Intramolecularly Coordinated Diorganyl Ditellurides: Thiol Peroxidase-like Antioxidants

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A series of diaryl ditellurides with and without coordinating amino/imino groups are synthesized by using either the Grignard route or the heteroatom-directed aromatic lithiation route. The chiral ditelluride (*R*),(*R*)-bis[2-(4-ethyl-2-oxazolinyl)phenyl] ditelluride is synthesized in an enantiomerically pure form by stereoselective *ortho*-lithiation. The thiol peroxidase activity of the ditellurides is studied by using H_2O_2 as a substrate and PhSH as a cosubstrate. The initial rates for the reduction of H_2O_2 catalyzed by diaryl ditellurides are much higher than those catalyzed by the corresponding diselenides. A comparison of the activities between various diorganyl ditellurides and diselenides shows that the presence of basic amino groups in the close proximity of tellurium enhances the reduction rates and the effect of amino groups on the activity is more pronounced in the case of ditellurides as compared to the corresponding diselenides. On the other hand, a correlation between the strength of Te···N intramolecular interactions and thiol peroxidase activity reveals that the strong Te···N interactions reduce the thiol peroxidase activity of amino/imino-substituted ditellurides. A plot of Te···N distances against ^{125}Te NMR chemical shifts shows a linear correlation.

Introduction

The construction of synthetic tellurium-containing peptides and proteins attracts considerable interest at present, mainly for the reason that it can be used to solve the phase problem in X-ray crystallography.[1] Although, replacement of sulfur by selenium is known to modify the biological activities considerably,[2] a similar role of tellurium in biosystems has not been discovered probably due to their great sensitivity to light and air. However, in recent years, the biological importance of tellurium has attracted considerable attention, as evidenced by several model studies on the antioxidant and photochemotherapeutic properties of synthetic organotellurium compounds.[3,4] In this direction, much attention has been directed toward the design and synthesis of organotellurium compounds[3b,c,e,j] that mimic the action of glutathione peroxidase (GPx). Apart from the GPx activity of several organoselenium compounds such ebselen (**1**) and other related compounds,[5,6] the thiol peroxidase activity of diaryl tellurides and ditellurides reported by Engman et al.[3b,c,e,j] and the use of tellurapyrylium dyes as catalysts for the H_2O_2 oxidation of benzenethiol reported by Detty et al.[4i] are significant examples in this area. GPx is a well-known selenoenzyme which catalyzes the reduction of harmful hydrogen peroxides and organic peroxides by glutathione (GSH) and protects the cell membrane from oxidative damage.[7] The enzyme catalytic site includes a selenocysteine residue in which the selenium undergoes a redox cycle involving the selenol (ESeH) as the active form which reduces hydrogen peroxides and organic peroxides. The selenol is oxidized to selenenic acid (ESeOH), which reacts with reduced glutathione (GSH) to form selenenylsulfide adduct (ESeSG). A second glutathione then regenerates the active form of the enzyme by attacking the ESeSG to form the oxidized glutathione (GSSG) (Scheme 1). Thus, in the overall process, 2 equiv of glutathione are oxidized to the

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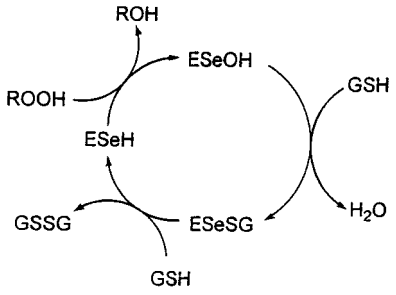
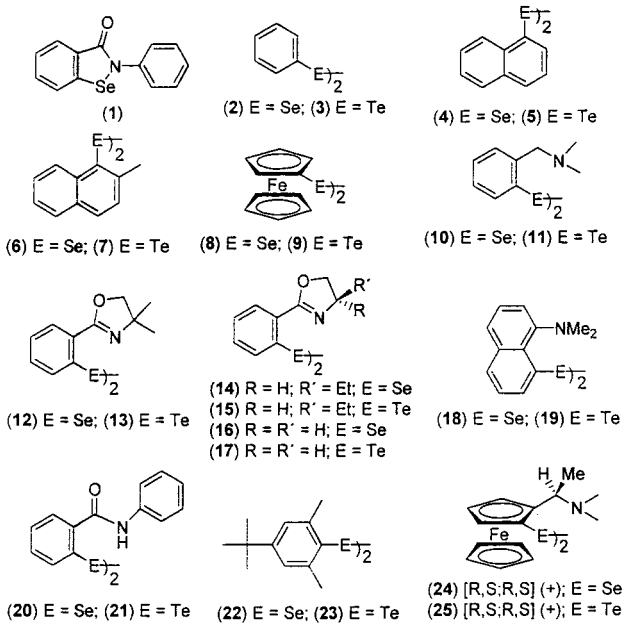
Scheme 1. Proposed Catalytic Mechanism of Glutathione Peroxidase



disulfide and water, while the hydroperoxide is reduced to the corresponding alcohol. In contrast to the cytosolic GPx, which uses GSH exclusively as cosubstrate, other enzymes such as plasma GPx or phospholipid hydroperoxide GPx readily accept many thiols other than GSH.[6b] Therefore, the selenium/tellurium compounds that reduce hydroperoxides by using thiols other than GSH can also be termed as GPx mimics or the activity of the compounds can be more properly described as a thiol peroxidase activity.[3e]

As part of our work on intramolecularly coordinated organochalcogens,[8] we have recently reported the GPx activity of a series of diaryl diselenides having intramolecular Se···N interactions.[9] It was found that the strong Se···N interactions reduce the GPx activity, although the basic amino groups in close proximity of selenium are essential for the catalytic GPx activity. In this paper we report a direct comparison of the thiol peroxidase activity of several tellurium compounds (**3**, **5**, **7**, **9**, **11**, **13**, **15**, **17**, **19**, **21**, **23**, **25**) with the selenium analogues (**2**, **4**, **6**, **8**, **10**, **12**, **14**, **16**, **18**, **20**, **22**, **24**) and delineate the effect of amino groups on the reactivity of organotellurium compounds as compared with the selenium analogues. In addition, we describe the synthesis and characterization of some new diorgano ditellurides including the first structural characterization of a novel diorgano ditelluride bearing chiral substituents. A correlation between intramolecular Te···N interactions and ^{125}Te NMR chemical shifts is also attempted.

Chart 1



Experimental Section

General Procedures. All reactions were carried out under nitrogen or argon using standard vacuum-line techniques. Solvents were purified by standard procedures[10] and were freshly distilled prior to use. Melting points were recorded in

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capillary tubes and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained at 300 and 75.42, respectively, in $CDCl_3$ on a Varian VXR 300S spectrometer. ^{1}H and ^{13}C chemical shifts are cited with respect to $SiMe_4$ as internal standard. The ^{77}Se and ^{125}Te NMR spectra were obtained at 95.35 and 94.75 MHz, respectively, in $CDCl_3$ on a Bruker AMX500 spectrometer using diphenyl diselenide and diphenyl ditelluride as external standards. Chemical shifts are reported relative to dimethyl selenide (^{77}Se) and dimethyl telluride (^{125}Te) (0 ppm) by assuming that the resonance of the standards are at 461 and 421 ppm, respectively. Elemental analyses were performed on a Carlo-Erba model 1106 elemental analyzer. Optical rotations were measured by a JASCO Model DIP 370 digital polarimeter.

Synthesis of Dinaphthyl Ditelluride (5).[11] In a 100 mL three-necked flask magnesium (0.36 g, 14.81 mmol) was added to 25 mL of anhydrous THF. 1-Bromonaphthalene (3.11 g, 15 mmol) was added dropwise with constant stirring under reflux conditions. The stirring was continued until the completion of the reaction, as indicated by the disappearance of magnesium. Tellurium powder (2.03 g, 15.83 mmol) was added to the reaction mixture in portions over a period of 30 min so as to maintain a gentle reflux. After 2 h reflux, the solution was poured into a beaker and kept overnight. The product was extracted with ether (2 × 25 mL). The ether solution was washed with water, and the organic layer was separated, dried over sodium sulfate, and evaporated under vacuum to give a brown solid, which was recrystallized from hexane. Yield: 1.5 g (37%), mp 110−112 °C (lit. 117−118 °C). Anal. Calcd for $C_{20}H_{14}Te_2$: C, 47.17; H, 2.77. Found: C, 47.49; H, 2.85. ^{1}H NMR ($CDCl_3$): δ 7.22−7.25 (m, 2H), 7.31−7.36 (m, 2H), 7.43−7.48 (m, 2H) 7.75−7.78 (m, 2H), 7.80−7.82 (m, 2H) 8.00−8.03 (m, 2H), 8.12−8.16 (m, 2H). ^{125}Te NMR ($CDCl_3$): δ 334.

Synthesis of 2-Methyl Dinaphthyl Diselenide (6). To a reaction mixture containing magnesium (0.24 g, 10 mmol) in 25 mL of anhydrous THF and a catalytic amount of iodine was added dropwise a solution of 1-bromo-2-methylnaphthalene (2.21 g, 10 mmol) in THF. The reaction mixture was stirred at room temperature until the completion of the reaction, as indicated by the disappearance of magnesium. Selenium powder (0.8 g, 10 mmol) was added to the reaction mixture in portions over a period of 30 min. After 2 h reflux, the solution was poured into a beaker and kept overnight. The product was extracted with ether (2 × 25 mL). The ether solution was washed with water, and the organic layer was separated, dried over sodium sulfate, and evaporated under vacuum to give an orange solid, which was recrystallized from a chloroform/hexane (1:2) mixture. Yield: 1.98 g (90%), mp 120−122 °C. Anal. Calcd for $C_{22}H_{18}Se_2$: C, 60.03; H, 4.12. Found: C, 59.57; H, 3.92. ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 6H), 7.18−7.36 (m, 6H), 7.68−7.71 (m, 4H) 8.15 (d, 2H). ^{13}C NMR ($CDCl_3$): δ 24.59, 125.05, 126.39, 127.88, 127.93, 128.88, 129.42, 129.89, 132.38, 135.87, 142.55. ^{77}Se NMR ($CDCl_3$): δ 356. IR (KBr): $\bar{\nu}$ 3045, 2927, 1617, 1586, 1551, 1500, 1030 (cm^{-1}).

Synthesis of 2-Methyl Dinaphthyl Ditelluride (7). To a reaction mixture containing magnesium (0.24 g, 10 mmol) in 25 mL of anhydrous THF and a catalytic amount of iodine was added dropwise a solution of 1-bromo-2-methylnaphthalene (2.21 g, 10 mmol) in THF. The reaction mixture was stirred at room temperature until the completion of the reaction, as indicated by the disappearance of magnesium. Tellurium powder (1.28 g, 10 mmol) was added to the reaction mixture in portions over a period of 30 min at room temperature. After stirring the mixture for 2 h at this temperature, oxygen was bubbled through the red solution for 10 min, and the resulting solution was poured into a beaker and kept overnight. The product was extracted with ether (2 × 25 mL). The ether solution was washed with water, and the organic layer was separated, dried over sodium sulfate, and evaporated under vacuum to give a brown solid. The crude product was loaded on a silica gel column, and the desired compound was eluted with hexane/ethyl acetate (5:1). Yield: 1.60 g (60%), mp 130−132 °C. Anal. Calcd for $C_{22}H_{18}Te_2$: C, 49.17; H, 3.37. Found: C, 49.07; H, 3.42. ^{1}H NMR ($CDCl_3$): δ 2.48 (s, 6H), 7.10−7.35 (m, 6H), 7.67−7.69 (m, 4H) 8.07 (d, 2H). ^{13}C NMR ($CDCl_3$): δ 30.74, 114.32, 125.06, 126.49, 126.78, 128.10, 130.14, 131.58, 134.53, 137.80, 145.28. ^{125}Te NMR ($CDCl_3$): δ 182. IR (KBr): $\bar{\nu}$ 3037, 2927, 1499, 1430, 1230, 1030 (cm^{-1}).

Synthesis of Diferrocenyl Ditelluride (9). Compound **9** was synthesized by following the literature method with slight modifications.[12] A stirred solution of ferrocene (2.24 g, 12 mmol) in dry THF (10 mL) was treated dropwise with a 1.6 M solution of t-BuLi in pentane (6.26 mL, 10 mmol) via a syringe at 0 °C. After stirring for 30 min at this temperature, the solution was warmed to room temperature. Tellurium powder (1.28 g, 10 mmol) was added under a brisk flow of N_2 gas, and stirring was continued for 1 h. The reaction mixture was then poured into a beaker, and oxygen was passed at a moderate rate for 30 min. The compound was extracted with 3 × 20 mL of CH_2Cl_2 and filtered. The filtrate was evaporated to dryness to give a brown solid. The crude product was chromatographed on a silica gel column. The unreacted ferrocene was eluted using hexane, and the diferrocenyl ditelluride was eluted using a 3:1 hexane/CH_2Cl_2 mixture. Slow evaporation of the CH_2Cl_2 solution gave red crystals of the desired compound. Yield: 0.6 g (19%), mp 138−140 °C (lit. 136 °C). Anal. Calcd for $C_{20}H_{18}Fe_2Te_2$: C, 38.44; H, 2.90. Found: C, 38.34; H, 2.92. ^{1}H NMR ($CDCl_3$): δ 4.13 (s, 10H), 4.27 (t, 4H), 4.36 (t, 4H). ^{125}Te NMR ($CDCl_3$): δ 383.

Synthesis of (*R*),(*R*)-Bis[2-(4-ethyl-2-oxazolinyl)phenyl] Ditelluride (15). A stirred solution of 4-*R*-(−)-ethyl-2-phenyloxazoline (1.78 g, 10.16 mmol) in dry THF (75 mL) was treated dropwise with a 1.6 M solution of n-BuLi in hexane (6.88 mL, 11 mmol) under N_2 at 0 °C. On stirring the reaction mixture for 1 h at this temperature, the lithiated product was obtained. Tellurium powder (1.28 g, 10 mmol) was added, and stirring was continued for an additional 15 min at 0 °C. The reaction mixture was then poured into a beaker containing cold aqueous $K_3Fe(CN)_6$ solution. The oily product was extracted with ether and then washed with water. The organic phase was separated, dried over Na_2SO_4, and filtered. The filtrate was concentrated to give a yellow oil. The compound was recrystallized from a dichloromethane/hexane (1:2) mixture to give pale yellow crystals. Yield: 1.07 g (35%), mp 128−130 °C. Anal. Calcd for $C_{22}H_{24}N_2O_2Te_2$: C, 43.79; H, 4.00; N, 4.64. Found: C, 43.80; H, 3.98; N, 4.65. ^{1}H NMR ($CDCl_3$): δ 1.12 (t, 6H), 1.81 (m, 4H), 4.16 (t, 2H) 4.60 (m, 2H), 4.42 (m, 2H) 7.10−7.30 (m, 4H), 7.80−8.16 (m,4H). ^{13}C NMR ($CDCl_3$): δ 10.46, 28.62, 67.18, 72.56, 126.24, 127.82, 128.23, 131.06, 132.07, 132.28, 163.32. ^{125}Te NMR ($CDCl_3$): δ 424. IR (KBr): $\bar{\nu}$ 3009, 2954, 2914, 2887, 1643, 1490, 1314, 1262, 1160, 1078, 1045 (cm^{-1}). $[\alpha]_D^{25}$ +102.3° (*c* 1, $CHCl_3$).

Synthesis of Bis[2-(4,4-dihydro-2-oxazolinyl)phenyl] Diselenide (16). A stirred solution of 4,4-dihydro-2-phenyloxazoline (1.47 g, 1.3 mL, 10 mmol) in dry ether (50 mL) was treated dropwise with a 1.6 M solution of n-BuLi in hexane (6.4 mL, 10.2 mmol) under N_2 at 0 °C. On stirring the reaction mixture for 1 h at this temperature, the lithiated product was obtained. Selenium powder (0.8 g, 10 mmol) was added, and stirring was continued for an additional 1 h at 0 °C and 2 h at room temperature. Oxygen was bubbled through the solution for 10 min, and the resulting mixture was poured into a beaker containing cold aqueous $NaHCO_3$ solution. Oxygen was bubbled for an additional 15 min. The yellow oily product was extracted with ether and then washed with water. The organic phase was separated, dried over Na_2SO_4, and filtered. The filtrate

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was concentrated to give a yellow solid. The compound was recrystallized from a dichloromethane/hexane (1:2) mixture to give yellow crystals of the desired compound. Yield: 1.35 g (60%), mp 218−220 °C. Anal. Calcd for $C_{18}H_{16}N_2O_2Se_2$: C, 48.04; H, 3.58; N, 6.22. Found: C, 48.23; H, 3.32; N, 6.22. ^{1}H NMR ($CDCl_3$): δ 4.25 (t, 4H), 4.47 (t, 4H), 7.20−7.27 (m, 4H), 7.82−7.87 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 54.9, 67.4, 125.6, 125.9, 129.7, 130.4, 131.4, 133.1, 164.3. ^{77}Se NMR ($CDCl_3$): δ 465. IR (KBr): $\bar{\nu}$ 2970, 2934, 2894, 2870, 1642, 1584, 1559, 1479, 1433, 1358, 1252 (cm^{-1}).

Synthesis of Bis[2-(4,4-dihydro-2-oxazolinyl)phenyl] Ditelluride (17). A stirred solution of 4,4-dihydro-2-phenyloxazoline (1.47 g, 1.3 mL, 10 mmol) in dry THF (50 mL) was treated dropwise with a 1.6 M solution of n-BuLi in hexane (6.4 mL, 10.2 mmol) under N_2 at 0 °C. On stirring the reaction mixture for 1 h at this temperature, the lithiated product was obtained. After the addition of tellurium powder (1.28 g, 10 mmol) at 0 °C, the reaction mixture was allowed to reach room temperature, and the stirring was continued for an additional 4 h. The reaction mixture was then poured into a beaker containing 10 mmol (3.29 g) of cold aqueous $K_3Fe(CN)_6$ solution. The red oily product was extracted with ether and then washed with water. The organic phase was separated, dried over Na_2SO_4, and filtered. The filtrate was concentrated to give an orange solid. Attempts to crystallize the compound led to oxygenated products with indefinite composition. Yield: 0.96 g (35%), mp 178−181 °C. Anal. Calcd for $C_{18}H_{16}N_2O_2Te_2$: C, 39.50; H, 2.94; N, 5.11. Found: C, 38.47; H, 3.53; N, 4.98. ^{1}H NMR ($CDCl_3$): δ 4.23 (t, 4H), 4.51 (t, 4H), 7.10−7.16 (m, 2H), 7.26−7.29 (m, 2H), 7.80−7.83 (m, 2H), 8.10−8.13 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 53.95, 68.10, 113.16, 126.47, 128.35, 128.95, 131.50, 139.16, 165.27. ^{125}Te NMR ($CDCl_3$): δ 420. IR (KBr): $\bar{\nu}$ 3057, 2965, 2874, 1644, 1611, 1565, 1368, 1256, 1084 (cm^{-1}).

Synthesis of Bis[2,5 dimethyl-4-*tert*-butylphenyl] Ditelluride (23). A 100 mL three-necked flask was equipped with a magnetic stirrer, a pressure-equalizing dropping funnel, and a reflux condenser mounted with a nitrogen source. To the flask were added 2-bromo-5-*tert*-butyl-*m*-xylene (**26**)[13] (2.42 g, 10 mmol), magnesium (0.24 g, 10 mmol), and ether (10 mL). The reaction was initiated by the addition of iodine. The reaction mixture was heated at reflux for 1 h, and then dry THF (25 mL) was added. The reflux was continued for a further 4 h to get a white slurry of **27**. While a slow stream of nitrogen was passed through a nitrogen inlet, Te powder (1.28 g, 10 mmol) was added. The reflux was continued until all the tellurium had reacted to give a red solution. The resulting solution was poured into a beaker, and oxygen was bubbled for 15 min. After evaporating the solvent completely, the red-colored solid was dissolved in dichloromethane, filtered through Celite, and dried over sodium sulfate. Evaporation of the solvent afforded a brown solid, which was recrystallized from hexane to give needle-shaped crystals of the desired compound. Yield: 5.01 g (90%), mp 110−112 °C. Anal. Calcd for $C_{24}H_{34}Te_2$: C, 49.92; H, 5.93. Found: C, 50.91; H, 6.20. ^{1}H NMR ($CDCl_3$): 1.20 (s, 18H), 2.35 (s, 12H), 7.04 (s, 4H). ^{125}Te NMR ($CDCl_3$): 197.

Kinetic Analysis. PhSH Assay. The reactions of model compounds with benzenethiol (PhSH) and H_2O_2 were studied by following the appearance of the disulfide absorption at 305 nm, at 25 °C. Each initial velocity was measured at least six times and calculated from the first 5−10% of the reaction. For the peroxidase activity, the rates were corrected for the background reaction between H_2O_2 and PhSH. The actual concentration of PhSH in the kinetic apparatus was measured from the 305 nm absorbance, and rates were corrected for any variation in the concentration of PhSH. The molar extinction coefficient of PhSSPh ($\epsilon_1 = 1.24 \times 10^3$ M^{-1} cm^{-1}) at the wavelength was much larger than that of PhSH ($\epsilon_2 = 9$ M^{-1} cm^{-1}). The concentration of PhSH (C) was therefore calculated from the absorbance (a) according to the following equation: $C = (\epsilon_1 C_0 - 2a)/(\epsilon_1 - 2\epsilon_2) \approx C_0 - 2a/\epsilon_1$. The initial reduction rate of H_2O_2 (v_0) was then determined by $1/v$ vs $1/[PhSH]$ plots. The concentration of the H_2O_2 stock was determined by permanganate titration. To investigate the dependency of rate on substrate concentrations, the reaction rates were determined at several concentrations of one substrate while keeping the concentration of the other constant. The Lineweaver−Burk plots were obtained using Grapher 1.09 version, 2D-Graphing System for windows program.[14] For each set of experiments the straight line was drawn by choosing the best fit method.

Table 1. Crystal Data and Structure Refinement for 11, 15, and 18

	11	**15**	**18**
empirical formula	$C_{18}H_{24}N_2Te_2$	$C_{22}H_{24}N_2O_2Te_2$	$C_{24}H_{24}N_2Se_2$
fw	523.59	603.63	498.37
cryst syst	orthorhombic	orthorhombic	monoclinic
space group	*Pcab*	$P2_12_12_1$	$P2_1/c$
a (Å)	9.098(3)	6.9679(4)	7.7149(5)
b (Å)	18.9503(17)	16.0795(10)	14.1747(18)
c (Å)	23.172(3)	20.1229(12)	19.9375(11)
α (deg)	90	90	90
β (deg)	90	90	90.623(5)
γ (deg)	90	90	90
V (Å^3)	3994.9(13)	2254.6(2)	2280.2(3)
Z	8	4	4
D(calcd) (Mg/m^3)	1.741	1.778	1.518
abs coeff (mm^{-1})	2.920	2.607	3.403
obsd reflens [$I > 2\sigma$]	4565	5117	4917
final $R(F)$ [$I > 2\sigma(I)$][a]	0.0285	0.0220	0.0459
$wR(F^2)$ indices [$I > 2\sigma(I)$]	0.0716	0.0490	0.0887
no. of data/restrains/params	4565/0/228	5117/0/280	4917/0/282
absolute structure param		−0.014(18)	
goodness of fit on F^2	1.161	1.048	1.018

[a] Definitions: $R(F_o) = \sum||F_o| - |F_c||/\sum|F_o|$ and $wR(F_o^2) = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_c^2)^2]\}^{1/2}$.

X-ray Crystallography. The X-ray diffraction measurements were performed on a Siemens R3m/V diffractometer for compounds **11** and **18** and on a Bruker SMART diffractometer for compound **15** using graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). The unit cell was determined from 25 randomly selected reflections using the automatic search index and least-squares routine. The data were corrected for Lorentz, polarization, and absorption effects. The structures were solved by direct methods and subjected to full-matrix least-squares refinement on F^2 (program SHELXL-97).[15] The hydrogens were partially located from difference electron-density maps, and the rest were fixed at calculated positions. Scattering factors were from common sources.[16] Some details of data collection and refinement are given in Table 1.

Results and Discussion

Synthesis. Dichalcogenides **10**,[17] **11**,[18] **12**,[9] **13**,[8a] **14**,[9] **18**,[9] **19**,[19] **20**,[20] **21**,[20] **22**,[9] **24**,[21] and **25**[22] used in the

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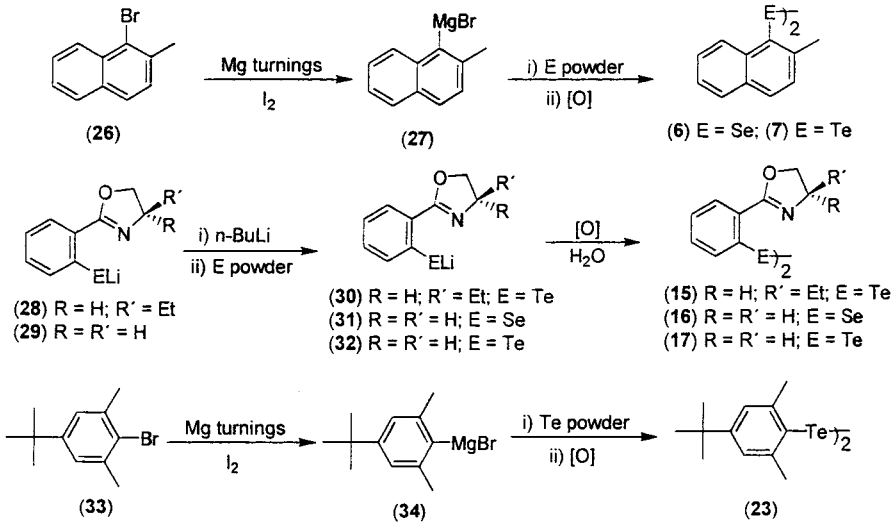
Scheme 2. Synthetic Routes to the Dichalcogenides



present study were prepared by the methods indicated. The dichalcogenides **4**,[11] **5**,[11] **8**,[12] and **9**[12] were synthesized by following literature methods with minor modifications. Dinaphthyl ditelluride **7** was synthesized from commercially available 1-bromonaphthalene by the Grignard route. Compounds **6** and **7** were also synthesized by the Grignard route by using 1-bromo-2-methylnaphthalene as the starting material (Scheme 2). Compound **9** was synthesized by following the literature method[12] with slight modifications, which include the use of ferrocene as the starting material instead of bromoferrocene. Monolithiation of ferrocene was achieved by the addition of t-BuLi to a solution of ferrocene in THF at 0 °C, which was further treated with finely ground tellurium to give the lithium arenetellurolate. Oxidative workup of the lithium arenetellurolate then gave the diferrocenyl ditelluride (**9**) in moderate yield. The quantity of THF used for the reaction was found to be crucial for the monolithiation and tellurium insertion reactions. The novel dichalcogenides (**6**, **7**, **15**−**17**, and **23**) were prepared from easily available starting materials.

The heteroatom-directed lithiation of *R*-(−)-4-ethyl-2-phenyloxazoline (**28**) with n-BuLi followed by tellurium insertion and oxidative workup afforded the novel chiral ditelluride **15** in an enantiomerically pure form. The dichalcogenides **16** and **17**, having no alkyl substituents in the five-membered oxazoline ring, were synthesized by following similar procedures starting from 4,4-dihydro-2-phenyloxazoline (**29**). Compound **18** was also synthesized by following the heteroatom-directed lithiation route.[9] Interestingly, two conformational polymorphs were obtained for compound **18** by the crystallization method. While polymorph **a** (**18a**) crystallized as yellow plates, polymorph **b** (**18b**) crystallized as white needles. Although the product mixture gave two strong signals in the ^{77}Se NMR spectra, the white needles isolated by crystallization exhibit only one signal at 485 ppm, which corresponds to a single conformer. The synthesis of compound **23** was first approached by the organolithium route. Addition of n-BuLi to an ethereal solution of 2-bromo-5-*tert*-butyl-*m*-xylene (**33**) produced a white precipitate of the lithiated compound. Since all attempts for the insertion of Te into the C−Li bond were unsuccessful, we decided to synthesize the desired compound by the Grignard route. Reaction of **33** with magnesium turnings produced arylmagnesium bromide (**34**). Addition of tellurium powder followed by oxidation afforded the desired ditelluride **23** as a dark brown solid in good yield.

Catalytic Activity: Initial Reduction Rates (v_0). The catalytic activity was studied according to the method reported by Tomoda et al.[6l] using benzenethiol (PhSH) as a glutathione alternative. The initial rates (v_0) for the reduction of H_2O_2 (3.75 mM) by thiol (1 mM) in the presence of various catalysts (0.1 mM) (eq 1) were determined in methanol medium by monitoring the UV absorption at 305 nm due to the formation of diphenyl disulfide (PhSSPh).

$$H_2O_2 + 2PhSH \xrightarrow{\text{catalyst}} 2H_2O + PhSSPh \qquad (1)$$

The relative activities of the compounds are summarized in Table 2. All the ditellurides were found to be much more efficient catalysts than the corresponding diselenides in reducing H_2O_2 with PhSH as a cosubstrate. Crucially, the best ditelluride catalyst (**11**, v_0 = 1629.56 (5.67) μM min^{-1}) is ca. 13 times more active than its selenium analogue (**10**, v_0 = 124.02 (7.89) μM min^{-1}). This is in agreement with a previous report that the hydrochloride salt of **11** is a more efficient thiol peroxidase-like catalyst than the hydrochloride salt of **10** in a ^{1}H NMR assay with *N*-acetylcysteine, *tert*-butylmercaptan, and 1-octylmercaptan as thiol cosubstrates.[3b] To know the effect of basic amino groups on the reactivity of tellurium catalysts, the activity enhancement of tellurium compounds was compared with the selenium analogues in both the presence and absence of amino substituents. The observed activities of the tellurium compounds **11**, **13**, **15**, and **19**, having basic amino groups, are much higher than those of the unsubstituted ditellurides **3**, **5**, and **9**. On the other hand, compounds **11** and **19**, having tertiary amino

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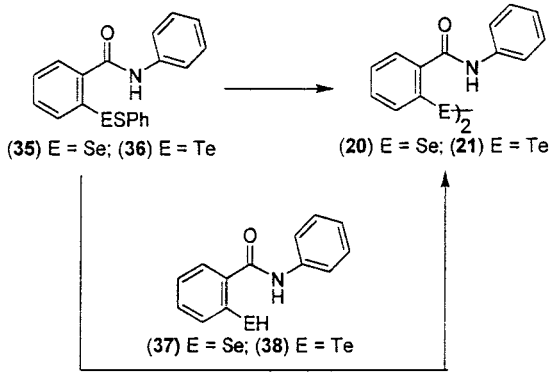
Table 2. Initial Reduction Rates (v_0)[a] of H_2O_2 (3.75 mM) with PhSH (1 mM) in the Presence of Various Dichalcogenide Catalysts (0.1 mM)

entry	catalyst (E = Se)	v_0,[b] μM min^{-1}	entry	catalyst (E = Te)	v_0,[b] μM min^{-1}
a	**2**	24.08(1.04)	b	**3**	59.52(3.58)
c	**4**	53.21(5.81)	d	**5**	142.97(5.17)
e	**6**	31.48(3.07)	f	**7**	70.47(5.40)
g	**8**	33.92(0.37)	h	**9**	77.61(6.08)
i	**10**	124.02(7.89)	j	**11**	1629.56(5.67)
k	**12**[c]	28.87(1.72)	l	**13**	135.09(10.04)
m	**14**[c]	18.53(1.32)	n	**15**	109.38(6.95)
o	**16**	41.64(1.48)	p	**17**	*e*
q	**18**[c]	45.34(2.81)	r	**19**	239.00(8.99)
s	**20**	3.52(0.87)	t	**21**	9.83(1.82)
u	**22**	inactive	v	**23**	inactive
w	**24**	574.01 (23.98)[d]	x	**25**	*e*

[a] Obtained by Lineweaver−Burk plots. [b] Standard deviations are shown in parentheses. [c] Inactive at lower concentration.[9] [d] Since the reduction rate was too fast to be determined at 0.1 mM concentration range, 0.01 mM was used for the experiments.[9] [e] Decomposed.

Scheme 3. Possible Conversions of Compounds 35 and 36



groups, were found to be more active than compounds **13** and **15**, possessing imino nitrogen in close proximity of tellurium. However, while the selenium compounds **12** and **14** are equally or less efficient than the unsubstituted diselenide **2**, the ditellurides **13** and **15** were found to be more efficient than the unsubtituted ditelluride **3**. These results clearly indicate that the presence of basic amino/imino nitrogen atom in close proximity of tellurium is important for high peroxidase activity. While diselenide **16**, containing no alkyl groups in the five-membered oxazoline ring, is more active than compounds **12** and **14**, having alkyl groups, the tellurium analogue of **16** could not be tested for the thiol peroxidase activity due to its instability during purification. Similarly, the tellurium analogue (**25**) of the most active compound **24** in the PhSH assay did not show any noticeable activity under identical experimental conditions since the ditelluride **25** decomposed completely in methanol, DMSO, and $CHCl_3$ to give elemental tellurium. Interestingly, compounds **20** and **21**, having secondary amino groups, were much less active than the compounds containing tertiary nitrogen atoms (**10**−**19**). This is probably due to the fact that the chalcogenyl sulfides (**35**, **36**) derived from reactions between **20** or **21** and PhSH may disproportionate to the corresponding dichalcogenides (**20**, **21**).[23] Moreover, the chalcogenyl sulfides **35** and **36** may react with the corresponding chalcogenols (**37**, **38**) to produce the dichalcogenides as shown in Scheme 3.[24]

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Table 3. Reduction Rates (v) Obtained by Changing the Thiol Concentration; the Concentrations of 10 and 11 Were Fixed to 0.01 mM

entry	[PhSH] (mM)	v (μM min^{-1}) for **10**	v (μM min^{-1}) for **11**
1	1.25	36.0	37.0
2	1.43	41.2	29.7
3	1.67	44.7	36.1
4	2.00	57.5	33.2
5	2.50	67.6	32.4
6	3.33	87.7	40.3
7	5.00	132.6	37.1

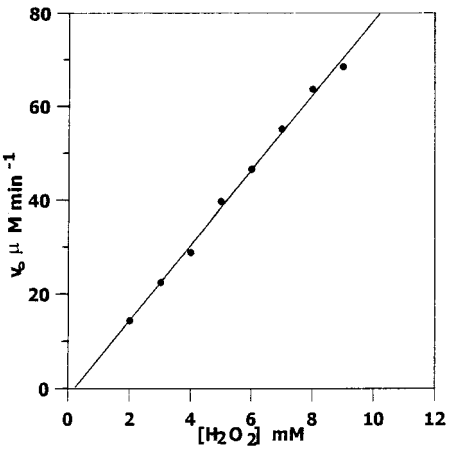

Figure 1. Plot of initial rates at 0.01 mM of catalyst **11** against H_2O_2 concentration. The initial PhSH concentration was fixed to 1.25 mM.

The striking feature of the kinetic data obtained for **10** and **11** is the difference in the effect of thiol (PhSH) on the reduction rate. While the initial reduction rate for **10** increased gratually with the thiol concentration, the rate for **11** was not affected by changing the thiol concentration from 1 mM to 5 mM (Table 3). On the other hand, a steady increase in the reduction rate was observed for **11** when the H_2O_2 concentration was increased (Figure 1). This is in contrast to the reduction rate by diselenides, which show only moderate effect on changing the H_2O_2 concentration.[6l] This indicates a basic difference between the reaction mechanisms of diselenides and ditellurides. It is also possible that the diselenides and ditellurides follow the same mechanism, but with different rate-determining steps. Since the mechanism (or the rate-determining step) of ditellurides differs considerably from that of diselenides, it may not be possible to compare the Michaelis constant (K_m) and maximum rate (V_{max}) for ditelluride-catalyzed reactions.

Crystal and Molecular Structures of 11, 15, and 18. The molecular structure of **11** with the atom-numbering scheme is given in Figure 2, and selected bond lengths and angles are summarized in Table 4. Since the crystal structure of compound **11** has been reported recently by Drake et al.[25] during the course of our present study, we compare only a few aspects of the structure which has a better *R*-value than the

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(25) Drake, J. E.; Hursthouse, M. B.; Kulcsar, M.; Light, M. E.; Silvestru, A. *J. Organomet. Chem.* **2001**, *623*, 153.

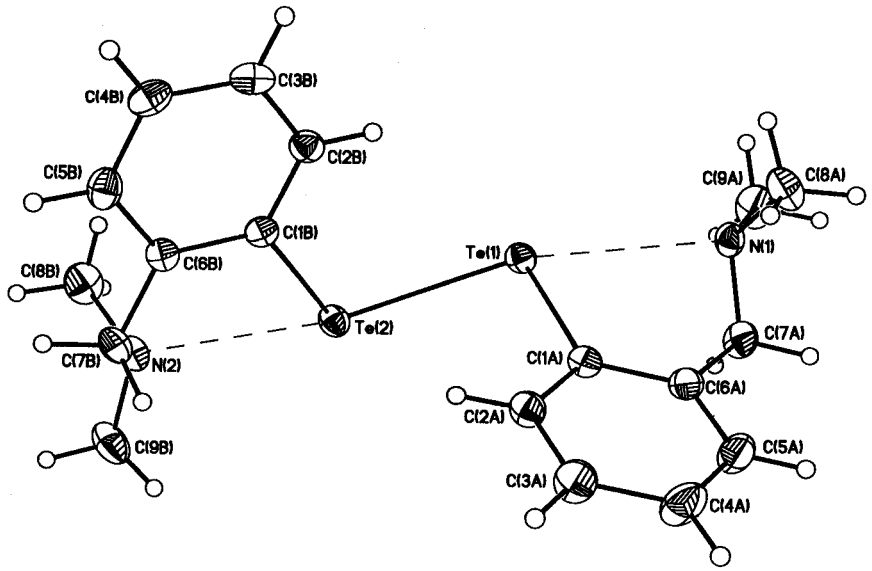

Figure 2. Molecular structure of compound **11**.

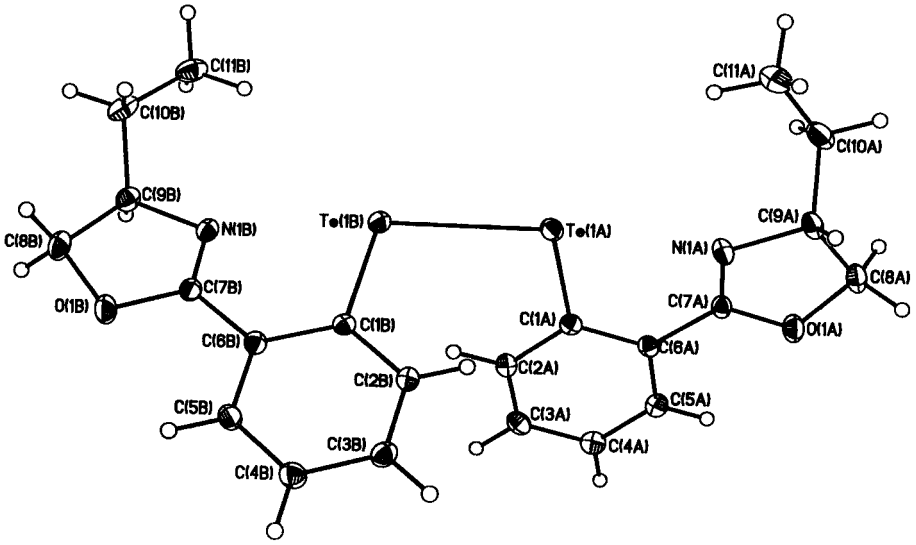

Figure 3. Molecular structure of compound **15**.

Table 4. Selected Bond Lengths (Å) and Angles (deg) for 11

Te(1)···N(1)	2.903	Te(2)···N(2)	2.848
Te(1)−C(1A)	2.135(4)	Te(1)−Te(2)	2.7479(7)
Te(2)−C(1B)	2.136(4)	N(1)−C(8A)	1.442(5)
N(1)−C(7A)	1.442(5)	N(1)−C(9A)	1.463(5)
N(2)−C(7B)	1.442(5)	N(2)−C(9B)	1.449(5)
N(2)−C(8B)	1.459(5)	C(1A)-Te(1)−Te(2)	98.92(10)
C(1B)−Te(2)−Te(1)	100.06(10)	C(8A)−N(1)−C(7A)	112.6(4)
C(8A)−N(1)−C(9A)	110.7(4)	C(7A)−N(1)−C(9A)	111.6(4)
C(7B)−N(2)−C(9B)	111.1(3)	C(7B)−N(2)−C(8B)	111.1(4)
C(9B)−N(2)−C(8B)	111.8(4)	C(2A)−C(1A)−Te(1)	121.1(3)
C(6A)−C(1A)−Te(1)	118.7(3)	C(2B)−C(1B)−Te(2)	122.0(3)
C(6B)−C(1B)−Te(2)	118.0(3)	N(2)−C(7B)−C(6B)	111.9(3)

Table 5. Selected Bond Lengths (Å) and Angles (deg) for 15

Te(1A)···N(1A)	2.792(5)	Te(1B)···N(1B)	2.755(8)
Te(1A)−C(1A)	2.141(3)	Te(1A)−Te(1B)	2.7559(3)
Te(1B)−C(1B)	2.147(3)	O(1A)−C(7A)	1.357(4)
O(1A)−C(8A)	1.444(4)	O(1B)−C(7B)	1.356(4)
O(1B)−C(8B)	1.458(4)	N(1A)−C(7A)	1.271(4)
N(1A)−C(9A)	1.479(4)	N(1B)−C(7B)	1.270(4)
N(1B)−C(9B)	1.473(4)		
C(1B)−Te(1B)−Te(1A)	98.78(8)	C(1A)−Te(1A)−Te(1B)	99.20(8)
C(7A)−N(1A)−C(9A)	107.8(3)	C(7B)−N(1B)−C(9B)	107.8(3)
C(2A)−C(1A)−Te(1A)	121.0(2)	C(6A)−C(1A)−Te(1A)	121.0(2)
N(1A)−C(7A)−O(1A)	117.8(3)	C(2B)−C(1B)−Te(1B)	121.1(2)
C(6B)−C(1B)−Te(1B)	120.2(2)	N(1B)−C(7B)−O(1B)	118.0(3)

reported structure. The intramolecular Te(1)···N(1) and Te(2)···N(2) distances of 2.903 and 2.848 Å, respectively, are identical with those of the reported values. The Te(1)−Te(2) length of 2.7479(7) Å and other bond lengths and angles are also identical with the literature values.

The molecular view of compound **15** with atom numbering is shown in Figure 3. Selected bond lengths and angles are summarized in Table 5. Compound **15** crystallizes in an orthorhombic system with four molecules per unit cell. The coordination geometry around the tellurium atoms is distorted T-shaped, with each tellurium atom bonded to a tellurium, a carbon, and a nitrogen atom. The Te(1A)−Te(1B) bond length of 2.7559(3) Å relates well to the Te−Te distance reported for the corresponding achiral analogue **13** [2.7387(5) Å][8a] and other ditellurides which normally range from 2.665 to 2.746 Å.[19] This distance is also close to the one

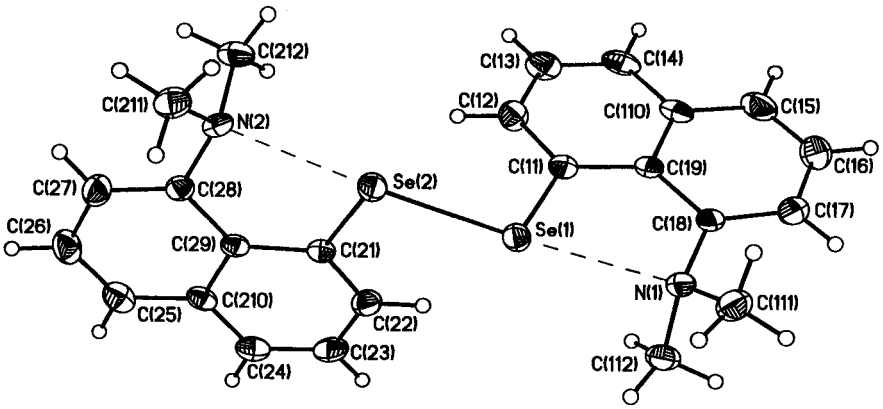

Figure 4. Molecular structure of compound **18**.

reported for a related compound, bis(2-naphthyl) ditelluride [2.7179(6) Å].[26] The Te−C bond lengths [Te(1A)−C(1A) 2.141(3), Te(1B)−C(1B) 2.147(3) Å] are also in agreement with the value of 2.14 Å suggested by Pauling[27] and the typical values for other ditellurides such as bis[2-(4,4-dimethyl-2-oxazolinyl)phenyl] ditelluride [2.136(4), 2.151(5) Å],[8a] bis(2-naphthyl) ditelluride [2.135(6), 2.127(5) Å],[26] and 8-(dimethylamino)-1-naphthyl ditelluride [2.130(5), 2.126(5) Å].[19] The interesting feature in this structure is the strong intramolecular interaction of the tertiary nitrogen with the tellurium. Atomic distances of Te(1A)···N(1A) and Te(1B)···N(1B) are 2.792(1) and 2.756(1) Å, respectively, both of which are larger than the sum of their covalent radii but significantly shorter than the sum of the corresponding van der Waals radii (3.61 Å). The Te···N distances in this compound differ significantly from the Te···N distances reported for the corresponding achiral analogue, as the corresponding distances are not equal in the latter case [2.864(5), 2.694(5) Å]. Moreover, the Te···N distances in **15** are shorter than those recently reported for bis[2-(hydroxyiminomethyl)phenyl] ditelluride [2.822 and 2.876 Å] where the nitrogen is also in sp^2 state.[28] In the case of **15**, the torsion angle C(1A)−Te(1A)−Te(1A)−C(1B) is 77.66(11)°, and therefore, the conformation can be termed as "cisoid". Since the ditelluride possesses two chiral centers in the oxazoline rings, the compound has crystallized in a chiral space group $P2_12_12_1$. Refinement of the Flack enantiopole parameter[29] led to a value of ∼0 for **15**, thus confirming that the crystals of **15** are enantiomerically pure.

The molecular structure of **18** with the atom-numbering scheme is shown in Figure 4, and selected bond lengths and angles are listed in Table 6. The crystals of compound **18** used in the present study can be considered as "conformational polymorphs" since the compound crystallized in different conformers. The crystal structure of another polymorph has been recently reported.[9] Polymorph **18a** is orthorhombic, space group $P2_12_12_1$, whereas polymorph **18b** is monoclinic, space group $P2_1/c$. Bond lengths and angles in the two polymorphs lie within normal ranges. The Se(1)···N(1) and Se(2)···N(2) distances of 2.672 and 2.617 Å, respectively, in **18b** are comparable to the corresponding distances [2.652, 2.628 Å] in **18a**. The Se(1)−C(11) [1.953(4) Å], Se(2)−C(21) [1.944(4) Å], and Se(1)−Se(2) [2.3723(6) Å] bond lengths in compound **18b** are comparable to those reported for the chiral polymorph **18a**.

Table 6. Selected Bond Lengths (Å) and Angles (deg) for 18

Se(1)···N(1)	2.672(1)	Se(2)···N(2)	2.617(1)
Se(1)−C(11)	1.953(4)	Se(1)−Se(2)	2.3723(6)
Se(2)−C(21)	1.944(4)	N(1)−C(18)	1.425(5)
N(1)−C(111)	1.452(5)	N(1)−C(112)	1.462(5)
N(2)−C(28)	1.425(5)	N(2)−C(211)	1.455(5)
C(11)−Se(1)−Se(2)	101.25(12)	C(21)−Se(2)−Se(1)	102.02(12)
C(18)−N(1)−C(111)	116.5(3)	C(18)−N(1)−C(112)	112.1(3)
C(111)−N(1)−C(112)	111.7(3)	C(28)−N(2)−C(211)	115.6(3)
C(28)−N(2)−C(212)	112.0(3)	C(211)−N(2)−C(212)	112.1(3)
C(19)−C(11)−Se(1)	120.4(3)	C(12)−C(11)−Se(1)	120.0(3)
C(22)−C(21)−Se(2)	121.4(3)	C(29)−C(21)−Se(2)	119.4(3)

Effect of the Te···N Interactions on the Reduction Rate. While the presence of a basic nitrogen atom in close proximity to the tellurium and subsequent interactions between tellurium and the heteroatom should be responsible for the activity enhancement of compounds **11**, **13**, **15**, and **19**, the strong Te···N interaction seems to be detrimental to the thiol peroxidase activity. The Te···N distances of **11** [2.903, 2.848 Å], **13** [2.864(5), 2.694(5) Å], **15** [2.792(4), 2.756(4) Å], and **19** [2.743(5), 2.699(5) Å] are significantly shorter than the van der Waals distance of these two atoms (3.61 Å). The Te···N distances of the most active compound, **11**, are considerably longer than the corresponding distances in other amino/imino-substituted compounds. The ^{125}Te NMR chemical shifts of **11** (374.6 ppm), **13** (417.1 ppm), **15** (423.5 ppm), and **19** (461.0 ppm) also indicate that the Te···N intramolecular interactions in **13**, **15**, and **19** are much stronger than that of **11**. To obtain a correlation between the ^{125}Te chemical shifts in solution and the strength of Te···N intramolecular interactions in the solid state, the chemical shifts were ploted against the Te···N distances. From Table 7 and Figure 5, it appears that the ^{125}Te NMR chemical shifts generally change with the strength of the Te···N interaction, with some exceptions. As in the case of ^{77}Se NMR chemical shifts,[8c] the ^{125}Te signals appear downfield when the Te···N interactions are strong.

The Te···N interactions alter the reactivity of the ditellurides and the intermediates involved in the

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Table 7. ^{125}Te NMR Chemical Shifts and Te···N Distances

compd	Te···N distance [Å]	^{125}Te (δ)	ref
11	2.876	375	this work
13	2.779	417	8a
15	2.774	424	this work
19	2.721	461	19
39[a]	2.713	709	19
40[b]	2.505	1124	8d
41[c]	2.366	1192	18
42[d]	2.966	493	30
43[e]	2.340	1229	28
44[f]	2.701	608	31
45[g]	2.185	1333	31

[a] 8-(Dimethylamino)-1-naphthylphenyl telluride. [b] 8-(Dimethylamino)-1-naphthyltellurium dithiacarbamate. [c] [2-(*N*,*N*-Dimethylaminomethyl)phenyl]tellurium iodide. [d] Bis[2-(4,4,-dimethyl-2-oxazolinyl)phenyl] telluride. [e] Bis[2-(phenylazophenyl-*C*,*N*′)] ditelluride. [f] Bis(diphenyltelluride)BISEN Schiff base. [g] 1,6-Bis(2-chlorotellurophenyl)2,5-diazahexa-1,5-diene.

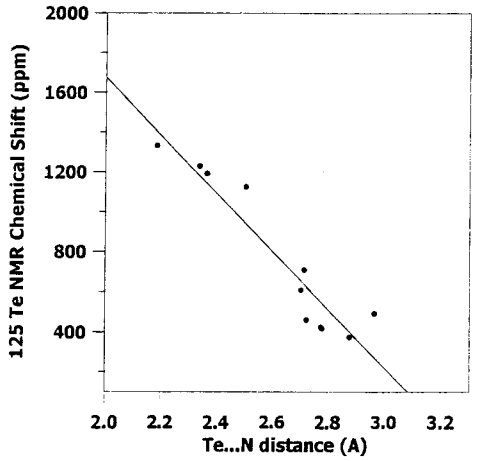
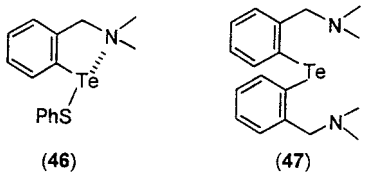


Figure 5. Plot of Te···N bond lengths against ^{125}Te NMR chemical shifts.

catalytic cycle. For example, ditelluride **11**, in which the Te−Te bond is activated by Te···N interactions, readily reacted with PhSH to give a signal at 964 ppm for the expected tellurenyl sulfide (**46**). It is also possible that the dichalcogenides may undergo dechalcogenation under certain conditions to form the corresponding monochalcogenides. It has been reported that the monotelluride (**47**) can be generated from the ditelluride **11** by using Pd in refluxing dioxane.[3e] However, the signal at 964 ppm is largely shifted downfield compared with that of **47** (545 ppm),[32] indicating the absence of such species during the course of reaction. The signal at 964 ppm can, therefore, be assigned to the tellurenyl sulfide (**46**) and the significant downfield shift of the signal in this compound is probably due to the presence of a basic amino group which strongly interacts with the tellurium to make a 3c−4e bonding environment around the N−Te−S moiety. As in the case of diselenides, the reactivity of tellurenyl sulfide toward the thiol might determine the peroxidase activity of the ditellurides. Since the strong Te···N interaction in the tellurenyl sulfide may preclude the possibility of a nucleophilic attack of thiol at sulfur, the regeneration of tellurol in the catalytic cycle becomes a less favored process.

Chart 2



Conclusion

We have shown that the diaryl ditellurides are much more efficient catalysts than the selenium analogues in reducing H_2O_2 by using PhSH as a thiol cosubstrate. The high thiol peroxidase activity of the tellurium compounds compared with the selenium analogues must be primarily ascribed to the ease of dissociation of tellurol as compared with selenol. While the basic amino group near the tellurium center shows a more pronounced effect on the thiol peroxidase activity than it does with the selenium, a strong Te···N interaction reduces the activity. The enhancement of reactivity of tellurium compounds as compared with selenium analogues may give some information regarding the question as to whether a tellurol instead of selenol in the active site of an enzyme can alter its kinetic parameters and modify the catalytic activity.

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Supporting Information Available: The details of kinetic measurements, tables giving crystal data and details of the structure determination, final atomic coordinates, bond lengths and angles, anisotropic displacement parameters, and hydrogen atom coordinates for **11**, **15**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) Compound **48** used in this study was synthesized from *N*,*N*-dimethylbenzylamine by *ortho*-lithiation followed by reaction with $Te(dtc)_2$ (dtc = diethyldithiacarbamate) or TeI_2 as described in refs 8d and 18.