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Photoswitchable vesicles

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ABSTRACT

Vesicles are self-assembled nanosized structures that result from the auto-organization of amphiphilic compounds into closed bilayers. These systems are highly attractive subjects of fundamental research owing to their role as biomimetic models of cell membranes and compartmentalization systems. Vesicles also display very interesting features and properties for practical applications, namely as superior nanocontainers for encapsulation of functional molecules and materials. Exerting control over the formation, dissociation and permeability of these containers is therefore of paramount importance for many of their potentials applications. Being light the stimulus of choice for remote spatiotemporal control, we have compiled and revised selected published works on photoresponsive vesicles with the aim of providing an overview of the main strategies, advantages and limitations of such systems.

1. Introduction

Self-assembled nanostructured materials formed from amphiphilic molecules found widespread applications in scientific and technological areas. Depending on the structure of the amphiphilic building block and medium conditions such example solvent, temperature, ionic strength, additives, different nanostructures can be formed. Micelles, vesicles or nanotubes are amongst the most frequently observed [1–7].

Vesicles are particularly interesting nanostructures self-assembled from amphiphilic compounds for different reasons. Amongst them, the possibility of using this aggregates as models of biological membranes, compartmentalization media or as superior nanocontainers owing to their ability to encapsulate both hydrophobic and hydrophilic payloads constitute archetypal examples [8–12].

The formation of vesicles (or other nanostructures) depends on a delicate balance between hydrophobic and hydrophilic molecular segments and as well on the packing parameter [13••,14••]. This subtle balance provides a fertile playground for the incorporation of chemically and/or physically switchable elements within the structure of the amphiphilic building blocks to trigger changes in the structure, size and aggregation behavior of nanosized assemblies with external inputs and ultimately control the functional behavior of the self-assembled material [15•]. The possibility to control their aggregation behavior through the application of external stimuli such as light, pH, redox, temperature, etc., further expand the functionality and the potential applications of such materials. These switchable properties are of particular interest for applications related with controlled uptake and release of functional cargo molecules such as drugs, genes, fragrances and flavors, catalysts, etc. [15•,16•].

Amongst the several possibilities, light is a preferred stimulus for many applications as it allows spatial, temporal and remote control of the self-assembled structures without introducing additional components in the system. Photoresponsive surfactants or photosurfactants are amphiphilic molecules that contain photochromic or photolabile units [17•]. While photochromic molecules are *reversibly* isomerized by light absorption returning to the thermodynamic stable state in the dark or by excitation at different wavelengths of light; photolabile or photocaged compounds are irreversibly cleaved by light irradiation [18–26]. This review focus on the self-assembly properties of photoresponsive surfactants that undergo self-organization in aqueous solutions to form vesicles or that can be incorporated into vesicular bilayers to impart photoresponsive properties to the self-assembled nanostructures. While in the first case the motivation is clearly dominated by the quest to develop soft-materials/containers with photocontrolled uptake and release properties; in the second case, and mainly in earlier pioneering works, there was a clear inspiration from biological systems in the sense that these membrane-embedded photoresponsive chromophores may be considered as primitive models of the photoreceptor membranes proteins that are responsible for the process of vision [27–31]. The article is organized according to the different classes of the most popular photoresponsive molecular switches in order to provide the reader with an idea of the potential advantages and limitations of the different photoactive units.

2. Azobenzenes

Azobenzenes are frequently chosen as functional unit to confer photoresponsive properties to amphiphilic molecules and their assemblies. The reason for this selection is most probably due to their

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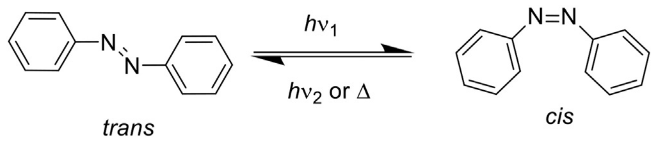
well-known photochemical properties and ease of synthesis and derivatization. These molecules can be found in two isomeric states: *trans* and *cis*, being the first one the thermodynamically stable state. *Trans* to *cis* isomerization can be promoted by light irradiation at appropriate wavelengths and the photogenerated *cis* isomer can be thermally reverted to *trans* in the dark (at very different rates depending on the substituents) or by light illumination at longer wavelengths (Scheme 1) [23]. The *trans-cis* photoisomerization is accompanied by a significant dipole moment change ($\Delta\mu \approx 3$ D) which contribute to modify lipophilic-hydrophilic balance of azobenzenes-based amphiphiles and perturb the self-assembled nanostructures [17•,15•,32].

Azobenzenes are frequently the molecule of choice to impart photochemical responsivity to biological, supramolecular and nanomaterials [32–36]. Amphiphiles are no exception and many derivatives containing azobenzene units were synthesized and reported (see Scheme 2 for some examples). The incorporation of azobenzene units in amphiphilic molecules was pioneered by Kunitake and co-workers [27–29]. These works were focused on the perturbation of vesicle membranes and phototriggered aggregate morphology transitions. The azobenzene derivatives **1** were suggested to form globular vesicles (bilayers) in water that transform into rod-like aggregates (micelles) after irradiation with 366 nm light. Although the nature of the aggregates was not unequivocally determined this is probably one of the first studies reporting a photoinduced vesicle-to-micelle transition. The system is reversible upon irradiation with visible light or upon heating the samples in the dark [27]. However, it should be noted that in systematic studies with structurally similar azosurfactants (**2**, **3**, **4** and **5**) the formation of vesicles was not reported but in the case of **2** the photoinduced transformation of large disklike micelles into smaller rodlike was suggested [31,37,38]. Double-tailed phospholipid and fatty acid derivatives bearing *trans*-azobenzene were synthesized(**6**–**11**) and characterized by Whitten et al. [39] However, contrary to conventional phospholipids, these amphiphiles do not self-assemble into closed bilayers able to entrap cargo molecules but into flat sheetlike structures observed by Cryo-TEM. Nevertheless, the authors were able to prepare vesicles from mixture of these amphiphiles with conventional D- and L-α-dipalmitoylphosphatidylcholine lipids. Using carboxyfluorescein (CF) as a fluorescent probe, it was shown that these vesicles could entrap CF without leakage for several days. Globular aggregates containing higher ratio of azobenzene phospholipids are disrupted by irradiation and the CF probe released.

The cationic photosurfactant **5** ($n = 2$, $R = C_4H_9$) was successfully employed to construct catanionic vesicles in the presence of anionic sodium dodecylbenzenesulfonate (SDBS) [40•]. The formation of spontaneous vesicles was observed for both anionic and cationic rich mixtures. In both cases reversible *trans-cis* photoisomerization was observed but, on the basis of turbidity measurements, it was proposed a different response of the aggregates to light stimulus, i.e., the anionic rich solutions do not show significant turbidity differences after irradiation while for cationic rich systems the turbidity increases upon light exposure. The photoreversible disruption of the vesicles was demonstrated by TEM micrographs. Spherical vesicles with 50–100 nm were transformed in unidentified elongated molecular aggregates after irradiation with UV light. Subsequent irradiation with visible light leads to the recovery of vesicles with average diameters of 50 nm. This photoresponsive system, constructed from **5** with SDBS and also with sodium dodecyl sulfate (SDS), was then employed has a non-viral vector to transport DNA into cells and release it after inducing the rupture of vesicle with UV illumination [41].



Scheme 1. Photochemically triggered *trans* – *cis* isomerization in azobenzenes.

Following their previous work on the catanionic system made from cationic azobenzene **5** ($n = 2$, $R = C_4H_9$) and anionic sodium dodecylbenzenesulfonate (SDBS) [40•], Sakai and co-workers reported a micelle to vesicle photoinduced transition that can be reversed also with light stimuli [42•]. The ternary phase diagram of **5**/SDBS/H_2O showed that for the regions with excess of one surfactant mixed micelles are formed (Fig. 1). Spontaneous vesicles were also observed in a wide range of concentrations both in the anion and cation-rich side of the diagram. Upon irradiation ca. 80% of *trans*-**5** is photoisomerized in the photostationary state independently of the **5**/SDBS ratio. For cation-rich mixtures, **5**/SDBS = 6:4, irradiation was observed to increase the turbidity of the solutions with differential interference microscopy showing 10–20 μm aggregates thus suggesting an appreciable change in the phase state. TEM micrographs showed the presence of 50 nm vesicles for non-irradiated solutions and large micrometer aggregates after UV-irradiation suggesting that the vesicles disintegrate after light absorption. Visible light irradiation leads to the reassembly of the vesicles demonstrating the reversibility of the system. At **5**/SDBS = 9:1, the DLS data suggests the formation of 50–200 nm vesicles for a total concentration of 1 mM while when the total concentration is 6.25 mM 6 nm particles, compatible with the formation of micelle-like aggregates, are observed. More interesting was the observation that for 1 mM concentration the size of the aggregates does not change upon irradiation while for 6.25 mM solution the observed size distribution greatly increased from 6 to 50–100 nm after UV-light illumination. These aggregates were confirmed to be vesicles by TEM observation. Again, irradiation with visible light recovered the 6 nm micelle-like aggregates demonstrating an all photonic reversible micelle to vesicle transition with UV and visible light. This work showed that the formation of vesicles can be triggered with UV light under certain conditions while for different conditions the vesicles can be also disintegrated. Conversely, vesicular aggregates can be formed in the dark thermodynamically stable state or in the photostationary metastable state depending on the **5**/SDBS ratio and total surfactant concentration.

More sophisticated azobenzene-based photosurfactants such as gemini **12** and bolaform **13** were also reported and characterized [43•,44,45•,46•,47•]. **12** forms polydisperse vesicles with sizes that range from few hundred nanometers to 10 μm as determined by FFTEM and no perturbation of the vesicle structures was observed after irradiation of the solutions with UV light (330–380 nm) [42•]. To improve the photoresponsivity of the vesicles, a mixture of cetyltrimethylammonium bromide (CTAB) and **12** in a 1:10 M ratio was prepared to obtain less stable bilayers. Under these conditions similar vesicular structures were observed but, in contrast with those formed from pure **12**, upon irradiation the vesicles are disrupted to give smaller objects that were not identified but proposed to be a mixture of micelles and small crystallites. However, the authors noted that the vesicles were not recovered despite of the reversibility of the azobenzene isomerization.

Bolaform **13** was studied in detail in the absence and presence of SDS [44,45•,46•,47•]. Mixed solutions of SDS and Bolaform **13** were studied in detail by Abbott et al. using quasi-elastic light scattering (QLS) and small-angle neutron scattering (SANS) experiments [47•]. These techniques showed the existence of vesicular aggregates with hydrodynamic diameters of 125–150 nm for samples containing *trans*-**13** and SDS in excess (Scheme 3). Analysis of the SANS data retrieved a bilayer thickness of 3.5 nm in agreement with the length of *trans*-**13** in a fully extended conformation. Illumination of these mixed solutions with UV light leads to a mixture of *cis*-**13** and *trans*-**13** at the photostationary state in a 80:20 M ratio. After the application of this stimulus, the scattering experiments confirmed a photoinduced morphology transition into aggregates with hydrodynamic diameters of 24 nm and cross sectional radii of 1.9 nm compatible with rod-like micelles. The vesicular