

Two Colors of Light Are Needed to Break Bonds and Release Small Molecules from the Surface of SiO₂–Au Core–Shell Nanoparticles

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S Supporting Information

ABSTRACT: The photothermal effect is not able to break bonds and release small molecules from the surface of SiO₂–Au core–shell nanoparticles unless the nanosystem is first exposed to visible light. Only after this light triggers the ring-opening reaction of dithienylethene chromophores attached to the surface of the nanoparticles can the heat generated by the NIR light induce reverse Diels–Alder reactions.

It should be unnecessary to convince a chemist that heat and light are two of the most versatile stimuli to induce chemical reactions and that processes from the synthesis of fine chemicals and polymers to lithography and drug delivery would be rendered almost useless without the ability to control them. The more recent use of nanoparticles and the surface plasmon effect to convert visible and near-infrared (NIR) light into heat has enabled many new technologies providing the user a heightened level of control of thermal processes in complex environments such as nanoscale devices and live cells. This photothermal effect has been effectively utilized in gene therapy and drug delivery,^{1–5} photodynamic therapy,^{6–9} chemical synthesis,¹⁰ and photolithography.¹¹

Our interests are to introduce “gating” mechanisms into nanosystems such as solid gold or gold–shell nanoparticles, which will offer the ultimate “on-command” control over where and when reactions on the surface of the nanoparticles occur. The true usefulness of the photothermal effect to break bonds and release small molecules will be realized by adding a second stimulus, which will prevent premature thermolysis and allow better spatial control. This concept is well appreciated by those researching molecular logic gates, where, for example, much like an AND gate, two input stimuli are required to achieve the desired output, in this case, bond-breaking and release.¹²

We and the group of Stefan Hecht have demonstrated the use of UV and visible light to “gate” Diels–Alder reactions in monomeric^{13–15} and polymeric materials.¹⁶ This was achieved by inducing reversible ring-closing and ring-opening reactions in diarylethene molecular backbones,^{17,18} one of the most versatile photoresponsive chromophores. In this communication, we demonstrate how specifically tailored diarylethenes can provide the control of the release of small molecules from the surface of nanoparticles by using two different colors of light.

Our proof-of-concept approach to use two colors of light to control the photorelease of small molecules from the surface of nanoparticles is illustrated in Scheme 1 and is based on the photoresponsive dithienylethene chromophore **1_o**. This chro-

mophore is prepared through the Diels–Alder reaction of maleimide **2** and the dithienylfuran **3**, which is reversible at elevated temperatures. The ligand **1_o** can be induced to undergo ring-closing (**1_o** → **1_c**) and ring-opening reactions (**1_c** → **1_o**) when exposed to UV and visible light, respectively.

Compound **1_o** can also be used to decorate SiO₂–Au core–shell nanoparticles through two Au–S bonds and can be either forced to undergo a reverse Diels–Alder reaction to release **3** when the nanosystem is exposed to NIR light, or a reversible, photochemical ring-closing reaction as in the case of the free ligand **1_o**. The key aspect to this design is the fact that the ring-closed isomers (**1_c** and **1_c**-NP) lack the cyclohexene rings required for the reverse Diels–Alder reactions and are, therefore, “locked” even when the systems are exposed to NIR light to trigger the photothermal effect.

Only after they are ring-opened with visible light can the heat (ambient or generated through the photothermal effect) trigger the spontaneous fragmentation of the ligand and release of **3**. Both visible and NIR light are required for the release process to occur.

The photochromic thiolated ligand **1_o** was prepared in good yield as proposed (Scheme 1) through the [4 + 2] cycloaddition of dithienylfuran **3** and maleimide **2**. The synthesis and characterization of all new compounds are described in the Supporting Information. Compound **1_o** undergoes ring-closing as expected (**1_o** → **1_c**) when a CH₃CN solution of it is exposed to 312 nm light (Figure 1b),¹⁹ as is evident by the disappearance of the strong absorption band corresponding to the ring-open isomer ($\lambda_{\text{max}} = 258$ nm) and the simultaneous growth of longer wavelength bands ($\lambda_{\text{max}} = 350$ and 524 nm) that correspond to the ring-closed isomer (**1_c**). The latter band for **1_c** explains why the initially colorless solution of **1_o** turns dark red during the photochemical reaction. These spectral changes are typical for the dithienylethene derivatives and parallel to those observed for our original Diels–Alder systems.¹⁴ In the case of the ring-closing of the free ligand (**1_o** → **1_c**), the spectral changes stop after 60 s of irradiation and produce a photostationary state containing 86% of the ring-closed isomer (**1_c**) as measured by comparing the respective signals in the ¹H NMR spectra.²⁰ Exposing this red solution to visible light of wavelengths greater than 434 nm triggers the photocycloreversion reaction (**1_c** → **1_o**) and regenerates the original spectrum. This ring-closing/ring-opening process can be carried out many times without observable degradation.²⁰

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Scheme 1. Reversible Light-Induced Cyclization Reaction of the Dithienylethene Backbone between Two Isomers That Have Different Electronic Connectivity between the Two Arms

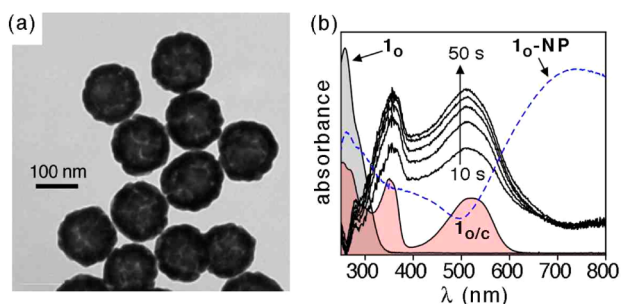
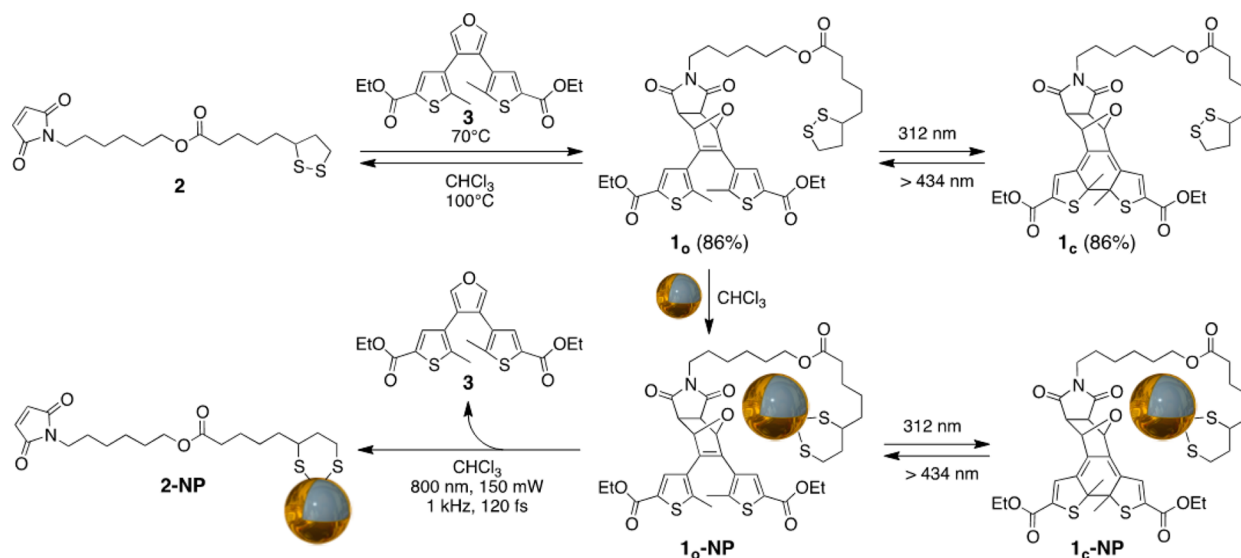


Figure 1. (a) TEM image of a CHCl_3 dispersion of chromophore-decorated SiO_2 -Au core-shell nanoparticles 1_o -NP (0.52 mg/mL) (average diameter = 134 ± 7 nm, average shell thickness = 18 ± 2 nm). (b) UV-vis absorption spectrum of a CHCl_3 solution of the photoresponsive core-shell nanoparticles 1_o -NP (0.52 mg/mL) before irradiation (broken blue line) and the difference spectra after irradiation with 312 nm light every 10 s for a total of 50 s (black lines). The spectra for a CH_3CN solution of the free ligand 1_o (50 μM) (gray shaded area) and the photostationary state containing 1_o and 1_c (red shaded area) are shown for comparison.^{2,31}

The photoresponsive nanosystems (1_o -NP) were prepared by first transferring aqueous soluble SiO_2 -Au core-shell nanoparticles (136 ± 9 nm)^{21–26} to CHCl_3 ²⁷ by ligand exchange with octadecylamine (ODA), where they can undergo a second ligand exchange reaction with 1_o .²⁸ The anticipated 45 nm bathochromic shifting of the absorption band of the SiO_2 -Au core-shell nanoparticles was observed as the nanoparticles were transferred between solvents, which can be attributed to the refractive index-dependence of the nanoparticles' surface plasmon resonance bands to the solvent.^{29,30} This dispersion of ODA-coated nanoparticles is stable up to 2 weeks at room temperature, after which time the appearance of a fine precipitate indicates an irreversible nanoparticle aggregation.

The photoresponsive ligands 1_o are anchored to the surface of the core-shell nanoparticles by stirring a mixture of the ODA-coated nanoparticles and ligand 1_o (1:21 w/w) in CHCl_3 at 20 °C overnight in the dark. The bivalent nature of the lipic acid anchor and the high affinity of the sulfur atoms to gold guarantee the displacement of the octadecylamine ligands by

ligand 1_o . The final nanosystems (1_o -NP) were isolated by removing any unbound ligands by centrifugation at 4 °C in the dark and resuspending the solid pellet in CHCl_3 . Transmission electron microscopy (TEM) imaging (Figure 1a) shows them to be 134 nm in diameter, and UV-vis absorption spectroscopy shows an additional but minor bathochromic shift of 7 nm due to the replacement ODA ligand with photoresponsive ligand 1_o . This dispersion of 1_o -NP is stable up to 1 week until any signs of aggregation or spectral changes are observed.

The number of molecules of the photoresponsive ligand (1_o) decorated onto the SiO_2 -Au nanoparticles was analyzed by UV-vis absorption spectroscopy and by measuring the dimensions of the nanoparticles using TEM. By calculating the number of particles in an aliquot amount of the stock solution of nanosystem 1_o -NP and the amount of ligand 1_o removed from the nanoparticles and converted to 1_c (using 312 nm light) after a similar sample was treated with excess dithiothreitol, a loading of approximately 23 000 molecules of 1_o per nanoparticle was estimated.²⁰ The photoresponsive ligands on the core-shell nanoparticles (1_o -NP) undergo similar spectral changes when exposed to 312 nm light (Figure 1b) as did the free ligand. Exposing the solution to visible light of wavelengths greater than 434 nm also triggered the photocycloreversion reaction and regenerated the original spectrum of 1_o -NP.

The “light-gated” photothermal release of small molecules from nanoparticles was demonstrated by monitoring the appearance of dithienylfuran **3** using high performance liquid chromatography (HPLC). The results are shown in Figure 2. After exposing a solution of 1_o -NP to 800 nm (150 mW, 1 kHz, 120 fs) pulsed-laser light, an aliquot amount of the supernatant was injected into an HPLC, and a new peak corresponding to the dithienylfuran **3** released during the photothermal process was observed (Figure 2b).^{32,33} This behavior is expected for 1_o because the ring-open isomer contains the cyclohexene required for the reverse Diels-Alder to occur. In this particular diene-dienophile pair, the thermal breakdown only proceeds at temperatures above 100 °C.¹⁴ We did not observe any temperature change of the bulk dispersion during the exposure of 1_o -NP to 800 nm laser light, which matches those in the

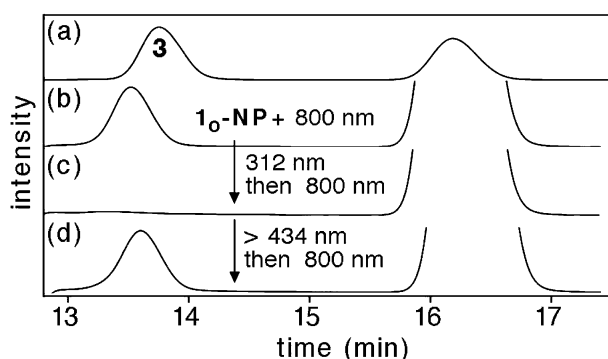


Figure 2. HPLC chromatographs of (a) dithienylfuran **3**, the supernatant obtained from a stock solution of the nanoparticles I_o -NP after (b) being exposed to 800 nm (150 mW, 1 kHz, 120 fs) pulsed-laser light for 120 s, (c) being exposed to 312 nm light for 6 min, followed by 800 nm (150 mW, 1 kHz, 120 fs) pulsed-laser light for 120 s, and (d) being exposed to 312 nm light for 6 min, followed by 800 nm (150 mW, 1 kHz, 120 fs) pulsed-laser light for 120 s, followed by light of greater than 434 nm for 30 min, and finally 800 nm (150 mW, 1 kHz, 120 fs) pulsed-laser light for 120 s. In each case, 30 μ L aliquot amounts in CHCl_3 were injected for analysis. The eluent used was 35% EtOAc in hexanes. All traces were referenced against *p*-nitroanisole, which appears at approximately 16–16.5 min.

literature.^{2,9} A multiphoton process where the photoresponsive ligands (I_o or I_c) on the nanoparticle are absorbing two 800 nm photons was ruled out by exposing solutions of them to the same conditions used for the release process. Neither isomer showed photoactivity under these conditions (see Figure S9).

Because the ring-closed isomer lacks the cyclohexene, there is no evidence of the thermal breakdown even after 24 h at 100 °C. When the solution of I_o -NP was exposed to 312 nm light for 6 min to generate the “locked” ring-closed isomer (I_c -NP), no peak corresponding to **3** was observed in the HPLC trace after the sample was subjected to the same photothermal conditions (800 nm, 150 mW, 1 kHz, 120 fs) pulsed-laser light (Figure 2c). The lack of this peak highlights the success of the “gating” concept. The fact that the ring-open isomers in nanoparticles I_o -NP can undergo the reverse Diels–Alder reaction, while the ring-closed isomers in nanoparticles I_c -NP cannot, is emphasized by exposing the sample of I_c -NP to visible light (of wavelengths greater than 434 nm), which triggers the ring-opening reaction, regenerates the ring-open isomers and I_o -NP, and turns the photothermal release process back “on”. A peak corresponding to **3** is observed (Figure 2d). Comparing the estimated average amounts of chromophore on the nanoparticles with the HPLC results suggests a quantitative release of **3**.

In this communication, we demonstrate how two colors of light are needed to control the photothermal release of small molecules from the surface of nanoparticles. One color (NIR) is required to induce the photothermal effect and generate heat, which is only able to trigger the spontaneous breaking of bonds after visible light is used to ring-open the organic chromophores. While “reloading” of the system may be feasible by adding more maleimide to regenerate I_o -NP, this is not necessary for delivery applications. It may be appealing for other applications, however.

We anticipate that this proof-of-concept study represents a general and versatile approach to potentially address the limitations of technologies such as drug delivery. These are the subjects of ongoing experiments, in which systems are being

prepared that have the photoresponsive component anchored to the nanoparticles in order to release maleimide and other biologically relevant compounds.

■ ASSOCIATED CONTENT

Supporting Information

Detailed descriptions of experimental methods, synthetic procedures, characterization of new compounds, and additional absorption spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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(20) See Supporting Information for details.

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(27) Compound **1_o** is insoluble in polar, protic solvents such as water, MeOH, and EtOH. It is freely soluble in common organic solvents such as CHCl_3 and CH_2Cl_2 .

(28) The decision to perform the Diels–Alder reaction prior to the decoration of the nanoparticles was based on synthetic considerations. This order of reactions maximizes the reaction yield and allows the removal of any unreacted starting material remaining in the mixture.

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(31) The apparent absorption below 700 nm is due to the scattering of light at these wavelengths as has been previously reported for SiO_2 –Au core–shell nanoparticles. The wavelengths used to induce the photoisomerization reaction are not absorbed by the nanoparticles. See: (a) Zhang, X.; Ye, S.; Zhang, X.; Wu, L. *J. Mater. Chem. C* **2015**, DOI: 10.1039/C4TC02780A. (b) Prasad, V.; Mikhailovsky, A.; Zasadzinski, J. A. *Langmuir* **2005**, *21*, 7528. (c) Bikram, M.; Gobin, A. M.; Whitmire, R. E.; West, J. L. *J. Controlled Release* **2007**, *123*, 219. (d) Sugawa, K.; Sakai, T.; Tanaka, D.; Akayima, T. *Jpn. J. Appl. Phys.* **2012**, *51*, 04DH04. (e) Oldenburg, S. J.; Averitt, R. D.; Westcott, S. L.; Halas, N. J. *Chem. Phys. Lett.* **1998**, *288*, 243.

(32) None of the other components involved in the reaction appear before 20 min in the HPLC traces.

(33) When the laser power was increased to 250 or 500 mW, the nanoparticles underwent restructuring as shown by TEM analysis (see Supporting Information for details). We attribute this restructuring to the thermal expansion of the Au nanoshell, followed by its dissociation from the SiO_2 core.