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Rational design of light-directed dynamic spheres†

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We created light-directed dynamic spheres based on simple azobenzene monomers showing (i) a high yield of reversible *trans* ↔ *cis* photoisomerization and (ii) noticeable phase transition from crystalline to isotropic states under UV light irradiation at ambient temperature.

The design and creation of dynamic aggregates (vesicles, micelles, bilayers, and spheres) capable of light-driven reversible self-assembly and disassembly have attracted extensive attention in photochemistry, biology, and medical fields for purposes including drug delivery and separation systems.[1] Most of the studies in this area have been concentrated on the laborious synthesis of block copolymers (BCP)[2] and surfactants[3] consisting of photochromic azobenzenes. In general, *cis*-azobenzene (μ = ~3 D) has a larger dipole moment than *trans*-azobenzene (μ = ~0 D),[4] but *cis*-azobenzene itself is not polar enough to dissolve in aqueous solution. Thus, efficient light-induced disassembly of self-assembled systems remains challenging.

The rod-shaped *trans* form stabilizes crystalline and liquid crystalline (LC) phases, whereas the bent-shaped *cis* form destabilizes the crystalline and LC phases. Accordingly, irradiation with UV light can cause an isothermal LC-to-isotropic phase transition in an aggregated state.[5] Nevertheless, there are only two reports on solid azobenzene compounds which liquefy under UV light even at room temperature.[6] Akiyama and Yoshida have demonstrated that fluidic orange droplets generated by UV light turned back to solid by visible light.[6b] The rational molecular design strategy considering an important balance between a homogeneous molecular structure without polydispersity and a steric factor inducing appropriate intermolecular interactions is desirable for light-induced transformation between assembled (crystalline and LC) and disassembled (isotropic) states.

Our purpose of this study is to design photoresponsive dynamic spheres based on simple azobenzene monomers showing not only high yield of reversible *trans* ↔ *cis* photoconversion but also phase transition from crystalline to isotropic states under UV light irradiation. Moreover, when a hydrophobic fluorescent dye is encapsulated inside the azobenzene sphere in aqueous solution, it can be released through disassembly of the sphere by UV light. The resulting solution becomes transparent and highly blue fluorescent, which allows us to distinguish between the sphere suspension and the UV-exposed solution.

We designed an amphiphilic azobenzene monomer (**EtO-Az-EG**, see Fig. 1) consisting of a hydrophobic azobenzene rod and a hydrophilic flexible tetra(ethylene glycol) chain. Interestingly, crystalline *trans*-**EtO-Az-EG** possessing its melting temperature at 50 °C becomes liquid at ambient temperature upon UV light irradiation (Fig. 1a and b, Fig. S1 and Movie S1, ESI†). The distorted *ortho*-alkylated azobenzene unit in **EtO-Az-EG** would experience weak intermolecular π–π stacking interactions between *trans*-azobenzenes,[7,8] which could be responsible for the low phase transition temperature from crystalline to isotropic states. The *cis* form is expected to become more hydrophilic with the aid of the tetra(ethylene glycol) chain, which may help to diffuse in water and other polar solvents.

Azobenzene spheres were produced simply by adding water into **EtO-Az-EG** THF solution (4.0×10^{-4} M, 1.5×10^{-3} M, 4.0×10^{-3} M, filtered through a PTFE syringe filter prior to use) under mild shaking conditions. With gradually increasing the water content, the THF–H_2O mixed solution turned orange-yellow turbid. Each suspension was well-dispersed with no evident precipitate over the 1 week storage period.

Transmission electron microscopy (TEM) images displayed spherical aggregates of approximately 0.4–2.0 μm in diameter

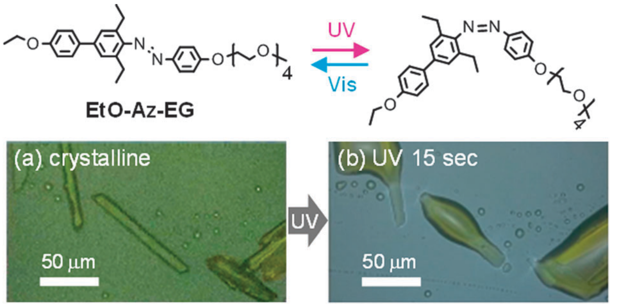

Fig. 1 (upper panel) Chemical structure of **EtO-Az-EG** and its photoisomerization. (lower panel) OM images of UV-induced liquefaction of **EtO-Az-EG**. (a) Before and (b) after UV light irradiation at ambient temperature (see Movie S1, ESI†).

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† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for **EtO-Az-EG** along with DSC (differential scanning calorimetry) data, UV-vis absorption spectra, additional TEM and OM images, DLS data of azobenzene spheres. See DOI: 10.1039/c2cc36443c

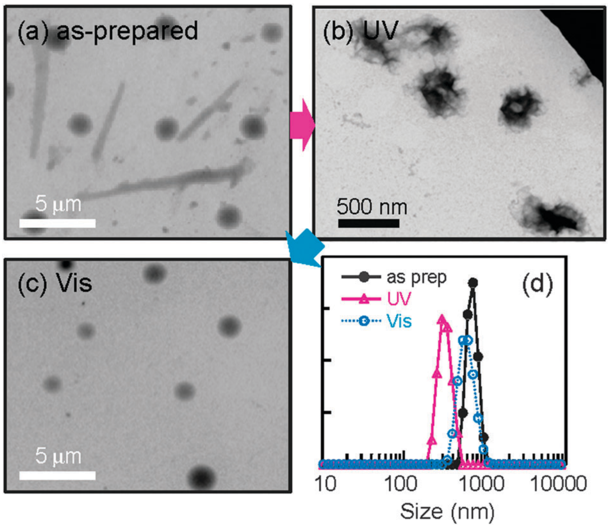

Fig. 2 Unstained TEM images of (a) **EtO-Az-EG** spheres obtained from 1.3×10^{-3} M THF/H_2O (4.0/8.2, v/v). (b) Exposure to UV light at 365 nm. (c) Subsequent exposure to visible light at 436 nm. (d) DLS measurements of size changes of azobenzene spheres upon UV and subsequent visible light irradiation.

for 1.3×10^{-3} M THF/H_2O (4.0/8.2, v/v) suspension, consistent with optical microscopy (OM) images (Fig. 2a and Fig. S2, ESI†). Dynamic light scattering (DLS) experiments also provided convincing evidence for generation of spheres with the size of 0.5–1.5 µm (Fig. 2d). The measured average size was independent of the azobenzene concentrations varying from 9.0×10^{-5} M to 1.3×10^{-3} M (Fig. S3, ESI†).

To examine light-driven reversible changes in the molecular conformation of the azobenzene unit and the resulting morphological transformation of azobenzene spheres under UV and visible light irradiation, a dilute azobenzene suspension (8.9×10^{-5} M THF/H_2O (2.0/7.0, v/v)) suitable for UV-vis absorption spectroscopy measurements was prepared. As clearly seen in Fig. 3, the azobenzene suspension shows a broad π–π* absorption band maximized at 354 nm and a conspicuously increased absorbance at 650 nm (indicated as turbidity), demonstrating formation of spherical aggregates. When compared to the typical monomer-like absorption spectrum of **EtO-Az-EG** (Fig. 3 and Fig. S4, ESI†), no noticeable absorption spectral shift originating from H- or J-aggregation was found.[9] This result suggests that the *ortho*-alkylated azobenzene unit is significantly distorted from coplanarity, resulting in modest intermolecular π–π stacking interactions between aromatic rings, as mentioned earlier.

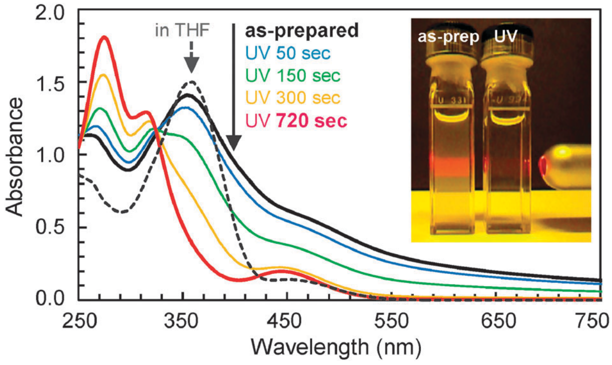

Fig. 3 UV-vis absorption spectral changes of 8.9×10^{-5} M THF/H_2O (2.0/7.0, v/v) as a function of exposure time of UV light. Inset photograph: red light from a red laser pointer is shone from the right side of the samples.

Exposure of the azobenzene suspension to UV light for inducing *trans*-to-*cis* photoisomerization led to a drastic decrease in the π–π* absorption band. Simultaneously, the scattered light intensity at 650 nm decreased substantially by ~98% (Abs = 0.003), and the suspension turned transparent (inset photograph in Fig. 3). The *cis* content was then estimated to be approximately 87%, based on the ^{1}H NMR and UV-vis absorption spectral results of **EtO-Az-EG** (Fig. 3 and Fig. S4, ESI†). In addition to the high photoisomerization yield, not only a large difference in the dipole moment between the *trans* and *cis* forms ($\mu_{cis} - \mu_{trans} = \sim 5.0$)[10] but also a hydrophilic tetra(ethylene glycol) chain covalently attached to the azobenzene unit becomes an important factor in making the *cis* form more hydrophilic. Therefore, the *cis*-azobenzene should efficiently diffuse in the THF–H_2O solution. However, we could occasionally observe largely disassembled objects as well as shrunken aggregates from TEM images of UV-exposed transparent aliquots (Fig. 2b). Their size, as measured by DLS, was calculated to be 0.2–0.5 µm (Fig. 2d). The existence of such shrunken objects seems to be due to the remaining small amount of *trans*-azobenzene (~13%) which stabilizes aggregated states.

Amazingly, subsequent irradiation with visible light for 5 min resulted in a prominent increase in the absorbance at 354 nm as well as a considerable recovery of turbidity (Fig. S5, ESI†), strongly indicating that rapid regeneration of spheres occurred through reverse *cis*-to-*trans* photoisomerization. The ratio of the *cis* to *trans* forms was then estimated to be 30/70 at the photostationary state. Unambiguously, TEM and DLS measurements provided strong evidence for the recovery of spherical aggregates with diameters of 0.3–1.5 µm (Fig. 2c and d). As shown in Fig. S5 (ESI†), the excellent assembly and disassembly process was repeatedly achieved together with reversible *trans* ↔ *cis* photoisomerization, without serious absorption spectral degradation.

Encouraged by the high *trans* ↔ *cis* photoisomerization of **EtO-Az-EG** as well as the dynamic transformation between spherical and disassembled objects, we next examined encapsulation and release of hydrophobic fluorescent dyes at a chosen light wavelength (Fig. 4b). A small amount of 9,10-diphenylanthracene (DPA, 4.0×10^{-5} M) was dissolved in **EtO-Az-EG** (4.0×10^{-3} M) THF solution. Slow addition of water into the mixed solution gave a turbid suspension (THF/H_2O = 4.0/8.2, v/v, see OM and DLS data in Fig. S6 and S7, ESI†). When excited at 365 nm, the suspension fluoresced very weakly and exhibited two discrete emission peaks with maxima at 429 nm and 532 nm, obviously different from the emission spectrum of the dilute single-component DPA solution[11] (Fig. 4c and d). Such striking emission spectral features seem to be closely associated with encapsulation of fluorescent dyes into azobenzene spheres. As the suspension was continuously exposed to UV light, the blue fluorescence centered around 407 nm significantly increased within 15 min. The fluorescence intensity improved by about

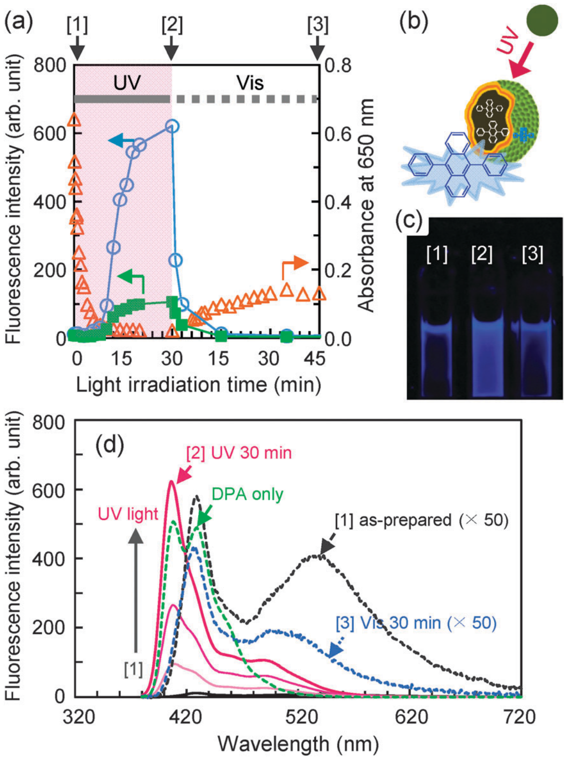

Fig. 4 (a) Changes of 1.3×10^{-3} M **EtO-Az-EG** THF/H_2O (4.0/8.2, v/v) including 1.3×10^{-5} M DPA in absorbance at 650 nm (orange triangle) and fluorescence intensities at 407 (blue circle) and 532 nm (green square) as a function of exposure time of UV light and subsequent visible light. Fluorescence intensities in (a) were based on fluorescence spectral changes in (d). (b) Schematic representation of release of fluorescent DPA from the azobenzene sphere. (c) Emission (under 365 nm irradiation) of suspensions containing **EtO-Az-EG** and DPA. [1] As-prepared suspension. [2] Highly fluorescent solution obtained after UV light irradiation. [3] Weakly fluorescent turbid suspension obtained after subsequent irradiation with visible light. (d) Fluorescence spectral changes of the **EtO-Az-EG** suspension including DPA upon irradiation with UV light and subsequent visible light.

60 times than that of the non-irradiated initial value. Simultaneously, the scattered light intensity became almost zero (Fig. 4a and Fig. S8, ESI†), confirming disruption of the large amount of spheres and the resulting release of DPA into the surrounding media.

In reverse, exposure to visible light gave rise to approximately 70 times reduction of blue fluorescence intensity along with a recovery of scattered light intensity ([2] → [3] in Fig. 4a, c and d). Additional TEM and DLS experiments exhibited substantial changes in spherical size in response to a chosen light wavelength (Fig. S7 and S9, ESI†). Photoswitching of fluorescence intensity was successfully performed through the reversible *trans* ↔ *cis* photoisomerization of **EtO-Az-EG**, and the resulting encapsulation and release of fluorescent dyes under UV and visible light irradiation (Fig. S10, ESI†).

In summary, we have demonstrated that a rationally designed azobenzene self-assembled into spherical aggregates in a THF–H_2O solution. The synthetic spheres underwent light-directed morphological transformation between spherical and disassembled states, which could be clearly seen as variations in turbidity with the naked eye. The dynamic photoswitching allowed azobenzene spheres to encapsulate fluorescent dyes which need to be released in a non-contact fashion. The light-responsive sphere system described in this investigation can be applied to drug delivery and emerging separation systems which require on-demand encapsulation/release at a specific light wavelength.

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