Novel Water-Soluble Diorganyl Tellurides with Thiol Peroxidase and Antioxidant Activity

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Novel water-soluble diaryl tellurides, alkyl aryl tellurides, and dialkyl tellurides carrying sulfopropyl groups were prepared and found to possess potent peroxide decomposing and chain-breaking antioxidative capacity. The dilithium, disodium, dipotassium, and bis-tetramethylammonium salts of bis(4-hydroxyphenyl) telluride (**4**) were treated with 2.3 equiv of 1,3-propanesultone in aqueous *tert*-butyl alcohol to give the corresponding salts **5** of bis-*O*-sulfopropylated diaryl telluride. A variety of diaryl ditellurides were reduced with sodium borohydride in ethanol. Upon addition of propanesultone to the resulting sodium arenetellurolates, the corresponding 3-aryltellurenylpropanesulfonic acid sodium salts **8** were precipitated. Diphenyl diselenide and dibutyl ditelluride reacted similarly to afford the sodium salts of 3-benzeneselenenylpropanesulfonic acid (**9**) and 4-telluraoctanesulfonic acid (**10**), respectively. The glutathione peroxidase-like activity of the water-soluble compounds was assessed at pH = 7.4 by using the coupled GSSG reductase assay. Dialkyl telluride **10** turned out to be the most efficient catalyst. Several alkyl aryl tellurides **8** were also more efficient than any of the previously tested organotellurium compounds in this model. Bulky and electron-withdrawing aryl substituents seemed to reduce activity, whereas electron-donating groups enhanced it. Alkyl aryl selenide **9** was void of any catalytic activity. The novel compounds were also assessed by ^{1}H NMR spectroscopy for their capacity to catalyze the hydrogen peroxide oxidation of *N*-acetylcysteine in D_2O under acidic conditions. In the presence of 0.01 mol % of the organotellurium catalyst, the thiol concentration was reduced to 50% within 12 min for the most active catalyst (compound **5b**). Although many of the compounds showed high catalytic activity, it was not possible to rationalize their relative efficiency. The capacity of the novel organotellurium compounds to act as a scavengers of 1,1-diphenyl-2-picrylhydrazyl (DPPH) was also investigated. The organotelluriums seem to act primarily as electron donors in their reaction with DPPH. Compounds **8d**, **10**, and **8b** were the most effective scavengers. Bulky or electron-withdrawing aryl substituents caused a reduction in activity, whereas electron-donating ones enhanced it. None of the compounds could match vitamin E in their scavanging capacity.

Introduction

It is now well established that oxidants, many of which are free radicals, are present in biological systems under normal physiological conditions. For example, the activation of polymorphonuclear leukocytes in response to inflammatory stimuli is known to result in the production of superoxide.[1] This species can dismutate to form hydrogen peroxide and, via the enzyme myeloperoxidase, be further converted to hypochlorous acid. In the presence of suitable transition-metal reductants, Fenton chemistry serves to further reduce hydrogen peroxide into the highly reactive hydroxyl radical. To prevent undesired radical-induced damage, the organism is equipped with several lines of antioxidant defense. These act either by interception of free radicals (superoxide dismutases, vitamin E, ascorbate, glutathione, and uric acid) or by destruction of precursors to free radicals (catalase and glutathione peroxidases). Under normal conditions, there is a balance between the production of oxygen-derived free radicals and their destruction. However, under certain conditions the antioxidant system becomes overwhelmed. The term "oxidative stress" has been introduced by biochemists to describe this situation of elevated cellular concentrations of oxygen-derived species,[2] and "antioxidant pharmacotherapy"[3,4] has emerged as a potential remedy for pathological conditions characterized by oxidative stress. For example, excessive radical production has been implicated in chronic inflammatory disorders, adult respiratory distress syndrome, atherosclerosis, ischemia/reperfusion injury, shock, and cataract.

Despite numerous reports on the activities and properties of the different antioxidant enzymes (catalase, superoxide dismutase, and glutathione peroxidases), their relative importance in the cell and their cooperation are still a subject of controversy. A recent study, focusing on cell survival against oxidative stress, concluded that all three enzymes are necessary for survival in normal conditions. It was observed, though, that the glutathione

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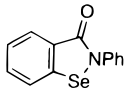
peroxidases were substantially more efficient on a molar basis than the other two enzymes.[5] The selenium-containing glutathione peroxidases[6] are selenoproteins, a class of enzymes of which less than a dozen repesentatives are known with respect to structure and function in mammals.[7] These enzymes catalyze the reduction of hydrogen peroxide, fatty-acid hydroperoxides, and phospholipid and cholesterol hydroperoxides using glutathione (GSH) and other thiols as stoichiometric reducing agents. The four varieties of the enzyme presently known serve their protective function in cells (GSH-Px-1),[8] plasma (GSH-Px-P),[9] membranes (PHGPX),[10] and the gastrointestinal tract (GSHPx-GI).[11] Considerable efforts have been made to find compounds that could mimic the properties of the glutathione peroxidase enzymes. Ebselen (2-phenyl-1,2-benzisoselenazol-3(2*H*)-one) (**1**) was



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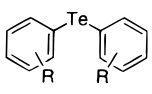

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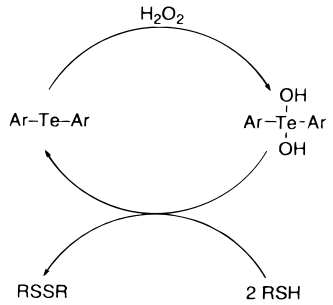
the first compound found to have this capacity.[12] In the presence of glutathione, Ebselen is readily ring-opened to give a selenosulfide. This species, the corresponding selenol and selenenic acid are then thought to be involved in the catalytic cycle responsible for the glutathione peroxidase-like properties of the compound.[13] Thus, compounds that could serve as precursors to any of these species could also be expected to have thiol peroxidase activity. Ebselen homologues,[14] selenenamides,[15] diselenides,[16] α-phenylselenoketones,[17] and selenium-containing enzymes,[18] antibodies,[19] and cyclodextrins[20] have all been demonstrated to catalyze the reduction of peroxides in the presence of thiols. Some time ago, we found that diorganyl ditellurides could also mimic the glutathione peroxidase enzymes.[21] The catalytic mechanism probably resembles that postulated for diselenides. The observed glutathione peroxidase-like properties of diaryl tellurides **2**[22,23] and other organotelluriums[24] rely on a distinctly different mechanism, the redox cycling of the heteroatom between the oxidation states II and IV (Scheme 1). Recent studies showed that compounds of this type could also inhibit azo-initiated peroxidation of linoleic acid in a two-phase system containing a thiol in the aqueous phase.[25] The thiol peroxidase activity certainly contributes to the antioxidative protection offered by these compounds.

Scheme 1



To also probe the catalytic concept of antioxidant protection in nonlipid environments, access to water-soluble diorganyl tellurides would be required. However, by examining the many thousands of known organotellurium compounds,[26] one finds only a very small fraction of water-soluble materials. In the following, we describe the preparation of novel water-soluble diaryl tellurides, aryl alkyl tellurides, and dialkyl tellurides with potent thiol peroxidase and antioxidant activity.

Results

Water solubility of organic compounds is frequently required for evaluation in biological systems and for applications in other hydrophilic environments. One commonly used method for enhancing the hydrophilicity involves introduction of sulfopropyl groups. Propanesulfonates of amines, alcohols, and phenols are conveniently prepared in the laboratory by ring-opening of 1,3-

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propanesultone (**3**).[27] Unlike the corresponding γ-lactone,

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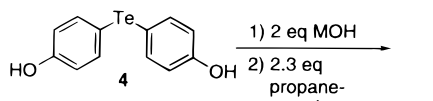
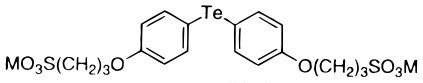
which behaves as an acylating agent in the reactions with nucleophilic agents, 1,3-propanesultone undergoes alkyl−O bond cleavage and behaves as a sulfoalkylating agent. In this way, a variety of compounds, including dyes,[28] lipids,[29] surfactants,[27,30] nucleosides,[31] and proteins,[32] were functionalized.

Preparation of Water-Soluble Organotellurium Compounds. Bis(4-hydroxyphenyl) telluride (**4**) (eq 1) is a readily available diaryl telluride with excellent antioxidative properties. To make it water-soluble, we

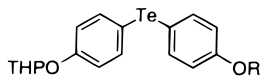




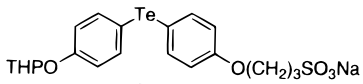
5a (M= Li)
b (M= Na)
c (M= K)
d (M= NMe_4)

tried to attach sulfopropyl groups to one or both of the phenolic oxygens. Treatment of telluride **4** with 1 equiv of base (LiOH, NaOH, or KOH) in 2-propanol or *tert*-butyl alcohol at 80 °C, followed by addition of a stoichiometric amount of propanesultone and continued heating, caused the precipitation of a mixture of mono- and bis-*O*-sulfopropylated telluride. Repeated recrystallization of this material failed to give a pure product. By increasing the amount of propanesultone and changing the solvent to aqueous *tert*-butyl alcohol, an 86% yield of essentially pure dilithium salt **5a** was isolated. Disodium salt **5b**, dipotassium salt **5c**,and bis(tetramethylammonium) salt **5d** were similarly isolated in 58%, 40%, and 49% yields, respectively. Attempts were also made to introduce sulfopropyl groups into bis(4-aminophenyl) telluride. However, under conditions similar to those used above, a dark red solid precipitate, insoluble in polar and nonpolar solvents, was formed.

In another attempt to mono-*O*-sulfopropylate telluride **4**, one of the phenolic groups was protected as a THP ether. Heating of telluride **4** with dihydropyran in methylene chloride in the presence of a catalytic amount of *p*-toluenesulfonic acid resulted in the formation of mixtures of mono- and dialkylated materials. Under the best conditions, a separable 7/1 mixture of compounds **6a** and **6b** was isolated in 56% yield. Sulfopropylation of com-



6a (R= H)
b (R= THP)



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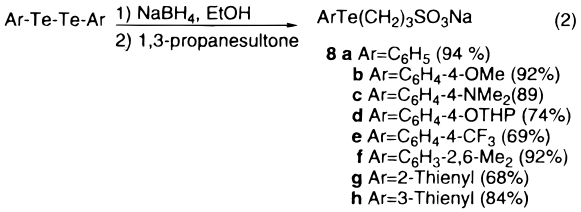
pound **6a**, employing sodium hydroxide as the base, proceeded in excellent yield (98%) under the above conditions to give telluride **7**. Unfortunately, successful hydrolysis of the THP ether under a variety of acidic conditions was always accompanied by decomposition/precipitation of elemental tellurium.

Ring opening of 1,3-propanesultone with highly nucleophilic arenetellurolate ion was considered for the preparation of water-soluble aryl alkyl tellurides. A variety of lithium arenetellurolates are readily available by insertion of elemental tellurium into the carbon−lithium bond of aryllithiums. The former are easily prepared from aryl bromides by lithium bromine exchange, employing 2 equiv of *tert*-butyllithium. Although in situ generated lithium arenetellurolates formed in this way in tetrahydrofuran were found to readily ring open 1,3-propanesultone, the poor crystallinity and propensity to hydrate formation of the resulting alkanesulfonic acid lithium salts made purification practically impossible. As observed already with the different bis-(propanesulfonate) salts **5**, the lithium salt is more difficult to purify than the sodium, potassium, and tetramethylammonium salts. Therefore, arenetellurolate sodium salts were prepared in ethanol by sodium borohydride reduction of the corresponding diaryl ditellurides (eq 2). Addition of pro-



8 a Ar=C_6H_5 (94 %)
b Ar=C_6H_4-4-OMe (92%)
c Ar=C_6H_4-4-NMe_2(89)
d Ar=C_6H_4-4-OTHP (74%)
e Ar=C_6H_4-4-CF_3 (69%)
f Ar=C_6H_3-2,6-Me_2 (92%)
g Ar=2-Thienyl (68%)
h Ar=3-Thienyl (84%)

panesultone and heating at 60 °C caused precipitation of the analytically pure aryl alkyl tellurides **8** in yields ranging from 68% to 94% (eq 2). Attempts to remove the THP protective group of compound **8d** under various acidic conditions failed to produce the desired phenolic compound. Again, decomposition and precipitation of elemental tellurium was observed. The chemistry described in eq 2 could also be extended to the preparation of aryl alkyl selenides. Thus, reduction of diphenyl diselenide with sodium borohydride in ethanol, followed by addition of 1,3-propanesultone, afforded the analytically pure alkanesulfonic acid sodium salt **9** in 94%

9 **10**

isolated yield. Attempts were also made to prepare water-soluble dialkyl tellurides. Readily available di-*n*-butyl ditelluride gave, after sodium borohydride reduction in

(27) A radical-based method, avoiding handling of the carcinogenic propanesultone, has also been used for the introduction of the sulfopropyl group. Ikenoue, Y.; Saida, Y.; Kira, M.; Tomozawa, H.; Yashima, H.; Kobayashi, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1694−1695. Schmitt, K. D. *J. Org. Chem.* **1995**, *60*, 5474−5479.

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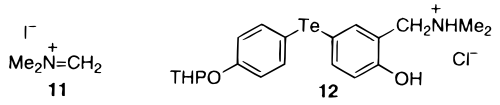
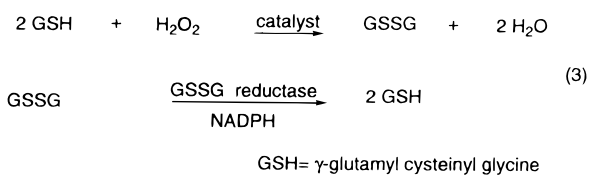
ethanol and addition of 1,3-propanesultone, an 84% yield of the crystalline sodium salt of 4-telluraoctanesulfonic acid (**10**).

The presence of ammonium groups is known to confer water solubility to organic compounds. In an effort to make diaryl tellurides carrying this functional group, THP-protected diaryltelluride **6a** was treated with Eschenmoser's salt [*N*,*N*-dimethylmethyleneammonium iodide (**11**)]. This compound is known to introduce dimethylaminomethyl groups into various phenolic compounds.[33] Prolonged heating of telluride **6a** with Eschenmoser's reagent in methylene chloride containing potassium carbonate, introduced a dimethylaminomethyl group ortho to the phenolic hydroxyl group (30% yield). Subsequent treatment of the oily telluride with an ether solution of HCl caused separation of the corresponding ammonium chloride **12**.



The solubility in water was determined for some of the newly prepared compounds. The solubility of compound **7**, the least soluble material, was 0.016 M at 20 °C. Some other compounds were significantly more soluble in water: compounds **5c**, **8a**, and **10** showed solubilities exceeding 0.031, 0.14, and 1.3 M, respectively.

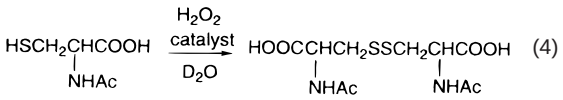
Thiol Peroxidase Activity. Thiol peroxidase activity can be assessed by several means.[34] The direct methods rely on monitoring the consumption of thiol or hydrogen peroxide with time in the presence of a catalyst. Glutathione peroxidase activity may also be indirectly assessed by performing the reaction in the presence of glutathione reductase and NADPH (eq 3). The progress



(3)

of reaction may then be conveniently followed spectrophotometrically by observing the fall in absorbance at 340 nm (NADPH). Poor catalyst water solubilty has previously been a problem in this coupled reductase assay. Usually, substantial amounts of dimethyl sulfoxide were added to the buffered aqueous medium to obtain a homogeneous system. The novel water-soluble organotellurium compounds prepared in this work could be evaluated in an aqueous phosphate buffer at physiological pH (7.4). The results are shown in Table 1. Catalyst activity (% catalysis) was determined as the initial rate increase (as compared with the uncatalyzed process) in the reaction between GSH and hydrogen peroxide. Some of the catalysts tested (compounds **8b**−**d** and **10**) turned out to be more active than any of the previously tested diorganyl tellurides in this system.[22]

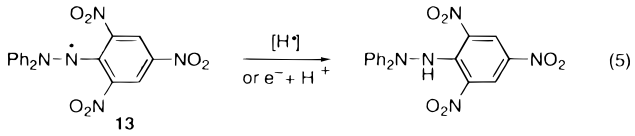
Some time ago, we introduced a ^{1}H NMR method for the assessment of thiol peroxidase activity.[21,23] In this assay, thiols are oxidized to the corresponding disulfides in CD_3OD/D_2O in the presence of hydrogen peroxide and the catalyst (0.3 mol %) to be evaluated. Catalyst efficiency was conveniently expressed as t_{50} values, the time required to reduce the thiol concentration by 50%. In this work, the novel organotellurium compounds were assessed for their ability to catalyze hydrogen peroxide oxidation of *N*-acetyl cysteine in unbuffered D_2O (eq 4).



(4)

To be able to conveniently monitor the progress of reaction by ^{1}H NMR spectroscopy, the amount of catalyst was reduced to 0.01 mol %. The results are shown in Table 1. Again, many of the tested compounds turned out to be more active than any of the previously tested diorganyl tellurides in this model.[23] Thus, catalysts **5**, **8a**−**e**, and **12** all showed t_{50} values shorter than that of compound **4**, the previously most active compund in this system.

The stable radical 1,1-diphenyl-2-picrylhydrazyl, DPPH (**13**), has been previously used for assessment of antioxidant capacity.[35,36] This densely colored radical is reduced by hydrogen atom/electron donors to a weakly absorbing hydrazine (eq 5). Thus, its interaction with reducing



(5)

agents is conveniently monitored by spectrophotometry. In the present study, $t_{1/2}$, the half-life of the 517 nm absorption of DPPH, was recorded in the presence of 0.5 molar equiv of the novel water-soluble organotellurium compounds. As indicated by the short $t_{1/2}$ values in Table 1, most of the water-soluble organotelluriums acted as scavengers of DPPH. The nonphenolic alkyl aryl telluride **8d** ($t_{1/2}$ = 4.5 min) and phenolic diaryl telluride **12** ($t_{1/2}$ = 5.5 min) were the most efficient quenchers. These compounds were significantly more reactive than the bisphenolic diaryl telluride **4** ($t_{1/2}$ = 14 min), suggesting that a phenolic group is not essential for quenching. However, none of the compounds tested could match the activity of vitamin E ($t_{1/2}$ = 0.5 min).

Discussion

1,3-Propanesultone is known to be ring-opened by a variety of heteroatom nucleophiles. It is therefore not surprising that bisphenolic diaryl telluride **4** and highly nucleophilic arene- and alkanetellurolates and selenolates are readily alkylated by this substance. Purification of water-soluble sulfopropylated products is troublesome. Often, one has to rely on reversed-phase preparative HPLC or ion-exchange chromatography/lyophilization to obtains products of sufficient purity. Fortunately, bis-*O*-

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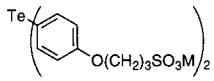
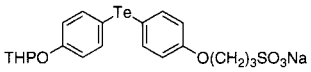
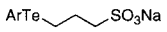
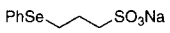
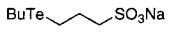
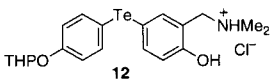
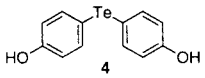
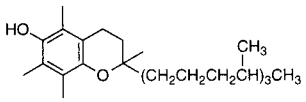
Table 1. Glutathione Peroxidase, Thiol Peroxidase, and Antioxidant Activity of Water-Soluble Organotellurium Compounds

compound, no.	Activity[a] Glutathione Peroxidase (% catalysis[b])	Thiol Peroxidase t_{50}[c] (min)	Antioxidant $t_{1/2}$[d] (min)
			
5a (M= Li)	1607	23	18.0
b (M= Na)	1696	12	10.5
c (M= K)	1389	13	11.0
d (M= Me_4N)	1603	13	11.0
 **7**	1325	21	14.0
			
8a (Ar= Ph)	1971	23	20.0
b (Ar= C_6H_4-4-OMe)	3521	33	9.5
c (Ar= C_6H_4-4-NMe_2)	3000	13	11.0
d (Ar= C_6H_4-4-OTHP)	2832	18	4.5
e (Ar= C_6H_4-4-CF_3)	1132	24	~300
f (Ar= C_6H_3-2,6-Me_2)	414	42	inactive
g (Ar= 2-Thienyl)	1028	42	~200
h (Ar= 3-Thienyl)	2103	46	20.5
 **9**	107	inactive	inactive
 **10**	7450	73	8.5
 **12**	1721	30	5.5
 **4**	1400[e]	42	14.0
	–	–	0.5

[a]For details see the Experimental Section. [b]The catalyst's percentage increase of the basal reaction rate between GSH and H_2O_2 was calculated as rate of NADPH consumption + 5 mol % catalyst (μM / min) / rate of NADPH consumption + vehicle (μM / min) X 100. [c]t_{50} is the time required to oxidize 50 % of the thiol in the presence of hydrogen peroxide and 0.01 mol % of the catalyst. [d]$t_{1/2}$ is the time required to reduce 50 % of the initial absorbance of DPPH in the presence of 0.5 molar equivalents of test substance. [e]From reference 22.

alkylated compounds **5** were found to crystallize as formed when the reaction was performed in aqueous *tert*-butyl alcohol containing excess 1,3-propanesultone and an alkali metal or tetramethylammonium hydroxide. In stoichiometric reactions, mono-*O*-sulfopropylated products could not be freed from bis-alkylated material. The purification of sodium propanesulfonates **8** was also very simple as the materials crystallized as formed when sodium arene- and alkanetellurolates and -selenolates were treated with 1,3-propanesultone in ethanol. Considering the ready availability of aliphatic and aromatic ditellurides and diselenides, this reaction would be useful for the preparation of a variety of water-soluble alkyl aryl tellurides and selenides.

Because glutathione is used as the stoichiometric reducing agent and the assay can be performed at pH 7.4, the coupled reductase method for assessment of thiol peroxidase activity mimics physiological conditions well. As seen from Table 1, bis-*O*-sulfopropylation of diaryl telluride **4** (1400% catalysis) causes only a modest increase in glutathione peroxidase-like activity (1325−1696%). Also, the effect of the sulfonate counterion (Li, Na, K, and Me_4N) is minimal. Because hydroxy and alkoxy groups have similar electron-donating capacities and the sulfopropyl groups are well separated from the phenolic oxygen, the electron density at tellurium is not expected to vary much among compounds **4** and **5**. Little mechanistic information is available concerning the oxidation and reduction steps of the catalytic cycle shown in Scheme 1. However, it seems reasonable to assume that oxidation involves nucleophilic attack of tellurium on hydrogen peroxide. The observed catalytic activity of sulfonate **7** (1325%) and ammonium compound **12** (1721%) are also in accord with the above analysis. Essentially, the different kinds of derivatization of compound **4** confer water solubility but retain glutathione peroxidase-like activity. Judging from the activities of compounds **8a**−**d**, alkyl aryl tellurides are intrinsicly better catalysts

than diaryl tellurides. This could be due to less steric hindrance around the heteroatom. Also, there is a tendency that electron-releasing *para*-substituents in the aryl moiety (OMe, OTHP, and NMe_2) enhance activity, whereas electron-withdrawing ones reduce it (CF_3). Steric hindrance in the aryl also causes a reduction in catalytic activity (compound **8f**). It is notewothy that catalyst **8h**, containing a 3-thienyl group bonded to tellurium, is significantly better than the 2-thienyl analogue **8g**. Maybe the sulfur lone pair is excerting some repulsive action toward hydrogen peroxide if positioned too close to the tellurium. The corresponding symmetrical diaryl telluride, bis(2-thienyl) telluride, has previously been found to possess low catalytic activity.[23] Compound **9**, the selenium analogue of compound **8a**, turned out to be inactive as a catalyst. Probably, its reaction with hydrogen peroxide is too slow for it to act in a catalytic fashion analogously to what is shown in Scheme 1. The water-soluble dialkyl telluride **10** turned out to be by far the most active catalyst in the coupled reductase system. This could again be due to steric factors.

The thiol peroxidase activity of the new compounds was also assessed by ^{1}H NMR monitoring of *N*-acetylcysteine consumption in D_2O in the presence of hydrogen peroxide (Table 1). Although the thiol peroxidase capacities of the water-soluble catalysts were superior to those of the lipophilic diorganyl ditellurides[21] and diorganyl tellurides[23] previously tested, their relative activity could not be easily rationalized. As expected, selenide **8** was inactive. However, the bis-*O*-sulfopropylated sodium, potassium, and tetramethylammonium compounds **5b**−**d** were significantly more active than the closely related lithium salt **5a**. Also, it is notable that dialkyl telluride **10** is one of the poorest performing compounds in this assay. Among aryl alkyl tellurides **8**, there appears to be no clear-cut substituent and steric dependence on activity. In fact, similar difficulties in rationalizing relative catalyst efficiencies in this system were previously encountered.[23] At this point, it seems premature to do extensive speculation as to the reasons for the inconsistency between the results obtained from the coupled reductase assay and the ^{1}H NMR method. Suffice to say that the thiols are different, the pH is different (7.4 as compared to ca. 2), and different steps in the proposed catalytic cycle (Scheme 1) could be rate-determining.

Chain-breaking, donating antioxidants act by donating a hydrogen atom or an electron to peroxyl radicals, thus eliminating these species from the catalytic cycle responsible for autoxidation. Thus, the ability of antioxidants to reduce the stable radical DPPH could serve as a simple measure of their chain-breaking antioxidant capacity. Because bis-*O*-alkylated derivatives of phenolic compound **4** (compounds **5** and **7**) show essentially the same activity as the parent compound, quenching seems to occur primarily by electron transfer. The poor quenching ability of electron-deficient compound **8e** and sterically hindered compound **8f** emphasize the importance of electronic and steric factors. With some exceptions, the glutathione peroxidase-like activity as assessed by the coupled reductase assay parallells the antioxidant activity as determined by the capacity to quench DPPH. The absorbance/time traces recorded for determination of $t_{1/2}$ values not only reflect the kinetics of the reaction but also give a hint as to the value of the stoichimetric factor *n*, the number of radicals that each antioxidant molecule can quench. Vitamin E is known to quench two molecules of DPPH. Because the same final absoption was arrived at (although more slowly) using diorganyl tellurides as quenchers, we conclude that the value of *n* for tellurides is also two. Probably, the organotellurium compounds are oxidized to the corresponding tellurium(IV)-dimethoxides in the reaction.

In conclusion, we have prepared a series of novel water-soluble diorganyl tellurides with potent peroxide decomposing and antioxidant properties. We are presently evaluating the protective/antioxidative properties of our materials in biological systems[37] and their stabilizing capacity in various types of synthetic and man-made polymeric materials.[38]

Experimental Section

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, using $CDCl_3$, CD_3OD, or D_2O as an internal reference. Tetrahydrofuran and diethyl ether were refluxed over sodium turnings under nitrogen atmosphere and then distilled prior to use. Dichloromethane was refluxed over CaH_2 under nitrogen atmosphere and then distilled prior to use. HPLC-grade methanol, ethanol, 2-propanol, and 2-methylpropane-2-ol were used without further purification. Diphenyl ditelluride,[39] bis(4-methoxyphenyl) ditelluride,[39] bis[4-(dimethylamino)phenyl] ditelluride,[39] bis(4-trifluoromethylphenyl) ditelluride,[39] bis(2-thienyl) ditelluride,[40] bis(3-thienyl) ditelluride,[41] di-*n*-butyl ditelluride,[42] and 4-(2-tetrahydropyranyloxy)phenyl bromide[43] were synthesized according to literature methods. Unless otherwise specified, all reactions were performed under an atmosphere of dry nitrogen. Elemental analyses were performed by Analytical Laboratories, Lindlar, Germany. Reduced glutathione, glutathione reductase (grade 1 from yeast), and NADPH were obtained from Sigma. **Caution:** propanesultone is a carcinogen. It should be handled in a well-ventilated hood, and any contact with it should be avoided.[44]

Bis(2,6-dimethylphenyl) Ditelluride. To a solution of 2,6-dimethylbromobenzene (3.0 g, 16.2 mmol) in tetrahydrofuran (45 mL) was added *tert*-butyllithium (19.1 mL 1.7 M; 32.5 mmol) in pentane at −78 °C. After 1 h, the cooling bath was removed, and finely ground elemental tellurium (2.07 g, 16.2 mmol) was added. When only traces of tellurium remained (ca. 0.5 h), the mixture was poured into a separatory funnel containing $K_3Fe(CN)_6$ (5.35 g, 16.2 mmol) in water. The ditelluride formed was extracted into methylene chloride. Drying and evaporation of solvent afforded a crude product, which was recrystallized from ethanol to give 3.05 g (80%) of the title compound as reddish orange needles, mp 151−153 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.38 (s, 6 H), 7.01−7.09 (several peaks, 3 H); ^{13}C NMR ($CDCl_3$) δ 30.2, 115.8, 125.9, 129.5, 146.2. Anal. Calcd for $C_{16}H_{18}Te_2$: C, 41.28; H, 3.91. Found: C, 41.11; H, 3.78.

Bis[4-(2-tetrahydropyranyloxy)phenyl] Ditelluride. To a solution of 4-(2-tetrahydropyranyloxy)phenyl bromide (1.250 g, 4.9 mmol) in tetrahydrofuran (30 mL) was added *tert*-butyllithium (7.6 mL 1.33 M, 10.1 mmol) in pentane at −78 °C. After 30 min, the cooling bath was removed, and finely

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ground elemental tellurium (0.638 g, 5.0 mmol) was added. When only traces of tellurium remained (ca. 1 h) the solution was poured into a separatory funnel containing $K_3Fe(CN)_6$ (1.70 g, 5.2 mmol) in water. The ditelluride formed was extracted into methylene chloride. Drying and evaporation of solvent afforded an oil, which was subjected to chromatographic purification (CH_2Cl_2) to afford 0.479 g (32%) of the title compound as dark red needles, mp 110−111 °C (dec): ^{1}H NMR ($CDCl_3$) δ 1.55−1.70 (several peaks, 3 H), 1.82−2.02 (several peaks, 3 H), 3.56−3.62 (several peaks, 1 H), 3.87 (dt, J = 10.3, 3.0 Hz, 2 H), 5.41 (t, J = 3.0 Hz, 1 H), 6.88 (d, J = 8.7 Hz, 2 H), 7.68 (d, J = 8.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.7, 25.2, 30.3, 62.1, 96.3, 98.6, 117.5, 140.1, 157.7. Anal. Calcd for $C_{22}H_{26}O_4Te_2$: C, 43.34; H, 4.31. Found: C, 43.07; H, 4.18.

Bis(4-hydroxyphenyl) Telluride (4). Into a three-necked round-bottomed flask equipped with a reflux condenser were placed $TeCl_4$ (27.2 g, 0.1 mol), phenol (25.4 g, 0.14 mol), CCl_4 (80 mL), and a stirring bar. After refluxing for 3 h, the resulting precipitate was filtered and then washed with CH_2Cl_2 (60 mL × 5) until the filtrate was colorless. Drying of the resulting yellow powder in vacuo for 3 h gave 4-hydroxyphenyltellurium trichloride in a quantitative yield. This material was dissolved into EtOAc (100 mL) in a three-necked round-bottom flask equipped with a dropping funnel. Into this solution was added sodium ascorbate (67 g, 0.33 mol) in water (116 mL) dropwise at 20 °C during 1 h (the color of the solution gradually changed to reddish black). The mixture was further stirred for 6 h, the organic phase was decantated, and the residual black aqueous phase was washed and extracted with EtOAc (60 mL × 3). The combined wine-red extracts were then heated at reflux with freshly prepared copper powder (38 g, 0.6 mol) until the solution had turned pale yellow (6−12 h). After filtration from black insoluble material (Cu and CuTe), the solution was passed through Celite (Φ 40 mm × 100 mm), and the residue was evaporated to give 13.5 g (86%) of the title compound as an orange solid. The physical and spectroscopic properties of the material were identical to those previously reported by us.[45]

Typical Procedure. Bis[4-(sulfopropyloxy)phenyl] Telluride Disodium Salt (5b). Bis(4-hydroxyphenyl) telluride (0.628 g, 2.00 mmol) and sodium hydroxide (0.160 g, 4.00 mmol) were mixed in *t*-BuOH/H_2O (10/1, 17 mL) at 80 °C and stirred for 30 min. Into this solution was added 1,3-propanesultone (0.529 g, 4.50 mmol). After the mixture stirred at 80 °C for 16 h, 0.701 g (58%) of colorless crystals, mp > 300 °C, of the title compound were filtered off: ^{1}H NMR (D_2O) δ 1.91 (quint, J = 7.0 Hz, 2 H), 2.77 (t, J = 7.0 Hz, 2 H), 3.72 (t, J = 7.0 Hz, 2 H), 6.49 (d, J = 8.5 Hz, 2 H), 7.35 (d, J = 8.5 Hz, 2 H); ^{13}C NMR (D_2O) δ 25.9, 49.5, 68.2, 106.6, 117.9, 141.5, 160.1. Anal. Calcd for $C_{18}H_{20}Na_2O_8S_2Te\cdot H_2O$: C, 34.86; H, 3.58. Found: C, 34.99; H, 3.42.

Bis[4-(sulfopropyloxy)phenyl] telluride dilithium salt (5a) was prepared using the procedure for compound **5b** (lithium hydroxide was used instead of sodium hydroxide): yield 86%; mp > 300 °C; ^{1}H NMR (D_2O) δ 1.95 (quint, J = 7.0 Hz, 2 H), 2.82 (t, J = 7.0 Hz, 2 H), 3.85 (t, J = 7.0 Hz, 2 H), 6.59 (d, J = 8.8 Hz, 2 H), 7.41 (d, J = 8.8 Hz, 2 H); ^{13}C NMR (D_2O) δ 26.0, 49.6, 68.2, 106.7, 117.8, 141.5, 160.1. Anal. Calcd for $C_{18}H_{20}Li_2O_8S_2Te\cdot H_2O$: C, 36.77; H, 3.78. Found: C, 36.88; H, 3.58.

Bis[4-(sulfopropyloxy)phenyl] telluride dipotassium salt (5c) was prepared using the procedure for compound **5b** (potassium hydroxide was used instead of sodium hydroxide): yield 40%; mp > 300 °C; ^{1}H NMR (D_2O) δ 1.97 (quint, J = 7.8 Hz, 2 H), 2.85 (t, J = 7.8 Hz, 2 H), 3.88 (t, J = 7.8 Hz, 2 H), 6.62 (d, J = 8.3 Hz, 2 H), 7.44 (d, J = 8.3 Hz, 2 H); ^{13}C NMR (D_2O) δ 26.0, 49.6, 68.4, 118.1, 127.3, 141.7, 160.2. Anal. Calcd for $C_{18}H_{20}K_2O_8S_2Te\cdot 0.5H_2O$: C, 33.60; H, 3.29. Found: C, 33.42; H, 3.05. Water solubility (20 °C) > 0.031 M.

Bis[4-(sulfopropyloxy)phenyl] telluride bis(tetramethylammonium) salt (5d) was prepared using the procedure for compound **5b** (tetrabutylammonium hydroxide was used instead of sodium hydroxide): yield 49%; mp 267−268 °C (dec); ^{1}H NMR (CD_3OD) δ 2.13 (quint, J = 7.0 Hz, 2H), 2.87 (t, J = 7.0 Hz, 2 H), 3.09 (s, 12 H), 4.00 (t, J = 7.0 Hz, 2 H)), 6.71 (d, J = 8.8 Hz, 2 H), 7.50 (d, J = 8.8 Hz, 2 H); ^{13}C NMR (CD_3OD) δ 26.3, 49.4, 55.8, 67.6, 105.3, 117.0, 140.9, 160.5. Anal. Calcd for $C_{26}H_{44}N_2O_8S_2Te\cdot H_2O$: C, 43.22; H, 6.43. Found: C, 43.37; H, 6.32.

4-Hydroxyphenyl 4-(2-Tetrahydropyranyloxy)phenyl Telluride (6a). Bis(4-hydroxyphenyl) telluride (1.254 g, 4.00 mmol), 3,4-dihydro-2*H*-pyrane (1.664 g, 1.480 mL, 16.00 mmol), *p*-TsOH·H_2O (0.022 g, 0.12 mmol), dichloromethane (50 mL), THF (10 mL), and a stirring bar were placed into a two-necked round-bottom flask equipped with a reflux condenser. After 16 h of refluxing and workup, involving washing with a saturated $NaHCO_3$ solution, drying over anhydrous Na_2SO_4, and removal of the solvent, chromatographic purification (CH_2Cl_2) of the resulting orange oil first gave 0.135 g (7%) of bis-[4-(2-tetrahydropyranyloxy)phenyl] telluride (**6b**) as pale yellow needles, mp 59−60 °C: ^{1}H NMR ($CDCl_3$) δ 1.56−2.01 (several peaks, 6 H), 3.54−3.60 (several peaks, 1 H), 3.82−3.90 (several peaks, 1 H), 5.38 (t, J = 3.4 Hz, 1 H), 6.89 (d, J = 8.3 Hz, 2 H), 7.61 (d, J = 8.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.7, 25.2, 30.3, 62.1, 96.2, 105.4, 117.8, 139.6, 157.2. Anal. Calcd for $C_{22}H_{26}O_4Te$: C, 54.81; H, 5.45. Found: C, 54.81; H, 5.48. Continued elution gave 0.783 g (49%) of the title compound as pale yellow needles, mp 100−101 °C: IR (KBr) 3274; ^{1}H NMR ($CDCl_3$) δ 1.54−2.05 (several peaks, 6 H), 3.56−3.62 (several peaks, 1 H), 3.84−3.92 (several peaks, 1 H), 5.40 (t, J = 3.4 Hz, 1 H), 5.53 (br s, 1 H), 6.65 (d, J = 8.6 Hz, 2 H), 6.89 (d, J = 8.8 Hz, 2 H), 7.57 (d, J = 8.6 Hz, 2 H), 7.58 (d, J = 8.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.7, 25.1, 30.2, 62.2, 96.3, 104.0, 105.7, 116.9, 117.8, 139.4, 140.2, 155.8, 157.0. Anal. Calcd for $C_{17}H_{18}O_3Te$: C, 51.31; H, 4.57. Found: C, 51.50; H, 4.59.

4-(Sulfopropyloxy)phenyl 4-(2-Tetrahydropyranyloxy)phenyl Telluride Sodium Salt (7). 4-Hydroxyphenyl 4-(2-tetrahydropyranyloxy)phenyl telluride (0.576 g, 1.45 mmol), sodium hydroxide (0.058 g, 1.46 mmol), 2-propanol (20 mL), water (0.1 mL). and a stirring bar were placed in a two-necked round-bottom flask (50 mL) and then stirred at 80 °C for 0.5 h. Into this solution was added 1,3-propanesultone (0.185 g, 1.52 mmol). After the mixture was heated at the same temperature for 4 h, filtration gave 0.652 g (98%) of the title compound as colorless microfine needles, mp 213−214 °C (dec): ^{1}H NMR (CD_3OD) δ 1.45−1.93 (several peaks, 6 H), 2.14 (quint, J = 7.0 Hz, 2 H), 2.89 (t, J = 7.0 Hz, 2 H), 3.46−3.52 (several peaks, 1 H), 3.72−3.80 (several peaks, 1 H), 4.00 (t, J = 7.0 Hz, 2 H), 5.32 (t, J = 3.4 Hz, 1 H), 6.72 (d, J = 8.4 Hz, 2 H), 6.81 (d, J = 8.4 Hz, 2 H), 7.47 (d, J = 8.4 Hz, 2 H), 7.52 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (CD_3OD) δ 19.9, 26.3, 26.3, 31.4, 49.1, 63.2, 67.6, 97.6, 105.1, 106.7, 117.0, 118.8, 140.4, 141.1, 158.5, 160.6. Anal. Calcd for $C_{20}H_{23}NaO_6STe\cdot H_2O$: C, 42.88; H, 4.15. Found: C, 42.52; H, 4.35. Water solubility (20 °C) 0.016 M.

3-(Benzenetellurenyl)propanesulfonic Acid Sodium Salt (8a). Typical Procedure. Into a suspension of diphenyl ditelluride (0.819 g, 2.00 mmol) in ethanol (20 mL) in a two-necked round-bottomed flask equipped with a reflux condensor was added sodium borohydride (0.200 g, 5.30 mmol) in small portions at 20 °C. After a further 30 min of stirring under the same conditions, 1,3-propanesultone (0.513 g, 4.20 mmol, 1.05 equiv) was added. The reaction mixture was then heated to 60 °C and stirred for 0.5 h. After this solution cooled to ambient temperature, 1.309 g (94%) of milky white crystals, mp 223−225 °C (dec), of the title compound was filtered off: ^{1}H NMR (CD_3OD) δ 2.15 (quint, J = 7.8 Hz, 2 H), 2.81 (t, J = 7.8 Hz, 2 H), 2.92 (t, J = 7.8 Hz, $^2J_{Te-H}$ = 29 Hz, 2 H), 7.08−7.21 (several peaks, 3 H), 7.64 (dd, J = 8.1, 1.5 Hz, 2 H); ^{13}C NMR (CD_3OD) δ 7.3 ($^1J_{C-Te}$ = 145 Hz), 28.5, 54.3, 112.5, 128.6, 130.2, 139.4. Anal. Calcd for $C_9H_{11}NaO_3STe$: C, 30.90; H, 3.18. Found: C, 30.89; H, 3.09. Water solubility (20 °C) > 0.143 M.

3-(4-Methoxybenzenetellurenyl)propansulfonic acid sodium salt (8b) was prepared according to the procedure for compound **8a** [bis(4-methoxyphenyl) ditelluride was used

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instead of diphenyl telluride]: yield 1.401 g (92%) of milky white crystals; mp 222−223 °C (dec); ^{1}H NMR (CD_3OD) δ 2.09 (quint, J = 7.6 Hz, 2 H), 2.79 (t, J = 7.6 Hz, 2 H), 2.82 (t, J = 7.6 Hz, $^2J_{Te-H}$ = 28 Hz, 2 H), 3.68 (s, 3 H), 6.69 (d, J = 9.7 Hz, 2 H), 7.59 (d, J = 9.7 Hz, 2 H); ^{13}C NMR (CD_3OD) δ 7.6 ($^1J_{C-Te}$ = 145 Hz), 28.4, 54.3, 55.6, 101.2, 116.2, 142.2, 161.4. Anal. Calcd for $C_{10}H_{13}NaO_4STe$: C, 31.51; H, 3.36. Found: C, 31.61; H, 3.46.

3-[4-(*N*,*N*-Dimethylamino)benzenetellurenyl]propansulfonic acid sodium salt (8c) was prepared according to the procedure for compound **8a** [bis(4-(*N*,*N*-dimethylamino)-phenyl) ditelluride was used instead of diphenyl telluride]: yield 89% of milky white crystals; mp 206−207 °C (dec); ^{1}H NMR (CD_3OD) δ 2.09 (quint, J = 7.5 Hz, 2 H), 2.75 (t, J = 7.5 Hz, $^2J_{Te-H}$ = 29 Hz, 2 H), 2.80 (t, J = 7.5 Hz, 2 H), 2.82 (s, 6H), 6.53 (d, J = 8.7 Hz, 2 H), 7.52 (d, J = 8.7 Hz, 2 H); ^{13}C NMR (CD_3OD) δ 7.4 ($^1J_{C-Te}$ = 154 Hz), 28.3, 40.5, 54.4, 95.9, 114.8, 142.3, 152.0. Anal. Calcd for $C_{11}H_{16}NNaO_3STe$: C, 33.62; H, 4.11. Found: C, 33.46; H, 4.02.

3-[4-(2-Tetrahydropyranyloxy)benzenetellurenyl]-propanesulfonic acid sodium salt (8d) was prepared according to the procedure for compound **8a** [bis(4-(2-tetrahydropyranyloxy)phenyl) ditelluride was used instead of diphenyl telluride]: yield 74% of white crystals; mp 206−207 °C (dec); ^{1}H NMR (CD_3OD) δ 1.48−1.95 (several peaks, 6 H), 2.11 (quint, J = 7.5 Hz, 2 H), 2.80 (t, J = 7.5 Hz, 2 H), 2.84 (t, J = 7.5 Hz, $^2J_{Te-H}$ = 29 Hz, 2 H), 3.50 (dt, J = 11.5, 5.0 Hz, 1 H), 3.77 (ddd, J = 11.5, 8.7, 3.1 Hz, 1 H), 5.33 (t, J = 3.1 Hz, 1 H), 6.81 (d, J = 8.6 Hz, 2 H), 7.58 (d, J = 8.6 Hz, 2 H); ^{13}C NMR (CD_3OD) δ 7.6 ($^1J_{C-Te}$ = 145 Hz), 19.9, 26.3, 28.4, 31.4, 54.3, 63.2, 97.6, 102.6, 118.7, 141.9, 158.7. Anal. Calcd for $C_{14}H_{19}NaO_5STe\cdot 0.5H_2O$: C, 36.63; H, 4.40. Found: C, 36.71; H, 4.12.

3-(4-Trifluoromethylbenzenetellurenyl)propanesulfonic acid sodium salt (8e) was prepared according to the procedure for compound **8a** [bis(4-trifluoromethyl)phenyl) ditelluride was used instead of diphenyl telluride]: yield 69%; mp 219−224 °C (dec); ^{1}H NMR (CD_3OD) δ 2.20 (quint, J = 7.5 Hz, 2 H), 2.84 (t, J = 7.5 Hz, 2 H), 3.04 (t, J = 7.5 Hz, $^2J_{Te-H}$ = 30 Hz, 2 H), 7.38 (d, J = 8.4 Hz, 2 H), 7.78 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (CD_3OD) δ 7.7 ($^1J_{C-Te}$ = 154 Hz), 28.6, 40.5, 54.2, 119.4, 125.8 ($^1J_{C-F}$ = 269 Hz), 126.6 ($^3J_{C-F}$ = 4 Hz), 130.3 ($^2J_{C-F}$ = 32 Hz), 138.5. Anal. Calcd for $C_{10}H_{10}F_3NaO_3STe$: C, 28.74; H, 2.42. Found: C, 28.70; H, 2.28.

3-(2,6-Dimethylbenzenetellurenyl)propanesulfonic acid sodium salt (8f) was prepared according to the procedure for compound **8a** [bis(2,6-dimethylphenyl) ditelluride was used instead of diphenyl telluride]: yield 94% of of white crystals; mp 182−185 °C (dec); ^{1}H NMR (CD_3OD) δ 2.01 (quint, J = 7.5 Hz, 2 H), 2.68−2.80 (several peaks, 4 H), 7.01 (s, 3 H); ^{13}C NMR (CD_3OD) δ 6.7 ($^1J_{C-Te}$ = 165 Hz), 28.7, 30.4, 54.8, 120.4, 127.2, 130.0, 146.5. Anal. Calcd for $C_{11}H_{15}NaO_3STe\cdot H_2O$: C, 33.37; H, 4.34. Found: C, 33.56; H, 4.15.

3-(2-Thiophenetellurenyl)propanesulfonic acid sodium salt (8g) was prepared according to the procedure for compound **8a** [bis(2-thienyl) ditelluride was used instead of diphenyl telluride]: yield 68% of milky white crystals; mp 173−175 °C (dec); ^{1}H NMR (CD_3OD) δ 2.12 (quint, J = 7.5 Hz, 2 H), 2.78 (t, J = 7.5 Hz, $^2J_{Te-H}$ = 34 Hz, 2 H), 2.80 (t, J = 7.5 Hz, 2 H), 6.85 (dd, J = 5.1, 3.6 Hz, 1 H), 7.30 (dd, J = 3.6, 1.2 Hz, 1 H), 7.42 (dd, J = 5.1, 1.2 Hz, 1 H); ^{13}C NMR (CD_3OD) δ 10.5 ($^1J_{C-Te}$ = 154 Hz), 28.2, 54.0, 98.4, 129.9, 135.4, 142.7. Anal. Calcd for $C_7H_9NaO_3S_2Te$: C, 23.62; H, 2.55. Found: C, 23.43; H, 2.47.

3-(3-Thiophenetellurenyl)propanesulfonic acid sodium salt (8h) was prepared according to the procedure for compound **8a** [bis(3-thienyl) ditelluride was used instead of diphenyl telluride]: yield 84% of milky white crystals; mp 218−220 °C (dec); ^{1}H NMR (CD_3OD) δ 2.11 (quint, J = 7.5 Hz, 2 H), 2.80 (t, J = 7.5 Hz, $^2J_{Te-H}$ = 30 Hz, 2 H), 2.81 (t, J = 7.5 Hz, 2 H), 7.15 (dd, J = 4.8, 1.0 Hz, 1 H), 7.27 (dd, J = 4.8, 3.0 Hz, 1 H), 7.51 (dd, J = 3.0, 1.0 Hz, 1 H); ^{13}C NMR (CD_3OD) δ 7.7 ($^1J_{C-Te}$ = 148 Hz), 28.5, 54.2, 102.3, 127.8, 134.5, 138.0. Anal. Calcd for $C_7H_9NaO_3S_2Te$: C, 23.62; H, 2.55.

3-(Benzeneselenenyl)propanesulfonic acid sodium salt (9) was prepared according to the procedure for compound **8a** (diphenyl diselenide was used instead of diphenyl telluride): yield 94% of a slightly bluish white powder; mp > 250 °C (dec); ^{1}H NMR (CD_3OD) δ 2.06 (quint, J = 7.5 Hz, 2 H), 2.84 (t, J = 7.5 Hz, 2 H), 2.96 (t, J = 7.5 Hz, $^2J_{Se-H}$ = 24 Hz, 2 H), 7.13−7.21 (several peaks, 3 H), 7.43 (d, J = 8.1 Hz, 2 H); ^{13}C NMR (CD_3OD/D_2O 1/1) δ 26.5 ($^1J_{C-Se}$ = 194 Hz), 27.0, 52.0, 128.0, 130.2, 133.5, 158.2. Anal. Calcd for $C_9H_{11}NaO_3SSe$: C, 35.88; H, 3.69. Found: C, 35.79; H, 3.62.

3-(*n*-Butanetellurenyl)propanesulfonic acid sodium salt (10) was prepared according to the procedure for compound **8a** (di-*n*-butyl ditelluride was used instead of diphenyl telluride): yield 84% of white crystals; mp 199−200 °C (dec); ^{1}H NMR (CD_3OD) δ 0.85 (t, J = 7.5 Hz, 3 H), 1.33 (sext, J = 7.5 Hz, 2 H), 1.65 (quint, J = 7.5 Hz, 2 H), 2.10 (quint, J = 7.5 Hz, 2 H), 2.60 (t, J = 7.5 Hz, $^2J_{Te-H}$ = 24 Hz, 2 H), 2.67 (t, J = 7.5 Hz, $^2J_{Te-H}$ = 25 Hz, 2 H), 2.81 (t, J = 7.5 Hz, 2 H). ^{13}C NMR (CD_3OD) δ 1.0 ($^1J_{C-Te}$ = 131 Hz), 2.6 ($^1J_{C-Te}$ = 149 Hz), 13.8, 26.1, 28.9, 35.6, 54.5. Anal. Calcd for $C_7H_{15}NaO_3STe$: C, 25.49; H, 4.59. Found: C, 25.37; H, 4.58. Water solubility (20 °C) >1.3 M.

4-(2-Tetrahydropyranyloxy)phenyl 3-(Dimethylaminomethyl)-4-hydroxyphenyl Telluride Hydrochloride (12). 4-Hydroxyphenyl 4-(2-tetrahydropyranyloxy)phenyl telluride (0.528 g, 1.33 mmol), *N*,*N*-dimethylmethyleneammonium iodide (0.258 g, 1.40 mmol), anhydrous potassium carbonate (0.276 g, 2.00 mmol), dichloromethane (20 mL), and a stirring bar were heated at reflux for 16 h. After the mixture was washed with a saturated $NaHCO_3$ solution and dried over anhydrous Na_2SO_4, removal of the solvent and chromatographic purification of the resulting oil, eluting with Et_2O and then MeOH, gave 0.186 g (30%) of 4-(2-tetrahydropyranyloxy)-phenyl 3-(dimethylaminomethyl)-4-hydroxyphenyl telluride as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.55−1.75 (several peaks, 3 H), 1.80−2.08 (several peaks, 3 H), 2.27 (s, 6 H), 3.53−3.63 (several peaks, 3 H), 3.86 (td, J = 10.3, 3.0 Hz, 1 H), 5.38 (t, J = 3.0 Hz, 1 H), 6.68 (d, J = 8.0 Hz, 1 H), 6.89 (d, J = 8.8 Hz, 2 H), 7.37 (m, 1 H), 7.53 (d, J = 8.0 Hz, 1 H), 7.56 (d, J = 8.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.7, 25.1, 30.3, 44.5, 62.1, 62.4, 96.2, 101.6, 105.8, 117.5, 117.7, 123.4, 138.9, 139.0, 139.7, 157.0, 158.6. 4-(2-Tetrahydropyranyloxy)phenyl 3-(dimethylaminomethyl)-4-hydroxyphenyl telluride (0.133 g, 0.286 mmol), an ether solution of HCl (1.0 M, 0.30 mL, 0.300 mmol), and ether (40 mL) were stirred at 20 °C for 16 h. Drying of the resulting precipitate in vacuo at 80 °C gave 0.145 g (quantitative yield) of the pure title compound as colorless microfine crystals: mp 77−79 °C (dec); IR (KBr) 3379; ^{1}H NMR (CD_3OD) δ 1.45−1.95 (several peaks, 6 H), 2.72 (s, 6 H), 3.45 (dt, J = 10.3, 3.0 Hz, 1 H), 3.73 (td, J = 10.5, 3.0 Hz, 1 H), 5.31 (t, J = 3.0 Hz, 1 H), 6.73 (d, J = 8.3 Hz, 1 H), 6.81 (d, J = 8.7 Hz, 2 H), 7.51 (d, J = 8.7 Hz, 2 H), 7.56−7.62 (several peaks, 2 H); ^{13}C NMR (CD_3OD) δ 19.9, 26.3, 31.4, 43.2, 57.8, 63.2, 97.6, 104.4, 117.4, 117.8, 118.9, 119.3, 140.8, 143.4, 143.6, 158.0, 158.7. Anal. Calcd for $C_{20}H_{26}ClNO_3Te\cdot H_2O$: C, 47.14; H, 5.55. Found: C, 46.92; H, 5.40.

Water Solubility. A weighed amount (ca. 0.090 g) of the compound was stirred in a beaker at 20 °C, and water was added by syringe in 0.5 mL portions until all of the crystals had completely dissolved.

Coupled Reductase Assay. The glutathione peroxidase-like activity of the compounds under study was assessed by their ability to catalyze the reaction between hydrogen peroxide and glutathione in an aqueous buffer at physiological pH. The oxidation of GSH to GSSG was measured indirectly by spectrophotometrically assessing the stimulated oxidation of NADPH in the presence of glutathione reductase. Incubations were conducted at room temperature in an Aminco Bowman Model 940 scanning double beam spectrophotometer recording at 340 nm with air as a reference. They were constructed in the following manner. Incubations in quartz cuvettes were with 50 mM potassium phosphate buffer pH 7.4 (1 mL). Additions and measurements were made in the order (all final concentrations): NADPH (250 μM), GSH (1 mM), test substance (50 μM), record baseline, GSSG reductase (1 unit), record, hydrogen peroxide (1 mM), record the decline in absorbance. Rate assessments were performed when the

decline in absorbance was constant for at least 20 s. The consumption of NADPH in the absence of test substance (control) was 28.0 ± 2 (n = 6) μM NADPH/min. In the catalyzed reactions, the following NADPH consumptions were recorded: compound no. [NADPH consumption (μM/min ± SD, n = 3], **5a** [450 ± 21], **5b** [475 ± 13), **5c** [389 ± 20], **5d** [449 ± 22], **7** [371 ± 25], **8a** [552 ± 39], **8b** [986 ± 52], **8c** [840 ± 29], **8d** [793 ± 53], **8e** [317 ± 24], **8f** [116 ± 10], **8g** [288 ± 11], **8h** [589 ± 38], **9** [31 ± 2], **10** [2086 ± 85], **12** [482 ± 30]. Control experiments revealed that the observed catalytic action of the compounds was not influenced by increasing amounts of GSSG reductase (0.5, 1.0, and 2.0 units) in the incubation. Controls also showed that none of the compounds directly interacted with the reduction of GSSG (250 and 500 μM) by the reductase.

Thiol Peroxidase Activity. To a solution of *N*-acetylcysteine (0.050 g, 0.31 mmol) and hydrogen peroxide (30%, 15.7 μL, 0.15 mmol) in D_2O (0.5900 mL) in an NMR tube (Φ 5 mm) was added an aqueous solution of the catalyst (10 μL 3.00 mM; 0.00003 mmol, 0.01 mol % based on thiol), and the ^{1}H NMR spectrum of the solution was recorded at intervals during ca. 1 h at 21 ± 0.5 °C. The conversion of thiol to disulfide [as determined by integration of the *N*-acetylcysteine methine and *N*-acetylcystine methylene peaks at δ 4.40 (t) and 3.08 (dd), respectively] was plotted against time to determine t_{50} values, the time required to obtain 50% conversion of thiol to disulfide. Values of t_{50} reported in Table 1 were based on duplicate determinations. Values usually varied ±15% between different experiments. In the absence of catalyst, the half-life of *N*-acetylcysteine was >30 h under the above conditions.

Antioxidant Activity. A Hewlett-Packard 8453 UV−visible spectrophotometer (514 nm), equipped with a LAUDA compact low-temperature thermostat RC6 CP, was used for the spectrophotometric measurements. Into 3.0 mL of a 50 μM methanolic solution of 2,2'-diphenyl-1-picrylhydrazyl in a 10 mm × 10 mm cuvette was added 100 μL of a 0.75 mM methanolic solution of the antioxidant by syringe, and the fall in absorbance, referenced to methanol, was recorded with time at 25.0 ± 0.2 °C. Values for $t_{1/2}$, the time required to reduce the 517 nm absorption by 50% (Table 1), were based on duplicate determinations.

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