# S-Nitrosocysteine-Decorated PbS QDs/TiO₂ Nanotubes for Enhanced Production of Singlet Oxygen

Chalita Ratanatawanate, Amy Chyao, and Kenneth J. Balkus, Jr.*

Department of Chemistry and the Alan G. MacDiarmid NanoTech Institute, The University of Texas at Dallas, 800 West Campbell Road, Richardson, Texas 75080-3021, United States

ⓢ Supporting Information

ABSTRACT: Nitric oxide (NO) is an endogenous diatomic molecule important in regulation of numerous physiological functions. The photorelease of NO in a controlled manner can potentially be used in photodynamic therapy (PDT). We present here a method to combine S-nitrosocysteine with TiO₂ nanotube-doped PbS quantum dots (PbS QDs) as a nitric oxide-releasing vehicle to promote production of singlet oxygen. The PbS QDs with a diameter ~3.6 nm (PbS/TNTs) were attached to the TiO₂ nanotube by using a thiolactic acid linker. S-Nitrosocysteine-decorated PbS/TiO₂ nanotubes were prepared by dipping PbS/TNTs in a cysteine solution followed by nitrosylation. The results suggest that this hybrid nanomaterial is capable of photoreleasing nitric oxide and producing singlet oxygen using near-IR light.
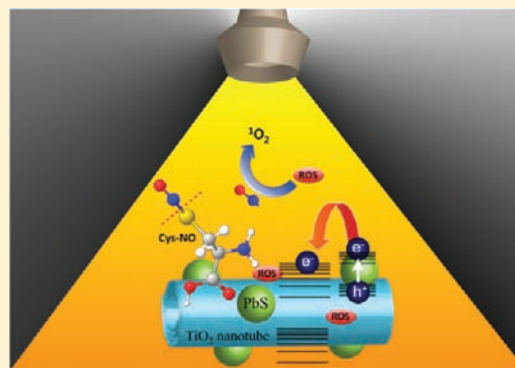
INTRODUCTION

Photodynamic therapy (PDT) is an emerging cancer treatment which may be site-specific, targeting only cells near the photosensitizer (PS), and noninvasive, avoiding the possible complications of surgery.[1] PDT is not affected by multiple drug resistance,[2] and enhances rather than suppresses the body's immune response,[3] overcoming two major problems faced in chemotherapy and radiotherapy. This technology has largely been applied to treatment of surface tumors.[1] In PDT, visible or near-infrared (NIR) light excites the PS molecules, which absorb the energy and then transfer this energy to molecular oxygen, generating reactive oxygen species (ROS) that kill tumor cells.[4] Singlet oxygen ($^1O_2$) is ideal for PDT because, unlike other ROS such as hydrogen peroxide and the hydroxyl radical, $^1O_2$ is not consumed by enzymes produced by tumor cells, including catalase and superoxide dismutase.[5]

In addition to efficiently generating $^1O_2$, an ideal photosensitizing agent should be excited by light wavelengths that are harmless and capable of deeper penetration into the body. The penetration of light is affected by many factors. For example, the light can be scattered at membranes, nuclei, etc., or absorbed by water, melanin, and hemoglobin.[6] The maximum of skin penetration depth appears in the range of 600–1100 nm which is the so-called "phototherapeutic window".[6–8] Therefore, a photosensitizing agent should efficiently absorb in the phototherapeutic window. In addition to using a dye molecule that sensitizes the triplet to singlet O₂ photocoversion in the near-IR, it may be possible to use chemicals that naturally form $^1O_2$ in the body to enhance the photochemical reduction of singlet oxygen. Nitric oxide generates $^1O_2$ in the body by reacting with reactive oxygen species.[9,10] This may account for in part the anticancer effect of nitric oxide.[11–13] Nitric oxide (NO)

has been well documented as a biological mediator in many biological processes, including neurotransmission, vascular smooth muscle relaxation, immune response, and vasodilatation.[14–17] Depending on the dose, NO can be therapeutic or toxic.[18–21] Therefore, there is interest in the design of controllable NO delivery systems. One approach is to use light as an on/off switch to precisely control the NO concentration. Photorelease of NO can be faster than other releasing mechanisms such as spontaneous thermolysis or metabolic transformation.[22] Various compounds have been tested as photocatalytic NO donors, including diazeniumdiolates, metal complexes, and S-nitrosothiols. Diazeniumdiolates have been shown to produce potentially carcinogenic nitrosamines and oxygen-substituted nitrites upon photorelease,[23] and metal complexes are limited by oxidation, thermal decomposition, and nonspecific NO release.[24–26] Surface-containing amino acids such as cysteines are implicated in many prolonged processes involving NO. The S-nitrosothiols (RSNOs) have been shown to be effective NO donors and may function as bioreservoirs for NO utilized by the body.[27] High quantum yields of NO can be achieved by photolysis of the S—NO bond.[27,28] RSNOs show great promise in PDT, as functionalization onto a photosensitizer can increase the NO photorelease 9-fold.[29] Therefore, the combination of S-nitroso-cysteine (cysteine—NO), which exhibits the above advantages of the RSNOs with a photosensitizer, may enhance $^1O_2$ production.[30]

Photoexcitation of titanium dioxide (anatase) has been shown to generate electron—hole pairs and, by redox reactions, can produce ROS, including hydroxyl radicals, hydrogen peroxide,

superoxide, and singlet oxygen.[31,32] However, there are two problems with TiO_2 as a PDT agent. (1) The band gap (3.2 eV) is too large to use near-IR light where the suitable band gap for use in the phototherapeutic window is in the range of 1.1−2.1 eV and (2) the generated $^1O_2$ has been shown to not diffuse away from the oxide surface in contrast to other ROS.[33] These ROS have been shown to react with NO in vivo to generate $^1O_2$ and peroxides, such as peroxynitrite.[9,34] Therefore, functionalization of a stable photocatalytic NO donor onto TiO_2 could provide a mechanism for generating $^1O_2$ away from the TiO_2 surface. TNTs can be catalytically active in the phototherapeutic window when they are doped with PbS QDs.[31,35]

Hence, the goal of the present work was to create a photosensitizing system which generates $^1O_2$ in the phototherapeutic window. High surface area TiO_2 nanotubes were synthesized and decorated with PbS quantum dots that absorb in the near-IR. The PbS/TNTs were then functionalized with cysteine−NO to enhance the production of singlet oxygen. Photorelease of NO was verified at wavelengths >600 nm. The generation of singlet oxygen was also confirmed by using a $^1O_2$ specific trap, sodium 1,3-cyclohexadiene-1,4-diethanoate.[36]

■ EXPERIMENTAL SECTION

Materials. P25 TiO_2 nanoparticles (80% anatase and 20% rutile) were donated by Evonik-Degussa. Nitric oxide and argon were purchased from Airgas (c.p. grade). Thiolactic acid (<95%) and sodium sulfide nonahydrate (<98%, ACS reagent) were purchased from Sigma-Aldrich, while lead nitrate (<99%, ACS reagent) was purchased from J. T. Baker, and L-cysteine was purchased from SAFC. Sodium 1,3-cyclohexadiene-1,4-diethanoate (CHDDE) was synthesized according to a published procedure.[37]

Synthesis of TiO_2 Nanotubes. TiO_2 nanotubes were prepared by hydrothermal synthesis according to a literature procedure.[38] A mixture of 0.5 g of P25 TiO_2 nanoparticles and 30 mL of 10 M NaOH aqueous solution was stirred at room temperature for 10 min. The mixture was then transferred to a Teflon-lined autoclave and heated at 150 °C for 24 h. The resulting white precipitate was stirred overnight with 0.1 M HCl and DI H_2O to perform a proton exchange to a pH of 7 and then dried at 90 °C for 10 h followed by annealing in air at 350 °C for 75 min.

Fabrication of PbS QD-Doped TiO_2 Nanotubes. TiO_2 nanotubes were pretreated with a 0.3 M thiolactic acid aqueous solution for 30 min and then dried at 50 °C for 10 h. A 25 mL amount of 0.2 M $Pb(NO_3)_2$ solution was then mixed with the pretreated TiO_2 nanotubes for 15 min to allow Pb^{2+} ions to bind to the thiol group of thiolactic acid. Then the TiO_2 nanotubes were combined with 25 mL of a 0.5 M Na_2S aqueous solution for 15 min to form the PbS QDs. The excess reagent after each deposition step was removed by washing with DI water.

Incorporation of L-Cysteine onto PbS/TiO_2 Nanotubes. A 0.25 g amount of PbS/TiO_2 nanotubes was stirred in a 0.6 M L-cysteine aqueous solution. The pH was then adjusted to 4 using a 0.1 M HCl solution. The product was centrifuged, and the precipitate was dried for 10 h at 60 °C.

Nitric Oxide Loading and Release. A 150 mg amount of PbS/TiO_2 nanotubes containing L-cysteine was placed in a 100 mL high pressure reactor. The reactor was filled with NO gas under 4 atm of pressure for 4 h. Afterward, the product was purged with argon to remove the free NO. As-synthesized PbS/TNTs with cysteine−NO sample (PbS/TNTs/Cys−NO) was protected from light during the synthesis process to ensure that NO remained bonded to the cysteine. To release the NO from PbS/TNTs/Cys−NO powder, the samples were irradiated in a dark box using a water-cooled 450 W Hanovia quartz mercury lamp with an argon purge. For the near-IR wavelengths, a

Ray-sorb reactor (optical filtration at wavelength <600 nm) was used. The argon gas carried the released NO into a 10 mL vial of deionized water, forming nitrite solution, from which a 300 μL aliquot was collected in 15 min intervals for 90 min. All experiments were done in triplicate. In a 20 mL scintillation vial, 100 μL of Griess Reagent, 100 μL of the nitrite containing sample, and 2.8 mL of DI H_2O were mixed and allowed to incubate for 30 min. UV−vis spectra of these samples were recorded at λ = 543 nm against a reference sample of 100 μL Griess Reagent with 2.9 mL of DI H_2O.

Singlet Oxygen Generation and Detection. A 80 mg amount of TNTs/Cys−NO and of PbS/TNTs/Cys−NO were placed in separate quartz reactors containing 100 mL of 1.6×10^{-4} M CHDDE aqueous solution. The system was irradiated with the Hanovia quartz mercury lamp using a Ray-sorb filter while stirring, and samples were collected in 15-min intervals from each reactor for 90 min. Collected samples were centrifuged, and the top liquid was collected into vials. UV−vis spectra were collected, and the concentration of CHDDE was determined from the absorbance at 270 nm.

■ RESULTS AND DISCUSSION

PbS/TNTs Combined with Cysteine−NO. Open-ended TiO_2 nanotubes with a 3−5 nm inner diameter were synthesized using the hydrothermal process first reported by Kasuga and co-workers.[38] The band gap of TNTs prepared by this method have been reported to be in the range of 3.3−3.87 eV,[39,40] meaning that only light with wavelengths <350 nm can excite the TNTs. The variation in reported band gap likely arises from compositional variance, which can include hydrogen and/or sodium titanate, TiO_2−B and anatase. Many studies reported that the mixture of TiO_2−B and anatase can be found after the H-exchange followed by annealing processes.[41,42] In our case, anatase is the major phase. In the present study, the anatase phase is the desirable phase compared to other TiO_2 phases (rutile and brookite) because it exhibits the highest photocatalytic activity. To access the near-IR, PbS QDs with a diameter 3−4 nm were grown on the TNTs by controlling the concentration of thiolactic acid linkers.[35] The excitation absorption of as-synthesized PbS QDs is around 760 nm, which falls in the phototherapeutic window.[35] The TEM image of the TNTs (Figure 1a) shows that the multiwall TNTs have 3−5 nm and 8−10 nm inner and outer diameters respectively, while the lengths of TNTs are several hundred nanometers. The TEM image of TNTs after deposition of the PbS QDs shown in Figure 1b indicates that the PbS QDs grow on both the inner and outer surface of the TNT pore. The PbS QDs located inside the TNT pore enhance the photocatalytic activity of the TNTs but to a lesser extent than the outside QDs because of partial pore blockage by the QDs.[31] The size distribution of the PbS QDs is 3.6 ± 0.2 nm which corresponds to a band gap of 1.63 eV. The PbS/TNTs were functionalized with cysteine before exposure to NO gas in the presence of oxygen to form S-nitrosocysteine. The process for the preparation of PbS/TNTs with cysteine−NO is outlined in Scheme 1. First, the TiO_2 nanotubes were prepared by a hydrothermal process. Then the PbS QDs were deposited on the surface of the TNTs by using thiolactic acid linkers.[35] Cysteine molecules were bound to the PbS/TNTs by adding cysteine to the PbS/TNTs under acidic conditions (pH ~ 4). S-Nitrosocysteines were formed on the surface of the PbS/TNTs by reacting the bound cysteine with nitric oxide. It should be noted that pure nitric oxide does not react with thiols. However, in the presence of trace amounts of oxygen, the NO can react with O_2 to form N_2O_3
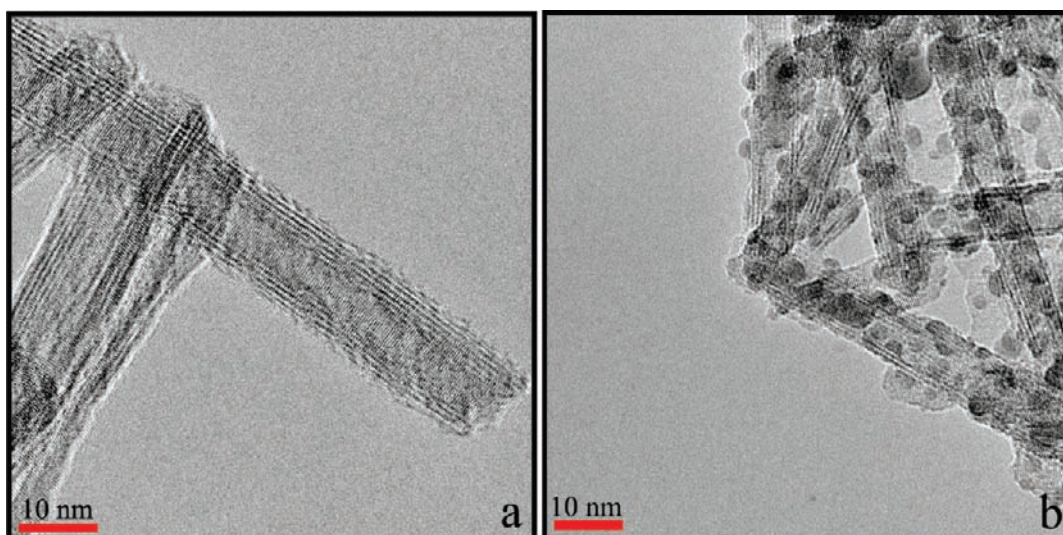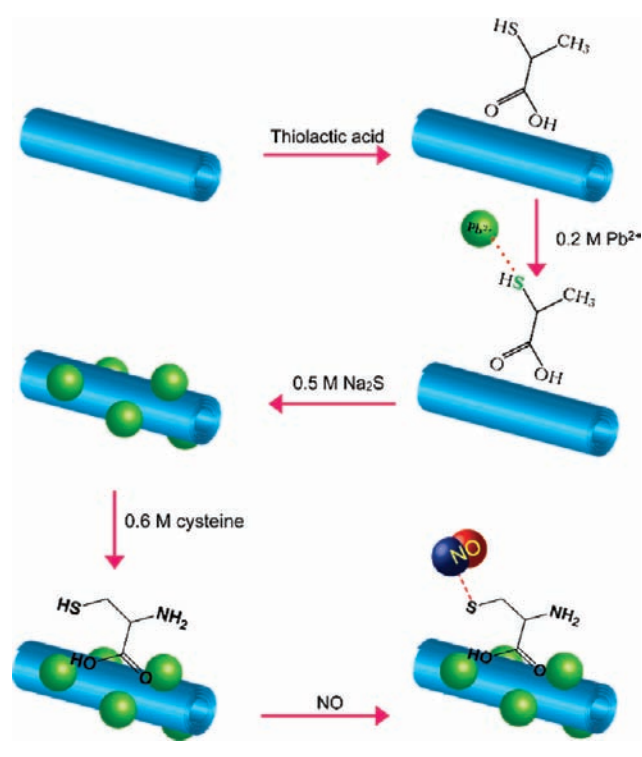
Figure 1. TEM images of photocatalysts: (a) TiO_2 nanotubes and (b) PbS-doped TiO_2 nanotubes.

Scheme 1. Preparation of PbS/TNTs with Cysteine—NO

Figure 2. FT-IR spectrum: (a) TNTs, (b) cysteine-treated TNTs, (c) Cys—NO/TNTs before NO release, and (d) Cys—NO/TNTs after NO release.

which readily reacts with thiols, resulting in formation of RSNO.[43] The formation of *S*-nitrosocysteine was followed using FT-IR spectroscopy. The FT-IR spectrum of the bare TNTs (Figure 2a) indicates an interaction between the Ti ions and molecular water (1630 and 3380 cm^{-1}). After treatment of the TNTs with an aqueous cysteine solution, the bands characteristic of CH_2 and SH stretching vibrations appear at 2983 and 2562 cm^{-1}, confirming the presence of cysteine.[44] The carboxylate group of cysteine reacts with the OH group on the surface of the TNTs resulting in a new band at 1506 and 1400 cm^{-1}, assigned to antisymmetric and symmetric vibrations of the carboxylate
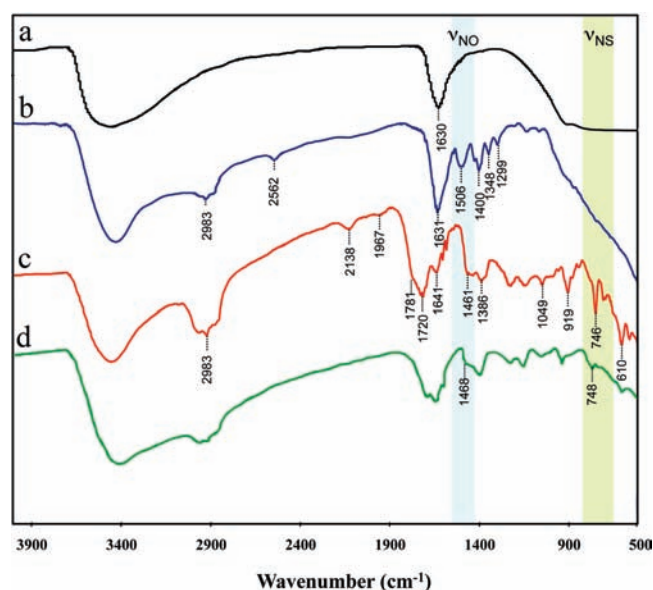
salts.[45] After infusion of NO, the formation of cysteine—NO can be verified from the bands at 1460—1500 and 610—700 cm^{-1}, corresponding to the ν_{NO} and ν_{NS}, respectively, as shown in Figure 2c.[46,47] These results show a close agreement with FT-IR spectra reported for *S*-nitrosothiols.[48] The band at 2138 cm^{-1} is characteristic of N_2O which disappears after purging with argon. Meanwhile, the absorption of NO on the TNT surface was also observed at 1967 cm^{-1} (ν_{NO}, Ti^{3+}—NO).[49] The FT-IR spectra after photorelease of NO (Figure 2d) shows a significant decrease in the ν_{NO} and ν_{NS} bands, indicating that S—NO bond was broken and that NO was released from the system. Note that the decrease in the ν_{NO} and ν_{NS} bands after photorelease of NO is the same for PbS/TNTs/Cys—NO (Supporting Information).
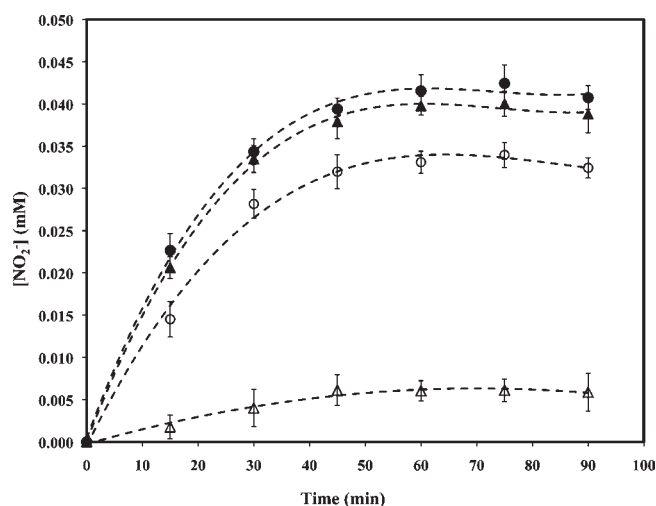
Figure 3. Photorelease profile of PbS/TNTs/Cys—NO (●), TNTs/Cys—NO (▲), PbS/TNTs/Cys—NO with Ray-sorb filter (○), and TNTs/Cys—NO with Ray-sorb filter (△).

Figure 4. Plot of CHDDE relative concentration versus irradiation time catalyzed by TNTs/Cys—NO (▲) and PbS/TNTs/Cys—NO (●) in the quartz reactor, and TNTs/Cys—NO (△) and PbS/TNTs/Cys—NO (○) in the Ray-sorb reactor.

Photorelease of Nitric Oxide. Irradiation of S-nitrosothiols (RSNOs) with UV light induces the homolytic cleavage of S—N bond in RSNOs, leading to the release of NO.[27,30,50,51] Upon UV light exposure, S-nitrosothiols can decompose to an NO and a RS radical.[52] These products can either recombine to form S-nitrosothiols (further decay to free NO during photolysis) or the RS$^{\bullet}$ can undergo dimerization with another thiol group, yielding a disulfide (RSSR).[48,50,52,53] S-nitrosothiols exhibit two absorption peaks in the range of 300—350 nm and 530—560 nm which corresponded to the $n_O{\rightarrow}\pi^*$ and $n_N{\rightarrow}\pi^*$ transitions, respectively.[48,50] Photocleavage of the S—NO bond can be achieved by promoting the $n_O{\rightarrow}\pi^*$ transition.[52] In this study, the 450 W mercury arc lamp used provides enough energy to break the S—N bond (S—N bond dissociation energy has been reported to be 20 to 32 kcal mol^{-1}),[54,55] resulting in NO release. A Ray-sorb reactor (optical filtration at wavelength <600 nm) was also used to better mimic the wavelength range of phototherapeutic window. A plot of the concentration of NO photoreleased versus time is shown in Figure 3. The amount of nitric oxide released from the PbS/TNTs with cysteine—NO is slightly higher than that released from only TNTs combined with cysteine—NO (TNTs/Cys—NO). However, when the samples are irradiated in a Ray-sorb reactor, the amount of NO released from the pure TNTs dropped dramatically because the filtered light does not provide enough energy for S—NO bond cleavage. Any NO released from the TNTs/Cys—NO comes from the nitric oxide that was weakly absorbed on the surface of the TiO$_2$. In the case of PbS/TNTs/Cys—NO, the photorelease of NO was still observed in the Ray-Sorb reactor. Thus, at longer wavelengths the mechanism of NO release likely involves reaction of ROS[57] and/or energy transfer from the QDs.[58] The NO release was also slower because the filtered light has a lower intensity above 600 nm. These results confirm that PbS QDs (~3.6 nm) help promote the release of NO from RSNO when irradiated in the phototherapeutic window probably by energy transfer and/or by reaction of the ROS generated on TiO$_2$ with the S-nitrosocysteine.

Photogenerated Singlet Oxygen. Singlet oxygen is the most important ROS generated for photodynamic therapy. In PDT, the photosensitizer should be able to produce singlet oxygen using near-IR light. Photogenerated singlet oxygen can
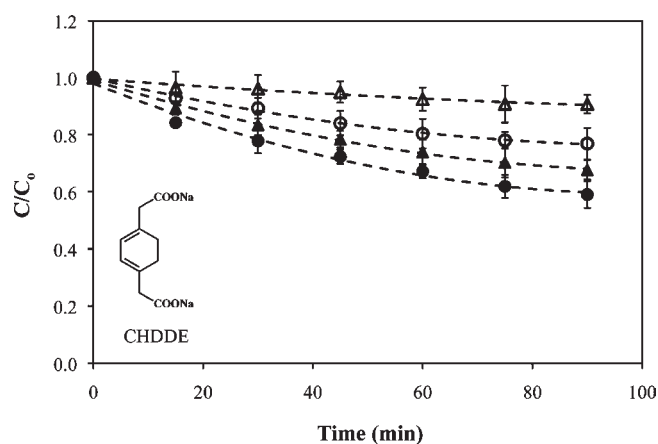
be monitored directly or indirectly by using a trap. The ideal properties of a $^1O_2$ trap for this study include (1) photostability, (2) highly reactive toward $^1O_2$ (not other ROS), (3) water-solubility, and (4) transparency in the UV and near-IR to avoid photosensitization by the trap itself. Nardello and co-workers reported the synthesis of sodium 1,3-cyclohexadiene-1,4-diethanoate (CHDDE) which meets all the requirements for a singlet oxygen trap.[37] The CHDDE structure (Figure 4) involves a 1,3-diene which can react with $^1O_2$ by a [4 + 2] cycloaddition, yielding a stable endoperoxide and a hydroperoxide.[56] Thus, the photogenerated singlet oxygen can be measured by following the photodegradation of CHDDE using UV—vis spectroscopy. CHDDE is stable under irradiation in the presence of TNTs and PbS/TNTs (without Cys—NO), and the amount of CHDDE absorbed on the surface of the TNTs and PbS/TNTs was determined to be negligible (data not shown). The results in Figure 4 show that the photooxidation of CHDDE catalyzed by PbS/TNTs/Cys—NO is higher than for TNTs/Cys—NO without quantum dots. This result suggests that PbS/TNTs/Cys—NO can produce more singlet oxygen upon irradiation with UV—vis light. After the light below 600 nm was filtered, the TNTs/Cys—NO did not catalyze the photodecomposition of CHDDE; meanwhile the production of $^1O_2$ was still observed for PbS/TNTs/Cys—NO. Photodecomposition of CHDDE can be approximated as pseudo-first-order kinetics. The linear relationship between $-\ln(C/C_o)$ and irradiation time is shown in Supporting Information (Figure S1). The amount of singlet oxygen produced with this system (after filtering out the light <600 nm), estimated from the amount of CHDDE consumed at 90 min irradiation time is 2.63×10^{-8} mol·min^{-1}. Because the PbS QDs (~ 3.6 nm) absorb at ~760 nm (in the target PDT window), electron transfer to the TNTs can occur to generate ROS. H$_2$O$_2$ has been reported to decompose S-nitrosocysteine[57] such that the photogenerated ROS could react directly with the nitrosothiol or with the photoreleased NO. The formation of peroxynitrite was previously not observed at neutral pH for the reaction of S-nitrosocysteine and H$_2$O$_2$ but could not be ruled out. Ford and co-workers reported that quantum dots could promote the photorelease of NO from NO photodonors through photoinduced energy transfer,[58] and this may be possible for our system. While cysteine may bind to both TNTs and PbS it is not

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known if SNO adducts form on the QDs. Nevertheless, the photochemical production of $^1O_2$ can be enhanced with a combination of *S*-nitrosocysteine and PbS QD/TNTs using PDT relevant wavelengths.

CONCLUSION

A hybrid nanoparticle, composed of a nitric oxide photodonor (cysteine−NO), a photosensitizer (PbS QDs), and a photocatalyst (TiO$_2$ nanotubes), can be used to enhance the production of singlet oxygen using visible light in the photodynamic therapy window. This type of photocatalyst may have potential as a next generation photodynamic therapy agent. Because PbS may present health and environmental issues, the synthesis of less toxic quantum dots for this system such as CuS, FeS$_2$ and Ag$_2$S is in progress.

ASSOCIATED CONTENT

ⓢ Supporting Information. Complete ref 21. Figures S1 and S2. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
balkus@utdallas.edu

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REFERENCES

(1) Juzenas, P.; Chen, W.; Sun, Y. P.; Coelho, M. A. N.; Generalov, R.; Generalova, N.; Christensen, I. L. *Adv. Drug Delivery Rev.* **2008**, *60* (15), 1600–1614.

(2) Reeves, K. J.; Reed, M. W. R.; Brown, N. J. *J. Photochem. Photobiol., B* **2009**, *95* (3), 141–147.

(3) Castano, A. P.; Mroz, P.; Hamblin, M. R. *Nat. Rev. Cancer* **2006**, *6* (7), 535–545.

(4) Chatterjee, D. K.; Fong, L. S.; Zhang, Y. *Adv. Drug Delivery Rev.* **2008**, *60* (15), 1627–1637.

(5) Cai, R.; Kubota, Y.; Shuin, T.; Sakai, H.; Hashimoto, K.; Fujishima, A. *Cancer Res.* **1992**, *52* (8), 2346–2348.

(6) Szacilowski, K.; Macyk, W.; Drzewiecka-Matuszek, A.; Brindell, M.; Stochel, G. *Chem. Rev.* **2005**, *105* (6), 2647–2694.

(7) DeRosa, M. C.; Crutchley, R. J. *Coord. Chem. Rev.* **2002**, *233–234*, 351–371.

(8) Vogel, A.; Venugopalan, V. *Chem. Rev.* **2003**, *103* (2), 577–644.

(9) Noronha-Dutra, A. A.; Epperlein, M. M.; Woolf, N. *FEBS Lett.* **1993**, *321* (1), 59–62.

(10) Khan, A. U. *J. Biolumin. Chemilumin.* **1995**, *10* (6), 329–333.

(11) Hirst, D.; Robson, T. *Curr. Pharm. Design* **2010**, *16* (4), 411–420.

(12) Sortino, S. *Chem. Soc. Rev.* **2010**, *39* (8), 2903–2913.

(13) Mocellin, S. *Curr. Cancer Drug Targets* **2009**, *9* (2), 214–236.

(14) Vincent, S. R. *Prog. Neurobiol.* **2010**, *90* (2), 246–255.

(15) Colasanti, M.; Persichini, T.; Venturini, G. *Nitric Oxide* **2010**, *23* (2), 94–100.

(16) Lundberg, J. O.; Weitzberg, E. *Biochem. Biophys. Res. Commun.* **2010**, *396* (1), 39–45.

(17) Tota, B.; Quintieri, A. M.; Angelone, T. *Curr. Med. Chem.* **2010**, *17* (18), 1915–1925.

(18) Tsumori, M.; Tanaka, J.; Koshimura, K.; Kawaguchi, M.; Murakami, Y.; Kato, Y. *Acta Biochim. Pol.* **2002**, *49* (1), 139–144.

(19) Efferth, T. *Curr. Drug Targets* **2006**, *7* (3), 237–238.

(20) Chakrapani, H.; Kalathur, R. C.; Maciag, A. E.; Citro, M. L.; Ji, X.; Keefer, L. K.; Saavedra, J. E. *Bioorg. Med. Chem.* **2008**, *16* (22), 9764–9771.

(21) Mijatovic, S.; Maksimovic-Ivanic, D.; Mojic, M.; Malaponte, G.; Libra, M.; Cardile, V.; Miljkovic, D.; Harhaji, L.; Dabideen, D.; Cheng, K. F.; Bevelacqua, Y.; Donia, M.; Garotta, G.; Al-Abed, Y.; Stosic-Grujicic, S.; Nicoletti, F. *Nitric Oxide* **2008**, *19* (2), 177–183.

(22) Barone, M.; Mascali, A.; Sortino, S. *New J. Chem.* **2008**, *32* (12), 2195–2200.

(23) Srinivasan, A.; Kebede, N.; Saavedra, J. E.; Nikolaitchik, A. V.; Brady, D. A.; Yourd, E.; Davies, K. M.; Keefer, L. K.; Toscano, J. P. *J. Am. Chem. Soc.* **2001**, *123* (23), 5465–5472.

(24) Rose, M. J.; Fry, N. L.; Marlow, R.; Hinck, L.; Mascharak, P. K. *J. Am. Chem. Soc.* **2008**, *130* (27), 8834–8846.

(25) Rose, M. J.; Mascharak, P. K. *Coord. Chem. Rev.* **2008**, *252* (18−20), 2093–2114.

(26) Ford, P. C. *Acc. Chem. Res.* **2008**, *41* (2), 190–200.

(27) Shishido, S. M.; Seabra, A. B.; Loh, W.; De Oliveira, M. G. *Biomaterials* **2003**, *24* (20), 3543–3553.

(28) Aravindakumar, C. T.; Veleeparampil, M. M.; Aravind, U. K. *Adv. Phys. Chem.* **2009**, *2009*, 1–5.

(29) Singh, R. J.; Hogg, N.; Joseph, J.; Kalyanaraman, B. *FEBS Lett.* **1995**, *360* (1), 47–51.

(30) Al-Sa'Doni, H.; Ferro, A. *Clin. Sci.* **2000**, *98* (5), 507–520.

(31) Ratanatawanate, C.; Tao, Y.; Balkus, K. J., Jr. *J. Phys. Chem. C* **2009**, *113* (24), 10755–10760.

(32) Konaka, R.; Kasahara, E.; Dunlap, W. C.; Yamamoto, Y.; Chien, K. C.; Inoue, M. *Free Radic. Biol. Med.* **1999**, *27* (3−4), 294–300.

(33) Tachikawa, T.; Majima, T. *Langmuir* **2009**, *25* (14), 7791–7802.

(34) Fukuto, J. M.; Ignarro, L. J. *Acc. Chem. Res.* **1997**, *30* (4), 149–152.

(35) Ratanatawanate, C.; Xiong, C.; Balkus, K. J., Jr *ACS Nano* **2008**, *2* (8), 1682–1688.

(36) Nardello, V.; Brault, D.; Chavalle, P.; Aubry, J. M. *J. Photochem. Photobiol., B* **1997**, *39* (2), 146–155.

(37) Nardello, V.; Azaroual, N.; Cervoise, I.; Vermeersch, G.; Aubry, J. M. *Tetrahedron* **1996**, *52* (6), 2031–2046.

(38) Kasuga, T.; Hiramatsu, M.; Hoson, A.; Sekino, T.; Niihara, K. *Adv. Mater.* **1999**, *11* (15), 1307–1311.

(39) Bavykin, D. V.; Gordeev, S. N.; Moskalenko, A. V.; Lapkin, A. A.; Walsh, F. C. *J. Phys. Chem. B* **2005**, *109* (18), 8565–8569.

(40) Jiang, Z.; Yang, F.; Luo, N.; Chu, B. T. T.; Sun, D.; Shi, H.; Xiao, T.; Edwards, P. P. *Chem. Commun.* **2008**, *47*, 6372–6374.

(41) Morgado, E., Jr; Jardim, P. M.; Marinkovic, B. A.; Rizzo, F. C.; De Abreu, M. A. S.; Zotin, J. L.; Araujo, A. S. *Nanotechnology* **2007**, *18*, 49.

(42) Beuvier, T.; Richard-Plouet, M.; Mancini-Le Granvalet, M.; Brousse, T.; Crosnier, O.; Brohan, L. *Inorg. Chem.* **2010**, *49* (18), 8457–8464.

(43) Williams, D. L. H. *Acc. Chem. Res.* **1999**, *32* (10), 869–876.

(44) Dong, A.; Caughey, W. S. *Methods Enzymol.* **1994**, *232*, 139–175.

(45) Bieri, M.; Burgi, T. *J. Phys. Chem. B* **2005**, *109* (20), 10243–10250.

(46) Perissinotti, L. L.; Estrin, D. A.; Leitus, G.; Doctorovich, F. *J. Am. Chem. Soc.* **2006**, *128* (8), 2512–2513.

(47) Roy, B.; D'Hardemare, A. D. M.; Fontecave, M. *J. Org. Chem.* **1994**, *59* (23), 7019–7026.

(48) Szacilowski, K.; Stasicka, Z. *Prog. React. Kinet. Mech.* **2001**, *26* (1), 1–58.

(49) Debeila, M. A.; Coville, N. J.; Scurrell, M. S.; Hearne, G. R. *Appl. Catal., A* **2005**, *291* (1−2), 98–115.

(50) Gow, A.; Doctor, A.; Mannick, J.; Gaston, B. *J. Chromatogr., B* **2007**, *851* (1−2), 140–151.

(51) Adam, C.; García-Río, L.; Leis, J. R.; Ribeiro, L. *J. Org. Chem.* **2005**, *70* (16), 6353–6361.

(52) Shishido, S. M.; De Oliveira, M. G. *Photochem. Photobiol.* **2000**, *71* (3), 273–280.

(53) Wang, P. G.; Xian, M.; Tang, X.; Wu, X.; Wen, Z.; Cai, T.; Janczuk, A. J. *Chem. Rev.* **2002**, *102* (4), 1091–1134.

(54) Lu, J. M.; Wittbrodt, J. M.; Wang, K.; Wen, Z.; Schlegel, H. B.; Wang, P. G.; Cheng, J. P. *J. Am. Chem. Soc.* **2001**, *123* (12), 2903–2904.

(55) Bartberger, M. D.; Mannion, J. D.; Powell, S. C.; Stamler, J. S.; Houk, K. N.; Toone, E. J. *J. Am. Chem. Soc.* **2001**, *123* (36), 8868–8869.

(56) Nardello, V.; Brault, D.; Chavalle, P.; Aubry, J. M. *J. Photochem. Photobiol., B* **1997**, *39* (2), 146–155.

(57) Coupe, P. J.; Williams, D. L. H. *J. Chem. Soc., Perkin Trans. 2* **1999**, *6*, 1057–1058.

(58) Neumann, D.; Ostrowski, A. D.; Mikhailovsky, A. A.; Absalonson, R. O.; Strouse, G. F.; Ford, P. C. *J. Am. Chem. Soc.* **2008**, *130* (1), 168–175.