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Singlet Oxygen Delivery Through the Porous Cap of a Hollow-Core Fiber Optic Device

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The development of the first photosensitizer/fiber optic device is reported. An oxygen-flowing, fiber-capped configuration is used for the application of heterogeneous, spatially confined singlet oxygen delivery in aqueous media. This is a unique device, unlike other heterogeneous photosensitizers, in which local concentrations of singlet oxygen can be delivered via introduction and withdrawal of the fiber tip.

Introduction

In 2008, we reported a photochemical approach to the clean generation of singlet oxygen in aqueous solution with a porous glass sensitizer [*meso*-tetra(*N*-methyl-4-pyridyl)porphine **1** adsorbed onto porous Vycor glass (PVG)].^{1,2} The porous glass sensitizer involved oxygen “collision” onto the matrix for the conversion of ground-state O₂ into ¹O₂, reflecting ¹O₂ diffusion into the bulk aqueous solution (Scheme 1).² Singlet oxygen was detected in water by time-resolved methods or reaction with an alkene molecule to give a hydroperoxide.¹ Our attention to a porous glass sensitizer stemmed from a desire to fix the photosensitizer to the end of a hollow fiber optic through which O₂ flows to “deliver” singlet oxygen site selectively on the microscale. Few reports have appeared on heterogeneous sensitizers coupled to fiber optics^{3–7} or the production of singlet oxygen by heterogeneous sensitizers in water.^{8,9} Clearly, at present, methods that generate singlet oxygen are not coupled into maneuverable delivery devices. We report here the first study of a hybrid sensitizer/fiber optic device for singlet oxygen generation at the fiber tip. The prototype device is based on micro-optic technology¹⁰ for localizing singlet oxygen in water and has the potential for use in cancer treatment and in water disinfection.

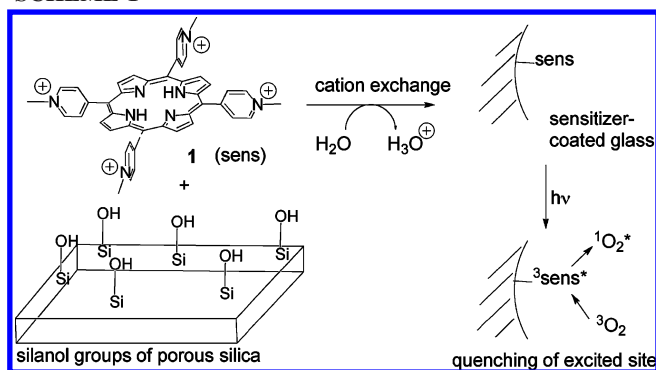
Results and Discussion

The singlet oxygen fiber device consisted of a porous Vycor cap coated with compound **1** (see Scheme 1) as sensitizer placed on the end of a hollow core photonic bandgap fiber. Compressed oxygen was delivered through the core of the fiber to the cap and into water solutions containing *N*-benzoyl-DL-methionine anion (0.02 M) as an indirect method to analyze singlet oxygen production. Oxygen flowed through the fiber, and irradiation with 532-nm laser light focused into the proximal end of the fiber led to the sulfoxide as the only product at the distal end in water. The same product was observed in D₂O and in H₂O. The experimental evidence suggesting the viability of the device in Scheme 2 includes the following: A hollow core photonic bandgap fiber HC-580 (capable of transmitting 520–630 nm light, core diameter of 4.9 μm, acrylate coating diameter of 220 μm) was coupled to a green LED or a 10-Hz Nd:YAG laser operating at 532 nm. The equation from Gaussian optics for the focal length with optimum mode matching the single-mode HC-580 fiber accounts for the preferred use of a 10× objective.¹¹

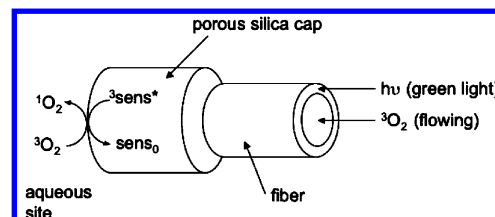
A Newport laser-to-fiber coupler with 0.1-μm *x-y-z* translation resolution aligned the microscope objective to focus green light into the optical fiber, and a Teflon-lined fiber chuck upon tightening accommodated the 220-μm fiber. The 532-nm beam exiting the distal end of the 30-cm length of fiber was 0.15 mW (LED) and 0.11 mJ/pulse (Nd:YAG). The intensity of the light exiting the fiber is a function of its length. The attenuation is ~1 dB/m, and bending the fiber does not increase the attenuation noticeably.

Previous studies of gas and light passage through hollow optical fibers^{12,13} suggested that ground-state O₂ could be delivered through our HC-580 fiber. A 406-μm channel was mechanically drilled through one side of a polystyrene cuvette (10 mm light path length, 12.5 mm² × 45 mm) using a micro diamond-head drill. The fiber was inserted into a ferrule collar glued into the hole in the cuvette with ethyl cyanoacrylate glue, where a 2-mm segment of the fiber protruded into the center of the cuvette (Figure 1A, B). The cuvette was placed into the center of the laser-to-fiber coupler, where the 532-nm beam passes through the opposite (unmodified) side of the quartz cuvette and entered the fiber (Figure 1B). A 3-mm hole was

SCHEME 1



SCHEME 2



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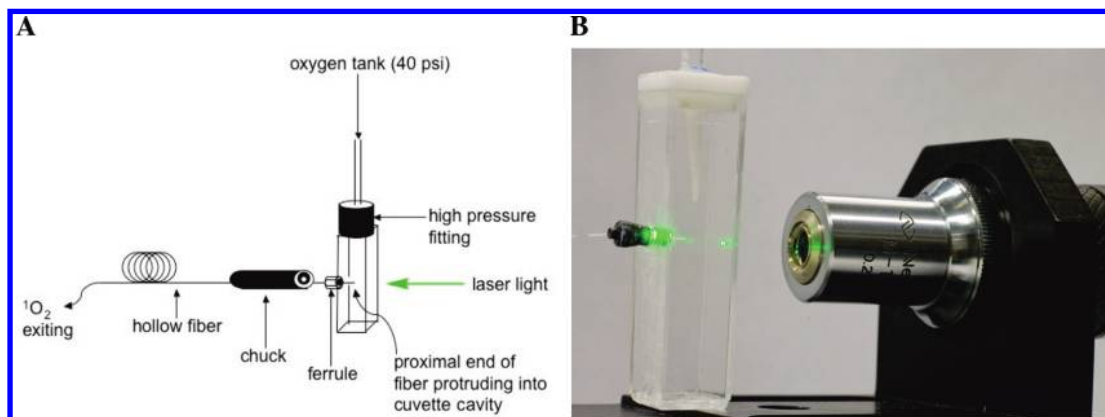


Figure 1. (A) A schematic drawing showing the compressed oxygen-to-fiber coupling and the use of a modified cuvette. Oxygen gas is delivered through a pipet at the top of the cuvette and enters the proximal end of the fiber to the left, which is protruding into the cuvette cavity. (B) A portion of the experimental setup showing the LED, the 10× objective, and modified cuvette in which green light is focused into the fiber.

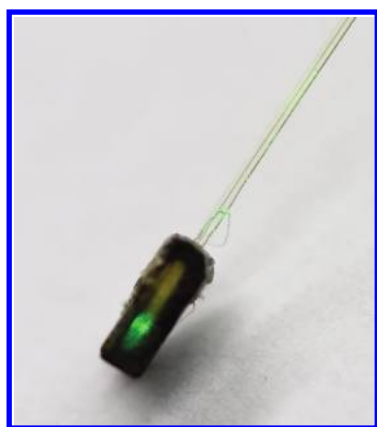


Figure 2. Image of the HC-580 fiber inserted into the silica cap (length = 2.38 mm, bore diameter = 0.38 mm). Green light exited the distal end of the fiber. The absorption of light by the sensitizer occurs in the PVG cap.

drilled into the square polytetrafluoroethylene cuvette cover (12.5 mm²) glued to the cuvette. A plastic 200 μ L pipet tip was inserted to about 1/4 of its length and glued in place. The top of the cuvette was connected to an oxygen tank, where compressed oxygen flowed at 40 PSI into the cuvette. The flow rate of oxygen through the uncapped hollow fiber was 0.12 mL/hour.

The end of the hollow fiber was capped with the porous glass photosensitizer [3×10^{-7} mol sensitizer **1** was adsorbed onto 0.013-g preshaped PVG (dimensions: 3 mm² \times 0.8 mm)]. The fiber acrylate coating was not removed so that the intensity of light was the same at the source and at the fiber–PVG junction. The colorless PVG cap was converted to deep red or black on adsorption of **1**. About 0.5% of the cap surface was covered with photosensitizer, and the photosensitizer remained adhered to the cap in contact with water.^{1,2} No desorption of **1** from PVG was observed at pH = 3, 7, and 10. Photobleaching of the fiber cap with the 5 mW laser was not evident up to 30 h of irradiation. Cap samples could be ground down to 0.6 mm, but any thinner led to cap leaking or cracking. A hole with the dimensions 2.38 mm \times 0.38 mm was drilled length-wise into the sensitizer-coated porous silica cap (Figure 2). The fiber was inserted into the cylinder hole and glued into place at the hole entrance. As desired, water did not fill the cap hole; neither did water fill the hollow fiber by capillary action. Excitation occurred by scattering of the light through the cap and absorption of the radiation by the sensitizer adsorbed to the surface. The sensitizer-coated surface faced the bulk solution, and O₂

TABLE 1: Quantities of Oxygen Delivered through a 30-cm Segment of the HC-580 Fiber into 100 μ L of H₂O from an Oxygen Tank at 40 PSI (room temperature)^a

uncapped fiber		capped fiber	
time (min)	ppm/O ₂ in H ₂ O	time (min)	ppm/O ₂ in H ₂ O
5.0	8.59	34.0	8.75
10.0	9.03	64.0	8.95
21.0	9.59	129.0	9.32
30.0	9.99	184.0	9.48
50.0	10.35	214.0	9.57

^a Porous Vycor glass cap (dimensions: 3 mm² \times 0.8 mm).

transport occurred by a pressure gradient, diffusing through the membrane cap; bubbles effused slowly. Parts per million oxygen delivered to a 100- μ L water sample via the fiber-compressed oxygen tank system in Figure 2 was determined with a pO₂ micro-oxygen electrode (Table 1). The capped fiber flowed O₂ about 20 times slower than the uncapped fiber. Other researchers have also demonstrated the transportation of gases through porous Vycor glass.^{14–17}

The experimental evidence suggested that singlet oxygen exited the distal end of the cap of the photosensitizer/fiber optic device and was trapped with *N*-benzoyl-DL-methionine anion (**2**, 0.02 M) in the surrounding aqueous solution (Figure 3). Only one product was formed—*N*-benzoyl-DL-methionine S-oxide anion (**3**)—which was monitored by ¹H NMR spectroscopy and is consistent with its literature assignment.^{18,19} Methionine **2**, as the anion, does not adsorb onto the PVG, and no trace of methionine molecules passes through the PVG membrane. The lifetime of ¹O₂ increases by 20-fold in D₂O as compared to H₂O;²⁰ however, the sulfoxidation reaction was found to be about 2 times faster in D₂O than H₂O (cf. 11% to 5%) after irradiation with the fiber device for 9 h at pH 8. The 2-fold increase of sulfoxide in D₂O as compared to H₂O was less than expected and may relate to a surface effect (some singlet oxygen adsorption or quenching of singlet oxygen by anionic Si–O[−]

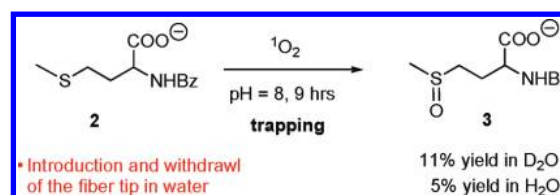


Figure 3. Photooxidation of *N*-benzoyl-DL-methionine anion **2** with the fiber device.

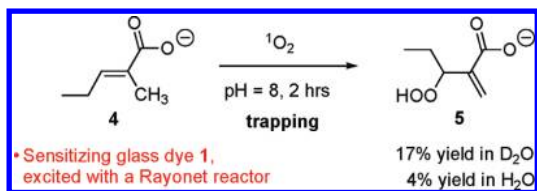


Figure 4. Photooxidation of *trans*-2-methyl-2-pentenoate anion **4** via “external” visible-light irradiation (ref 1).

sites). The exchange of Si–OH groups with D_2O to make Si–OD, potentially reducing surface physical quenching of singlet oxygen, was not examined.²¹

Steady-state (i–iv), control (v), and time-resolved experiments (vi) point to a singlet oxygen mechanism for the heterogeneous PVG sensitizer. (i) Quenching studies carried out with the singlet oxygen quencher sodium azide (2 mM) in D_2O led to the reduced production of methionine S-oxide **3** (cf. 17% to 5%). (ii) Product yields were identical for the photooxidation of methionine **2** carried out in the presence of the radical scavenger *D*-mannitol (33 mM). (iii) Cumyl radical-derived products were not observed when using cumene radical scavenger in high concentrations; that is, when cumene was used as solvent. (iv) Previous studies¹ showed the photooxidation of *trans*-2-methyl-2-pentenoate anion (**4**) afforded one main product, the hydroperoxide **5** from the singlet oxygen “ene” reaction (^1H NMR spectra indicate 1–2% byproduct derived from type I reactions with oxygen radicals) (Figure 4). (v) Sulfoxidation of **2** did not take place in the dark. (vi) $^1\text{O}_2$ molecules were generated in aqueous media; in the absence of oxidizable reagents, $^1\text{O}_2$ was converted to $^3\text{O}_2$ physically and was monitored by time-resolved $^1\text{O}_2$ ($^1\Delta_g$) phosphorescence at 1270 nm.¹ From studies of singlet oxygen diffusion, the square of distance (d) that an oxygen molecule travels during time (t) with the diffusion coefficient (D_0) is given by the equation $d^2 = 6D_0t$.^{22–24} Thus, singlet oxygen is expected to diffuse a short distance (~ 150 nm) away from the silica cap into bulk H_2O .

Conclusion

This manuscript describes the development of a prototype (portable) singlet oxygen delivery device. The above data demonstrate that the oxygen-flowing fiber-capped configuration is suited for the heterogeneous generation of singlet oxygen in aqueous solution. The device is unique. Local concentrations of singlet oxygen can be delivered via introduction and withdrawal of the fiber tip.

Experimental Section

General Aspects. Porous Vycor glass (Corning 7930) was purchased from Advanced Glass and Ceramics (Holden, MA). *N*-Benzoyl-DL-methionine sodium salt (Aldrich), sodium azide (Aldrich), cumene (Aldrich), *D*-mannitol (Aldrich), *meso*-tetra(*N*-methyl-4-pyridyl)porphine tetratosylate (Frontier Scientific), and adipic acid (Monsanto Chemical Co.) were used as received. Deuterium oxide- d_2 (Aldrich), chloroform- d_1 (Aldrich), and acetonitrile- d_3 (Isotec, Inc.) were of spectrophotometric grade. Deionized H_2O was from a U.S. Filter Corporation deionization system (Palm Desert, CA). The 532-nm excitation source was either a AAA battery-powered green LED (5 mW, Astro Aimer II) or a New Wave Research Minilase 10-Hz Nd:YAG Q-switched laser (~ 4 ns fwhm, 3 mJ/pulse) (Fremont, CA). A hollow core photonic bandgap fiber HC-580 was used [core diameter of 4.9 μm , holey region diameter of 31 μm , silica cladding diameter of 89 μm , acrylate coating diameter of 220

μm , numerical aperture was 0.12 (Crystal Fiber Inc., Birkerød, Denmark)]. A Newport high-precision single-mode laser-to-fiber coupler (F-915) with an M-10 \times microscope objective focused the 532-nm light into the HC-580 fiber. The effective focal length of the M-10 \times microscope objective was 16.5 mm, and its numerical aperture was 0.25. A Newport Teflon-lined fiber chuck (FPH-J) was used. The radiant power of the 532-nm light exiting the fiber was measured with a Nova energy meter (Ophir Optonics, Logan, UT). Fibers were cleaved with a 90° diamond wedge scribe, and the ends of the fibers were polished with diamond lapping polishing sheets (3 and 6 μm grain sizes) (Thor Laboratories, Newton, NJ). UV–visible spectra were collected on a Hitachi UV–vis U-2001 instrument. NMR data were collected on a Bruker DPX400 NMR instrument. Mass spectrometry data were acquired on an Agilent Technologies 6890N GC/MS instrument with a 5973 mass selective detector (MSD) and a HP-5MS column. A Rayonet photoreactor was used with Sylvania F8T5/CW 8-W bulbs that emit at ~ 425 –650 nm. Dissolved oxygen was measured with a pO_2 micro oxygen electrode (2 mm tip) (Lazar Research Laboratories).

Fiber Modifications. A hole with the dimensions of 406 $\mu\text{m} \times 12.5$ mm was drilled into one wall of a polystyrene cuvette (10 mm path length, 4.5 mL, 12.5 mm² \times 45 mm) (Fisherbrand). A diamond-head drill bit was used (UKAM Industrial Superhard Tools, Valencia, CA). Glued into this channel was a 0.25 mm ferrule (Valco Instruments, Houston, TX) so that the fiber could be threaded. The fiber protruded 2 mm beyond the ferrule collar and into the cuvette cavity. The cuvette was modified further by drilling a 3-mm hole into its PTFE cover and inserting a 200- μL Redi-tip (Fisherbrand). After gluing the cap and tip to the cuvette, the top of the cuvette was coupled to a 200 PSI compressed oxygen tank (gas regulator set to 40 PSI).

Cap Preparation, Adsorption, and Desorption Studies. The sensitizer **1**-impregnated PVG cap was prepared for placement on the distal end of the hollow fiber. With silicon carbide sandpaper, PVG was sanded into a cylindrical (7.5 mm L \times 3.5 mm diameter) or rectangular shape (3 mm² \times 0.8 mm). The adsorption of **1** onto a 0.013 g rectangular piece of PVG was achieved by soaking the PVG cap in 15 mL of 3.3×10^{-5} M aqueous solution of **1** for 48 h. A plateau was reached when there was 2.5×10^{-7} mol **1** adsorbed onto the PVG cap. The amount of **1** adsorbed onto the PVG cap was calculated from the difference in absorbance of the solution before introduction of PVG, and the absorbance of the same solution, after the removal of PVG. The adsorption process was followed by monitoring the largest of the four Q-bands of **1**-ads at $\lambda = 525$ nm. The sensitizer-coated caps were rinsed with distilled water prior to use to remove any unbound **1**. A 2.38-mm \times 0.38-mm core was drilled lengthwise into the sensitizer-coated PVG cap. The 220- μm -o.d. fiber was inserted into the cap hole and glued into place at the hole entrance. Desorption of **1** was not observed when sensitizer-coated PVG (7.5×10^{-7} mol **1** onto 1.5 g PVG) was placed into 2 mL of H_2O solution at pH = 3, 7, and 10 and stirred for 8 h. No desorption of **1** was observed with Soxhlet extraction, in which acetonitrile and methanol were used as solvents; neither was desorption of **1** observed in a Soxhlet extractor with 2 N NaOH solution for 48 h. Desorption of **1** ($\sim 70\%$) took place when the PVG cap was in a Soxhlet extractor in 2 N HCl over 48 h.

Methionine Trapping Studies. Methionine trapping studies were conducted in 100 μL of H_2O and D_2O containing 0.02 M methionine **2**. The ratio of the void space inside the PVG cap to the 100- μL bulk solvent volume was $\sim 1:300$, in which $\sim 0.3\%$ of the solution volume resides in the cap relative to bulk

solution. A sensitizer-coated PVG cap was immersed into H₂O and D₂O while connected to the fiber optic device. Oxygen flowed through the fiber during the irradiation of samples with the green LED for 9 h. The long irradiation times were due to the low intensity of the radiation through the fiber cap. At <15% conversion, methionine S-oxide **3** was detected as the sole product on the basis of ¹H NMR. Sulfone or cleavage products from (*S*)-hydroperoxysulfonium ylide chemistry were not observed.^{25,26} The internal standard adipic acid (0.02 M) was added to determine the concentration of the photooxidation samples. The percent yield was determined by comparison of the sulfoxide with the methylene protons of adipic acid (internal standard) by ¹H NMR spectroscopy. The structure of *N*-benzoyl-DL-methionine S-oxide anion was elucidated by ¹H NMR (D₂O) δ 2.24 (m, 1H), 2.40 (m, 1H), 2.71 (s, 3H), 2.99 (m, 2H), 4.54 (m, 1H), 7.54 (m, 2H), 7.63 (m, 1H), 7.82 (m, 2H).

Further Experiments. Additional experiments included the following: (1) A 1.0-mL D₂O solution containing methionine **2** (20 mM) and 2.5 × 10⁻⁷ mol **1** adsorbed onto 0.097 g PVG placed in the dark for 10 h, in which formation of methionine S-oxide **3** was not observed. (2) O₂ was bubbled into a 1.0-mL D₂O solution containing methionine **2** (20 mM) and 5 × 10⁻⁷ mol **1** adsorbed onto 0.34 g PVG and into a 1.0-mL D₂O solution containing methionine **2** (20 mM), *D*-mannitol (33 mM), and 5 × 10⁻⁷ mol **1** adsorbed onto 0.34 g PVG. Both solutions were irradiated with the Rayonet reactor for 4 h, and both led to methionine S-oxide **3** in 21% yield. (3) O₂ was bubbled into a 2.0-mL D₂O solution containing methionine **2** (20 mM) and 5 × 10⁻⁷ mol **1** adsorbed onto 0.34 g PVG and into a 2.0-mL D₂O solution containing methionine **2** (20 mM), sodium azide (2 mM), and 5 × 10⁻⁷ mol **1** adsorbed onto 0.34 g PVG. Both solutions were irradiated with the Rayonet reactor for 4 h; the formation of methionine S-oxide **3** was reduced in the latter case by 3-fold. (4) O₂ was bubbled into a 2.0-mL cumene solution containing 5 × 10⁻⁷ mol **1** adsorbed onto 0.34 g PVG and was irradiated with the Rayonet reactor for 11 h. Formation of solvent radical-derived products, such as olefins, were not observed.

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