in fairly high efficiencies (Table I). Excited benzene is formed even when **1** is excited at the red-edge of its absorption (335 nm) where benzene exhibits no detectable absorption (Figure 1). The fluorescence excitation spectra of **1** and **2** monitored at the red-edge of benzene emission are the same as their absorption spectra indicating that excited benzene is derived from the excited dimers. It is not certain at this moment whether the higher efficiency of excited benzene formation from **2** is related to its higher energy content or the higher symmetry in the cycloreversion process.

Since the energy content of excited benzene is 110 kcal/mol[11] while that of the exciting light at 335 nm is only 85.3 kcal/mol, the result clearly demonstrates that a part of the chemical energy liberated from the photochemical dissociation of **1** or **2** is available for the excitation of benzene during the adiabatic conversion. Adiabatic photochemical reactions generally occur with light more energetic than that needed for the excitation of the product.[9] Previous contributions by Turro and his co-workers demonstrated the "red light-to-blue light uphill conversions" in the generation of n,π^* excited states of acetone from the direct or sensitized photolysis of tetramethyldioxetane,[12] but such upconversions have a propensity to occur in the triplet manifold. Therefore, our finding on the photon up-conversion in the singlet manifold of such an efficiency is unprecedented.

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[12] Turro, N. J.; Lechtken, P.; Lyons, A.; Hautala, R. R.; Carnahan, E.; Katz, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 2035-2037. Turro, N. J.; Brewer, D.; Farneth, W.; Ramamurthy, V. *Nouv. J. Chem.* **1978**, *2*, 85-89.

Tellurapyrylium Dyes as Photochemotherapeutic Agents. Surprising Tellurium Atom Effects for the Generation of and Rates of Reaction with Singlet Oxygen

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Photochemotherapy (PCT) is a relatively new treatment of localized neoplasia which depends upon the light-activation of a tumor-specific photosensitizer.[1] At the present time, the limiting factor on the successful application of PCT has been the lack of a photosensitizer that absorbs light with a high degree of penetrance in tissue (wavelength range of 700–1200 nm for maximum penetration).[2] Near-infrared-absorbing tellurapyrylium dyes, including **1** and **2**, have been identified as potential photochemotherapeutic agents from in vitro studies.[3] Related non-tellurium-containing dyes do not show the phototoxic effect. We report our preliminary findings on the photochemistry of tellurapyrylium dyes **1–3** in air-saturated aqueous solution. Photoproducts derived from formal oxidative addition of hydrogen peroxide across one tellurium atom were isolated from photooxidation of **1** and **2**. From an analysis of the kinetics of photooxidation, the oxidizing species is not hydrogen peroxide but is singlet oxygen generated in a dye-sensitized process. The photooxidation products are not observed for **4** and **5**, non-tellurium-containing chalcogenapyrylium dyes.

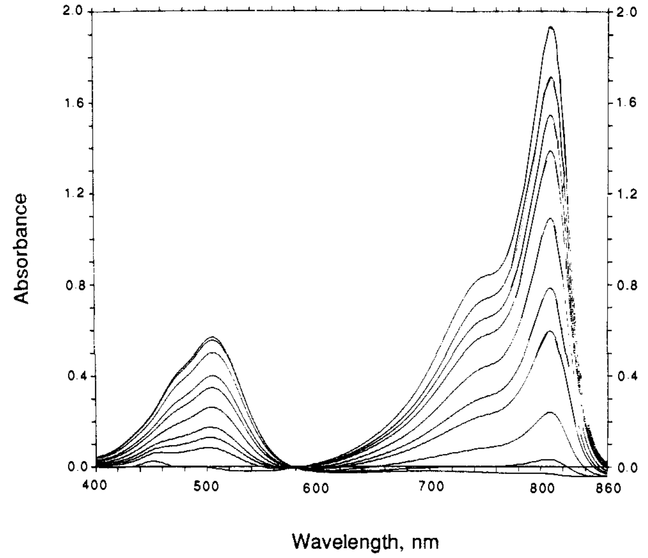
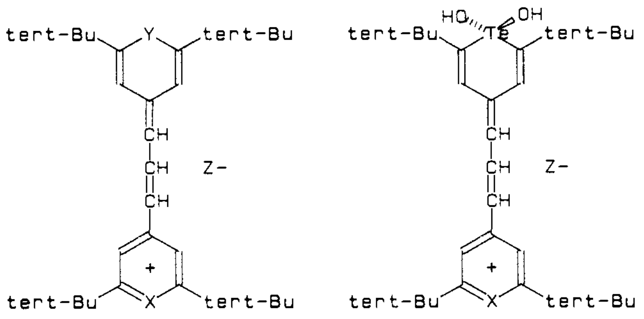


Figure 1. Isosbestic behavior for the conversion of **1** (5×10^{-5} M) to **6** in water. Total irradiation time was 3 min in a 1-cm square-quartz cell held 15 cm from a GE Sunlamp. Sampling was every 5 s for the first three points, every 20 s for the next three, and every 35 s for the final three.



1, X=Y=Te, Z=BF_4^-

2, X=Te, Y=Se, Z=ClO_4^-

3, X=Te, Y=O, Z=ClO_4^-

4, X=Se, Y=O, Z=ClO_4^-

5, X=Y=O, Z=ClO_4^-

6, X=Te, Z=BF_4^-

7, X=Se, Z=ClO_4^-

As shown in Figure 1, irradiation of an air-saturated, aqueous solution of **1** (5×10^{-5} M), with an unfiltered, tungsten bulb, gave rapid disappearance of the dye chromophore and clean formation of a new product, **6**, with an isosbestic point at 580 nm.[4] Similar behavior was observed upon irradiation of an aqueous solution of **2** (5×10^{-5} M, isosbestic point at 560 nm) to give a new product, **7**.[4] In carefully degassed aqueous solutions, no loss of chromo-

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[1] (a) Powers, S. K. In *Application of Lasers in Neurosurgery*; Cerullo, L. J., Ed.; Yearbook Medical Publishers, Inc.: Chicago, 1988. (b) Oseroff, A. R.; Ohuoha, D.; Ara, G.; McAuliffe, D.; Foley, J.; Cincotta, L. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 9729. (c) Dougherty, T. J.; Boyle, D. G.; Weishaupt, K. R.; Henderson, B. A.; Potter, W. R.; Bellnier, D. A.; Wityk, K. E. In *Porphyrin Photosensitization*; Kessel, D., Dougherty, T. J., Eds.; Plenum: New York, 1983. (d) Balchum, O. J.; Dorion, D. R.; Huth, G. C. In *Porphyrin Localization and Treatment of Tumors*; Dorion, D. R., Gomer, C. J., Eds.; Liss: New York, 1984. (e) Dahlman, A.; Wile, A. G.; Burns, R. G.; Mason, G. R.; Johnson, F. M.; Berns, M. W. *Cancer Res.* **1983**, *43*, 430.

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Table I. Quantum Efficiencies [$\Phi(^1O_2)$] for the Generation of and Rates of Reaction [$k(^1O_2)$] with Singlet Oxygen for **1–5**[a]

compd	λ_{max},[b] nm (log ϵ)	$\Phi(^1O_2)$ (in MeOH)	$k(^1O_2)$, M^{-1} s^{-1} methylene blue[b]	$k(^1O_2)$, M^{-1} s^{-1} rose bengal[b]
1	810 (5.27)	0.13 ± 0.01	(15.5 ± 0.8) × 10^7	(15.3 ± 0.8) × 10^7
2	770 (5.22)	0.09 ± 0.01		
3	700 (5.27)	0.06 ± 0.01	(7.5 ± 0.5) × 10^7	(8.1 ± 0.5) × 10^7
4	660 (5.35)	0.005 ± 0.001	(0.2 ± 0.1) × 10^7	(0.4 ± 0.1) × 10^7
5	593 (5.31)	0.0004 ± 0.0001	*c*	(0.2 ± 0.1) × 10^7

[a] For experimental procedures, see ref 6. [b] In 50% aqueous methanol. [c] The methylene blue absorption peak overlapped the absorption peak of the dye.

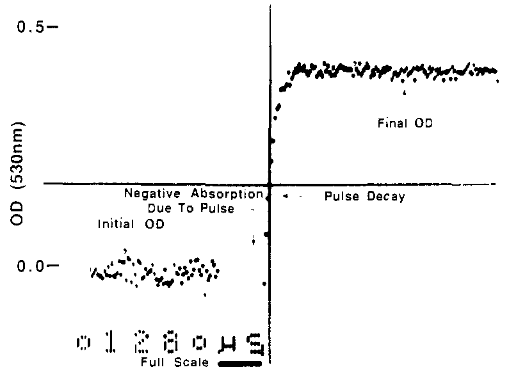


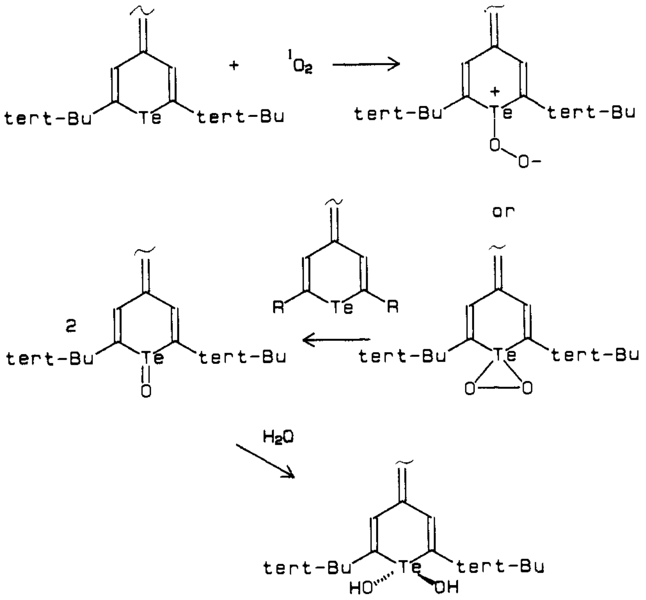
Figure 2. Time-resolved absorption at 530 nm reflecting the production of **6** following UV-filtered xenon pulse excitation of 10^{-5} M **1** in air-saturated 50% aqueous methanol in a 25-cm cell. The time scale is 5 μs per point. The 530-nm absorption (representing about 4% conversion to product) is fully present or nearly so at the end of the exciting pulse, which decays over a period of ~50 μs.

phore from either **1** or **2** was observed after several hours of irradiation suggesting that the presence of dioxygen was necessary for the photochemical reaction.

The addition of hydrogen peroxide to aqueous solutions of both **1** and **2** generated products identical with the photochemical reaction products, **6** and **7**, in each case by both UV–vis absorption and ^1H NMR spectroscopies.[4] Isolation of **6** and **7** from either the photolysis reactions or the hydrogen peroxide addition reactions gave maroon solids which regenerated **1** and **2**, respectively, upon standing. The oxidative addition of halogens to the tellurium atoms of **1** and **2** to give trigonal bipyramidal tellurium(IV) species has been described as having reductive elimination reactions from the oxidized species.[5]

In air-saturated methanol, **1** produces singlet oxygen (as monitored by the photooxidation of the acceptor 1,3-diphenylisobenzofuran)[6] with a quantum efficiency, $\Phi(^1O_2)$, of 0.13. Oxygen quenching of methylene blue triplets is known to generate singlet oxygen with nearly unit efficiency.[7] The methylene blue sensitized fade of **1** also yields **6** quantitatively and permits calculation of a rate constant for reaction between **1** (at 10^{-5} M, the quantum efficiency of photooxidation is a function of the concentration of dye) and singlet oxygen, $k(^1O_2)$, of 1.1 × 10^9 M^{-1} s^{-1} in water.[6] In deuterium oxide as solvent, the quantum efficiency of photooxidation of **1** (at 10^{-5} M) increases by an order of magnitude relative to water as expected from the increased lifetime of singlet oxygen in the deuteriated solvent.[7,8]

Scheme I



Although rapid bleaching of **1** following absorption of a photon can be inferred from the lifetime of singlet oxygen (~3.5 μs in 50% aqueous methanol),[9] the steady-state photolysis experiments indicate only that **6** is formed from **1** within a few seconds. More precise information is provided by flash photolysis measurements such as in Figure 2. In the flash photooxidation of **1** (10^{-5} M in air-saturated 50% aqueous methanol), the formation of **6** is concurrent with the exciting pulse, which decays over ~50 μs, establishing a value of ≤50 μs for the lifetime of **6**.

The thermal reaction between **1** and hydrogen peroxide is much slower. With 0.01 M hydrogen peroxide in 50% aqueous methanol (a much higher concentration than could be produced in the photolysis experiments), **1** reacts to form **6** at a rate of only 3.3 × 10^{-3} s^{-1} which suggests that hydrogen peroxide is not the oxidant in the photooxidations.

The increase in values of $\Phi(^1O_2)$ in methanol (Table I), as the chalcogen atoms in the dyes **1–5** become heavier, probably reflects increased spin-orbit coupling allowing faster intersystem crossing to the triplet state. The increased quantum yield of triplet formation is expected to lead to higher values of $\Phi(^1O_2)$. The tellurium atom effect on $\Phi(^1O_2)$ is much larger than one might expect based on the rather small effect of selenium atom incorporation.

The rate constants for reaction of **1–5** with singlet oxygen [$k(^1O_2)$] generated in air-saturated 50% aqueous methanol by both methylene blue (excitation at 634 nm) and rose bengal (excitation at 544 nm) photosensitization are compiled in Table I.[6] The self-sensitized photooxidation rates for the dyes are consistent with the $\Phi(^1O_2)$ and $k(^1O_2)$ values. The tellurium-containing dyes **1–3** react with singlet oxygen approximately 20–80 times faster than the non-tellurium containing dyes **4** and **5**. Doubling the number of tellurium atoms (**1** versus **3**) approximately doubles the reaction rate.

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(4) For **6**: ^1H NMR (CD_3OD) δ 8.88 (d × d, 1 H, *J* = 12.0, 14.8 Hz), 8.68 (s, 2 H), 7.33 (s, 1 H), 7.28 (d, 1 H, *J* = 14.8 Hz), 7.02 (d, 1 H, *J* = 12.0 Hz), 6.72 (s, 1 H), 1.68 (s, 18 H), 1.52 (s, 9 H), 1.47 (s, 9 H); IR (KBr) 3400 cm^{-1}; λ_{max} (50% aqueous MeOH) 510 nm (ϵ = 56 000 ± 3000 L m^{-1} cm^{-1}). Anal. Calcd for $C_{29}H_{45}O_2Te_2{\cdot}BF_4$: C, 45.4; H, 5.9. Found: C, 45.9; H, 6.0. For **7**: ^1H NMR (CD_3OD) δ 8.81 (d × d, 1 H, *J* = 12.0, 15.1 Hz), 8.69 (s, 2 H), 7.36 (s, 1 H), 7.33 (d, 1 H, *J* = 15.1 Hz), 7.07 (d, 1 H, *J* = 12.0 Hz), 6.74 (s, 1 H), 1.65 (s, 18 H), 1.52 (s, 9 H), 1.48 (s, 9 H); IR (KBr) 3400 cm^{-1}; λ_{max} (50% aqueous MeOH) 502 nm (ϵ = 55 000 ± 3000 L m^{-1} cm^{-1}). Anal. Calcd for $C_{29}H_{45}O_2SeTe{\cdot}ClO_4$: C, 47.6; H, 6.2. Found: C, 48.0; H, 6.3.

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(6) Procedures for measuring $\Phi(^1O_2)$ values using 1,3-diphenylisobenzofuran and for obtaining $k(^1O_2)$ values are described in the following: Merkel, P. B.; Smith, W. F. *J. Phys. Chem.* **1979**, *83*, 2834.

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(8) Rodgers, M. A. J. *J. Am. Chem. Soc.* **1983**, *105*, 6201.

(9) Nilsson, R.; Merkel, P. B.; Kearns, D. R. *Photochem. Photobiol.* **1972**, *16*, 117.

The mechanism of photooxidation of **1–3** can be compared to the well-studied oxidation of sulfides to sulfoxides with singlet oxygen.[10] Both persulfoxide and thiadioxirane intermediates have been proposed for this oxidation.[10a] Similar intermediates can be proposed, as shown in Scheme I, for the reaction of the tellurapyrylium dyes with singlet oxygen (with the initial oxidized intermediate reacting with unoxidized dye). The final photoproducts **6** and **7** are hydrated forms of telluroxides. The hydration of telluroxides to give dialkyl and diaryl dihydroxy telluranes has been described and would be expected to be rapid in aqueous solvent.[11] Values of $k(^1O_2)$ for **1** are very sensitive to water concentration, increasing from 8×10^6 M^{-1} s^{-1} in 99% methanol to 1.5×10^6 M^{-1} s^{-1} in 50% aqueous methanol to 1.1×10^9 M^{-1} s^{-1} in water. These values suggest that water is involved in the rate-determining step of the photooxidation perhaps by adding to an initial pertelluroxide or telluradioxirane intermediate.

The photooxidation products **6** and **7** have been detected in vitro in cell cultures treated with tellurapyrylium dyes **1** and **2** and light. Extraction of cell cultures treated first with **1** or **2** followed by washing and irradiation gives detectable amounts of **6** or **7** by absorption spectroscopy. Yellow-green intracellular fluorescence (emission maximum ≈ 530 nm) has been observed with an epifluorescent microscope in cells cultured on multichamber tissue culture slides and treated with **2**.[3] We are actively investigating the relationship between the solution photochemistry of tellurapyrylium dyes and phototoxicity in vivo and in vitro.

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Pentalenene Biosynthesis and the Enzymatic Cyclization of Farnesyl Pyrophosphate. Inversion at C-1 during 11-Membered-Ring Formation

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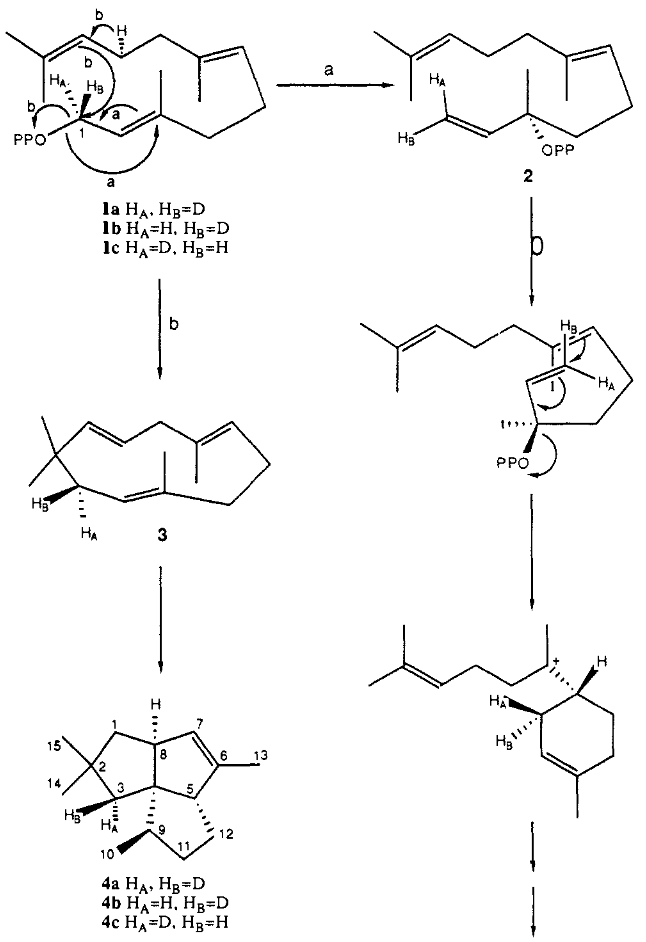
Farnesyl pyrophosphate (FPP, **1**) is the universal biosynthetic precursor of the sesquiterpenes, which encompass a wide variety of carbon skeletal types.[1] Current biogenetic theory holds that cyclizations of FPP proceed through carbocationic intermediates resulting from loss of pyrophosphate from C-1, followed by electrophilic attack on the central or distal double bond. Further cyclizations and/or hydrogen or alkyl migrations and elimination or capture of the resulting carbocation by nucleophiles gives rise to the natural sesquiterpenes.[1]

For sesquiterpenes derived from attack on the central double bond, initial isomerization of FPP to nerolidyl pyrophosphate (NPP, **2**) is required to avoid formation of 6-membered rings containing a trans double bond.[1-3] Considerable evidence has accrued to support this concept, including several studies of the overall stereochemistry of reaction at C-1 of both FPP[1,4,5] and geranyl pyrophosphate in analogous monoterpene cyclizations.[1,6] In these cases, isomerization with a suprafacial 1,3-shift of the pyrophosphate group[2] must be followed by rotation about the C-2,3 bond in order to bring the two π systems (C-1,2 and C-6,7) into proximity for subsequent reaction (e.g., path a, Scheme I). This sequence results in displacement of pyrophosphate and formation of a new C–C bond with net retention of configuration at C-1 of FPP. There is no requirement for isomerization of the C-2,3 bond, however, when initial attack occurs at the C-10,11 double bond to generate, for example, humulene (**3**) (path b, Scheme I).[7,10,11] We now report direct proof of inversion at C-1 of FPP in the biosynthesis of pentalenene (**4**), the parent hydrocarbon of the pentalenolactone family of sesquiterpene antibiotics,[5b,12,13] based on deuterium NMR analysis of pentalenene derived from both (1*R*)- and (1*S*)-[1-^{2}H]FPP.

Scheme I



1a H_A, H_B=D
1b H_A=H, H_B=D
1c H_A=D, H_B=H

4a H_A, H_B=D
4b H_A=H, H_B=D
4c H_A=D, H_B=H

For the first experiment, [1,1-$^2H_2$;12,13-^{14}C]farnesyl pyrophosphate (**1a**)[14] was prepared by reduction of farnesal with

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[1] (a) Cane, D. E. *Acc. Chem. Res.* **1985**, *18*, 220. (b) Cane, D. E. *Tetrahedron* **1980**, *36*, 1109.

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[6] Croteau, R.; Felton, N. M.; Wheeler, C. J. *J. Biol. Chem.* **1985**, *260*, 5956. Croteau, R. *Chem. Rev.* **1987**, *87*, 929.

[7] Isomerization is not required in the conversion of FPP to humulene[8] but there is strong indirect evidence for the intermediacy of NPP in formation of longifolene and sativene.[9] See: Croteau, R.; Cane, D. E. *Meth. Enzymol.* **1985**, *110*, 383.

[8] Croteau, R.; Gundy, A. *Biochem. Biophys.* **1984**, *233*, 838.

[9] Arigoni, D. *Pure Appl. Chem.* **1975**, *41*, 219.

[10] Hanson and co-workers have reported experiments that appear to support net inversion of configuration at C-1 of FPP in the biosynthesis of illudin M, based on an assumed retention of configuration during a subsequent oxidation: Hanson, J. R.; Marten, T.; Nyfeler, R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 876. Cf.: Cane, D. E. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W., Spurgeon, S. L., Eds.; Wiley: New York, 1981; Vol. 1, pp 332-333.

[11] In the cyclization of FPP to longifolene via an initial 11-membered ring and sativene via an initial 10-membered ring, subsequent hydride shifts of the H-1 hydrogens precluded direct stereochemical analysis of the initial configurational changes at C-1.

[12] Cane, D. E.; Tillman, A. M. *J. Am. Chem. Soc.* **1983**, *105*, 122.

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