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Light-Controlled Formation of Vesicles and Supramolecular Organogels by a Cholesterol-Bearing Amphiphilic Molecular Switch

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Abstract: A new responsive material composed of an amphiphilic light-switchable dithienylethene unit functionalized with a hydrophobic cholesterol unit and a hydrophilic poly(ethylene glycol)-modified pyridinium group has been designed. This unique single-molecule system shows responsive light-switchable self-assembly in both water and organic solvents. Light-triggered reversible vesicle formation in aqueous solutions is reported. The molecule shows a different behavior in apolar aromatic solvents, in which light-controlled formation of organogel fibers is observed. The light-triggered aggregation behavior of this molecule demonstrates that control of a supramolecular structure with light can be achieved in both aqueous and organic media and that this ability can be present in a single molecule. This opens the way toward the effective development of new strategies in soft nanotechnology for applications in controlled chemical release systems.

Introduction

The self-assembly of small functional molecules into supramolecular structures,[1] including nanofibers,[2] nanotubes,[3] vesicles,[4] micelles,[5] and gels,[6] is central to the construction of molecular-based soft nanotechnological devices and materials for applications as diverse as drug delivery,[7] controlled cell growth,[8] and sensing.[9] Despite considerable progress, control over the organization by physical and chemical trigger elements remains a major challenge.[10] A highly promising approach towards this goal is the use of responsive, or smart, materials through the integration of addressable functionality, for example, intrinsic photoresponsive moieties, within the supramolecular building blocks.[11] This approach opens the possibility to control self-assembled nanostructures formed from individual molecules or to change the properties of supramolecular arrays noninvasively in time and space, by using light.[3] Dithienylethene photoswitches[12] have played a central role in addressing such supramolecular systems, including nanofibers,[13] nanotubes,[14] metal complexes,[15] surfaces,[16] organogels,[17] polymer aggregates,[18] and liquid crystals.[19] However, most of these systems form supramolecular aggregates only in organic media, which severely limits the possibilities for biological applications.

Herein, we report a unique single-molecule system that shows responsive assembly, in both water and organic solvents, which enables reversible photochemical control over both vesicle and organogel formation, by using the amphiphilic photochromic diaryl ethene **1**, functionalized with a cholesterol unit and a poly(ethylene glycol)-modified pyridinium moiety (Scheme 1). The cholesterol unit provides hydrophobic functionality with possible applications to biological membranes. The poly(ethylene glycol)-modified pyridinium group facilitates sufficient hydration in aqueous environments, in which aggregation is predominantly driven by hydrophobic interactions.

The aggregation behavior of **1** in aqueous solutions represents one of the very few examples of fully reversible light-driven control over vesicle formation in aqueous media[20] and is, to the best of our knowledge, the first system based on a single compound as opposed to a mixture of compounds.[10] Photoresponsive organogelation is a well-described phenomenon, but this property is not frequently observed for compounds that also form distinct aqueous supramolecular aggregates, and it offers insight into the behavior of the compound.[21] This behavior could provide opportunities in applications as diverse as controlled release of compounds in biological systems, selective labeling, and control of cell growth.

Results and Discussion

The synthesis of compound **1o** (Scheme 2) is described in the Supporting Information, and its structure was confirmed by ^{1}H

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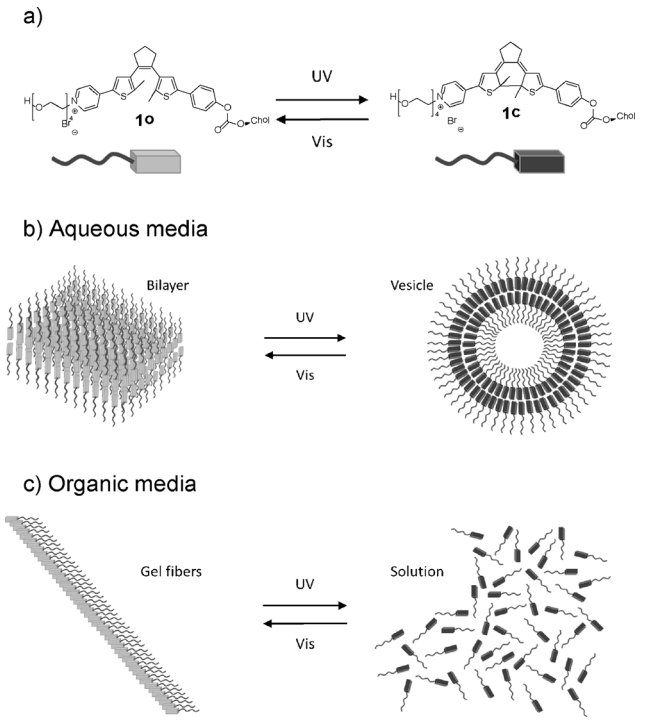


Scheme 1. Dynamic self-assembly behavior of **1** in aqueous and organic media upon light-induced switching. Chol: cholesterol; **1o**: open form of **1**; **1c**: closed form of **1**).

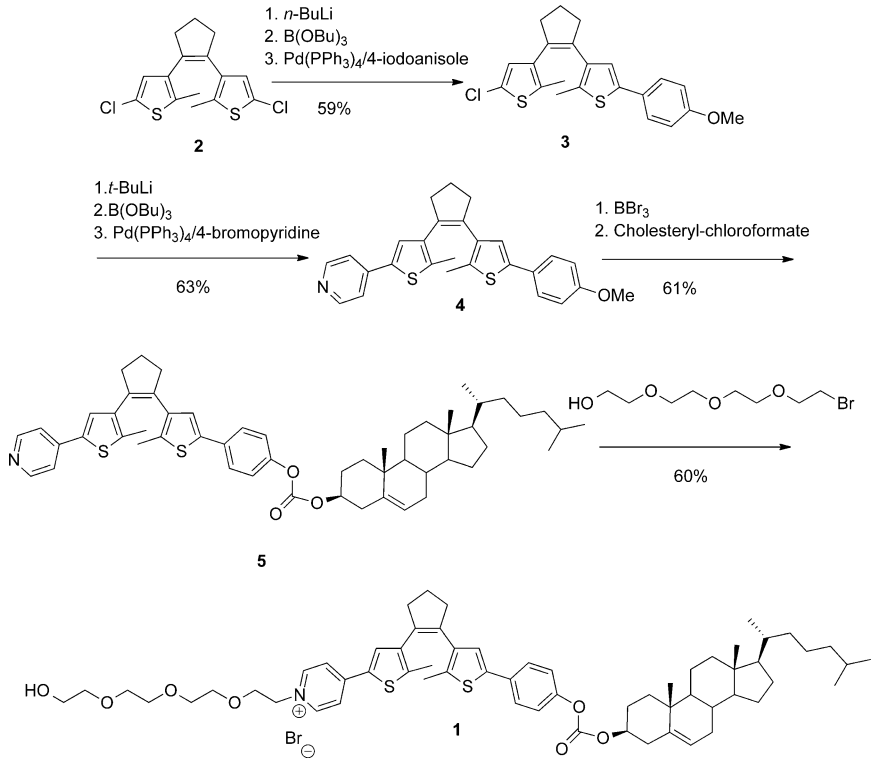
and ^{13}C NMR spectroscopy, elemental analysis, and MALDI-TOF mass spectrometry. The photochromic behavior of **1** was characterized in toluene and H_2O (Figure 1). As expected, compound **1** shows reversible changes in absorbance and fluorescence intensity upon alternate irradiation with ultraviolet ($\lambda = 365$ nm) and visible ($\lambda > 500$ nm) light. Upon irradiation in toluene at $\lambda = 365$ nm, the colorless solution turned blue and the absorption band assigned to **1c** appeared at 649 nm (Figure 1a). Concomitantly, the absorbance of **1o** at 372 nm ($\varepsilon = (1.9 \pm 0.1) \times 10^4\ M^{-1}\,cm^{-1}$) decreased. The ratio of **1c** to **1o** in the photostationary state (pss) was found to be higher than 98:2.[22] Upon irradiation at $\lambda > 500$ nm, the blue color faded and the open-ring isomer **1o** was regenerated.

The absorption maxima of **1o** and **1c** in H_2O are 377 ($\varepsilon = (1.3 \pm 0.1) \times 10^4\ M^{-1}\,cm^{-1}$) and 647 nm, respectively (Figure 1e). In the open state, **1o** is fluorescent, whereas the closed form, **1c**, is not fluorescent, which allows the switching process to be followed readily. Compound **1o** fluoresces at 516 nm ($\lambda_{exc} = 380$ nm) in toluene (Figure 1b), at 610 nm in ethanol (Figure 1d), and at 550 nm in water (Figure 1f). The shift in the emission maximum is most likely solvatochromic, with the molecules experiencing the most polar environment in ethanol, in which they are fully dissolved; in water, aggregation (see below) somewhat reduces the effect. The fluorescence in both organic and aqueous solution could be switched off and on by irradiation at $\lambda = 365$ and > 500 nm, respectively (Figure 1e, insert).[23]

The gelation behavior of **1o** was determined in a range of solvents (Table 1). Stable gels were formed in *o*-, *m*-, and *p*-xylene (1 mg mL^{-1}), benzene and toluene, as was confirmed by rheometry measurements (see Figure 2).

The rheological strain sweep measurements (Figure 2a) show a plateau region until a strain of 1%, which hints that larger strains result in the (partial) breakup of the fiber network. The frequency dependence (Figure 2b) of the gels was found to be largely frequency independent, with the storage modulus (G') dominating the loss modulus (G''). This behavior, typical of gels, was lost once the samples were converted to the closed form photochemically (Figure 2a).

Cryo transmission electron microscopy (cryo-TEM) images of these organogels in xylene and toluene indicate that fibers were the dominant supramolecular structure formed (Figure 3b and c). These images are the first examples reported of cryo-TEM performed by using xylene as the solvent.[24] The thickness of the gel fibers ((17.0 ± 1.0) nm) is uniform and ex-



Scheme 2. Synthesis of amphiphilic dithienylethene **1**.

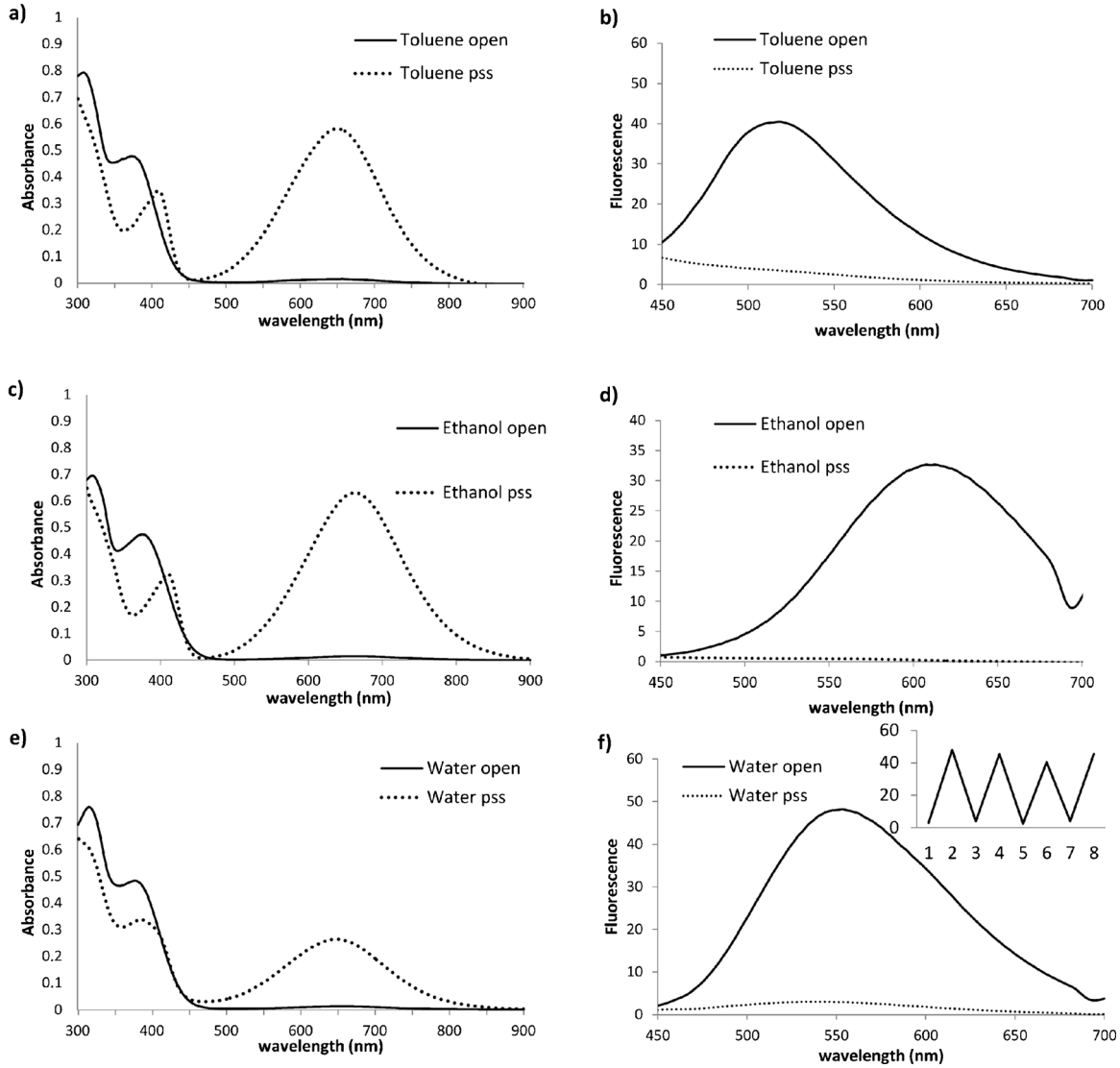


Figure 1. UV/Vis absorbance (a, c, and e) and fluorescence (b, d, and f) spectra of **1** in a, b) toluene ($(2.6\pm0.1)\times10^{-5}$ M), c, d) ethanol ($(3.2\pm0.1)\times10^{-5}$ M), and e, f) H_2O ($(2.0\pm0.1)\times10^{-5}$ M). Insert: Modulation of fluorescence at 550 nm in water over several switching cycles. PSS: photostationary state.

ceeds the maximum length of compound **1** (3.6 nm) to a large extent, which indicates that the aggregation occurs at several hierarchical levels. Both cholesterol[25] and dithienylethene moieties[17] have been shown to be able to form organogels under certain conditions and it is therefore likely that the aggregation of compound **1o** is due to the cumulative effect of both moieties.

Table 1. Gelation properties of **1o** in organic solvents.

Solvent	State[a]	Solvent	State[a]
hexane	i	1,2-dichloroethane	s
cyclohexane	p	1-octanol	s
n-butyl acetate	p	ethanol	s
o-, *m*-, *p*-xylene	g (1)	THF	s
toluene	g (5)	1,2-dichlorobenzene	s
benzene	g (10)	1-propanol	s
2-propanol	p	tetraline	s
acetonitrile	p	DMSO	s
1,4-dioxane	s	DMF	s

[a] i: insoluble; p: precipitate; g: gel; s: solution at 40 mg mL^{-1}. The number in parentheses indicates the minimal gelation concentration in mg mL^{-1}.

Upon irradiation of an organogel formed by **1o** in toluene at $\lambda=365$ nm, a gel-to-sol transition was observed within seconds. The system could be switched fully reversibly between a gel and the solution state by photochemical ring closing or opening of the photochromic dithienylethene unit. The sol–gel transition upon irradiation was confirmed by CD spectroscopy. In toluene, **1o** shows a positive Cotton effect at 402 nm ($\Delta\varepsilon=34.7$ M^{-1}cm^{-1}) in the gel state, with a signal at around 330 nm attributed to an exciton coupling, which indicates the presence of tightly packed chiral structures (Figure 4a).[13,17] After irradiation at $\lambda=365$ nm to form **1c**, the CD signal decreases and eventually disappears, which indicates a loss of the induced CD signal of the dithienylethene units due to dissolution of the gel fibers. The lack of a CD signal for both **1o** and **1c** in

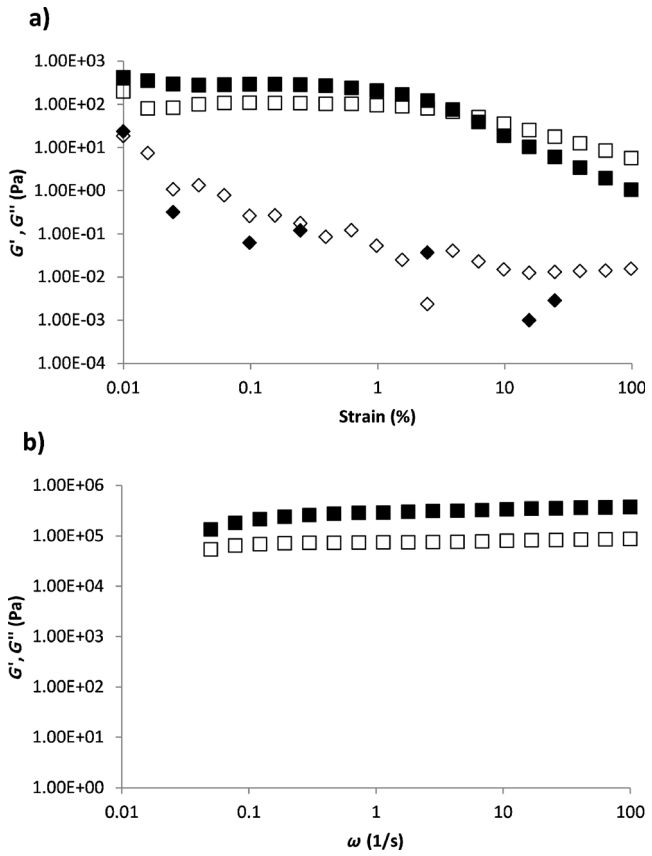


Figure 2. a) Strain sweep ($\omega = 1.0\ s^{-1}$) of a toluene gel of compound **1** (10 mg mL^{-1}) before (■, □) and after (◆, ◇) photoinduced ring closure. Black markers indicate the storage modulus (G') and white markers indicate the loss modulus (G''). b) Frequency sweep ($\gamma = 0.1\%$) of a toluene gel of compound **1**.

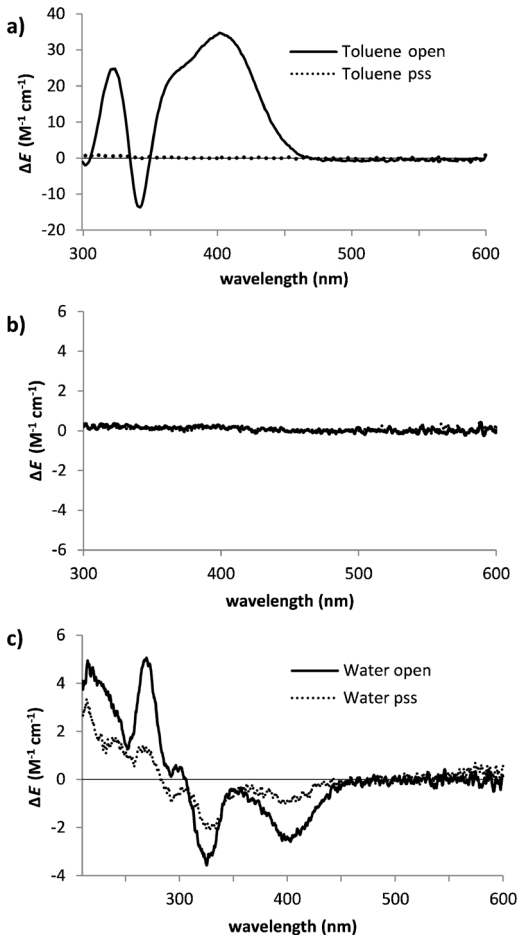


Figure 4. CD spectra of **1** in the open and the photostationary states in a) toluene ($(2.6 \pm 0.1) \times 10^{-5}$ M), b) ethanol (3.2×10^{-5} M), and c) water ($(2.0 \pm 0.1) \times 10^{-5}$ M) before and after irradiation with UV light at $\lambda = 365$ nm to form the photostationary state.

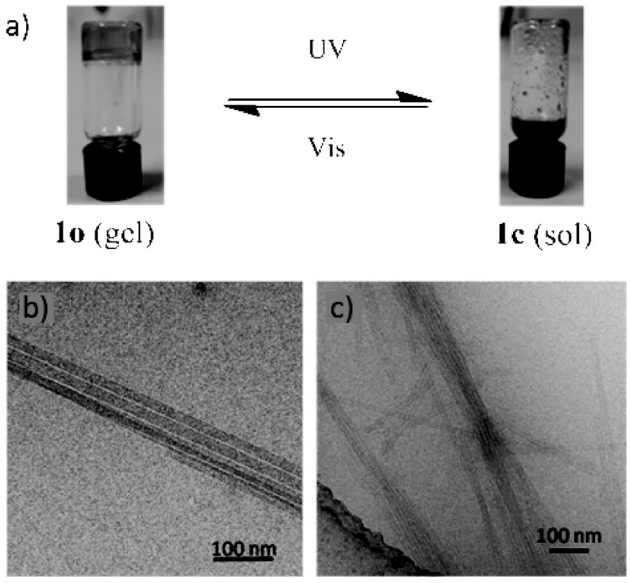


Figure 3. a) Sol–gel phase-transition behavior of **1** (3 mM in toluene) after irradiation with UV ($\lambda = 365$ nm) and visible ($\lambda = 500$ nm) light. Cryo-TEM images of **1o** in b) *m*-xylene and c) toluene.

ethanol confirms earlier observations that **1o** and **1c** are fully dissolved in this solvent (Figure 4b).

In aqueous solutions, the CD signal is much stronger in the open state (**1o**) than in the closed state (**1c**; Figure 4c). The decrease in signal is a manifestation of a change in the packing parameters and is likely to be due to less tight stacking in the closed state (see below). In water, **1o** forms supramolecular assemblies, as evidenced by cryo-TEM (Figure 5a and b). The images show lamellar aggregates, which most likely form due to aggregation driven by hydrophobic interactions of the cholesterol and the dithienylethene moieties, which are both known to be capable of (co)forming vesicular aggregates in aqueous solvents.[23,26]

Upon switching of **1o** into its photostationary state (predominately **1c**) by irradiation at $\lambda = 365$ nm, vesicles were observed (Figure 5c and d). In contrast to the results in organic solvents, in which ring closing led to the disappearance of the supramolecular aggregates, in aqueous systems, the distinct packing parameters of the amphiphilic molecule now led to the formation of vesicles, probably due to a less tight packing of **1c** in the supramolecular aggregate than **1o**.

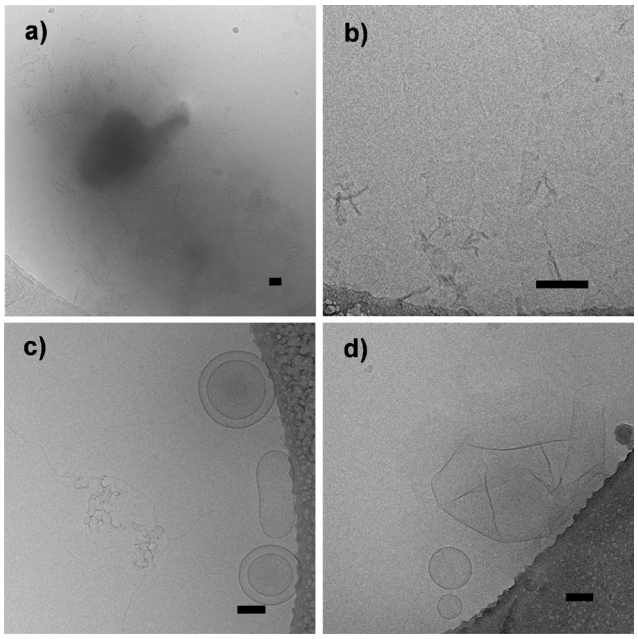


Figure 5. a, b) Cryo-TEM images of **1o** in water (scale bars: 1 μm and 100 nm, respectively). c, d) Cryo-TEM images of **1c** after irradiation at $\lambda = 365$ nm (scale bars: 1 μm and 100 nm, respectively).

The changes in packing arise most likely from two cumulative effects. The cholesterol and ethylene glycol chain are forced into a specific orientation by the switch moiety when it is in its rigid closed state. The molecule can adopt more favorable orientations of these side groups in the open, less rigid, state of the switch, because rotations around more bonds become available. A second factor that affects the packing is that, in the closed form, the methyl groups are attached to a tetrahedral (sp^3) hybridized carbon atom instead of a trigonal (sp^2) hybridized carbon atom. As a result, the methyl groups are oriented out of plane and thus interfere more with the packing of the otherwise flat dithienylethene. The less tight packing provides increased lateral mobility of the individual molecules and allows for a greater curvature in the aggregates, which thus provides the right circumstances to form vesicles from pre-existing lamellar bilayers (Figure 5 d).[27]

Conclusion

In conclusion, we report a new responsive material composed of a light-switchable dithienylethene unit functionalized with a hydrophobic cholesterol unit and a hydrophilic poly(ethylene glycol)-modified pyridinium group. The incorporation of the light-switchable functionality allows for photochemical control over vesicle formation in water and for light-controlled self-assembly of organogel fibers in apolar aromatic solvents. These features demonstrate that light control of a supramolecular structure can be achieved in aqueous as well as organic media and that this ability can be present in a single molecule. This opens the way toward the effective development of new strategies in soft nanotechnology for applications in controlled chemical release systems.

Experimental Section

UVASOL grade solvents were used for spectroscopic measurements. UV/Vis measurements were performed on a JASCO V-630 spectrophotometer. CD spectra were recorded on a Jasco J-815 CD spectrometer. Fluorescence spectra were recorded by using a Jasco FP-6200 fluorimeter. Cryo-TEM was performed on a Philips CM 120 instrument. Rheological measurements were performed on a MCR 300 rheometer (Anton Paar) by using a parallel plate setup, equipped with a 25 mm plate (PP25 SS). Samples were introduced as liquids at 50 °C, after which the sample was sealed and allowed to cool to 25 °C and rest for at least 60 min before measurement.

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