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Photoresponsive Nanoparticles

A UV-Blocking Polymer Shell Prevents One-Photon Photoreactions while Allowing Multi-Photon Processes in Encapsulated Upconverting Nanoparticles**

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The use of low-energy two-photon excitation to provide information about where and when non-invasive photorelease[1–5] and photodynamic therapy (PDT)[6–9] processes occur avoids the need for high-energy UV or visible light. Although this is an effective way to activate photoresponsive agents while minimizing damage to cells and increasing penetration depth into tissue, it does not take into account one serious issue—it does not eliminate the direct activation by the one-photon process. This fact explains why, after therapy, patients often need to avoid excessive exposure to sunlight or ambient light for a period of time to reduce phototoxicity.[10] Avoiding unwanted photochemistry requires a UV-selective filter to block the high-energy light reaching the photoresponsive agent while still retaining the activation by multi-photon processes using longer wavelength light.

Herein, we demonstrate an effective way to reduce the access of ultraviolet light to photoresponsive compounds and how they can still be activated by generating the necessary high-energy light using near infrared (NIR) light and upconverting nanoparticles (UCNPs). Our strategy is illustrated in Scheme 1 and takes advantage of lanthanide-doped $NaYF_4$ nanoparticles wrapped in a UV-blocking organic polymer. A photochromic dithienylethene derivative is used as a model to demonstrate our concept, which can be applied to photorelease and other phototherapeutic processes.

Monodispersed core–shell $NaYF_4$ nanocrystals containing trivalent Tm^{3+} and Yb^{3+} ions (**$NaYF_4$:TmYb**) offer an effective way to generate UV and visible light using NIR light.[11–13] These UCNPs absorb several NIR photons (980 nm) and convert them into emissions in the UV and visible regions of the spectrum. We have already shown how these UCNPs can be used to perform photochemistry, release small molecules, and turn 'on' and 'off' fluorescent markers in polymers, in solution and even in live organisms.[14–21] Most of this work was done using photoresponsive dithienylethenes (DTEs), which undergo ring-closing and ring-opening reactions between two isomers when exposed to UV and visible light, respectively.[22–24] Because they are relatively well behaved and have different optical properties depending on the isomer, they provide a versatile proof-of-principle model to demonstrate our concept. The two systems (inorganic nanoparticles and organic photoresponsive chromophores) can be combined to generate **1o-NP** (Scheme 1) in which the DTE is anchored to the surface of the UCNPs using "click" chemistry.[15,19]

On the right of Scheme 1 is our hybrid system. The decorated nanoparticles (**1o-NP**) are wrapped in a polymer shell composed of polyamide containing PEG chains, one of which is terminated with a known UV-blocking compound.[25] The completely assembled system (**1o-NP-P1**) has five distinct layers. The UCNP lies at the core and acts as the NIR-to-UV "light bulb". It is surrounded by a layer of photoresponsive DTEs, whose role is to report on the success of the concept. The amphiphilic nature of the comb-shaped polymer results in a hydrophobic layer, which stabilizes the assembly, keeps the inner hydrophobic components away from contact with water and ensures the photochemistry of the DTE is maintained, surrounded by a hydrophilic layer as a result of the two PEG chains that project away from the nanoparticle and out into the aqueous environment. The longer of the two PEG chains is terminated with the UV-blocking hydroxy benzophenone,[25] which forms the final UV-light-filtering layer. Because all the layers are transparent to NIR light, this light can still reach the nanoparticle core and be converted into blue and UV light, which will be emitted back out to the photoresponsive layer to trigger the ring-closing reaction. On the other hand, UV light should not penetrate the outer layer. In this way, the multi-photon process can be selectively used and any direct activation of the photochromic DTE by ambient light should be minimized.

Details of all synthetic steps are provided in the Supporting Information. The key step is the assembly of the polymer shell around the DTE-decorated nanoparticles (**1o-NP**). Two separate polymers were used to encapsulate these surface modified nanoparticles. The first (**P1**) contains the UV-blocking compound, the other (**P2**) does not and is used as a control for our studies. We used the encapsulation method described by Raymo and co-workers[26] and recently used by

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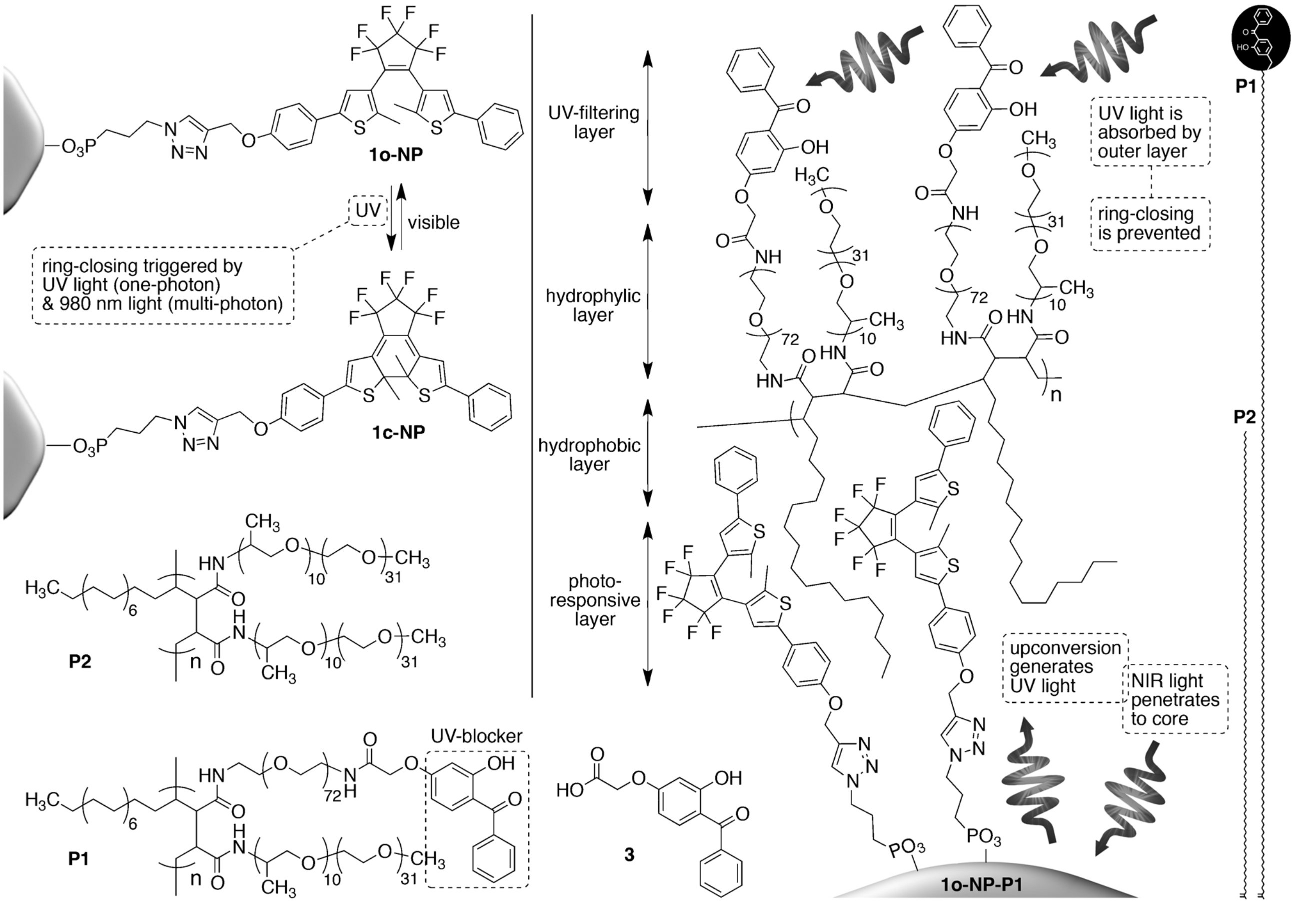

Scheme 1. Left: The reversible photo-induced ring-closing and ring-opening of photochromic dithienylethenes on the surface of lanthanide-doped $NaYF_4$ nanoparticles (**1o-NP**) using ultraviolet and visible light. The two polymers (**P1** and **P2**) used to wrap the nanoparticles and the UV-blocker (**3**) are also shown. Right: The direct ring-closing reaction using UV light is minimized while retaining the NIR-to-UV upconverting process. The schematic representation on the far right show the relative length the polymers **P1** and **P2** extending from the nanoparticle surface starting from the disuccinic diamide.

us[21] and others[27–29] to assemble the two final water-dispersible systems (**1o-NP-P1** and **1o-NP-P2**). Transmission electron microscopy showed these two nano-systems have an average size of 29 nm.[30]

As is typical for dithienylethenes, the photoresponsive derivative anchored to the nanoparticles in both nanoparticle systems (**1o-NP-P1** and **1o-NP-P2**) undergo photochemical reactions that are easily monitored by examining the UV/Vis absorption spectra when solutions of them are irradiated with UV light. As shown in Figure 1 a, the ring-open isomer has no absorption bands in the visible region. Exposing aqueous solutions of either nano-system to 365 nm light causes significant changes in the spectra. The high-energy absorption bands decrease in intensity and new broad absorptions appear in the visible region of the spectra, which accounts for the change in the color of the solutions from colorless to blue. Based on these changes in absorption, the ratio of "blue filter" **3** to the photoresponsive dithienylethene **1o/c** can be estimated to be 2:1.[30]

The DTE in **1o-NP-P1** and **1o-NP-P2** have the same optical behavior as the free chromophore in organic solvent showing that there are no major changes when the compound is encapsulated in the nano-system.[30] The spectral changes stop after a few minutes when the photostationary states are reached. We assume that these states contain the same 72% of the ring-closed isomer **1c** based on the analysis of the

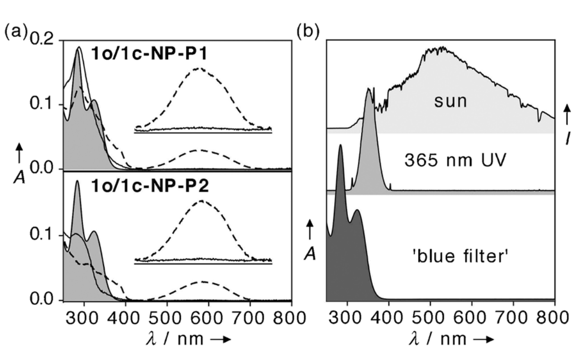

Figure 1. a) UV/Vis absorption spectra of H_2O solutions of top: **1o-NP-P1** (3.4×10^{-6} M)[31] and bottom: **1o-NP-P2** (1.3×10^{-6} M)[31] before (solid lines) and after irradiation with 365 nm light (broken lines). The gray shaded area in each absorption spectrum corresponds to the absorption of a CH_3CN solution of the UV-blocker **3** (1.0×10^{-4} M) to highlight the spectral overlap. b) Luminescent spectra of top: sunlight measured for a typical day. Middle: the 365 nm UV light source used for these studies, and bottom: the absorbance spectrum of **3**.

photostationary state for the free compound (**1o/1c**) by ^{1}H NMR spectroscopy.

Figure 1a also shows how the absorption spectrum of the pure "blue filter" (**3**) overlaps with the absorption bands for the ring-open isomer of the photoresponsive dithienylethene and illustrates how it can potentially act to block the UV light from reaching the chromophores anchored to the nanoparticles. This "filter" should effectively reduce the amount of light coming from the sun (Figure 1b) and prevent the one-photon excitation of the DTE.

Figure 2 illustrates how the nano-system containing the "blue filter" (**1o-NP-P1**) selectively blocks the UV light from penetrating into the interior of the encapsulated nanoparticles and activating the photoresponsive dithienylethenes. When aqueous solutions of both systems (**1o-NP-P1** and **1o-NP-P2**) are exposed to UV light (365 nm) from a hand-held lamp at the distance that corresponds to the intensity of the UV component in sun light,[32] the absorbance corresponding to the ring-closed isomer (at 590 nm) appears to a significantly lesser extent than it does for the nano-system without the "blue filter" (**1o-NP-P2**). The basic photochemistry of the dithienylethene is not affected since exposing both samples to intense UV light (365 nm) saturates the filter and produces the same intensity of the band at 590 nm. As expected from these initial experiments, the same outcome results when the two nano-systems are taken outdoors and exposed to sunlight (Figure 2). Once again, the absorption corresponding to the ring-closed isomer (**1c**) in **1o-NP-P1** is significantly reduced in intensity when compared to that for **1o-NP-P2**. These differences are visually apparent. Colorless solutions of both nano-systems turn dark blue when exposed to high intensity UV light, however, only the system lacking the "blue filter" (**1o-NP-P2**) turns deep blue when exposed to sun light.[30]

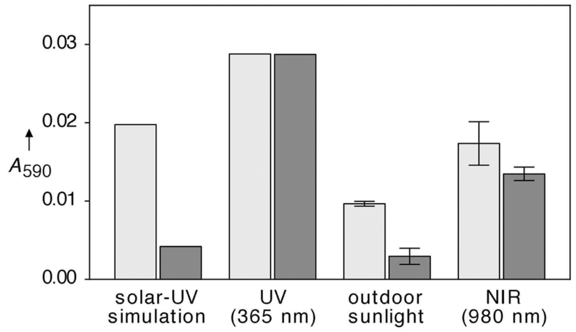

Figure 2. Absorption values at 590 nm for nanoparticles **1o/c-NP-P1** (dark shaded) and **1o/c-NP-P2** (light shaded) when exposed to different light sources. The values for sun light and NIR light are average values from three separate measurements. The solar-UV simulation conditions employ a 365 nm light source placed at a distance that matches the emission intensity of the UV component in sunlight. Exposure times are 2 min for solar-UV, 2 min for UV (365 nm), 2 min for outdoor sunlight and 30 min for 980 nm light.

The multi-photon process of the UCNPs is not affected by the presence of the 'blue filter' and the photochemical ring-closing of the DTE chromophore occurs equally for both **1o-NP-P1** and **1o-NP-P2** when they are exposed to 980 nm light (Figure 2).[30] This simple experiment demonstrates the success of our concept. Exposure to this NIR light resulted in no changes in the absorption spectra for either system even after 12 h of continuous irradiation. Sunlight also resulted in no observable degradation. Interestingly, neither **1o-NP-P1** nor **1o-NP-P2** are effected by typical indoor lighting (fluorescence or halogen).[30] When the emission spectra are examined the explanation is clear. Neither light source has a UV component intense enough to trigger the ring-closing reaction.

In conclusion, we have designed a water-dispersible nano-system that undergoes multi-photon driven photochemistry when exposed to 980 nm NIR light because this light can penetrate the UV-blocking shell and turn on the upconverting nanoparticle "light bulb", while minimizing direct activation with UV light. We believe that our nano-system will offer a heightened level of control over photochemistry in many applications.

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[30] See Supporting Information for more details.

[31] All concentrations are those for the encapsulated chromophores obtained using the concentrations of the ring-closed isomers at their photostationary state (as measured by UV/Vis spectroscopy) divided by percentage of ring-closed isomers in this state (as measured by ^{1}H NMR spectroscopy).

[32] This distance was measured to be 65 cm. See Supporting Information for more details.