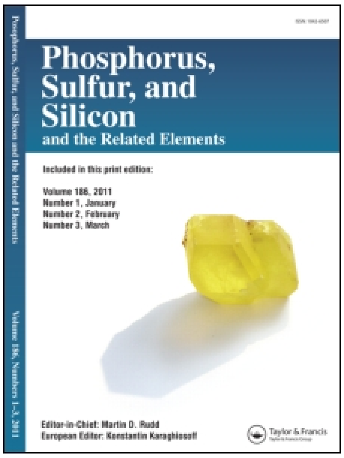

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Heavy Atom Effects in Tellurapyrylium Dyes Useful in Photodynamic Therapy and Catalytic Generation of H_2O_2

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HEAVY ATOM EFFECTS IN TELLURAPYRYLIUM DYES USEFUL IN PHOTODYNAMIC THERAPY AND CATALYTIC GENERATION OF H_2O_2

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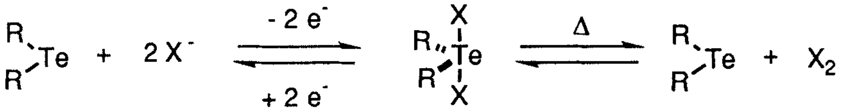
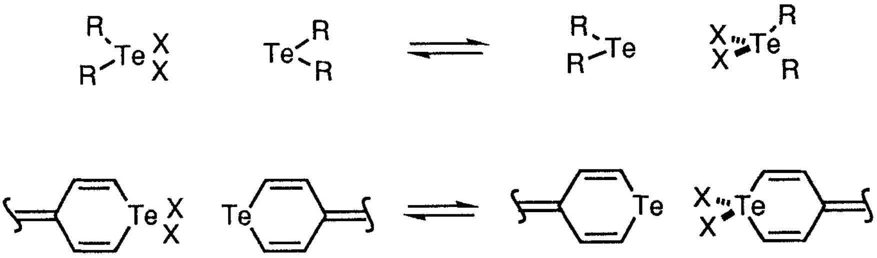
Abstract The large rate of intersystem crossing between singlet and triplet states of tellurapyrylium dyes leads to efficient generation of singlet oxygen in irradiated air-saturated aqueous solutions containing these dyes. One reaction of tellurapyrylium dyes with singlet oxygen and water is the formation of dihydroxy tellurane [tellurium(IV)] species. We have found that the photochemical generation of dihydroxy telluranes is reversible thermally. The tellurapyrylium dye is regenerated while a molecule of hydrogen peroxide is produced. The thermal generation of hydrogen peroxide coupled with a photochemical generation of singlet oxygen allows a catalytic cycle to be devised for the conversion of oxygen and water to hydrogen peroxide. The dihydroxy telluranes are efficient two-electron oxidizing agents and can be used as catalysts to accelerate reactions using hydrogen peroxide as a two-electron oxidizing agent. Examples of tellurapyrylium dye-mediated reactions of hydrogen peroxide include reactions of leucodyes normally oxidized by horseradish peroxidase and hydrogen peroxide. These processes lead to thermal and photochemical reactions that are potentially cytotoxic following the generation of singlet oxygen in photodynamic therapy. The regeneration of the original catalyst allows repeated treatment from a single dose.

INTRODUCTION

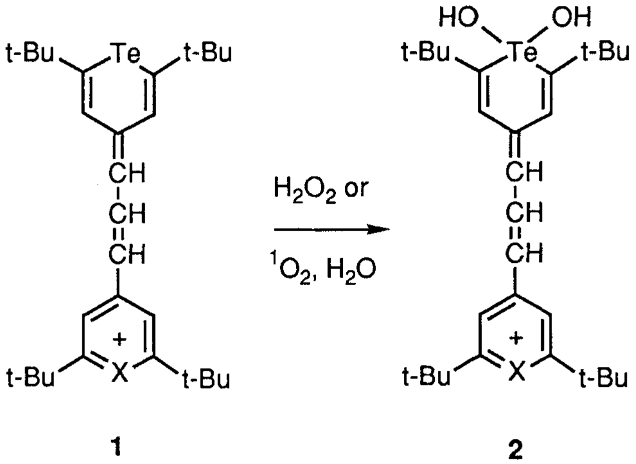
Organotellurium compounds undergo facile oxidative addition and reductive elimination reactions with the halogens to give interconversion of tellurium(II) and tellurium(IV) states. Both thermal[1] and electrochemical[2] reactions appear to be two-electron oxidations and reductions with discrete tellurium(III) intermediates being undetected. These reactions are not typically observed in organosulfur and organoselenium compounds.



Tellurium-halogen exchange reactions have been observed between organotellurium(II) and organotellurium(IV) species. Nefedov et al. employed isotopic labeling to follow halogen exchange between diphenyltellurium dihalides and diphenyltelluride[3] while Detty and Luss used line-shape analysis from variable-temperature ^{1}H NMR to follow tellurium-halogen exchange in tellurapyrylium dyes.[4] In these studies, exchange pathways involving both second-order and first-order reactions were observed with two-electron changes in oxidation state.



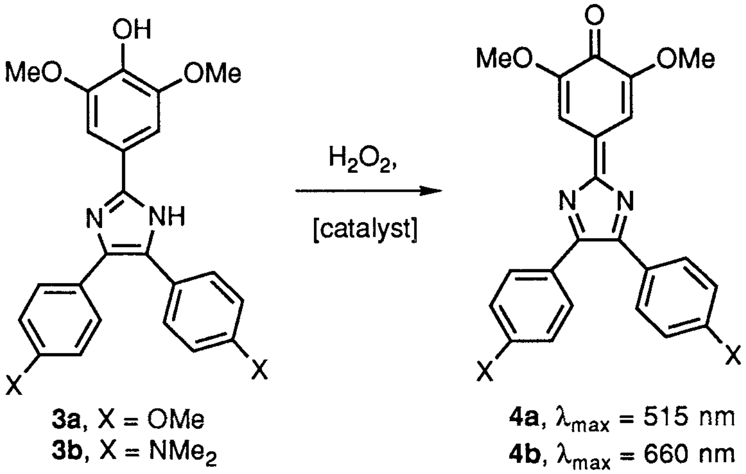
Oxidation of tellurapyrylium dyes **1** with either hydrogen peroxide or with singlet oxygen in the presence of water gives tellurane dyes **2**.[5] The dihydroxy telluranes **2** display a variety of unusual properties[6] which include increased acidity of the protons of the hydroxyl groups and the ability of the tellurium(IV) center in these molecules to oxidize an adjacent carbon center. Like their dihalide analogues, these materials undergo exchange of hydroxy ligands between tellurium(II) and tellurium(IV) as observed by ^1H NMR spectroscopy. Rates for reductive elimination of hydrogen peroxide from the tellurium(IV) center as well as equilibrium constants for **1**, **2**, and hydrogen peroxide have been measured.



X = O,S,Se,Te

Tellurapyrylium dye **1** (X = Se) has been found useful as a photosensitizer for photodynamic therapy of neoplastic tissue.[7] During irradiation in vitro or in vivo, dihydroxy tellurane **2** (X = Se) was formed. The thermal and photochemical reactions of species such as **2** have not been explored in vitro or in vivo.

In a preliminary communication, we described catalytic reactions of one tellurapyrylium dye (**1**, X = Te) in which tellurium(IV) species **2** was produced as an intermediate.[8] In one reaction, **1** is oxidized to **2** via irradiation of air-saturated aqueous solutions. Thermal reductive elimination of hydrogen peroxide regenerates **1**, allowing the net photochemical conversion of oxygen and water to hydrogen peroxide. In a second reaction, the formation of **2** (X = Te) leads to a two-electron reduction of hydrogen peroxide and oxidation of leucodyes **3** to dyes **4**. In both of these systems, a tellurium(II)-tellurium(IV)-tellurium(II) cycle avoids the use of a sacrificial electron donor.



3a, X = OMe
3b, X = NMe_2

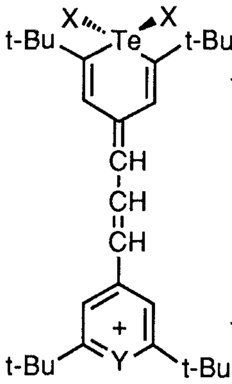
4a, λ_{max} = 515 nm
4b, λ_{max} = 660 nm

The catalytic behavior described above has not been observed with selena- or thiapyrylium dyes. Nor has catalytic behavior been observed with neutral tellurium(II) species as well as with other organosulfur(II) or organoselenium(II) species. In this manuscript, we examine a variety of different tellurapyrylium dyes with respect to their ability to catalyze the two-electron oxidation of leucodyes **3** to **4** with hydrogen peroxide and to catalyze the conversion of oxygen and water to hydrogen peroxide. We also examine the structural parameters necessary for the catalytic tellurium(II)-tellurium(IV)-tellurium(II) cycles with both tellurapyrylium dyes and other organotellurium species. We also examine a tellurium(II)-tellurium(IV)-tellurium(III)-tellurium(II) cycle with dihydroxy telluranes 2 in the presence of electron donors and light.

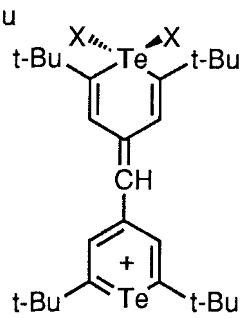
RESULTS AND DISCUSSION

Electrochemical Studies

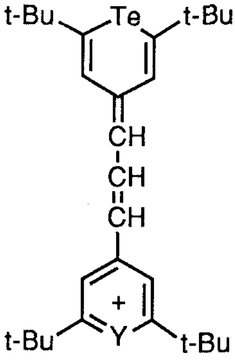
Diorganotellurium(IV) halides display irreversible two-electron reductions by cyclic voltammetry.[2,4] One would expect dihydroxy telluranes **2**, similar in structure to the dihalo telluranes, to show similar behavior. In 10% aqueous acetonitrile (0.2 M tetra-n-butylammonium fluoroborate as supporting electrolyte), irreversible reductions were observed for the dihydroxy telluranes **5** and **6** via cyclic voltammetry (5 x 10^{-4} M in **2**, Pt disk electrode, 100 mv sec^{-1} scan rate). The initial reduction was followed by a second reduction (quasireversible or irreversible in aqueous acetonitrile) characteristic of the corresponding tellurapyrylium dye **7** or **8**. Values for the reduction potentials of **5** and **6** are compiled in Table I.



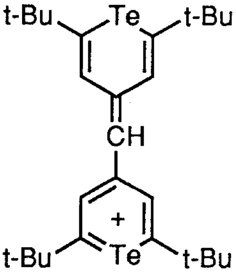
5a, X=OH, Y=S
b, X=OH, Y=Se
c, X=OH, Y=Te
9a, X=Br, Y=S
b, X=Br, Y=Se
c, X=Br, Y=Te



6, X=OH
10, X=Br



7a, Y=S
b, Y=Se
c, Y=Te



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These values can be compared to those of the corresponding dibromo telluranes **9** and **10** which are also compiled in Table I. In each comparison, the reduction of the dihydroxy tellurane is at more negative potential than the corresponding dibromo tellurane.

Bulk electrolyses of solutions of **5** and **9** in aqueous acetonitrile were indicative that the initial irreversible reductions are two-electron processes (Table I). Spectroscopic examination of the electrolyzed solutions shows only the chromophore for the reduced tellurapyrylium dye **7**. Similarly, cyclic voltammograms of the reduced solutions are indicative of reduced tellurapyrylium dyes **7**.

Since the addition of hydrogen peroxide or halogens to tellurium appears to be a two-electron oxidation at tellurium and since the tellurane intermediates undergo two-electron reductions (or reductive eliminations), tellurapyrylium dyes should serve as two-electron shuttles for redox reactions. The reduction potentials listed in Table I suggest that the telluranes should function as mild oxidants. The utility of these dyes as catalysts for the oxidation of leucodyes **3** to dyes **4** with hydrogen peroxide or as catalysts for the photochemical conversion of oxygen and water to hydrogen peroxide was explored.

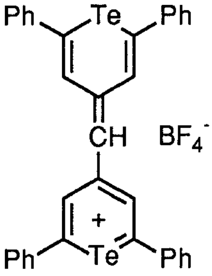
TABLE I Electrochemical reduction potentials of dihydroxy telluranes **5** and **6** and dibromo telluranes **9** and **10** in 10% aqueous acetonitrile with 0.2 M tetrabutylammonium fluoroborate as supporting electrolyte at a platinum disk electrode at a scan speed of 0.10 V/s.

Compd	Epc^1, V (vs SCE)	N, Faradays/mol	Epc^2, V (vs SCE)
5a	-0.18	1.91	-0.48
5b	-0.22	1.84	-0.45
5c	-0.10	2.06	-0.42
6	-0.10	--	-0.55
9a	-0.05	1.84	-0.48
9b	+0.10	--	-0.44
9c	+0.24	1.95	-0.45
10	+0.18	--	-0.55

Oxidation of Leucodyes with Hydrogen Peroxide Using Tellurapyrylium Catalysts

In aqueous solutions (pH 6.8) containing 1 x 10-4 M leucodye **3** and 0.01 M hydrogen peroxide, dyes **4** are formed with pseudo-first-order rate constants of <1 x 10^{-8} s^{-1} for **3a** and 1.57 x 10^{-7} s^{-1} for **3b** at 298 K. The addition of 1 x 10^{-10} M horseradish peroxidase

(HRP) catalyzes the oxidation of **3a** to **4a** with a pseudo-first-order rate constant of 7.05 x 10^{-3} s^{-1} while the addition of 3 x 10^{-11} HRP catalyzes the oxidation of **3b** to **4b** with a pseudo-first-order rate constant of 5.00 x 10^{-3} s^{-1} for **3b** at 298 K (Table II). The enzymatic reaction proceeds with a conversion rate of 7.05 x 10^{12} nmol/s/mol of HRP for **3a** and a conversion rate of 1.67 x 10^{13} nmol/s/mol of HRP for **3b**. Turnover numbers are >10^6 for HRP in these reactions.



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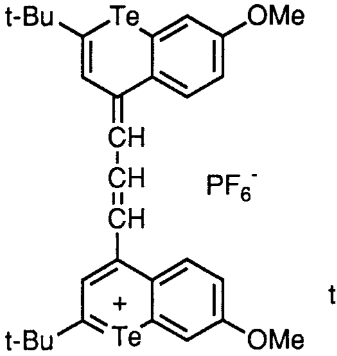

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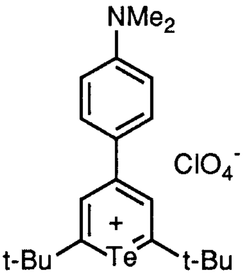

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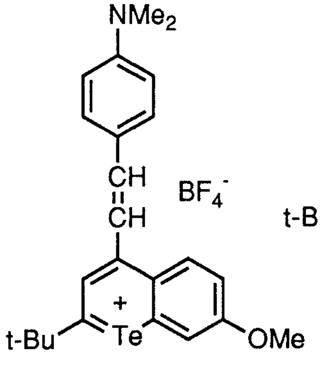

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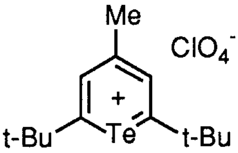

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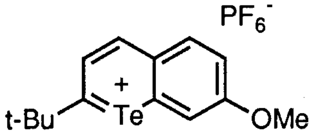

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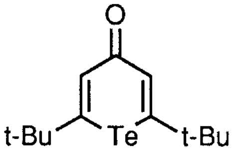
Tellurapyrylium dyes also catalyze the oxidation of leucodyes **3** to dyes **4** with hydrogen peroxide in aqueous solutions (pH 6.8). Values of the pseudo-first-order rate constants for oxidation of leucodyes **3** (1×10^{-4} M) with hydrogen peroxide (0.01 M) as well as conversion rates are compiled in Table II. A variety of dye structures catalyzed the oxidation. The most efficient were dyes **7** (as the chloride salts for **7b** and **7c** and as the hexafluorophosphate salt for **7a**) followed by the monomethine analogues **8** (as the hexafluorophosphate salt) and **11**. The benzo-analogue **12** and the dimethylanilino analogues **13** and **14** were one to two orders of magnitude less efficient. The simple tellurapyrylium salts **15** and **16** show little if any catalytic activity.

Neutral tellurium(II) compounds display no catalytic activity for the oxidation of leucodyes **3** with hydrogen peroxide (Table II). Tellurapyranone **17**, β-aryltellurocinnamic acid **18**, and diaryltelluride **19** all gave conversion rates of **3** to **4** of less than 2.0×10^3 nmol/s/mol of catalyst.



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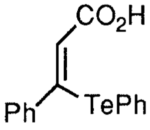

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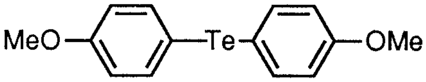

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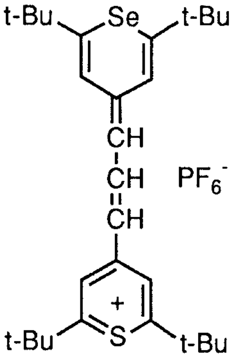

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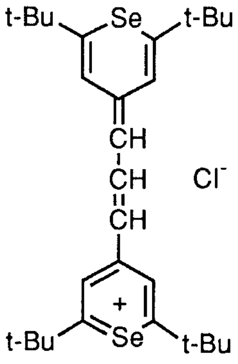

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Table II Pseudo-first-order rate constants (k) and conversion rates for chalcogenapyrylium dyes.

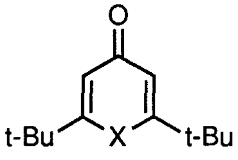
Catalyst	Conc., M	Leuco-dye	k, s^{-1}	Conversion Rate, nmol **3**/s/mol catalyst
none	--	**3a**	$<1 \times 10^{-8}$	--
		3b	1.57×10^{-7}	--
HRP	1.0×10^{-10}	**3a**	7.05×10^{-3}	7.05×10^{12}
	3.0×10^{-11}	**3b**	5.00×10^{-3}	1.67×10^{13}
7a	1.0×10^{-5}	**3a**	9.12×10^{-4}	9.12×10^{6}
		3b	1.62×10^{-3}	1.62×10^{7}
7b	1.0×10^{-5}	**3a**	1.19×10^{-3}	1.19×10^{7}
		3b	1.33×10^{-3}	1.33×10^{7}
7c	1.0×10^{-5}	**3a**	2.25×10^{-3}	2.25×10^{7}
		3b	1.98×10^{-3}	1.98×10^{7}
	1.0×10^{-6}	**3a**	1.86×10^{-4}	1.86×10^{7}
8	1.0×10^{-5}	**3a**	1.65×10^{-4}	1.65×10^{6}
11	1.0×10^{-5}	**3a**	1.18×10^{-4}	1.18×10^{6}
		3b	2.05×10^{-5}	2.05×10^{5}
12	1.0×10^{-5}	**3a**	3.82×10^{-5}	3.82×10^{5}
		3b	3.82×10^{-5}	3.82×10^{5}
13	1.0×10^{-6}	**3a**	1.24×10^{-5}	1.24×10^{6}
		3b	1.02×10^{-5}	1.02×10^{6}
14	1.0×10^{-5}	**3a**	5.52×10^{-6}	5.52×10^{4}
15	2.0×10^{-5}	**3a**	1.08×10^{-6}	5.40×10^{3}
		3b	1.82×10^{-5}	9.10×10^{4}
16	2.0×10^{-5}	**3a**	8.10×10^{-8}	4.05×10^{2}
17	2.0×10^{-5}	**3a**	$<1 \times 10^{-8}$	$<10^{2}$
	1.0×10^{-4}	**3b**	1.71×10^{-6}	1.71×10^{3}
18	1.0×10^{-5}	**3b**	8.70×10^{-8}	8.70×10^{2}
19	1.0×10^{-5}	**3a**	$<1 \times 10^{-8}$	$<10^{2}$
20	1.0×10^{-5}	**3a**	8.12×10^{-7}	8.12×10^{3}
21	1.0×10^{-4}	**3a**	7.57×10^{-7}	7.57×10^{2}
	1.0×10^{-5}	**3b**	2.75×10^{-8}	2.75×10^{2}

Selenapyrylium and thiapyrylium dyes **20** and **21** are much poorer catalysts for the oxidation of **3** to **4** with hydrogen peroxide than their tellurium analogues **7** (Table II). Conversion rates with **20** are three orders of magnitude poorer than tellurapyrylium dyes **7** while conversion rates with **21** are four orders of magnitude poorer.

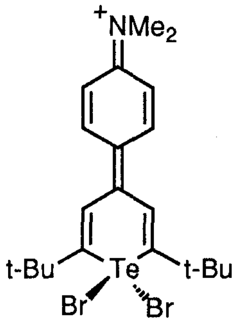
The data in Table II are indicative that the tellurapyrylium dyes are more efficient as catalysts for the oxidation of leucodyes **3** with hydrogen peroxide than are simple tellurapyrylium salts (**15** and **16**) or neutral organotellurium(II) compounds (**17-19**). Oxidative addition of hydrogen peroxide to either **15** or **16** would destroy the aromaticity of the tellurapyrylium ring as well as destabilize the positive charge. Tellurapyrylium dyes **7**, **8**, and **11-14** contain a second aromatic nucleus which maintains delocalization and stabilization of the positive charge. Thus, one might expect the rate of oxidative addition of hydrogen peroxide for the dyes **7**, **8**, and **11-14** to be much greater than for simple tellurapyrylium salts such as **15** or **16**.

Reductive elimination from the dihydroxy tellurane formed from the tellurapyrylium dye would regenerate the tellurapyrylium nucleus. The reduction potentials of the dihydroxy telluranes **5** and **6** are positive relative to reduction potentials observed for neutral tellurium(IV) species. Although we were unsuccessful in our attempts to measure reduction potentials for the dihydroxy tellurane analogues of **17-19**, comparison to dihalo analogues illustrate the effect of the positive charge on reduction potential.

The telluranes **22-24** have been prepared by the oxidative addition of peracetic acid, chlorine, and bromine, respectively, to tellurapyranone **17**.[4] Similarly, **25** was prepared by the oxidative addition of bromine to **13**[4] while **26** was prepared by the oxidative addition of chlorine to **8**. Reduction potentials for **9c**, **10**, and **22-26** were determined by cyclic voltammetry in dichloromethane with 0.2 M tetrabutylammonium fluoroborate as supporting electrolyte at a platinum disk electrode and a scan rate Of 0.1 V/s. Data are compiled in Table III.



17, X=Te
22, X=Te(OAc)$_2$
23, X=TeCl$_2$
24, X=TeBr$_2$



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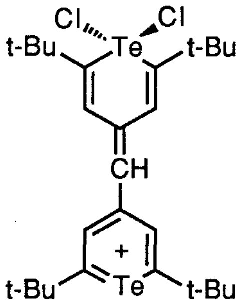

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TABLE III Electrochemical reduction potentials of dihydroxy telluranes **5** and **6** and dibromo telluranes **9** and **10** in dichloromethane with 0.2 M tetrabutylammonium fluoroborate as supporting electrolyte at a platinum disk electrode at a scan speed of 0.10 V/s

Compd	E_{pc}^{1}, V (vs SCE)	N, Faradays/mol	E^{o2}, V (vs SCE)
22	-1.14	--	-1.60
23	-0.68	--	-1.60
24	-0.46	2.10	-1.60
25	+0.48	1.90	-0.45
26	+0.28	--	-0.42
9c	+0.17	--	-0.30
10	+0.35	--	-0.42

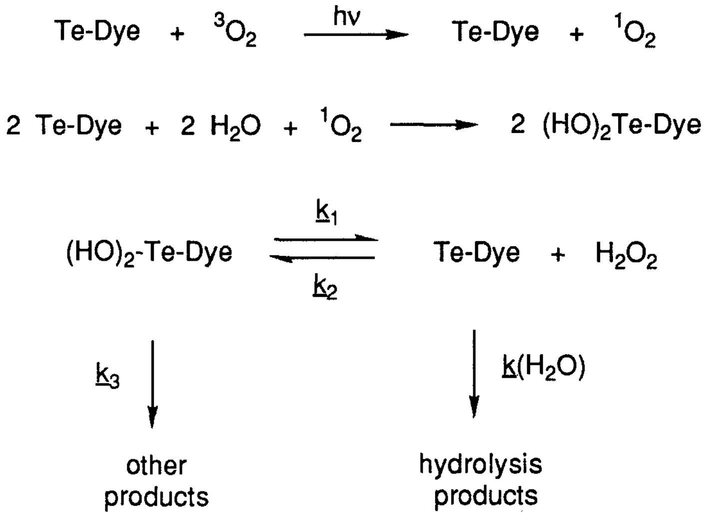
The positive charge in the dihalo telluranes derived from tellurapyrylium dyes leads to reduction potentials that are 0.6-1.0 V more positive than dihalo telluranes derived from neutral tellurapyranone**17**. If similar difference in reduction potential were observed between dihydroxy telluranes derived from tellurapyrylium dyes **7**, **8**, and **11**-**14** and dihydroxy telluranes derived from neutral organotellurium compounds **17**-**19**, then the dihydroxy telluranes derived from the tellurapyrylium dyes would be more powerful oxidants. Thus, dihydroxy telluranes derived from **17**-**19** would be expected to be poorer oxidants for leucodyes **3** for both kinetic and thermodynamic reasons.

Catalytic Generation of Hydrogen Peroxide from Irradiation of Chalcogenapyrylium Dyes

The development of methods for light-to-chemical energy conversion is important for application to solar-energy storage. While the major emphasis in such research has been the splitting of water for the production of hydrogen,[9-14] the photoproduction of other energy-rich compounds such as hydrogen peroxide has also received attention.[8c,15-17] In metal-based systems for the production of either hydrogen or hydrogen peroxide as well as in dye-mediated systems, a sacrificial electron donor is required to minimize electron back-transfer from the electron relay.

We have reported the photochemical conversion of oxygen and water to hydrogen peroxide using tellurapyrylium dye **7c** as a catalyst.[8] In this process, the photochemical generation of singlet oxygen is followed by the rapid reaction of singlet oxygen and water to produce the dihydroxy tellurane **2**. A slower thermal reaction produces hydrogen peroxide and regenerates the tellurapyrylium catalyst via a reductive elimination reaction. No sacrificial electron donor is required since the tellurapyrylium dye acts as a two-electron shuttle. The catalyst is lost by competitive thermal or photochemical reactions which include hydrolysis of the dye. The entire process is summarized in Scheme 1.

SCHEME 1



The photochemical process determines the efficiency of the system while the thermal reaction will determine the rate of peroxide production. The quantum yield for hydrogen peroxide generation is given in Eq. 1:

$$\Phi(H_2O_2) = \Phi(^1O_2) \times \frac{k(ox) \times [Dye]}{1/\tau + k(ox)[Dye]} \times n \times f \qquad (1)$$

where $\Phi(H_2O_2)$ is the photochemical quantum yield for hydrogen peroxide production, $\Phi(^1O_2)$ is the quantum yield for dye-sensitized generation of singlet oxygen, $k(ox)$ is the rate of reaction of singlet oxygen with the dye, τ is the lifetime of singlet oxygen in the medium, n is the number of tellurium atoms in the molecule and *f* is the frequency of hydrogen peroxide production from the catalyst in the entire process. Values for these parameters are compiled in Table IV for the dyes **7**, **8**, and **11** in water at 10^{-5} M. Under these conditions, τ is 10 μs. The assumption was made for monomethine dyes **8** and **11** that the value of $k(ox)$ was similar to the value measured for **7c**.

The quantum yield for hydrogen peroxide generation is quite sensitive to solvent because of the effect of solvent on the rate of reaction of singlet oxygen with catalyst. At 298 K, the value of $\underline{k}$(ox) for **7c** decreases from 8.0 x 10^8 $\underline{M}^{-1}s^{-1}$ in water to 1.8 x 10^8 $\underline{M}^{-1}s^{-1}$ in 50% aqueous methanol to 9.0 x 10^6 $\underline{M}^{-1}s^{-1}$ in 99% methanol with corresponding quantum yields for hydrogen peroxide production of 1.7 x 10^{-2}, 2.4 x 10^{-3}, and 4.8 x 10^{-5}, respectively.

TABLE IV Parameters for determining quantum efficiencies of hydrogen peroxide generation at 10^{-5} $\underline{M}$ catalyst in water at 298 K

Catalyst	$\Phi(^1O_2)$	$\underline{k}$(ox), $\underline{M}^{-1}s^{-1}$	*f*	Turnover number	$\Phi(H_2O_2)$
7a	0.07	4.2 x 10^8	0.92	11.1 +/- 2.9	2.7 x 10^{-3}
7b	0.09	4.0 x 10^8	0.84	5.1 +/- 0.5	3.0 x 10^{-3}
7c	0.12	8.0 x 10^8	0.89	7.7 +/- 1.4	1.7 x 10^{-2}
8	0.07	8.0 x 10^8	0.60	1.5 +/- 0.4	6.7 x 10^{-3}
11	0.09	8.0 x 10^8	0.62	1.7 +/- 0.4	8.9 x 10^{-3}

The thermal component of Scheme 1 determines the rate at which hydrogen peroxide is produced. An initial steady-state concentration of dihydroxy tellurane is reached photochemically followed by a slower change to an equilibrium concentration of catalyst, dihydroxy tellurane, and hydrogen peroxide. The first order rate constants ($\underline{k}_1$) for decomposition of the dihydroxy telluranes are sensitive to solvent as are the second order rate constants ($\underline{k}_2$) for the reaction of hydrogen peroxide with tellurapyrylium catalyst. Table V contains values of $\underline{k}_1$ for dihydroxy tellurane **5c** as well as values of $\underline{k}_2$ for tellurapyrylium dye **7c** in various combinations of methanol and water as well as values for $\underline{k}$(ox) in the various solvents. While $\underline{k}$(ox) and $\underline{k}_2$ decrease with decreasing water concentration, $\underline{k}_1$ increases complicating the process shown in Scheme 1.

TABLE V Solvent-dependent values of k(ox) and k_2 for tellurapyrylium salt **7c** and solvent-dependent values of k_1 for dihydroxy tellurane **5c**

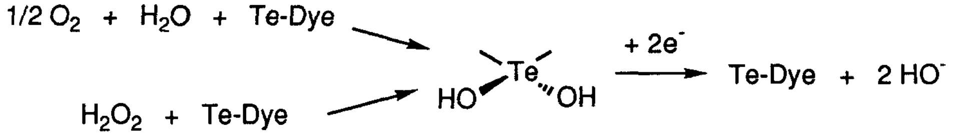
Solvent	k(ox) $M^{-1}s^{-1}$	k_1, s^{-1}	k_2, $M^{-1}s^{-1}$
water	8.0×10^8	2.24×10^{-5}	2.0
50% MeOH	1.8×10^8	2.83×10^{-4}	0.33
90% MeOH	--	2.47×10^{-3}	0.080
99% MeOH	9.0×10^6	1.10×10^{-2}	0.013

The dihydroxy telluranes can be used as photooxidants as well. As shown above, formation of the dihydroxy tellurane from the tellurapyrylium catalyst with hydrogen peroxide leads to oxidation of leukodyes **3** to **4**. At 298 K in distilled water, **3b** is oxidized by **5c** with a second order rate constant of 44.1 $M^{-1}s^{-1}$. At 1×10^{-5} M in **7c** and 10^{-3} M in **3b**, the observed pseudo-first-order rate constant for the reaction of **5c** (generated photochemically) with **3b** is approximately 4×10^{-2} s^{-1} which is much larger than k_1 for the reductive elimination of hydrogen peroxide in water.

At an initial concentration of 3.0×10^{-6} M, **7c** will oxidize 1.56×10^{-4} M **3a** (initially 10^{-3} M) to **4a** upon irradiation before the catalyst is consumed in air-saturated 99% methanol. Similarly, at an initial concentration of 1.0×10^{-6} M, **7c** will oxidize 5.13×10^{-5} M **3b** (initially 10^{-3} M) to **4b** upon irradiation before the catalyst is consumed in air-saturated 99% methanol. These values represent turnover numbers of >50 for **7c**.

The ability of tellurapyrylium dyes to function as two-electron catalysts for the oxidation of leucodyes **3** is summarized in Scheme 2. The formation of the dihydroxy tellurane intermediate with either singlet oxygen and water or with hydrogen peroxide is the key step in this process. Oxidation of the leucodye regenerates the tellurapyrylium catalyst and two molecules of water.

Scheme 2



$$3 \xrightarrow{-2e^-} 4 + 2H^+$$

Applications of Dihydroxy Tellurane Chemistry to Photodynamic Therapy

The irradiation of tellurapyrylium dye **7b** in vivo or in vitro produces singlet oxygen as a cytotoxic reagent and generates dihydroxy tellurane **5b**.[7] The cytotoxic effects of the dihydroxy telluranes have been described in vitro for inhibition of cytochrome c oxidase activity in isolated tumor mitochondria.[18] The observed inhibition is a photochemical phenomenon. The addition of catalase as a peroxide scavenger and the addition of mannitol as a scavenger of hydroxyl radicals show some decrease in the inhibition of cytochrome c oxidase while scavengers of superoxide (superoxide dismutase) and singlet oxygen or lowered oxygen concentrations show no effect on the observed inhibition. The cytochrome c oxidase activity in isolated mitochondrial suspensions is not affected by treatment with dihydroxy tellurane **5b** in the dark.

These data are consistent with a photochemical mechanism involving the generation of hydroxy radicals from either dihydroxy tellurane **5b** or from hydrogen peroxide generated thermally from **5b**. In membrane bound **5b**, the dihydroxy tellurane might be in contact with a molecule capable of acting as an electron donor to an excited state of **5b**. If this "reduced" state of **5b** were to dissociate to hydroxy or hydroperoxy radicals at a rate competitive with back-electron transfer to the donor, then the photogeneration of radical species within the membrane might alter the membrane sufficiently to inhibit biological function.

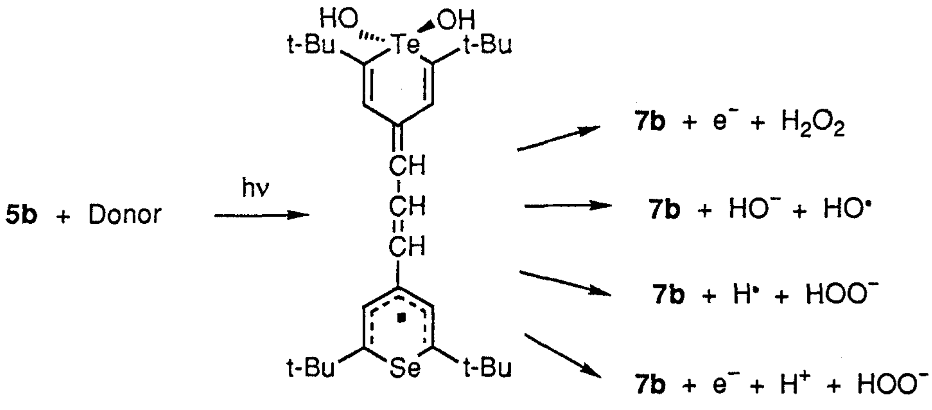
Photochemical Studies and ESR Studies of 5b in Aqueous Solution in the Presence of 0.01 M Tryptophan

The ability of tryptophan to act as an electron donor to dihydroxy tellurane **5b** was explored in distilled water. A mixture of 0.01 M tryptophan and 2 x 10^{-5} M **5b** in distilled water shows a slow thermal conversion of **5b** to **7b** at 281 K (k_1 = 8.21 x 10^{-6} s^{-1}).

Irradiation of tryptophan-containing solutions of **5b** with 489 nm filtered light (+/- 5 nm) from a 500 W tungsten filament lamp at 281 K in water-jacketed cells gives a five-fold increase in the rate of formation of **7b** from **5b**. These data are consistent with a photochemically induced interaction of **5b** and tryptophan leading to reduction of **5b** to **7b**, perhaps involving photochemically induced electron transfer.

If dihydroxy tellurane **5b** were to act as an electron acceptor, the resulting odd-electron species could generate **7b** via a number of routes. Some of these routes are summarized in Scheme 3. If either hydroxy or hydroperoxy radicals were being produced photochemically, it should be possible to detect them using ESR techniques.[19]

Scheme 3



5,5-Dimethyl-1-pyrroline-N-oxide (DMPO) has been utilized as a spin trap for the detection of hydroxy and hydroperoxy radicals generated both in aqueous solvent and in biological systems.[19] DMPO reacts with hydroxy radicals with a rate constant of approximately 2 x 10^9 $M^{-1}s^{-1}$.[19] In aqueous solvent, the DMPO-hydroxy radical adduct displays a simple, four-line pattern in ESR spectra (A_N = A_H = 1.487 mT).[19b] Methods exist, as well, to distinguish hydroxy and hydroperoxy radicals with DMPO since thermal and chemical conversion of the DMPO-hydroperoxy radical adduct to the DMPO-hydroxy radical adduct does occur.

In order to test for the generation of radical species during the thermal reduction of **5b** to **7b** in the presence of tryptophan, samples of **5b** (4 x 10^{-4} M) in distilled water were heated at 323 K in the presence of DMPO (0.1 M) and tryptophan (0.01 M). The reaction mixtures were examined by ESR spectroscopy every hour for 8 h. The patterns characteristic of hydroxy or hydroperoxy radical adducts with DMPO were not detected.

Control solutions of the DMPO-hydroxy radical adduct were studied under concentrations similar to those for the thermal conversion of **5b** to **7b**. An aqueous solution of hydrogen peroxide (4 x 10^{-4} M) and DMPO (0.1 M) in a 5-mm, quartz ESR tube was irradiated for 300 s at a distance of 20 cm from a General Electric sun lamp. A weak, four-line signal for the DMPO-hydroxy radical adduct was obtained with A_N = A_H = 1.47 mT. Irradiation of a similar solution for 1 h with the 489 nm (=/- 5 nm) filtered light from the 500 W tungsten filament lamp gave no ESR signal.

These experiments were repeated in the presence of added 0.1 M tryptophan with identical results. The ESR signal was weaker for the the tryptophan-containing sample irradiated with the sun lamp.

A solution of **5b** (4 x 10^{-4} M) and DMPO (0.1 M) was heated in the dark at 323 K for 1 h giving complete disappearance of **5b**. No ESR signal was detected. When a similar solution was irradiated with the 489 nm filtered light, no ESR signal was detected.

Tryptophan (0.01 M) was added to the solution of **5b** and DMPO and the resulting solution was irradiated for 2 h at 281 K. A weak

ESR signal was obtained, containing the four-line signal for the DMPO-hydroxy radical adduct ($\underline{A}_{\underline{N}} = \underline{A}_{\underline{H}} = 1.47$ mT).

The ESR studies suggest that hydroxy radicals are generated in irradiated aqueous solutions of **5b** containing DMPO and tryptophan. In the absence of added tryptophan, no ESR signal was detected. If membrane bound **5b** were to undergo photochemical reactions similar to those observed in solution, then the generation of hydroxy radicals as well as other radical species might be responsible for the observed photodynamic effects of **5b** in isolated mitochondrial suspensions.

The regeneration of tellurapyrylium dye **7b** via photoinduced electron transfer suggests that a tellurium(IV)-tellurium(III)-tellurium(II) reduction pathway is available to the dihydroxy telluranes.

SUMMARY AND CONCLUSIONS

The heavy-atom effect of tellurium yields high quantum yields for triplet formation and, as a consequence, for singlet oxygen generation.[5] The tellurium atoms of tellurapyrylium dyes react rapidly with singlet oxygen in the presence of water to produce dihydroxy telluranes. The dihydroxy telluranes are also produced by the oxidative addition of hydrogen peroxide. The dihydroxy telluranes function as mild oxidizing agents for leucodyes **3**. The dihydroxy telluranes also form hydrogen peroxide via a thermal process which regenerates the starting tellurapyrylium dye.

The photochemical generation of hydrogen peroxide effectively stores 100 kJ/mol of light energy as chemical energy. Subsequent reactions of the hydrogen peroxide release this energy. The quantum yields for hydrogen peroxide production with tellurapyrylium dyes, water, and oxygen are reasonably high. The rate of reductive elimination from the dihydroxy telluranes, which are formed as intermediates, determines the rate of hydrogen peroxide production. A far more efficient use of the stored photochemical energy would be the direct utilization of the dihydroxy telluranes as a reactive form of hydrogen peroxide.

The oxidation of leucodyes **3** with the dihydroxy telluranes is an example of the direct use of the dihydroxy telluranes as a two-electron oxidant. The oxidation of the leucodye yields dye **4**, the reduced tellurapyrylium dye, and two molecules of water. No sacrificial electron donor is required. The substitution of other reactants oxidizable by dihydroxy telluranes might lead to the development of fuel cells based on this chemistry.

The photochemical, single-electron transfer from tryptophan to dihydroxy tellurane **5b** provides a dual-mechanism approach to photodynamic therapy that has not been observed in other photosensitizers. Both Type I and type II processes are available with the production of singlet oxygen from irradiation of the tellurapyrylium dye **7b** and the production of hydroxy radicals from the irradiation of dihydroxy tellurane **5b**. The regeneration of the tellurapyrylium dye from the thermal and/or photochemical reduction of **5b** allows repeated treatments from a single dye treatment. The development of more stable dyes that retain these features should provide more effective treatment with photodynamic therapy.

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