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Photoactive Fluoropolymer Surfaces that Release Sensitizer Drug Molecules

Goutam Ghosh[†], Mihaela Minnis[†], Ashwini A. Ghogare[†], Inna Abramova[†], Keith Cengel[‡], Theresa M. Busch[‡], and Alexander Greer^{†,*}

[†]Department of Chemistry, Brooklyn College, City University of New York, Brooklyn, New York 11210, United States

[‡]Department of Radiation Oncology, University of Pennsylvania, Philadelphia, Pennsylvania 19104, United States

Abstract

We describe a physical-organic study of two fluoropolymers bearing a photoreleasable PEGylated photosensitizer which generates $^1\text{O}_2$ [chlorin *e*₆ methoxy tri(ethylene glycol) triester]. The surfaces are Teflon/polyvinylalcohol (PVA) nanocomposite and fluorinated silica. The relative efficiency of these surfaces to photorelease the PEGylated sensitizer [shown previously to be phototoxic to ovarian cancer cells (Kimani, S. et al *J. Org. Chem* **2012**, 77, 10638)] was slightly higher for the nanocomposite. In the presence of red light and O_2 , $^1\text{O}_2$ is formed, which cleaves an ethene linkage to liberate the sensitizer in 68–92% yields. The fluoropolymers were designed to deal with multiple problems. Namely, their success relied not only high O_2 solubility and drug repellency, but that the C–F bonds physically quench little $^1\text{O}_2$ for its productive use away from the surface. The results obtained here indicate that Teflon-like surfaces have potential uses of delivering sensitizer and singlet oxygen for applications in tissue repair and photodynamic therapy (PDT).

Keywords

Polymer photooxidation; singlet oxygen; fluorination; PEGylation; vibrational quenching; drug delivery

INTRODUCTION

Solid supports have been used as platforms for the photorelease of drug molecules.^{1,2} However, there are gaps in data on whether Teflon-like^{3,4} or superhydrophobic surfaces⁵ can efficiently photorelease drugs. To address this issue, two photoactive fluoropolymers have been synthesized and compared (Figure 1). One is made of fluorinated silica [glass coated with $(\text{CH}_3\text{O})_3\text{SiCH}_2\text{CH}_2\text{CF}_2\text{CF}_2\text{CF}_2\text{CF}_3$] and the other is a Teflon/polyvinyl alcohol

Alexander Greer (agreer@brooklyn.cuny.edu).

Supporting Information Available: Absorption, FT-IR, HRMS, and ^1H and ^{13}C NMR spectra for **1–5**. Absorption and FT-IR spectra of solids **7** and **10**. This information is available free of charge via the Internet at <http://pubs.acs.org>

(PVA) nanocomposite which has $-(CF_2-CF_2)_m-$ and $-(CH_2-CH(OH))_n-$ chains. Figure 1 also shows the sensitizer drug to be photoreleased is PEGylated.

While the delivery of PEGylated compounds is an active area of research,^{6–8} they tend to adhere to surfaces.^{9–11} Even though solid state sensitizers have been established,^{12–14} few have been designed to release PEGylated compounds,¹⁵ and none have capitalized on fluoropolymers' nonstick repellent properties¹⁶ for better molecule discharge from the surface. Thus, we anticipated that fluoropolymer sensitizer release systems with repellent properties *and* visible light activation could be established.

Visible light and NIR photocleavage reactions are known^{17–24} and actually represent a burgeoning area of research.^{25,26} For example, the sensitized generation of 1O_2 (1g) has been used with labile ethene linkers for photorelease reactions. We^{27,28} and others^{29–31} have published papers devoted to 1O_2 -based drug release and a book chapter has also appeared.³² Singlet oxygen is a potentially therapeutic species and is photogenerated by PAHs,^{33,34} chlorins,^{35,36} porphyrins and phthalocyanines, and their fluorinated analogs.^{37–41} In 2011, Röder et al. reported the deposition of perfluorinated phthalocyanines on silica gel as a composite material for generating 1O_2 for sterilization.⁴² A Teflon ponytail fullerene (i.e. C_{60} adduct with $CH_2[CO_2(CH_2)_3(CF_2)_7CF_3]_2$) has also been prepared for 1O_2 generation.⁴³ Favorable properties of surface *fluorination* for 1O_2 and drug potency through *PEGylation* would make such a combination be desirable. However, solid materials that are *both* fluorinated and PEGylated are rather uncommon.⁴⁴ Taken together, the above topics reveal the potential utility of a Teflon-supported PEGylated-drug release system and point to the need for new studies.

Our hypothesis was that a Teflon/PVA nanocomposite will photorelease the PEGylated sensitizer more efficiently than fluorinated silica because of the higher number of C–F bonds in the former. Thus, we report here the synthesis and study of two fluoropolymers illustrated in Figure 1 to give us insight into the photosensitizer release mechanism. We show that these surfaces have (i) high solubility of ground-state oxygen, which is advantageous for photooxidation chemistry; (ii) relatively low adsorptivity for the PEGylated sensitizer, for good turnout; (iii) facile breakage of the ethene linker bond; and (iv) longer singlet oxygen lifetimes (τ) because the C–F bonds *sap* the polymer's ability to physically quench 1O_2 (i.e. paucity of C–H and O–H bonds limit unwanted vibrational relaxation of 1O_2 to 3O_2). The fluoropolymers we describe are biocompatible (e.g., for surgery)^{45,46} and our mechanistic study provides results which may be useful for applications in localized delivery of sensitizer to desired surfaces (e.g. wounds or diseased tissue) where the released photosensitizer is active upon subsequent illumination.

EXPERIMENTAL

General Aspects

Reagent grade solvents methanol, hexane, toluene, DMF, THF, CH_2Cl_2 , $CHCl_3$, $CDCl_3$, CCl_4 , and *n*-butanol were used. Hydrofluoric acid, sodium sulfate, sodium bicarbonate, sodium periodate, sodium borohydride, osmium tetroxide, acetic acid, succinic acid, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC), *N,N*-dimethyl-4-

aminopyridine (DMAP), (3-iodopropyl)trimethoxysilane, 3,3,4,4,5,5,6,6,6-nonafluorohexyltrimethoxysilane, tri(ethylene glycol) monomethyl ether, chlorin e₆, rose bengal, polyvinyl alcohol (MW 89,000–98,000, and 99% hydrolyzed), poly(tetrafluoroethylene) (PTFE: 60 wt % solid content, 5.9 wt % nonionic surfactant, 22.3 nm average particle size, and 2.20 g/mL density) were used as received from commercial suppliers. Solid samples were cleaned with refluxing methanol in a Soxhlet extractor. Proton and carbon NMR data were recorded at 400 MHz and 100.6 MHz, respectively. UV–vis and IR spectrophotometers, a GC/MS instrument, a muffle furnace, and a portable pO₂ oxygen sensor were also used. HRMS data were collected at the mass spectrometry facility in University of California, Riverside.

Synthesis of 3-Formyl-17³,15²,13¹-Chlorin e₆ Methoxy Tri(ethylene glycol) Triester (2) (Figure 2)

Yield 12.0 mg (60%); purity: 98%. Chlorin e₆ was converted to triPEG chlorin **1** (i.e. methoxy triethylene glycol attached at the ester bonds for a 3:1 conjugate) by a previously described procedure.⁴⁷ To the 20.0 mg (0.019 mmol) of **1** in 15 mL THF, 7.68 mg (0.03 mmol) of OsO₄ in 20 μ L CCl₄ was added at 0 °C under N₂ atmosphere. Reaction mixture was stirred under 0–5 °C temperature for 25 min. 82.8 mg (0.38 mmol) of NaIO₄ was dissolved in 1% AcOH solution and added to the reaction mixture. Reaction was stirred overnight at room temperature. A drop of saturated sodium bicarbonate solution was added to neutralize the acid. The reaction mixture was extracted with 50 mL of CH₂Cl₂ and washed with water. The organic layer was dried over sodium sulfate. After evaporating the organic solvent, the residue was purified by column chromatography using 1.1% methanol–CH₂Cl₂. R_f = 0.69 in 3% methanol–CH₂Cl₂. HPLC: t_R = 12.2 min in gradient mixture of methanol and H₂O. ¹H NMR (400.0 MHz, CDCl₃) δ 11.56 (s, 1H), 10.28 (s, 1H), 9.70 (s, 1H), 8.97 (s, 1H), 5.48 (d, *J* = 18.4 Hz, 1H), 5.30 (d, *J* = 18.4 Hz, 1H), 4.96 (m, 1H), 4.89 (m, 1H), 4.51 (m, 2H), 4.35 (m, 2H), 4.16 (m, 4H), 3.86 (m, 3H), 3.84 (s, 3H), 3.82 (m, 3H), 3.71 (t, *J* = 4.8 Hz, 3H), 3.65 (m, 5H), 3.56 (m, 10H), 3.44 (t, *J* = 4.8 Hz, 3H), 3.37 (s, 3H), 3.34 (m, 4H), 3.30 (s, 3H), 3.23 (s, 3H), 3.22 (s, 3H), 3.18 (t, *J* = 4.8 Hz, 2H), 2.60 (m, 1H), 2.25 (m, 2H), 1.77 (m, 8H), –1.24 (br s, 1H), 1.76 (br s, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ 188.3, 173.0, 172.2, 168.9, 168.5, 167.6, 155.1, 151.5, 144.9, 138.3, 138.1, 137.9, 136.6, 136.0, 134.0, 131.9, 128.6, 125.8, 103.4, 101.3, 100.7, 95.5, 71.9, 71.8, 71.6, 70.7, 70.6, 70.5, 70.4, 70.2, 70.1, 69.2, 69.0, 68.9, 65.2, 64.3, 63.6, 59.0, 58.9, 58.8, 53.4, 48.7, 38.5, 31.0, 29.7, 29.5, 23.3, 19.6, 17.5, 12.4, 11.4, 11.3. HRMS (+ESI) *m/z* calculated for C₅₄H₇₇N₄O₁₆ [M+H]⁺ 1037.5335, found: 1037.5357. UV–vis (CHCl₃) $\lambda_{\max}$ 418 and 694 nm.

Synthesis of 3¹-Hydroxyl-17³,15²,13¹-Chlorin e₆ Methoxy Tri(ethylene glycol) Triester (3)

Yield 10.0 mg (77%); purity: 92%. To 13.0 mg (0.012 mmol) of **2** in 4:1 mL methanol–CH₂Cl₂ at 5–10 °C, 1.0 mg (0.025 mmol) of NaBH₄ was added. A sudden color change from brown to green was observed. The reaction was monitored by TLC. It was completed in 0.5 h. The reaction mixture was quenched with water and extracted by CH₂Cl₂. The organic layer was dried over sodium sulfate and evaporated by a rotavapor system. R_f = 0.50 in 3% methanol–CH₂Cl₂. HPLC: t_R = 7.79 min in gradient mixture of methanol and H₂O. ¹H NMR (400.0 MHz, CDCl₃) δ 9.72 (s, 1H), 9.55 (s, 1H), 8.76 (s, 1H), 5.87 (s, 2H),

5.44 (d, $J = 18.8$ Hz, 1H), 5.29 (d, $J = 19.6$ Hz, 1H), 4.93 (m, 1H), 4.88 (m, 1H), 4.47 (m, 2H), 4.32 (m, 2H), 4.11 (m, 4H), 3.85 (m, 3H), 3.79 (m, 3H), 3.70 (t, $J = 4.8$ Hz, 2H), 3.60 (m, 5H), 3.55 (t, $J = 4.8$ Hz, 3H), 3.48 (m, 11H), 3.40 (m, 2H), 3.36 (s, 3H), 3.30 (s, 3H), 3.28 (s, 3H), 3.20 (m, 4H), 3.16 (m, 3H), 3.11 (m, 2H), 3.02 (t, $J = 4.8$ Hz, 2H), 2.27 (m, 1H), 2.16 (m, 1H), 2.09 (m, 2H), 1.86 (m, 2H), 1.75 (m, 7H), -1.58 (br s, 1H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 173.0, 172.4, 169.7, 168.8, 166.8, 154.5, 148.9, 145.0, 139.1, 136.6, 136.0, 135.7, 135.5, 135.2, 132.5, 129.4, 123.7, 102.6, 102.0, 98.2, 93.7, 71.9, 71.7, 71.5, 70.7, 70.6, 70.3, 70.1, 70.0, 69.2, 68.8, 65.0, 64.3, 63.5, 59.0, 58.9, 58.7, 56.3, 53.4, 52.9, 49.3, 38.6, 30.9, 29.7, 29.6, 23.0, 19.6, 17.6, 14.1, 12.4, 11.3, 11.1; HRMS (+ESI) m/z calculated for $\text{C}_{54}\text{H}_{79}\text{N}_4\text{O}_{16}$ $[\text{M}+\text{H}]^+$ 1039.5491, found: 1039.5490. UV-vis (CHCl_3) λ_{max} 404 and 661 nm.

Synthesis of 3¹-Succinate-17³,15²,13¹-Chlorin e₆ Methoxy Tri(ethylene glycol) Triester (4)

Yield 8.0 mg (73.4%); purity: 90%. To the 10.0 mg (0.0096 mmol) of **3** in 10 mL of dry CH_2Cl_2 under nitrogen atmosphere, 5.65 mg (0.048 mmol) of succinic acid, 4.57 mg (0.024 mmol) of EDC and 2.9 mg (0.024 mmol) of DMAP were added. Reaction was stirred for 36 h under N_2 at room temperature after which 15 mL CH_2Cl_2 was added. The organic layer was washed with water and dried over sodium sulfate. The organic layer was evaporated and **3** was purified by 2% methanol- CH_2Cl_2 . $R_f = 0.37$ in 3% methanol- CH_2Cl_2 . HPLC: $t_R = 7.79$ min in gradient mixture of methanol and H_2O . ^1H NMR (400.0 MHz, CDCl_3) δ 9.73 (s, 1H), 9.58 (s, 1H), 8.80 (s, 1H), 6.46 (s, 2H), 5.44 (d, $J = 18.4$ Hz, 1H), 5.29 (d, $J = 19.6$ Hz, 1H), 4.92 (m, 2H), 4.48 (m, 2H), 4.30 (t, $J = 4.8$ Hz, 2H), 3.80 (m, 6H), 3.70 (t, $J = 4.8$ Hz, 2H), 3.62 (s, 3H), 3.55 (m, 4H), 3.51 (s, 3H), 3.47 (s, 3H), 3.45 (m, 4H), 3.36 (m, 8H), 3.23 (s, 3H), 3.11 (s, 3H), 3.07 (m, 2H), 2.99 (t, $J = 4.8$ Hz, 2H), 2.88 (m, 2H), 2.82 (m, 2H), 2.75 (m, 2H), 2.69 (m, 2H), 2.48 (m, 2H), 2.29 (m, 4H), 1.86 (m, 2H), 1.74 (dd, $J = 16.4$ Hz, 11.6 Hz, 6H), -1.67 (br s, 1H). HRMS (+ESI) m/z calculated for $\text{C}_{58}\text{H}_{83}\text{N}_4\text{O}_{19}$ $[\text{M}+\text{H}]^+$ 1139.5652, found: 1139.5634.

Synthesis of Spacer Alkene-3¹-Succinate-17³,15²,13¹-Chlorin e₆ Methoxy Tri(ethylene glycol) Triester (5)

Yield 1.9 mg (52%); purity: 91%. To the 3.0 mg (0.0026 mmol) of **4** in dry CH_2Cl_2 in nitrogen atmosphere, 2.0 mg (0.0073 mmol) of spacer alkene alcohol, 1.06 mg (0.0052 mmol) of EDC and 1.0 mg (0.0078 mmol) of DMAP were added. Reaction was stirred for 36 h under N_2 at room temperature after which 15 mL CH_2Cl_2 was added. Organic layer was washed with water and dried over sodium sulfate. The organic layer was evaporated and **5** was purified by 1.5% methanol- CH_2Cl_2 . $R_f = 0.64$ in 3% methanol- CH_2Cl_2 . HPLC: $t_R = 9.24$ min in gradient mixture of methanol and H_2O . ^1H NMR (400.0 MHz, CDCl_3) δ 9.73 (s, 1H), 9.58 (s, 1H), 8.80 (s, 1H), 7.32 (d, $J = 8.4$ Hz, 2H), 7.01 (d, $J = 8.4$ Hz, 2H), 6.97 (d, $J = 8.4$ Hz, 2H), 6.71 (d, $J = 8.4$ Hz, 2H), 6.45 (s, 2H), 5.91 (d, $J = 3.2$ Hz, 1H), 5.71 (d, $J = 3.2$ Hz, 1H), 5.44 (d, $J = 18.8$ Hz, 1H), 5.27 (d, $J = 18.4$ Hz, 1H), 4.89 (m, 4H), 4.61 (s, 2H), 4.47 (m, 2H), 4.33 (m, 2H), 4.14 (m, 5H), 3.83 (m, 3H), 3.77 (m, 3H), 3.70 (t, $J = 4.8$, 4H), 3.62 (m, 5H), 3.56 (m, 10H), 3.50 (s, 3H), 3.43 (m, 3H), 3.36 (s, 3H), 3.33 (s, 3H), 3.29 (s, 3H), 3.21 (m, 7H), 3.14 (t, $J = 4.8$ Hz, 2H), 2.80 (m, 2H), 2.74 (m, 2H), 2.55 (m, 1H), 2.19 (m, 3H), 1.73 (m, 7H), -1.40 (br s, 1H), -1.65 (br s, 1H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 173.5, 173.0, 172.4, 172.2, 172.0, 169.5, 168.7, 167.1, 157.0, 156.7, 145.0, 138.6, 136.7,

136.2, 135.6, 135.5, 135.2, 134.0, 130.7, 129.8, 129.7, 129.6, 128.4, 127.6, 123.9, 116.1, 115.8, 101.9, 98.3, 94.0, 71.9, 71.8, 71.5, 70.7, 70.6, 70.5, 70.4, 70.1, 69.2, 68.9, 66.8, 66.0, 65.0, 64.7, 64.3, 63.5, 59.0, 58.9, 58.8, 57.6, 53.4, 53.0, 49.2, 38.7, 38.6, 34.0, 31.0, 30.4, 29.7, 29.6, 29.3, 29.2, 28.9, 24.4, 23.8, 23.0, 22.9, 19.6, 17.7, 14.1, 14.0, 12.4, 11.3, 11.0. HRMS (+ESI) m/z calculated for $C_{74}H_{97}N_4O_{22}$ $[M+H]^+$ 1393.6594, found: 1393.6592. UV-vis ($CHCl_3$) λ_{max} ($\epsilon/M^{-1}cm^{-1}$) 400 nm (338680), 661 nm (92760).

TriPEG Chlorin-Modified Fluorinated Silica (7) (Figure 3)

Fluorinated glass **6** was prepared based on the methods established from our previous work.⁴⁸ Briefly, Vycor pieces were added to the nonafluorotrimethoxysilane in 0.07 wt/wt % in toluene and refluxed for 24 h under N_2 . Unreacted nonafluorotrimethoxysilane was washed off of the silica by Soxhlet extraction in methanol for 24 h. TriPEG chlorin **5** reacted with (3-iodopropyl)trimethoxysilane and was added to 0.33 g fluorinated silica **6** [shaped into pieces sized $\sim 5\text{ mm} \times \sim 8\text{ mm}$ ($d \times l$)] in refluxing toluene for 24 h to reach **7**. Washings with CH_2Cl_2 , THF, methanol and hexane were followed by a Soxhlet extraction in methanol for 24 h to remove any adsorbed sensitizer from the silica. No sensitizer leaching from the surface was observed in the dark or under subdued light. UV-vis (λ_{max} , air) 400 and 661 nm. After dissolution of silica **7** by HF treatment and extraction with $CHCl_3$, evidence suggested the liberation of sensitizer (Soret band observed at 400 nm), $HOCH_2C_6H_4OCH=CHOC_6H_4CH_2OCH_2CH_2CH_2SiF_3$ (+ESI) m/z calculated for $C_{19}SiH_{20}O_4F_3$ = 398, found = 399, and $HOCH_2C_6H_4OCH=CHOC_6H_4CH_2OCH_2CH_2CH_2Si(OH)_3$ (+ESI) m/z calculated for $C_{19}H_{24}O_7Si$ = 392, found = 391. The amount of sensitizer that was loaded into **7** was 90 nmol/g of silica.

TriPEG Chlorin-Modified Teflon/PVA (10) (Figure 4)

Teflon/PVA **8** was prepared from a literature procedure and is a polymeric nanocomposite material of a PVA matrix filled with Teflon nanospheres.⁴⁹ Teflon suspension was added to a PVA solution (PVA dissolved in boiling H_2O with stirring for 5 h) in a 6:1 Teflon:PVA mass ratio. The mixture was stirred at room temperature and atmospheric pressure for 2.5 h using a mechanical agitator. Samples were placed in a mold and dried at room temperature and atmospheric pressure for 1 week. FT-IR (cm^{-1}): 3600–3100, 2950–2850, 1419–1325, 1203, 1147. UV-vis (λ , air): transparent. Succinic acid (0.100 g, 8.5 mmol) was dissolved in 1 mL anhydrous DMF and added to five pieces (ea. 0.22 g) of Teflon/PVA in 15 mL anhydrous CH_2Cl_2 . EDC (0.081 g, 0.425 mmol), and DMAP (0.052 g, 0.425 mmol) were added and the mixture was stirred under nitrogen atmosphere for 5 days. The samples were washed with CH_2Cl_2 , THF, methanol, toluene, and hexane, and then Soxhlet extracted with methanol for 24 h to reach Teflon/PVA **9**. FT-IR (cm^{-1}): 1723. UV-vis (λ , air): transparent. TriPEG chlorin **5** (6 mg, 4.3 μmol), EDC (0.010 g, 0.052 mmol), and DMAP (0.010 g, 0.082 mmol) were added to 0.21 g Teflon/PVA **9** [sized $\sim 4\text{ mm} \times \sim 7\text{ mm}$ ($d \times l$)] in 10 mL CH_2Cl_2 in N_2 atmosphere. The reaction mixture was stirred for 5 days. After reaction the samples were washed with several solvents (CH_2Cl_2 , THF, methanol, toluene, hexane) and Soxhlet extracted using methanol for 24 h. FT-IR (cm^{-1}): 1731. UV-vis (λ , air): 396 and 660 nm. The amount of sensitizer attached onto the succinic acid sites of Teflon/PVA was

determined to be 23.4 nmol/g by UV–vis spectroscopy. IR data were unable to distinguish whether the excess EDC used converted many of the surface acid sites to diesters (Figure S22, Supporting Information). Teflon/PVA **10** was stable in the dark; the sensitizer did not leach off to any measurable extent after CH₂Cl₂, methanol, THF and hexane solvent washings or Soxhlet extraction with methanol.

Photorelease of Sensitizer **13** from Surfaces **7** and **10** (Figure 5)

The photolysis setup included a continuous wave diode laser (669 nm output) where the light was passed through an SMA port, and out of the end of a borosilicate optical fiber with SMA optical fiber coupling as has been described in our previous work.⁴⁸ Under subdued light, *n*-butanol solutions were presaturated with O₂ for 20 min and then illuminated with red light for 1.5 h, upon which ¹O₂ was generated and trapped by the alkene sites on the solid supports. These heterogeneous photolysis reactions contained 0.328 and 0.214 g of solids **7** and **10**, respectively. Concentrations of **13** were measured based on calibration curves, which followed its Q–band absorption at 665 nm. The number of broken alkene bond was quantified by the amount of sensitizer detected in after Soxhlet extraction in methanol. Control experiments demonstrated that the photorelease does not deviate from Beer's Law in the UV–vis detection of sensitizer. Compound **13**: HRMS (+ESI) *m/z* calculated for C₆₆H₈₉N₄O₂₁ [M+H]⁺ 1273.6014, found: 1273.6018. UV–vis (CHCl₃) λ_{max} 399 and 660 nm. No other products were found in solution based on GC/MS and NMR spectroscopy.

Lifetime Measurements

The singlet oxygen lifetime was determined using the output of a Continuum Surelite I-20 Nd:YAG pumped Surelite OPO Plus (type I BBO broadband) laser producing 5-ns pulses of 460 nm light at ~0.2 mJ/pulse and a Hamamatsu H10330B-45 photomultiplier tube at an operating voltage of 650 V. Four-milliliter O₂-saturated solutions of acetone-*d*₆ were used containing 2.5×10^{−4} M rose bengal and 75–150 μm sized silica and ~300–400 μm sized Teflon particles. The ¹O₂ luminescence intensity was monitored at a right angle through an interference filter centered at 1270 nm. The ¹O₂ signal was recorded on a 600 MHz oscilloscope (LeCroy WaveSurfer) and processed with OriginPro software.

RESULTS AND DISCUSSION

O₂ Solubility Enhancements (Table 1)

Table 1 shows that the O₂ solubility increases in the presence of the fluorinated materials (fluorinated silica **6** and Teflon/PVA nanocomposite **8**) compared to native PVA and silica. Table 1 also shows an O₂ solubility increase in Teflon/PVA **8** compared to fluorinated silica **6**, where a 1.2 ppm increase is shown. O₂ solubility increases in fluororous media has been observed previously in fluorinated artificial bloods,⁵⁰ ionic liquids,⁵¹ solvents^{52–54} and biological systems.^{55,56} As we will see the fluorinated solids provide an opportunity to enhance the production of ¹O₂ due to higher local O₂ concentrations.

PEGylated Sensitizer Photorelease from the Fluoropolymers (Figure 6 and Table 2 and Table 3)

Figure 5 and Table 2 show that the percent of PEGylated sensitizer **13** photoreleased into *n*-butanol was higher for Teflon/PVA **10** than for fluorinated silica **7**. The emergence of sensitizer **13** in *n*-butanol was quantified by monitoring its Q-band absorption by UV-vis. Control experiments show that the red light and O₂ were needed to cause the photorelease of **13**. Control experiments also showed that the ester groups of **7**, **10**, and **13** remained intact under dark reaction conditions. We did not find any evidence for ester bond hydrolysis under the conditions wherein all sensitizer release was due to reaction of ¹O₂ with the ethene sites. In terms of loading, the quantity of sensitizer loaded onto **7** was greater than **10**. “High” loading of sensitizer molecules is undesirable especially when porphyrin sites are within the ~15 Å Förster radius producing self-quenching for a photothermal⁵⁷ rather than a photosensitizer polymer. This led us to examine the number and type of bonds on our fabricated surfaces. Table 3 shows the absolute number of Si-OH, C-OH, C-F, C-H groups and sensitizer sites in fluorinated silica **7** and Teflon/PVA **10**. The number of O-H bonds for **10** is 4.8 fold greater than in **7**. For **10** compared to **7**, there are also 1.2-fold more C-F bonds and 1.8-fold less C-H bonds. A driving force in sensitizer adsorption may be the higher number of H-bonding sites in **10** (C-OH 6.2×10²⁰) compared to **7** (Si-OH 1.3×10²⁰). There is a greater number of O-H sites on **10** than **7**, which led us to study the adsorptive affinity of sensitizer **13**.

Testing the Fluorinated Surfaces for Sensitizer Adsorption (Figure 7)

We wondered what levels of unwanted adhering of the PEG sensitizer **13** would occur with our fluoropolymer supports. Figure 7 shows the amount of sensitizer that adsorbs onto fluoropolymers (here “sensitizer-less” **6** and **9** were examined) placed in 10-μM *n*-butanol solution of **13**. The sensitizer’s ability to adsorb to the surfaces was increased for **9** compared to **6**. This can be understood by the tendency of PEGylated compounds to adhere to surfaces with O-H groups. This result is similar with our recent work⁴⁸ where a pheophorbide sensitizer increased its adsorptive affinity for silica with higher quantities of O-H groups. The number of O-H bonds was important to tabulate because they can serve as adsorption sites. Next, we examined the physical quenching of ¹O₂ by the fluoropolymers, where less would be better.

Lifetime Measurements (Table 4)

Table 4 shows that the total rate constants (*k_T*) of ¹O₂ decreased in the presence of fluorinated silica **6**, Teflon/PVA **8**, and Teflon particles compared to native silica. In these experiments, the 1270 nm signal of ¹O₂ was followed with added quantities of the solid particles in acetone-*h*₆ at 25 °C. Native silica, **6**, **8**, and Teflon were used because they lacked the sensitizer heads of **7** and **10**, where a constant concentration of rose bengal was used in the heterogeneous mixtures. Teflon, **6** and **8** contain a high number of C-F oscillators which do not efficiently physically quench ¹O₂ compared to C-H or O-H oscillators due to electronic to vibronic overlap.^{59,60} Consistent with this notion, for native silica the *k_T* value increased by 2–3-fold because of greater numbers of O-H bonds. The “poor” R square values in entries 3 and 4 (Table 4) are not a cause for concern where

Teflon/PVA **8** and Teflon were ground to flakes that were larger and harder to stir as a slurry than the silica particles. Clearly, the data show success in using fluorinated surfaces due to their reduced physical quenching of $^1\text{O}_2$. The low k_T values we observe are encouraging since less wasted $^1\text{O}_2$ by the fluorinated surface is vital to its success for drug photorelease as is described next.

Mechanism of Sensitizer Photorelease from the Teflon-like Surfaces (Figure 8)

A proposed mechanistic explanation of the results is as follows:

(i) O_2 solubility—There is enhanced O_2 solubility with our fluoropolymers than non-fluorinated media so more $^1\text{O}_2$ can be generated. Fluoropolymer surface topology likely relates to O_2 solubility increases based on previous NMR studies⁶¹ where shapes of perfluoro sites and the existence of cavities in the liquid phase dominate over any direct interactions of O_2 with the fluorine atoms, such as charge-transfer interactions.

(ii) Steric Effects—Singlet oxygen is generated by surfaces **7** and **10**, mainly from surface $^3\text{sensitizer}^*$ quenching by O_2 that leads to a dioxetane. We know that the dioxetane is not stable^{62,63} and spontaneously breaks apart at room temperature so the covalent bond between the sensitizer and the surface is lost. As yet increased *kinetic* persistence of dioxetanes through sterics, as has been noted in adamantaneadamantylidene dioxetane which is stable at room temperature⁶⁴ cannot be attributed to our fluoropolymers. But compare parts A and B of Figure 8 where the fluorine groups are oriented differently. Because the fluorinated silica **7** consists of branched fluorosilane (high “aspect ratio”) groups they are more subject to dynamical motion.⁶⁵ Whereas, Teflon/PVA **10** consists of continuous end-on carbon-fluorine chains in which Teflon $-\text{[CF}_2\text{-CF}_2\text{]}_m-$ may also coil into a helix due to repulsion between vicinal fluorine atoms.⁶⁶ The importance of steric interactions of the fluorosilane is consistent with our observation of a reduced photocleavage efficiency in **7** compared to **10**, but this is confounded by factors such as repelling and quenching (described below). Although, it seems obvious, crowding by branched fluorosilanes can prevent $^1\text{O}_2$ accessibility to the ethene site. Indeed, dioxetane experiments come to mind probing mechanical,⁶⁷ cage and chemiluminescence,^{68–70} and dynamical features of the $\sim 1.2\text{-nm}$ length fluorosilane, i.e. nano-heterogeneity, of **7** and **10** but are beyond the scope of the present study.

(iii) Resistance to Adsorption—After the ethene is photooxidized and broken, there is a partition between surface release and adsorption channels. The shuttling⁷¹ or mobility of the sensitizer on the surface prior to departure was not scrutinized with our fluoropolymers. However, the small decrease in the adsorptive affinity of **13** for **10** than **7** is attributed to the higher number of surface O–H groups in **10** than **7**. But does the adsorptive affinity interfere with further ethene photooxidation? Tying up some of sensitizer **13** in an adsorbed state means that autocatalytic-assisted release kinetics are unavailable unlike more repellent hydrophobic sensitizers.⁷²

(iv) Reactive Ethene Sites; Inert Support—For our fluoropolymers **7** and **10**, the ethene sites are photooxidized. The data point to fluorinated media and an increase in τ due

to inefficient radiationless deactivation of $^1\text{O}_2$ by C–F bonds compared to O–H and C–H bonds.^{73–75} Unlike polyfunctionalized compounds or proteins,^{76,77} the reaction center for **7** and **10** is the ethene site. Other than the ethene site, the surfaces do not chemically react with $^1\text{O}_2$, as would be expected of Teflon-like materials that are known to resist oxidation.^{78–81} We find the PEGs groups of **7** and **10** were not susceptible to photooxidation. This is not the case of oxygen radicals, e.g., via autoxidation, where PEG hydroperoxides can form and degrade.⁸²

In summary, we find that the presence of C–F bonds in these materials lead to efficient photocleavage of the PEGylated sensitizer. The Teflon/PVA **10** provides a slight advantage with respect to the sensitizer photorelease application compared to fluorinated silica **7**.

CONCLUSION

We have developed two fluoropolymers and examined their ability to photorelease a PEGylated sensitizer drug. The presence of C–F bonds in the polymers is beneficial for high O_2 solubility, repelling action, and low physical quenching of $^1\text{O}_2$. Designing photoactive repellent surfaces so that drugs are released rather than retained is largely an empirical endeavor and remains a challenge. However, opportunities exist by integrating methodologies from the photosciences to engineering to address the problem.

Future Directions

We have synthesized surfaces that are Teflon-like so a PEGylated sensitizer drug that is otherwise quite sticky can be photoreleased into the surrounding solution, however further advancements could be made. The fluoropolymers could be shaped into device tips to discharge controlled sensitizer and $^1\text{O}_2$ quantities for tissue repair^{83,84} or pointsource photodynamic therapy⁸⁵ *in vivo*. The fluorinated materials provide intriguing possibilities for generating new types of device tips for manual precision in singlet oxygen delivery. Next, we will turn to *in vivo* experiments to examine the fluoropolymers' functional capacity in a mouse tumor model for sensitizer delivery and tumor killing but not biofouling.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Design of fluoropolymer surfaces tailored for $^1\text{O}_2$ -initiated sensitizer drug photorelease reactions. The sensitizer, a chlorin derivative PEGylated with triethylene glycol, was bound to surface OH groups of (A) fluorinated silica (Vycor glass monolith coated with nonafluorosilane), and (B) a Teflon/polyvinyl alcohol nanocomposite. Red light irradiation leads to the reaction of $^1\text{O}_2$ with the ethene, resulting in the formation of a dioxetane. A second step follows with cleavage to release the sensitizer.

Figure 2.
Synthesis of spacer triPEG chlorin **5**.

Figure 3.
Synthesis of sensitizer-conjugated organically to fluorinated silica **7**.

Figure 4. Synthesis of sensitizer-conjugated organically to Teflon/PVA nanocomposite **10** and by-product formation of surface diester sites.

Figure 5. The photooxidation of fluorinated silica **7** and Teflon/PVA nanocomposite **10** leads to the photorelease of sensitizer **13**.

Figure 6. Evolution of the sensitizer **13** which photo-departed away from the fluorinated silica **7** (●) and Teflon/PVA **10** (■) into *n*-butanol solution at 25 °C. Error bars represent the standard deviation obtained from 3 measurements.

Figure 7. Percent of PEGylated sensitizer **13** adsorbed onto fluorinated surfaces [fluorinated silica **6** (●) and Teflon-PVA **9** (■)] in *n*-butanol. The samples were immersed in *n*-butanol, which contained 10 μ M sensitizer **13** and then samples were removed at the indicated times.

Figure 8. Mechanism of photorelease of sensitizer drug bound to (A) fluorinated silica **7**, and (B) Teflon/PVA **10**. The green spheres are fluorine atoms.

Table 1Oxygen Solubility Enhanced by Fluorinated Materials in Solution^a

Solid	ppm	mM
Native silica	14.9±0.4	0.47±0.02
Fluorinated silica 6	16.7±0.4	0.522±0.01
Native PVA	14.9±0.03	0.466±0.001
Teflon/PVA 8	17.9±0.07	0.559±0.003

^aPyrex test tubes contained 5.0 mL of O₂-saturated *n*-butanol with 0.58 g of solid at 25 °C. A pO₂ electrode was used to measure the O₂ solubility. After removing the solids from solution, the O₂ solubility returns to 14.9 ppm (0.466 mM).

Table 2Photorelease of Sensitizer on Fluorinated Surfaces^{a,b}

solid support	Sens Loading (nmol)	sens 13 photocleaved (nmol)	% sens photocleaved	Sens Adsorbed (nmol)	ethene linker bonds broken (nmol)
Fluorinated silica 7	89.4	12.7	68.3	48.4	61.1
Teflon/PVA 10	21.7	6.5	91.7	13.4	19.9

^a Red light from a diode laser was used to photocleave the sensitizer. Absorption spectroscopy was used to quantitate the amount of sensitizer **13** in the surrounding *n*-butanol solution.^b The data show a weights for **7** and **10** normalized to 1.0 g.

Table 3
Absolute Number of Bonds or Functional Groups on the Fabricated Surfaces per Gram^a

solid support	Si-OH	C-OH	C-H	C-F	sens	C-OH: C-F:sens	Si-OH: C-F:sens
fluorinated silica 7	1.3×10^{20}	-	3.5×10^{21}	7.8×10^{21}	5.5×10^{16}	-	2400:142000:1
Teflon/PVA 10	-	6.2×10^{20}	1.9×10^{21}	9.6×10^{21}	1.3×10^{16}	48000:750000:1	-

^a Fluorinated silica **7** contains pendent nonafluorosilane groups. Teflon/PVA **10** contains repeating $-(CF_2-CF_2)_{17}-$ and $-(CH_2-CH(OH))_{17}-$ units. The penetration depth of sensitizer into solid **7** was 0.08 mm and into solid **10** was 1.0 mm.

Table 4

Rates of Reaction with Singlet Oxygen by Native Silica, Fluorinated Silica **6**, Teflon/PVA **8**, and Teflon in Acetone^a

Entry	Sample	k_T (L g ⁻¹ s ⁻¹)	R square
1	Native silica ^a	71±6	0.09
2	Fluorinated silica 6 ^a	27±3	0.99
3	Teflon/PVA 8 ^c	29±9	0.84
4	Teflon ^d	10±8	0.60

^a Heterogeneous mixture of particles [**6** (75–150 μm) and **8** (~300–400 μm)] in acetone-*h*₆ at 25 °C. Average of 2–3 experiments.