dimethylaminophenyl) telluride (**1**) was the most potent telluride, exhibiting an IC_{50} of 30 nM. This compound also showed the lowest oxidation potential in the series (0.50 V). The analogous selenium compound **16** was much less efficient (IC_{50} = 0.9 μM). Figure 1 shows the relationships between concentration and antioxidative effect of the most and least potent diaryl tellurides (compounds **1** and **13**, respectively) in the microsome system. A plot of the peak oxidation

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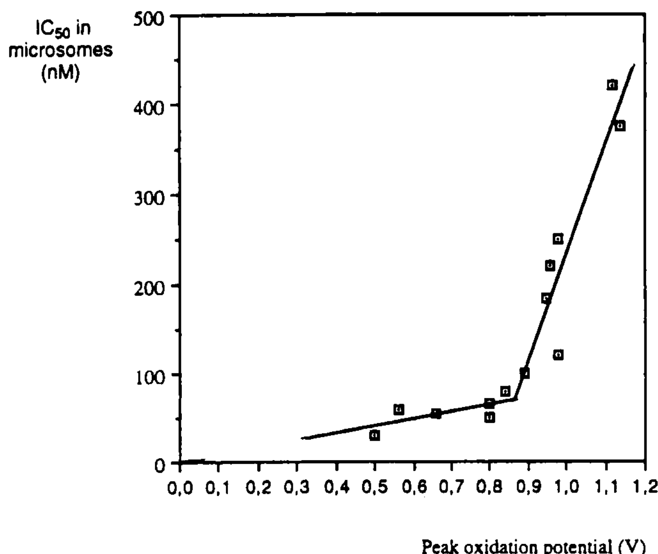

FIGURE 2 Plot of the oxidation potential versus the IC_{50} value for the series of diaryl tellurides in the microsomal peroxidation system. Regression analysis was performed by the method of least squares.

potentials for the tellurides versus IC_{50} in the microsome system (Figure 2) shows a significant correlation between these two parameters. The graph indicates a point of inflection around 0.85 V.

In addition to the results on peroxidation inhibition over 30 minutes of incubation, we also determined the effects of compounds **1** and **13** on the time-course of lipid peroxidation in microsomes (Figure 3). Control peroxidation followed fairly linear kinetics after a 5 minute lag phase, and was maximal after 90 minutes of incubation. It can be seen that both compounds elicited a dose-dependent delay of the onset of peroxidation at concentrations ranging from just under their respective IC_{50}s (30 nM and 375 nM for compounds **1** and **13**, respectively) to concentrations about threefold higher.

The data obtained from the microsomal system were largely reflected in the purely chemical peroxidation system, but a smooth correlation of antioxidant capacity versus redox potential was not obtained. However, the most potent antioxidants in this system, except for compound **11**, exhibited oxidation potentials of 0.84 V or less. These included the 4-amino substituted derivatives **(1-3)** and the 4-hydroxy and 4-phenyl analogues **(5,6)**. Compounds **1-6** all showed high activity in this assay as compared with the selenium analogue **14** (IC_{50} = 35 μM) or Ebselen (**15**, IC_{50} = 50 μM). As in the microsomal system, compounds **7-10** and **13** possessed weaker antioxidant activity, whereas the two fluorine-containing derivatives **(11,12)** proved to be amongst the most active antioxidants in this system.

When the effects of compounds **1-13** were tested on tBH-induced lipid peroxidation in hepatocytes, all compounds demonstrated protective activity (IC_{50}s from 0.2 μM to 3.0 μM). However, unlike in the simpler microsomal and chemical peroxidation assays, the antioxidant capacity showed no correlation with oxidation potential (Table 1). All of the organotellurium compounds, however, showed higher activity as compared with the organoselenium compounds **(14-16)**.

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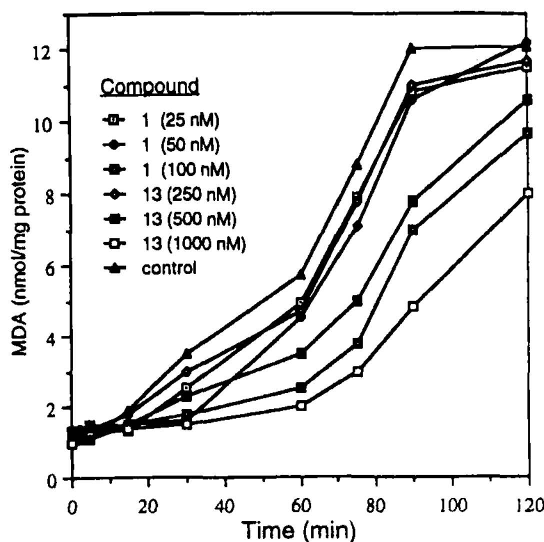

FIGURE 3 The concentration dependency of the effect of compounds 1 and 13 on the time course of microsomal lipid peroxidation. Microsomal incubations were constructed and the effects of the compounds on the accumulation of TBARs determined at several time points up to 2 hours, as described in Materials and Methods.

TABLE 1
A comparison of the peak oxidation potentials of diaryl tellurides and their antioxidant activity in biological and chemical systems undergoing free radical-mediated lipid peroxidation

Compound no	Oxidation Potential (V)[1]	Microsomes (nM)	IC_{50}[2] Hepatocytes (μM)	PC/Org (μM)
1	0.50	30	1.0	3.0
2	0.56	60	1.5	<1.0
3	0.66	55	0.2	<1.0
4	0.80	65	0.4	3.0
5	0.80	50	3.0	<1.0
6	0.84	80	0.5	<1.0
7	0.89	100	0.5	25
8	0.95	185	1.0	30
9	0.96	220	1.5	>50
10	0.98	120	1.0	>50
11	0.98	250	2.0	<1.0
12	1.12	420	0.5	3.0
13	1.14	375	2.0	35
14	0.80	2000	10	35
15	nd	3000	35	50
16	0.68	900	3.0	nd

1) Oxidation potential determined by cyclic voltammetry in acetonitrile/-Et_4NClO_4.
2) IC_{50} is the concentration of compound required to inhibit the observed peroxidation by 50%. Curves were constructed with at least 10 points in each case, from the determination of MDA at fixed time points. PC/org = phosphatidyl choline in chlorobenzene. nd = not determined.

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DISCUSSION

The peroxidation of unsaturated lipids is known to occur via a free radical chain mechanism. In a completely peroxide-free system the reaction sequence is initiated by hydrogen abstraction from an allylic position by a highly reactive species such as the hydroxyl radical. Under aerobic conditions the initial carbon-centered radical rapidly combines with oxygen to generate a peroxyl radical. In the case of polyunsaturated lipids this process is usually preceded by an allylic rearrangement. The peroxyl radical is sufficiently reactive to abstract a hydrogen atom from an unsaturated lipid molecule and thus propagate the reaction. Termination of the chain reaction occurs via various combinations of radical species.[21-22]

We have previously demonstrated that diaryl selenides can interrupt free radical processes occurring in the lipid membranes of biological material.[11] The efficacy of these antioxidant molecules was dependent both on their lipid solubility and their oxidisability, suggesting that the organoselenium compounds act as antioxidants either by preventing initiation or in a chain breaking manner.

In contrast to the series of diaryl selenides, all of the diaryl tellurides tested were potent antioxidants. The most active compound, bis(4-dimethylaminophenyl) telluride (**1**) (IC_{50} = 30 nM) is among the most potent antioxidant in the microsomal system ever reported. In agreement with the findings using the selenium compounds, there was also a correlation between the oxidation potential of the diaryl tellurides and their antioxidant capacity. However, the most potent tellurium analogues are generally 30–100 times more active than the corresponding selenium compounds. This does not appear to be due to differences in oxidation potential or lipid solubility.

The above IC_{50} data for the diaryl tellurides were obtained from screening experiments in which one fixed time point was used for the assessment of TBARs. As it is known that microsomal lipid peroxidation stimulated by ADP-Fe^{2+}-ascorbate does not follow linear kinetics, we performed experiments with compounds **1** and **13** to test their effects on the time-course of peroxidation over two hours (Figure 3). The data again clearly demonstrate a dose-dependent inhibition of peroxidation at 30 minutes but also illustrate dose-dependent inhibition of the onset of the linear phase of lipid peroxidation for both compounds. However, compound **13** was required at 10 times the concentration of compound **1** in order to produce the same effects. In addition to validating the data generated from single-point determinations, the above results also corroborate the chain-breaking nature of the antioxidant activity of the series of diaryl tellurides represented by these two compounds.

Electrochemical oxidation of diaryl selenides and tellurides is known to irreversibly produce tetravalent compounds,[23] in an aqueous milieux most probably the Se(IV) and Te(IV) oxides. It is reasonable to assume that such oxides are also formed in the present peroxidising systems. It may be envisaged that these oxides react with substantially different rates with reducing agents, such as GSH or ascorbate, to regenerate diaryl tellurides more efficiently than the corresponding selenides, thus accounting for the superior antioxidant capacity of the former (Figure 4). In an experiment performed to validate this hypothesis, equimolar amounts of compounds **17a** and **17b** were allowed to compete for two equivalents of benzyl thiol in an NMR tube in CD_3OD. The telluroxide was considerably more reactive than the selenoxide (95% of compound **17b** and <5% of compound **17a** were consumed). Particularly in the microsomal assay, ascorbate[24] may also serve to regenerate the chalcogenide antioxidants.

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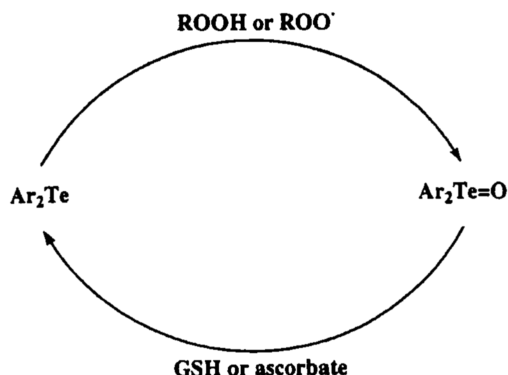

FIGURE 4 Proposed mechanism of antioxidant action of diaryl tellurides.

Commercially-available lipids are usually contaminated with lipid hydroperoxides. Diaryl chalcogenides could conceivably also exert an antioxidant effect by decomposing these species to alcohols. As a model system, diaryl chalcogenides **4** and **18** were treated with excess tBH in CD_3OD in an NMR tube. Much to our surprise it was found that telluride **4** was rapidly and cleanly oxidised to its corresponding oxide **17b** (100% conversion after 8 min) whereas the selenide **18** reacted only very sluggishly (< 5% conversion after 1 h; 87% conversion after 20 days). Further studies indicated that some diaryl tellurides, in contrast to diaryl selenides, indeed possess glutathione peroxidase-like activity.[25]

With the exception of the fluoro- and trifluoromethyl-substituted compounds (**11** and **12**), the ability of the tellurides to inhibit AIBN-induced peroxidation of PC in chlorobenzene correlated qualitatively with their oxidation potentials. The compounds rank similarly with respect to potency in this chemical assay and in the microsomal assay. However, all of the tellurides behaved similarly in the assay using intact hepatocytes. The equipotency of the compounds in this model may indicate that the most active compounds are present essentially in the inactive telluroxide form (a large excess of tBH was used to initiate peroxidation). Alternatively, oxidative metabolism or insufficient reducing capacity of the hepatocytes could prevent the full expression of the antioxidant capacity of the more readily oxidised test compounds.

In summary, a series of diaryl telluride antioxidants are described which possess extremely potent, chain-breaking antioxidant activity in model biological and chemical systems. The potencies of the compounds, particularly in comparison with organoselenium analogues, suggest that they may produce regenerable products (telluroxides) during the inhibition of the peroxidation process. It remains to be examined whether this type of biological antioxidants will produce pharmacologically useful effects in more complex models.

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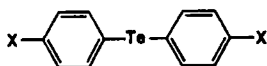
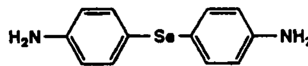


1 X=NMe₂
2 X=NH₂
3 X=NHPh
4 X=OMe
5 X=OH
6 X=Ph
7 X=Me
8 X=H
9 X=Br
10 X=Cl
11 X=F
12 X=CF₃
13 X=NO₂



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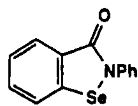

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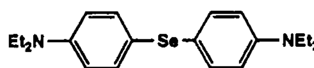

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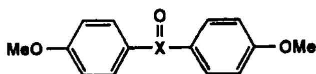
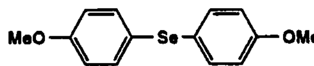


17 a X=Se
b X=Te



18

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Accepted by Prof. H. Sies

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