Articles

Thiol Peroxidase Activity of Diorganyl Tellurides

Lars Engman,* David Stern, and Mikael Pelcman

Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden

Carl M. Andersson

Department of Medicinal Chemistry, Preclinical R & D, Astra Draco AB, P.O. Box 34, S-221 00 Lund, Sweden

Received August 17, 1993•

A number of diorganyl tellurides, including diaryl tellurides, diheteroaryl tellurides, and alkyl aryl and dialkyl tellurides, were found to catalyze the reaction of hydrogen peroxide with thiols. The thiol peroxidase activity of the compounds was assessed by using a ^{1}H NMR method previously developed in our laboratories. In this assay, thiols (*N*-acetylcysteine, *tert*-butyl mercaptan, and 1-octyl mercaptan) were oxidized in the presence of hydrogen peroxide and catalyst (0.3 mol %) and the time required to reduce the thiol concentration with 50%, t_{50}, determined. In a series of 4,4′-disubstituted (R = H, Me, OH, OMe, NH_2, NMe_2, NHPh, CF_3) diphenyl tellurides **5**, the catalytic activity increased when mesomerically electron-donating substituents were present. Attempts to correlate the catalytic efficiency, expressed as log t_{50}^{-1}, with Hammett σ_p^+-values were successful in the 1-octyl mercaptan (r = 0.97; n = 8) and *tert*-butyl mercaptan (r = 0.92; n = 8) systems. In order to study the effect of coordinating, basic, acidic, or neutral substituents on catalyst efficiency, a series of 2,2′-disubstituted (R = CH_2OH, CH_2NMe_2, COOH, COOMe, OH, OMe, NH_2) diphenyl tellurides **6** were prepared and evaluated in the three thiol systems. As compared with their 4,4′-disubstituted counterparts, the 2,2′-disubstituted compounds were generally less active. The poor catalytic activity of bis(2,6-dimethylphenyl) telluride indicates the importance of steric factors. A two-step mechanism, involving H_2O_2-oxidation of the diorganyl telluride to a tellurium(IV) dihydroxide and reduction by thiol with disulfide formation, is proposed to account for the observed catalysis. The similar t_{50} values obtained in the *tert*-butyl mercaptan and 1-octyl mercaptan systems seem to indicate that oxidation is rate-determining in the catalytic process. This view was also corroborated by the structure/activity results obtained with the 4,4′-disubstituted diphenyl tellurides **5**, ^{1}H NMR experiments and results obtained using a poorer oxidant (*tert*-butyl hydroperoxide) in the standard 1-octyl mercaptan assay.

Introduction

Since the discovery by Foltz and Schwarz[1] in 1957 that selenium is an essential microelement to man, it has been recognized that this element exerts its most important biological function in the selenium-containing glutathione peroxidases. Of the two kinds of selenium-containing enzymes presently known, one (GSH-Px) is capable of reducing hydrogen peroxide as well as a number of other hydroperoxides whereas the other one (PH-GSH-Px, phospholipid hydroperoxide glutathione peroxidase) is an interfacial enzyme acting on lipid hydroperoxides.[2] Both enzymes require thiols as stoichiometric reducing agents. However, out of the many endogenous thiols available, only glutathione (GSH; γ-glutamylcysteinylglycine) will serve as a substrate for GSH-Px (eq 1). On the other hand, the substrate specificity for PH-GSH-Px is markedly different since many thiols other than glutathione are readily accepted by this enzyme (eq 2).[2] The activity shown by PH-GSH-Px would therefore be more properly described as a thiol peroxidase activity.

$$\mathrm{ROOH} + 2\,\mathrm{GSH} \xrightarrow{\text{GSH-Px}} \mathrm{ROH} + \mathrm{GSSG} + \mathrm{H_2O} \quad (1)$$

R = alkyl or H

$$\mathrm{R'OOH} + 2\,\mathrm{RSH} \xrightarrow{\text{PH-GSH-Px}} \mathrm{R'OH} + \mathrm{RSSR} + \mathrm{H_2O} \quad (2)$$

R′ = phospholipid

Hydroperoxides are believed to be involved in a number of pathological processes, including atherosclerosis, ischemia, inflammation, and related conditions.[3] Thus, it has been of therapeutic interest to manipulate the production and accumulation of these species. Ebselen (2-phenyl-1,2-benzisoselenazol-3(2*H*)-one (**1**)) was the first compound suggested for hydroperoxide-inactivating therapy.[4] In the presence of glutathione, Ebselen catalyzed the reduction of hydrogen peroxide to water, thus mimicking the properties of GSH-Px.[5] The thiol peroxidase

• Abstract published in *Advance ACS Abstracts,* March 15, 1994.

(1) Schwarz, K.; Foltz, C. M. *J. Am. Chem. Soc.* **1957**, *79*, 3292.

(2) Wendel, A. *Phosphorus Sulfur Silicon*, **1992**, *67*, 405.

(3) . *Oxidative Stress;* Sies, H., Ed.; Academic Press: London and New York, 1991. Parnham, M. J.; Graf, E. *Biochem. Pharmacol.* **1987**, *36*, 3095.

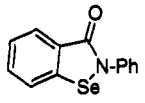
(4) Sies, H. *Free Radical Biol. Med.* **1993**, *14*, 313.

(5) Müller, A.; Cadenas, E.; Graf, P.; Sies, H. *Biochem. Pharmacol.* **1984**, *33*, 3235. Wendel, A.; Fausel, M.; Safayhi, H.; Tiegs, G.; Otter, R. *Biochem. Pharmacol.* **1984**, *33*, 3241. Parnham, M. J.; Kindt, S. *Biochem. Pharmacol.* **1984**, *33*, 3247.

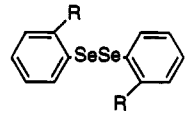
0022-3263/94/1959-1973$04.50/0

activity of Ebselen was recently demonstrated using dihydrolipoate as the stoichiometric reductant.[6]

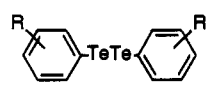
Several attempts have been made recently to prepare simple synthetic compounds with thiol peroxidase activity. Diphenyl diselenides **2**[7] and α-(phenylselenenyl)acetophenone derivatives[8] were more efficient than Ebselen in catalyzing the reaction of H_2O_2 with glutathione using the classical coupled reductase assay. Selenosubtilisin[9] (a synthetic selenoprotein), glutaselenone[10] (γ-glutamylselenocysteinylglycine), and some isoselenazolidin-3-one derivatives[11] were also recently shown to possess glutathione peroxidase-like properties.



1

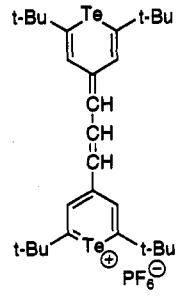


2 a R = H
b R = CH_2NMe_2



3

Concerning organotellurium compounds, we reported some time ago the thiol peroxidase activity of a series of diaryl ditellurides **3**, using the coupled reductase assay and a newly developed ^1H NMR method.[12] By using an ^1H NMR assay similar to ours, Detty and Gibson recently reported the successful use of tellurapyrylium dye **4** (but *not* other tellurium(II) compounds) as a catalyst for the hydrogen peroxide oxidation of thiophenol.[13] These results have prompted us to disclose our finding that a variety of tellurium(II) compounds show thiol peroxidase activity.



4

Results

Diorganyl tellurium(II) compounds are known to be readily oxidized to the corresponding telluroxides by many oxidants.[14] Since these materials can be reduced to diorganyl tellurides by thiols,[15] we thought it worthwhile to probe the catalytic activity of a series of diorganyl tellurides using our ^1H NMR method for the assessment of thiol peroxidase activity.[12]

In this assay, thiols are oxidized to the corresponding disulfides in CD_3OD or CD_3OD/D_2O in the presence of hydrogen peroxide and the catalyst to be evaluated. The time required to reduce the thiol concentration by 50%, t_{50}, is determined as a measure of the thiol peroxidase activity of the catalyst. Thiols useful in this assay must be clearly distinguishable by ^1H NMR from their corresponding disulfides and also unreactive toward hydrogen peroxide in the uncatalyzed reaction. We found that *N*-acetylcysteine, *tert*-butyl mercaptan, and 1-octyl mercaptan all fulfilled these requirements. *N*-Acetylcysteine was studied in a 4/1 mixture of D_2O/CD_3OD under acidic conditions (aqueous pH ≈ 2) whereas the other two thiols, with vastly different steric requirements, were studied in CD_3OD.

In the present study we chose to focus on diaryl tellurides (Table 1, entries 1–19 and 21). In these compounds, the electron density at the central atom can be easily controlled by para-substitution. By the proper choice of ortho substituents, it is also possible to study the steric requirements of the catalyst and the influence of coordinating ligands. Some diheteroaryl tellurides (Table 1, entries 22, 23), an alkyl aryl telluride (entry 24) and a dialkyl telluride (entry 25) were also included in the study, as typical representatives of other classes of tellurium(II) compounds.

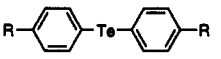
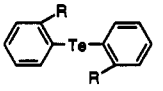
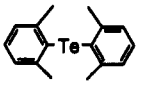
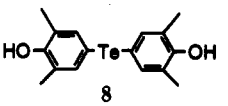
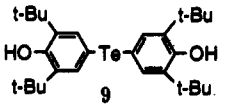
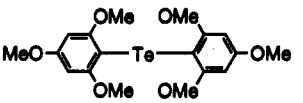
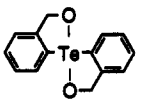
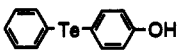
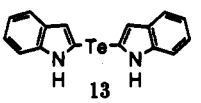
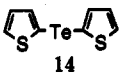
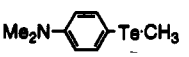
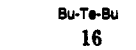
Many of the diaryl tellurides studied were prepared by detelluration of the corresponding diaryl ditellurides (Scheme 1). Activated copper powder is known as a versatile reagent for this transformation.[16] However, with some diaryl ditellurides carrying coordinating 2,2′-substituents (CH_2NMe_2, OMe, NH_2), the standard procedure (refluxing dioxane, 10 equiv of copper powder) did not cause any detelluration. Of other transition metals tried, with higher affinity for tellurium (Ra-Ni, Pd), palladium on carbon was found to give the best results (56, 75, and 37% yields, respectively, of compounds **6b**, **6f**, and **6g**). In the preparation of the 2,2′-disubstituted diaryl telluride **6e** (56% yield from 2-bromophenol) detelluration of the corresponding ditelluride was effected in refluxing ethanol.

The required ditellurides were prepared by either of three methods (Scheme 1). Potassium ferrocyanide oxidation of lithium arenetellurolates, obtained from aryllithiums and elemental tellurium, was used in the preparation of compounds **5a**,**b**,**h**, **6b**,**e**–**g**, **10**, **13**, and **14**. The aryllithium reagents were conveniently prepared, *via* lithiation, from the corresponding aryl bromides. In the case of diaryl tellurides **6b**, **10**, **13**, and **14**, direct lithiation of the corresponding aromatic or *N*-protected (compound **13**) aromatic compound provided the desired aryllithium reagent.

The reduction of aryltellurium trichlorides is a well-known method for the preparation of diaryl ditellurides (Scheme 1).[18] With activated aromatic compounds, the required tellurium compounds can be obtained by aromatic electrophilic substitution using tellurium tetrachloride. In this way, 2,6-dimethylphenol and 2,6-di-*tert*-butylphenol were converted, *via* ditellurides, to diaryl tellurides **8** and **9**, respectively, in 48 and 15% yields.

(6) Haenen, G. R. M. M.; De Rooij, B. M.; Vermeulen, N. P. E.; Bast, A. *Mol. Pharmacol.* **1990**, *37*, 412.
(7) Wilson, S. R.; Zucker, P. A.; Huang, R-R. C.; Spector, A. *J. Am. Chem. Soc.* **1989**, *111*, 5936.
(8) Cotgreave, I. A.; Moldéus, P.; Brattsand, R.; Hallberg, A.; Andersson, C. M.; Engman, L. *Biochem. Pharmacol.* **1992**, *43*, 793.
(9) Wu, Z-P.; Hilvert, D. *J. Am. Chem. Soc.* **1990**, *112*, 5647. House, K. L.; Dunlap, R. B.; Odom, J. D.; Wu, Z-P.; Hilvert, D. *J. Am. Chem. Soc.* **1992**, *114*, 8573.
(10) Soda, K. *Phosphorus Sulfur Silicon* **1992**, *67*, 461. Esaki, N.; Oikawa, T.; Tanaka, H.; Soda, K. *Biomed. Res. Trace Elem.* **1990**, *1*, 261.
(11) Reich, H. J.; Jasperse, C. P. *J. Am. Chem. Soc.* **1987**, *109*, 5549.
(12) Engman, L.; Stern, D.; Cotgreave, I. A.; Andersson, C. M. *J. Am. Chem. Soc.* **1992**, *114*, 9737. A preliminary account of this work was presented at the 6th International Conference on the Chemistry of Selenium and Tellurium, July 9–13, 1991, Osaka, Japan (abstract OP 09).
(13) Detty, M. R.; Gibson, S. L. *Organometallics*, **1992**, *11*, 2147.
(14) Irgolic, K. J. In *Houben-Weyl. Methods of Organic Chemistry*; Klamann, D., Ed.; Thieme: Stuttgart, 1990; Vol E 12 b, p 642.
(15) Ley, S. V.; Meerholz, C. A.; Barton, D. H. R. *Tetrahedron Suppl.* **1981**, *37*, 213.
(16) Sadekov, I. D.; Bushkov, A. Yu.; Minkin, V. I. *Zh. Obshch. Khim.* **1973**, *43*, 815.
(17) Engman, L.; Persson, J. *J. Organomet. Chem.* **1990**, *388*, 71.
(18) See ref 14 p 274.

Table 1. Thiol Peroxidase Activity of Diorganyl Tellurides As Determined by ^1H NMR Spectroscopy

entry	catalyst	*N*-acetylcysteine	*tert*-butyl mercaptan	1-octyl mercaptan
	 5			
1	**5a**: R = H	22	34	38
2	b: R = Me	161	34	26
3	c: R = OH	1	19	21
4	d: R = OMe	36	21	17
5	e: R = NH_2	3	9	7
6	f: R = NMe_2	6	15	7
7	g: R = NHPh	232	16	7
8	h: R = CF_3	inactive	95	136
	 6			
9	**6a**: R = CH_2OH	5	inactive	426
10	b: R = CH_2NMe_2	21	332	99
11	c: R = COOH	94	inactive	inactive
12	d: R = COOMe	324	147	76
13	e: R = OH	6	74	17
14	f: R = OMe	26	42	38
15	g: R = NH_2	11	35	32
16	 7	inactive	inactive	inactive
17	 8	8	14	8
18	 9	b	15	12
19	 10	113	9	10
20	 11	3	inactive	387
21	 12	1	30	26
22	 13	240	118	63
23	 14	174	273	245
24	 15	1	21	5
25	 16	22	138	4

[a] t_{50} is the time required to reduce the thiol concentration with 50%. [b] Solubility problems, cloudy solutions.

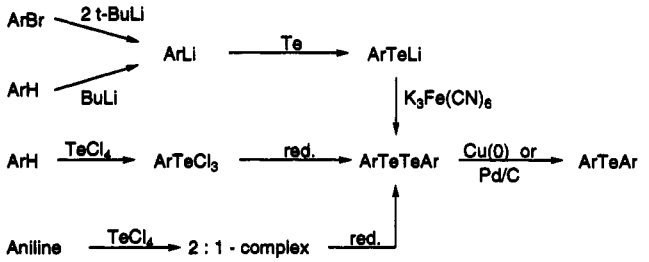
The three 4-amino substituted diaryl tellurides **5e–g** were prepared, *via* ditellurides, by reduction of 2/1 complexes formed from the corresponding anilines and tellurium tetrachloride according to a method recently developed in our laboratories.[19]

The reaction of 2-(carbomethoxy)phenyldiazonium tetrafluoroborate with sodium telluride was used for the low-yield (28%) preparation of the new diaryl telluride **6d**. Similar methodology, using potassium tellurocyanide,[20] was employed for the synthesis of tellurides **5d, 6c and 7.**

(19) Engman, L.; Persson, J. *Organometallics* **1993**, *12*, 1068.

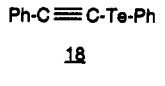
(20) Engman, L. *J. Org. Chem.* **1983**, *48*, 2920.

Scheme 1

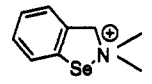


The known[21] telluride **6a** was prepared in a one-pot reaction in 92% yield from ortho,O-dilithiated benzyl alcohol and the tellurium(II)-equivalent **17**.[22] A phenyltellurium(II) equivalent recently developed in our laboratories, phenyl phenylethynyl telluride **18**,[23] was allowed to react with para,O-dilithiated phenol (from 4-bromophenol) to afford the unsymmetrical telluride **12** in 72% yield.

17



18



19

The thiol peroxidase activity of compounds **5–16**, expressed as t_{50}, the time required to reduce the thiol concentration by 50%, was determined in the three thiol systems using 0.3 mol % (based on thiol) of the catalysts. These data are presented in Table 1. When the progress of the catalyzed reactions could not be clearly distinguished from the uncatalyzed oxidation rate, the catalyst was classified as inactive (the t_{50} values in the uncatalyzed reactions were 55 h, ≫100 h, and ≈100 h, respectively, in the *N*-acetylcysteine, *tert*-butyl mercaptan, and 1-octyl mercaptan systems).

Some oxidations of thiols to disulfides were followed by ^{1}H NMR to 100% conversion, corresponding to turnover numbers of 340 (based on thiol). Attempts to increase the turnover number beyond this value with catalyst **5c** in the *N*-acetylcysteine system were successful using 0.1% catalyst (turnover number = 1110) but failed on the 0.01% level.

Discussion

The diorganyl tellurides studied in the present work are the most potent catalysts found to date, using our assay for thiol peroxidase activity.[12] Some of the compounds were also recently tested, and found to be active, using the coupled reductase assay.[24]

Concerning substituent effects, the results with the eight 4,4′-disubstituted diaryl tellurides **5** indicate that the introduction of conjugatively electron-donating substituents (OH, NH_2, NMe_2, NHPh) reduces t_{50} values, as compared to the unsubstituted compound **5a**. On the other hand, the electron withdrawing CF_3 group had the opposite effect. Attempts to correlate log t_{50}^{-1} with Hammett σ_p^+

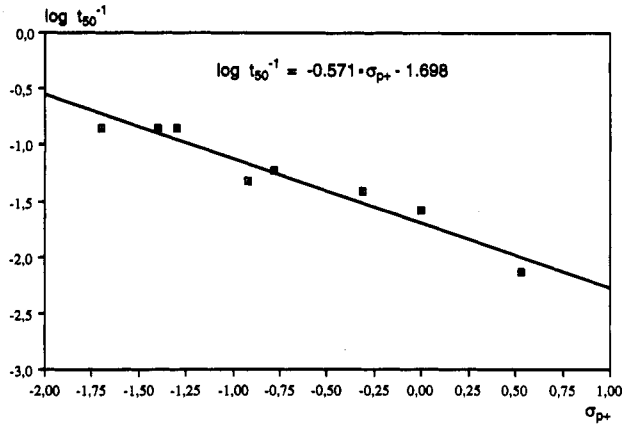


Figure 1. Plot of log t_{50}^{-1} versus σ_{p+} for 4,4′-disubstituted diphenyl tellurides **5** (1-octyl mercaptan system).

values resulted in good correlations in the 1-octyl mercaptan (Figure 1, $r = 0.97$, $n = 8$) and *tert*-butyl mercaptan systems ($r = 0.92$, $n = 8$ not shown) whereas a considerably poorer correlation ($r = 0.61$, $n = 8$) was obtained in the *N*-acetylcysteine system. This is in part due to the high activity of the hydroxy-substituted telluride **5c**. In fact, this compound was among the most potent catalysts tested in the *N*-acetylcysteine system (t_{50} = 1 min). Since Hammett σ_p^+ values correlate well with cyclovoltammetric peak oxidation potentials for 4,4′-disubstituted diaryl tellurides,[25] the catalyst efficiency, expressed as log t_{50}^{-1}, would also correlate well with the oxidation potentials of the compounds. In conclusion, para-substituents which facilitate oxidation of the central atom generally increase the thiol peroxidase activity.

Spector and co-workers observed a 5-fold increase in glutathione peroxidase-like activity of the 2,2′-disubstituted diselenide **2b**, as compared to the parent compound **2a**.[7] It was proposed that this effect was due to formation of a cyclic selenenamide species **19** as a highly reactive intermediate in a catalytic cycle. Alternatively, it was also hypothesized that the amine may facilitate the reaction by acting as a base toward thiol, or, in protonated form, by acting as a proton source. Although the diaryl selenide corresponding to diselenide **2b** was devoid of any glutathione peroxidase-like activity in the coupled reductase assay,[7] we thought it was interesting to study the effects of ortho substitution on our diaryl telluride catalysts. Therefore, a series of compounds **6**, carrying coordinating, basic, acidic, or neutral substituents in the 2,2′-positions was prepared. The introduction of ortho substituents did not have a dramatic influence on the catalytic efficiency (Table 1). As compared to the corresponding 4,4′-disubstituted catalysts (entries 3 and 13; 4 and 14; 5 and 15) the 2,2′-disubstituted compounds were generally less active, probably as a result of increased steric hindrance. The hydroxymethyl-substituted compound **6a** was considerably more active than diphenyl telluride (**5a**) in the *N*-acetylcysteine system and considerably less active than the parent compound in the other two systems. This was also true for the spirocyclic tellurium(IV) compound **11**, the dehydrated form of the oxide of compound **6a**. In one experiment benzoic acid (1 equiv based on thiol) was present in the 1-octyl mercaptan system using catalyst **6a**.

(21) Sadekov, I. D.; Maksimenko, A. A.; Minkin, V. I. *Khim. Get. Soedin.* **1981**, *117*, 122.
(22) Bergman, J.; Engman, L. *J. Am. Chem. Soc.* **1981**, *103*, 2715.
(23) Engman, L.; Stern, D. *Organometallics* **1993**, *12*, 1445.
(24) Andersson, C. M.; Hallberg, A.; Brattsand, R.; Cotgreave, I. A.; Engman, L.; Persson, J. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2553.
(25) Engman, L.; Persson, J.; Andersson, C. M.; Berglund, M. *J. Chem. Soc. Perkin Trans. 2.* **1992**, 1309.

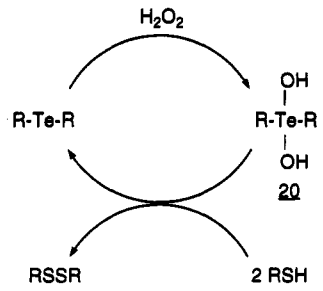


Figure 2. Proposed mechanism for the thiol peroxidase activity of diorganyl tellurides.

This did not significantly change the t_{50} value as compared with the standard conditions.

The poor catalytic activity of 2,2′,6,6′-tetramethyl substituted diphenyl telluride **7**, shows that the diaryl telluride catalysts are sensitive to steric hindrance by ortho substituents. On the other hand, substitution in the 3,3′- and 5,5′-positions (compounds **8** and **9**), even by bulky *tert*-butyl groups, did not change the catalytic activity much. The hexamethoxy-substituted diphenyl telluride **10** has a lower oxidation potential (0.44 V versus Ag/AgCl) than any of the 4,4′-disubstituted compounds **5**. This compound also turned out to be one of the most active catalysts in the *tert*-butyl mercaptan and 1-octyl mercaptan systems.

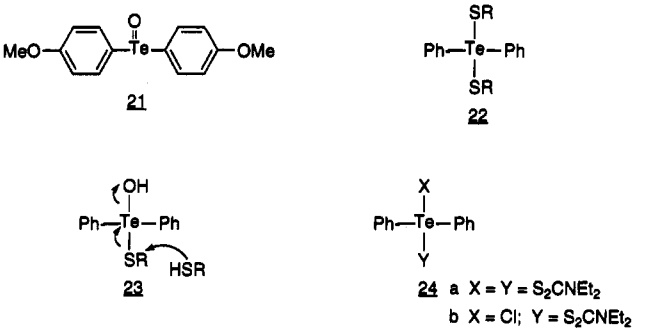
The similar performance in all three thiols systems of compounds **12** and **5c** shows that only one 4-hydroxy substituent is required to obtain a highly potent catalyst.

Substitution of one aryl group for methyl in the active (in all three systems) compound **5f** gave a slightly more (in two of the systems) potent catalyst **15**. This may be due to decreased steric hindrance around the central atom in combination with maintained or only marginally decreased oxidizability. Substitution of both phenyl groups of diphenyl telluride for alkyls (compound **16**) did not affect the activity in the *N*-acetylcysteine system. However, the activity was increased in the 1-octyl mercaptan and decreased in the *tert*-butyl mercaptan systems.

The diheteroaryl tellurides **13** and **14** both turned out to be poorer catalysts than most of the diaryl tellurides tested.

Concerning the mechanism of organotellurium-catalyzed H_2O_2 oxidations of thiols, Detty and Gibson[13] concluded, from work with compound **4**, that the heteroatom undergoes rapid cycling between the oxidation states +II and +IV. We propose a similar mechanism to explain the catalytic activity of diorganyl tellurides (Figure 2). Since telluroxides are readily hydrated, we formulate the tetravalent compound as a diorganyltellurium dihydroxide **20**, rather than a telluroxide. When telluroxide **21** was added as a catalyst under standard conditions in the *tert*-butyl mercaptan and 1-octyl mercaptan systems, the t_{50} values (26 and 19 min, respectively) were very similar to those recorded for the corresponding tellurium(II) compound **5d** (21 and 17 min, respectively).

Although little mechanistic information is available concerning the oxidation and reduction steps of the proposed catalytic cycle, the H_2O_2 oxidation of diorganyl tellurides is likely to involve nucleophilic attack by tellurium on oxygen. The reduction of tellurium(IV) compounds could either involve reductive elimination from a tellurium(IV) dithiolate **22** or nucleophilic attack by thiol on a tellurium(IV) hydroxide thiolate **23**. The reductive elimination of tellurium(IV) dithiolates appears to have



some precedence in the literature. For example, tellurium tetrachloride was first believed to form tetrakis(alkylthio)-tellurium when reacted with 4 equiv of a thiol.[26] However, a more recent investigation has shown that the isolated product was a mixture of bis(organothio)tellurium and the corresponding diorganyl disulfide.[27,28] Similarly, diaryltellurium dialkoxides rapidly afforded a polymeric disulfide when treated with a dithiol.[29] When diphenyltellurium dichloride was treated with sodium diethyldithiocarbamate, diphenyl telluride was formed, probably *via* the unstable disubstituted compound **24a** or the monosubstituted compound **24b**.[30]

With some exceptions, the t_{50} values obtained in the *tert*-butyl mercaptan and 1-octyl mercaptan systems with various catalysts were very similar (Table 1). Considering the different steric requirements of the two thiols, this suggests that oxidation, rather than reduction, is rate-determining in the catalytic process. This view is also corroborated by the finding that catalyst efficiency increases with increasing oxidizability for 4,4-disubstituted diaryl tellurides.

Since both the oxidation and reduction steps are fast, even with relatively inactive catalysts, it was not possible to study the separate steps by ^{1}H NMR spectroscopy (for example, both compounds **5d** and **5h** were oxidized within minutes by hydrogen peroxide, and their respective oxidation products were reduced within minutes by thiols). Kinetic studies using UV detection were also difficult to perform since diaryl tellurides and their corresponding tellurium(IV) dihydroxides have similar absorption spectra. *tert*-Butyl hydroperoxide was found to oxidize tellurides **5d** and **5h** more slowly than hydrogen peroxide. The time required to oxidize 50% of the compounds in a stoichiometric experiment were 1.3 and 6.6 min, respectively, as determined by ^{1}H NMR spectroscopy. Upon addition of 1-octyl mercaptan (2 equiv), both tellurium(IV) compounds were completely reduced at the time (<2 min) the first ^{1}H NMR spectrum was recorded. Compounds **5d** and **5h** were also tested as catalysts in the 1-octyl mercaptan system, with *tert*-butyl hydroperoxide replacing hydrogen peroxide in the standard assay. The larger t_{50} values for compounds **5d** and **5h** (71 and 386 min, respectively, as compared with 17 and 136 min under standard conditions) are also indicative of rate-determining oxidation in the catalytic system. By using an increased amount (3%) of catalyst **5h** under otherwise unchanged conditions in the *tert*-butyl mercaptan system, it was

(26) Nakhdjavan, B.; Klar, G. *Liebigs Ann. Chem.* **1977**, 1683.
(27) Stukalo, E. A.; Yur'eva, E. M.; Markovskii, L. N. *Zh. Org. Khim.* **1983**, *19*, 343.
(28) ref 14, p 38.
(29) Wieber, M.; Kaunzinger, E. *J. Organomet. Chem.* **1977**, *129*, 339.
(30) Bond, A. M.; Dakternieks, D.; Di Giacomo, R.; Hollenkamp, A. F. *Organometallics* **1991**, *10*, 3310.

possible to determine the resting state of the catalyst. As judged by ^{1}H NMR in comparison with authentic samples, >98% of the catalyst was present in the telluride form during the experiment.

With some catalysts (entries 10, 13, 24, 25), there was a substantial difference in the t_{50} values obtained in the *tert*-butyl mercaptan and 1-octyl mercaptan systems. In all cases, 1-octyl mercaptan was oxidized faster than *tert*-butyl mercaptan under otherwise identical conditions. The effect is most obvious with dialkyl telluride **16** and alkyl aryl telluride **15**. For some reason, the reduction step appears to become slow enough to be rate-determining with these catalysts.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra[12] were obtained at 250 MHz in $CDCl_3$ solutions containing Me_4Si as internal standard. Elemental analyses were performed by Analytical Laboratories, Engelskirchen, Germany. Diphenyl telluride,[16] bis(4-methylphenyl) telluride,[16] bis(4-hydroxyphenyl) telluride,[25] bis(4-methoxyphenyl) telluride,[20] bis(4-aminophenyl) telluride,[19] bis[4-(phenylamino)phenyl] telluride,[19] bis[4-(trifluoromethyl)phenyl] telluride,[25] bis(2-carboxyphenyl) telluride,[20] bis(2,6-dimethylphenyl) telluride,[20] 1,2-benzo[*c*]oxatellurol-2-spiro-2-[1,2-benzo[*c*]oxatellurol],[21] bis(2-thienyl) telluride,[23] 4-(dimethylamino)phenyl methyl telluride,[31] dibutyl telluride,[32] 2,5-dihydrotellurophene-yl 1,1-dichloride,[22] phenyl phenylethynyl telluride,[23] bis(4-methoxyphenyl) telluroxide[15] were prepared according to literature methods. The oxidation potential of compound **10** was determined as described in a literature procedure.[25] Hammett σ-values were from ref 33 (except for the *N*-phenylamino substituent[34]).

Bis[2-(hydroxymethyl)phenyl]Telluride (6a). To a stirred solution of 2-bromobenzyl alcohol (2.34 g, 12.5 mmol) in tetrahydrofuran (75 mL) under argon at −78 °C was added *n*-butyllithium (10 mL 2.5 M, 25.0 mmol). After 1 h, 2,5-dihydrotellurophene-yl 1,1-dichloride (1.58 g, 6.25 mmol) in tetrahydrofuran (30 mL) was added dropwise and the cooling-bath removed. Evaporation of the solvent after 2 h, addition of water (100 mL) and methylene chloride (150 mL), separation of the organic phase, drying ($MgSO_4$), evaporation, and recrystallization from CH_2Cl_2/hexanes afforded 1.97 g (92%) of compound **6a**, mp 103–4 °C (lit.[21] 108.5–109.5 °C).

Bis[2-[(dimethylamino)methyl]phenyl] Telluride (6b). Bis[2-[(dimethylamino)methyl]phenyl ditelluride[12] (1.1 g, 2.1 mmol) and palladium 5% on carbon (7.1 g, 3.3 mmol) were heated at reflux in dioxane (50 mL) until the color of the solution had disappeared (80 min). Filtration and evaporation of the solvent afforded 0.46 g (56%) of compound **6b**: mp 110 °C (EtOH); ^{1}H NMR δ 2.21 (s, 12H), 3.52 (s, 4H), 6.96 (t, 2H), 7.11–7.23 (several peaks, 4H), 7.57 (d, 2H). Anal. Calcd for $C_{18}H_{24}N_2Te$: C, 54.60; H, 6.11. Found: C, 54.37; H, 5.97.

Bis[2-(carbomethoxy)phenyl] Telluride (6d). Finely ground elemental tellurium (2.24 g, 17.5 mmol) and sodium borohydride (1.45 g 96%, 36.8 mmol) were heated in ethanol (75 mL) at reflux under argon for 45 min. After cooling to ambient temperature, 2-(carbomethoxy)phenyldiazonium tetrafluoroborate (8.77 g, 35.1 mmol; prepared in 53% yield in analogy with a literature procedure[35]) was added in portions (foaming, exothermic reaction) and stirring continued for 90 min. The reaction mixture was then poured into CH_2Cl_2/H_2O (1/1, 300 mL) and the organic phase separated after filtration from some insoluble material. Drying, evaporation, and flash chromatography (SiO_2; CH_2Cl_2/hexanes = 1/1) afforded 1.92 g (28%) of compound **6d**: mp 120–1 °C (CH_2Cl_2/hexanes); ^{1}H NMR δ 3.93 (s, 6H), 7.22–7.37 (several peaks, 4H), 7.72 (dd, 2H, J = 1.3 and 7.6 Hz), 8.00 (dd, 2H, J = 1.7 and 7.5 Hz). Anal. Calcd for $C_{16}H_{14}O_4Te$: C, 48.30; H, 3.55. Found: C, 48.34; H, 3.47.

Bis(2-hydroxyphenyl) Telluride (6e). *tert*-Butyllithium (10 mL, 1.7 M, 17.0 mmol) was added at −78 °C under N_2 to a stirred solution of 2-bromophenol (0.98 g, 5.7 mmol) in dry THF (40 mL). After 1 h the cooling-bath was removed and the temperature allowed to rise to ambient. Finely ground elemental tellurium (0.73 g, 5.7 mmol) was then added and stirring continued for 1 h when only trace amounts of unreacted tellurium remained. The solution was then poured into water (100 mL) containing $K_3Fe(CN)_6$ (1.87 g, 5.7 mmol) and acidified with acetic acid. Extraction with CH_2Cl_2 (3 × 50 mL) afforded a mixture of telluride and ditelluride. This was heated at reflux in EtOH for 1.5 h to extrude elemental tellurium. Flash chromatography (SiO_2; CH_2Cl_2) afforded 0.50 g (56%), of compound **6e**: mp 133–4 °C; ^{1}H NMR δ 5.85 (s, 2H), 6.78 (m, 2H), 6.96 (d, 2H), 7.25 (m, 2H), 7.51 (d, 2H). Anal. Calcd for $C_{12}H_{10}O_2Te$: C, 45.93; H, 3.25. Found: C, 46.05; H, 3.25.

Bis(2-methoxyphenyl) Telluride (6f). Bis(2-methoxyphenyl) ditelluride[12] (0.50 g, 1.07 mmol) was treated with palladium 5% on carbon (3.40 g, 1.40 mmol), as described for the preparation of compound **6b**, to give 0.27 g (75%) of compound **6f**: mp 76–8 °C (hexanes); ^{1}H NMR δ 3.85 (s, 6H), 6.77–6.89 (several peaks, 4H), 7.26–7.40 (several peaks, 4H). Anal. Calcd for $C_{14}H_{14}O_2Te$: C, 49.19; H, 4.13. Found: C, 49.38; H, 4.05.

Bis(2-aminophenyl) Telluride (6g). Following the procedure for the preparation of compound **6b**, bis(2-aminophenyl) ditelluride[12] (0.40 g, 0.91 mmol) was refluxed with palladium 5% on carbon (3.88 g, 1.82 mmol) in dioxane (30 mL) for 3 h. After flash chromatography (SiO_2; EtOAc/hexanes = 3/7), 0.99 g (37%) of compound **6g** was obtained: mp 73–4 °C; ^{1}H NMR δ 4.16 (s, 4H), 6.59 (m, 2H), 6.76 (dd, 2H, J = 1.2 and 8.0 Hz), 7.15 (m, 2H), 7.66 (dd, 2H, J = 1.5 and 7.6 Hz). Anal. Calcd for $C_{12}H_{12}N_2Te$: C, 46.22; H, 3.88. Found: C, 46.33; H, 3.85.

Bis(3,5-dimethyl-4-hydroxyphenyl) Telluride (8). 2,6-Dimethylphenol (4.0 g, 32.8 mmol) and tellurium tetrachloride (4.4 g, 16.3 mmol) were stirred in CCl_4 (50 mL) for 70 h. The green solid formed was filtered off, washed with CCl_4, and dried to give 5.4 g of 3,5-dimethyl-4-hydroxyphenyl tellurium trichloride. This material (2.0 g, 5.6 mmol) was dissolved in MeOH (30 mL), and sodium ascorbate (3.3 g, 16.8 mmol) in water (6 mL) was added dropwise with stirring. After 1.5 h, CH_2Cl_2 was added and the reaction mixture washed with water. After evaporation of the organic layer, the resulting mixture of telluride and ditelluride was dissolved in dioxane (50 mL) and refluxed with copper powder (1.5 g) for 2 h. Flash chromatography (CH_2Cl_2) of the product afforded 0.50 g (48%) of compound **8**: mp 135 °C; ^{1}H NMR δ 2.19 (s, 12H), 4.60 (s, 2H), 7.37 (s, 4H). Anal. Calcd for $C_{16}H_{18}O_2Te$: C, 51.95; H, 4.90. Found: C, 51.83; H, 4.92.

Bis[3,5-di-*tert*-butyl-4-hydroxyphenyl]Telluride (9). 2,6-Di-*tert*-butylphenol (1.02 g, 4.94 mmol) and $TeCl_4$ (1.33 g, 4.94 mmol) in CCl_4 (25 mL) were refluxed for 30 min. Elemental tellurium precipitated and darkened the solution. A solution of $Na_2S_2O_5$ (3.0 g, 15.8 mmol) in H_2O (25 mL) was added. The mixture was stirred for 15 min, filtered and transferred to a separatory funnel containing additional H_2O (30 mL) and CH_2Cl_2 (30 mL). The phases were separated and the aqueous phase was shaken with an additional portion of CH_2Cl_2 (25 mL). The combined organic phases were dried ($MgSO_4$) and evaporated. The solid residue was dissolved in dioxane and refluxed for 30 min with activated copper. After cooling, the mixture was filtered with Celite and evaporated. Flash chromatography (SiO_2; CH_2Cl_2/hexanes 9/1 → 5/5) afforded 0.18 g (15%) of compound **9** as a yellow microcrystalline powder: mp 121–2 °C dec; ^{1}H NMR δ 1.38 (s, 36H), 5.22 (s, 2H), 7.50 (s, 4H). Anal. Calcd for $C_{28}H_{42}O_2Te$: C, 62.48; H, 7.86. Found: C, 62.36; H, 7.80.

Bis(2,4,6-trimethoxyphenyl) Telluride (10). To a stirred solution of 1,3,5-trimethoxybenzene (1.0 g, 6.0 mmol) in dry THF (15 mL) under argon at −78 °C, *tert*-butyllithium (3.5 mL 1.7 M, 6.0 mmol) was added dropwise and stirring continued for 5 h. The cooling bath was then removed and freshly crushed elemental tellurium (0.77 g, 6.0 mmol) added. After 3 h, when most of the tellurium had disappeared, the reaction mixture was poured into water (100 mL) containing $K_3Fe(CN)_6$ (1.97 g, 6.0 mmol). Extraction with CH_2Cl_2, drying, and evaporation afforded crude

(31) Engman, L.; Hellberg, J. S. E. *J. Organomet. Chem.* **1985**, *296*, 357.
(32) Bergman, J.; Engman, L. *Synthesis* **1980**, 569.
(33) Exner, O. *Correlation Analysis of Chemical Data*; Plenum Press: New York, 1988.
(34) Exner, O. In *Correlation Analysis in Chemistry*; Chapman, N. B.; Shorter, J., Eds.; Plenum Press, New York, 1978.
(35) Roe, A. *Org. React.* (*N.Y.*) **1949**, *5*, 193.

bis(2,4,6-trimethoxyphenyl) ditelluride which was dissolved in dioxane (50 mL) and heated at reflux with 3.8 g (60 mmol) of activated copper powder until the red colour of the solution disappeared. Filtration, evaporation, and flash chromatography (SiO_2; CH_2Cl_2) afforded 0.335 g (24%) of compound **10**: mp 161 °C dec; ^1H NMR δ 3.65 (s, 12H), 3.80 (s, 6H), 6.10 (s, 4H). Anal. Calcd for $C_{18}H_{22}O_6Te$: C, 46.80; H, 4.80. Found: C, 46.57; H, 4.75.

4-Hydroxyphenyl Phenyl Telluride (12). To a stirred solution of 4-bromophenol (0.34 g, 1.97 mmol) in dry THF under argon, *tert*-butyllithium (3.48 mL 1.7 M; 5.9 mmol) was added dropwise at −78 °C. After 15 min a solution of phenyl phenylethynyl telluride (0.60 g, 1.97 mmol) in dry THF was added dropwise and stirring continued for 1 h. Workup, including hydrolysis at −78 °C, warming of the reaction mixture, dilution with water and CH_2Cl_2 extraction, evaporation, and recrystallization from CH_2Cl_2/hexanes afforded 0.42 g (72%) of compound **12**: mp 65 °C; ^1H NMR δ 4.81 (s, 1H), 6.73 (d, 2H), 7.14–7.26 (several peaks, 3H), 7.57 (m, 2H), 7.68 (d, 2H). Anal. Calcd for $C_{12}H_{10}OTe$: C, 48.40; H, 3.38. Found: C, 48.62; H, 3.26.

Bis(2-indolyl) Telluride (13). To a stirred solution of *N*-(benzenesulfonyl)indole[36] (1.50 g, 5.8 mmol) in dry THF (30 mL) at −78 °C under argon was added *tert*-butyllithium (3.5 mL 1.7 M, 5.9 mmol). After 45 min, the temperature was raised to ambient and finely crushed elemental tellurium (0.75 g, 5.9 mmol) added. Stirring was continued for 2 h when most of the tellurium had disappeared. The reaction mixture was then poured into water (100 mL) containing $K_3Fe(CN)_6$ (1.90 g, 5.8 mmol). After extraction with CH_2Cl_2, drying, and evaporation, the residue was dissolved in dioxane (50 mL) and heated at reflux with activated copper (1.90 g, 30 mmol) for 1 h. Filtration, evaporation and flash chromatography (CH_2Cl_2/hexanes = 1/1) afforded 0.96 g (51%) of crude bis[*N*-(benzenesulfonyl)-2-indolyl] telluride.

This material (0.60 g, 0.94 mmol) was heated at reflux in a mixture of MeOH (20 mL) and water (5 mL) containing K_2CO_3 (0.80 g, 5.8 mmol) for 10 h, when the solution was clear and homogenous. Workup with CH_2Cl_2/H_2O afforded 0.30 g (88%) of compound **13**: mp 181–2 °C (EtOH); ^1H NMR δ 6.95 (dd, 2H, J = 0.8 and 2.0 Hz), 7.08 (m, 2H), 7.14 (m, 2H), 7.26 (d, 2H), 7.57 (d, 2H), 8.09 (br s, 2H). Anal. Calcd for $C_{16}H_{12}N_2Te$: C, 53.40; H, 3.53. Found: C, 53.28; H, 3.53.

^1H NMR Assay. The determination of t_{50} values by ^1H NMR spectroscopy in the *N*-acetylcysteine, *tert*-butyl mercaptan, and 1-octylmercaptan systems was carried out as previously described[12] using 2.7×10^{-7} mol of the diorganyl telluride catalyst. The t_{50} values reported in Table 1 were in most cases based on a single determination. In case of duplicate determinations, the average value is reported. In a series of experiments carried out to examine the reproducibility of the method, the t_{50} values usually varied ±15% between different experiments.

As suggested by one reviewer, t_{50} values were determined in buffered and unbuffered solution, respectively, to investigate the possible influence of a pH effect on rates. As determined by the standard procedure for the *N*-acetylcysteine system (using neat D_2O as solvent and catalyst **5e**), the t_{50} value was the same (1 min) in the unbuffered and the buffered (containing 6 equiv of oxalic acid monopotassium salt, pH = 1.3) experiment.

In some experiments *tert*-butyl hydroperoxide (6.3 μL, 70% in H_2O, 0.046 mmol) replaced hydrogen peroxide in the standard 1-octyl mercaptan system.

When catalyst **5c** (2.7×10^{-7} mol) was added to a solution of *N*-acetylcysteine (0.050 g, 0.30 mmol) and hydrogen peroxide (30%, 15.7 μL, 0.15 mmol) in D_2O (0.6 mL) and CD_3OD (0.15 mL) in an NMR tube, all thiol was oxidized to the corresponding disulfide within 5 min. This corresponds to a turnover number based on thiol of 1110.

***tert*-Butyl Hydroperoxide Oxidation of Compounds 5d and 5h.** To a solution of bis(4-methoxylphenyl) telluride (0.0114 g, 0.033 mmol) in CD_3OD (0.75 mL) in an NMR tube was added *tert*-butyl hydroperoxide (5.0 μL, 70% aqueous; 0.037 mmol) and the ^1H NMR spectrum recorded at intervals during 30 min. From integration of the ^1H NMR spectrum (doublet at 6.78 ppm corresponding to telluride **5d**, doublet at 7.09 ppm corresponding to the oxidation product), the time required to oxidize 50% of the starting material, t_{50}, was calculated by intrapolation (t_{50} = 1.3 min). The ^1H NMR spectrum recorded 2 min after addition of 1-octyl mercaptan (12.7 μL, 0.074 mmol) showed only signals corresponding to compound **5d**.

Compound **5h** similarly gave a t_{50} value of 6.6 min (doublet at 7.53 ppm corresponding to telluride **5h**, doublet at 8.12 ppm corresponding to the oxidation product). Addition of 1-octyl mercaptan resulted in the rapid (<2 min) formation of bis[4-(trifluoromethyl)phenyl] telluride.

Acknowledgment. Financial support by the Swedish Natural Science Research Council and the National Swedish Board for Technical Development is gratefully acknowledged.

(36) Sundberg, R. J.; Russell, H. F. *J. Org. Chem.* **1973**, *38*, 3324.