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Reversible Disassembly−Assembly of Octa Acid−Guest Capsule in Water Triggered by a Photochromic Process

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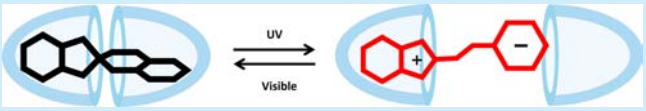
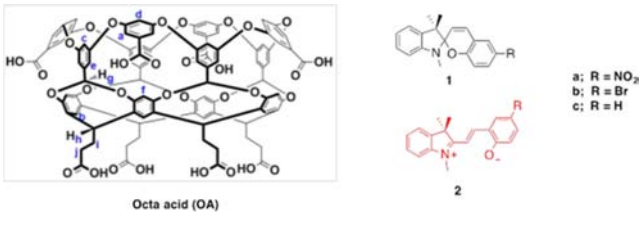
Supporting Information

ABSTRACT: Octa acid (OA), a calixarene-based cavitand, forms a 1:2 capsular assembly with neutral 1,3,3-trimethyl-6′-nitrospiro[2*H*-1]benzopyran-2,2′-indoline and 1:1 cavitandplex with its open zwitterionic merocyanine form. Photochromic interconversion between the spiropyran and merocyanine leads to unprecedented reversible capsular disassembly and assembly. OA provides stability to the merocyanine in both the ground and excited states. The photochemically controlled disassembly and assembly process established here points toward the opportunity of using the OA capsule in delivering small molecules at the desired locations.



Considerable progress has been made during the last three decades toward modifying the known excited state behavior of organic molecules through supramolecular approaches.[1] Among the photoreactions explored within supramolecular assemblies, photochromic ring-opening reaction of spiropyrans is noteworthy due to its application in optical switching, data storage, ophthalmic lenses, and drug delivery.[2] For this process to gain value as a biological probe, solubility and stability in water of the reactant spiropyran and the product merocyanine are necessary. The widely used spiropyran named 1,3,3-trimethyl-6′-nitrospiro[2*H*-1]benzopyran-2,2′-indoline (**1a**) and its open merocyanine form **2a** (Scheme 1) are unfortunately insoluble in water. Attempts at

Scheme 1. Structure of Water-Soluble Octa Acid (OA) Cavitand and the Guest Molecules



solubilizing **1a** with water-soluble hosts such as micelles,[3−6] cyclodextrins,[7,8] cucurbiturils,[9,10] calixarenes,[11] and proteins[12] have been less successful. Of the various supramolecular assemblies, cholic acid micelles and dioctadecyldimethylammonium bromide vesicles were better but had limited solubilizing ability (∼50 μM). We were thus prompted to exploit octa acid (OA; Scheme 1),[13] a cavitand that has been successfully used to modify the excited state behavior of organic molecules, for photochromic studies of **1a** in water.[14] Our goals were to solubilize both **1a** and **2a** in water, stabilize them under photolytic and thermolytic conditions, and photochemically toggle between the two forms within the confined space of OA. We had previously established that (a) a guest with a charged headgroup would form an open 1:1 cavitandplex with OA while a neutral guest would prefer a closed 1:2 (guest to host) or 2:2 capsuleplex[15] and (b) interior micropolarity of OA capsule is benzene/toluene-like despite the aqueous environment.[16] We anticipated that the hydrophobic, neutral **1a** with its nonpolar environment preference would form a closed capsule, while the partially hydrophilic zwitterionic **2a** would prefer a 1:1 open cavitandplex. The photochemical conversion of **1a** to **2a** involving a sudden large change in dipole moment (from ∼4 to ∼18 D)[2] and generation of a zwitterionic species from a neutral reactant would provide an opportunity to investigate the OA capsular disassembly−assembly process. We envisioned the controlled disassembly of OA to aid strategic release in the future of small hydrophobic molecules at desired locations in an aqueous environment. Toward these possibilities, we have explored the photochromic behavior of **1a** and **2a** included within OA. Highlights of our results include the following: (a) both **1a** and **2a** solubilize at the 1 mM level in water at pH 9 (and at 10 μM level at pH 7) in OA; (b) while **1a** upon inclusion within OA senses a nonpolar environment (toluene-like), the ring-opened zwitterionic product **2a** senses an aqueous environment; (c) the photochromic process of **1a** and **2a** leads to capsular disassembly and assembly; (d) inclusion of **2a** within OA protects it from acid/base catalyzed decomposition; (e) there is an observed enhancement in the excited-state singlet lifetime (S_1) of **2a** that we believe is due to slower cyclization of **2a** to **1a** within OA.

Since the initial report by Hirshberg and Fisher,[17] examination of numerous spiropyrans has revealed that the presence of an electron-withdrawing group (e.g., NO_2) is essential to make the open form thermodynamically stable so that the closing will be slow under ambient conditions. This has resulted in the use of **1a** as the model system for most studies. We have examined the photochemical behavior of three

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systems **1a**, **1b**, and **1c**, of which only **1a** showed experimentally observable photochromic behavior. The other two merocyanines reversed thermally to the spiropyran instantaneously. Results for **1b** and **1c** are included as Supporting Information (Figures S1−S5) and those for **1a** are presented below.

Spiropyran **1a** insoluble in borate buffer went into solution in the presence of OA. In Figure 1 are provided the ^{1}H NMR

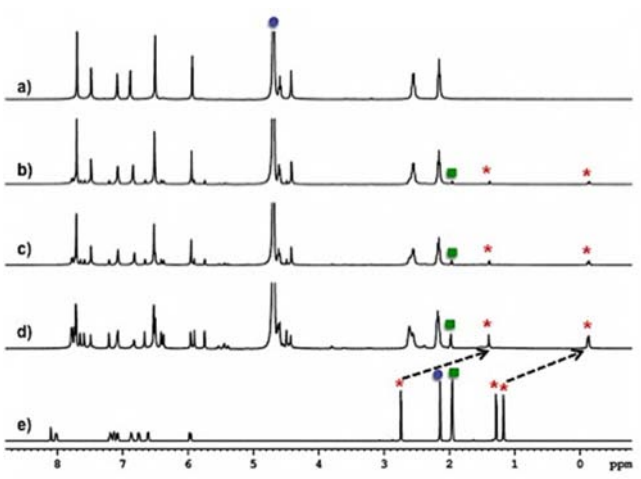


Figure 1. ^{1}H NMR (500 MHz) spectra of (a) OA([OA] = 1 mM) in 10 mM $Na_2B_4O_7$ buffer/D_2O; (b) **1a**@OA_2 ([OA] = 1 mM), [**1a**] = 0.125 mM) in 10 mM $Na_2B_4O_7$ buffer/D_2O; (c) **1a**@OA_2 ([OA] = 1 mM), [**1a**] = 0.25 mM) in 10 mM $Na_2B_4O_7$ buffer/D_2O; (d) **1a**@OA_2 ([OA] = 1 mM), [**1a**] = 0.50 mM) in 10 mM $Na_2B_4O_7$ buffer/D_2O; (e) **1a** in CD_3CN. Key: * indicates bound guest proton peaks; ● and ■ represent the residual solvent peaks of D_2O and CD_3CN, respectively.

spectra of OA and solutions containing various ratios of **1a** and OA in borate buffer (pH ∼ 8.9) and **1a** in CD_3CN (for experimental details, see the SI). Upon addition of **1a** to the aqueous solution containing OA, the chemical shifts of both are affected, confirming interaction between the two. In these spectra, the signals due to the three methyl groups of **1a** are upfield shifted, with the $\Delta(\delta_{OA} - \delta_{CD3CN})$ ranging between −1.3 and −1.4 ppm, a clear indication of guest inclusion within OA.[13] Titration experiments revealed that addition of more than 0.5 equiv of **1a** showed no change in the spectra, further suggesting the guest to host ratio to be 1:2. In addition, the integration of the guest methyl and selected host signals as well as the diffusion constant measured by DOSY (1.35×10^{-6} cm^2/s; Figure S6, SI) were consistent with the formation of a capsule containing one molecule of **1a** and two molecules of OA (represented as **1a**@OA_2). This is further supported by the appearance of two signals in the ^{1}H NMR spectrum for several chemically equivalent protons of OA in the region δ 6.5−8 ppm because the unsymmetrical guest **1a** (along the short axis) imparts magnetic nonequivalence to the two halves of the capsule, further supporting the **1a**@OA_2 capsule. The appearance of a single set of signals for the guest methyl groups suggested the absence of free **1a** in water. Thus, ^{1}H NMR spectra provided unequivocal evidence for the solubilization of **1a** in water by OA by including it within a hydrophobic capsule. NOESY correlation between the three methyl groups of the guest and the host OA protons (H_d, H_c and H_e) (NOESY spectra see Figure S7, SI) suggested that all three methyl groups are located at the middle region of the capsule.

The colorless aqueous solution of **1a**@OA_2 upon irradiation (365 ± 20 nm; see the SI for experimental details) turned red with an absorption in the region 450−620 nm (Figure 2 and

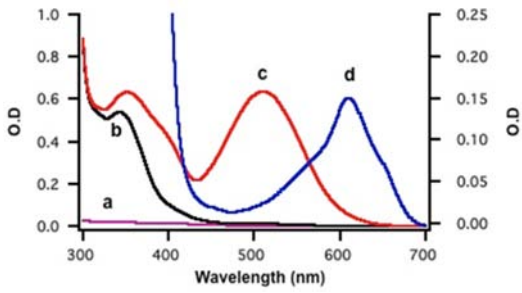
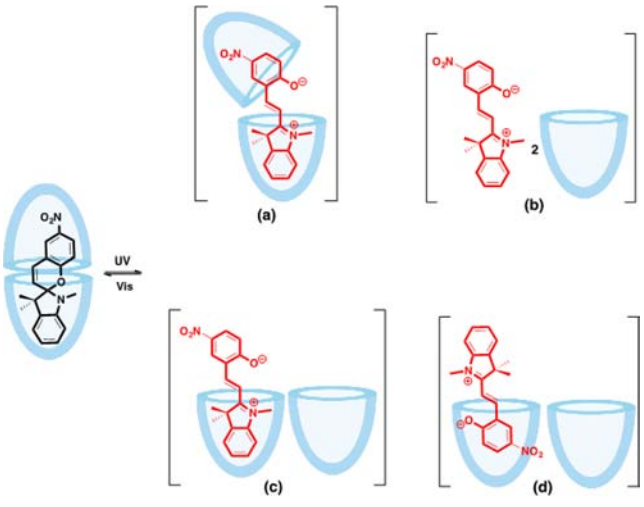


Figure 2. Absorption spectra of (a) **2a** in buffer; (b) **1a**@OA_2 in buffer; (c) **2a**@OA in buffer; and (d) **2a** in benzene. The *Y*-axis scale on the left side (0 to 1.0) corresponds to the spectra a−c, and the scale on the right side (0 to 0.25) corresponds to the spectrum d.

Figure S8, SI). The recorded absorption is consistent with the merocyanine **2a** spectra reported in the literature.[18] The ^{1}H NMR spectrum did not reveal any new peaks even though the solution turned red, suggesting the conversion was not high enough to be detected by this technique. It must be noted that in organic solvents also the conversion is less than 10%. One of the most important observations is the λ_{max} of the absorption within OA (511 nm), one considerably blue-shifted relative to that in benzene (600 nm) and most organic solvents (615 to 512 nm).[6,18] Had **2a** remained within OA capsule it would be in a benzene/toluene-like environment with an absorption maximum at 600 nm.

Thus, we infer the zwitterionic merocyanine to be in an environment closer to the methanol−water mixture (absorption at 512 nm)[6] and not confined within the hydrophobic capsule where it was generated. We expect the merocyanine with zwitterionic character and high dipole moment to be less hydrophobic than the spiropyran and prefer a polar environment rather than a hydrophobic one. The absorption characteristic of **2a** is consistent with the conclusion that the ring-opening process has prompted a capsular disassembly (Scheme 2) exposing **2a** (fully or partially) to water. This

Scheme 2. Capsule Disassembly and Assembly Triggered by the Photochromic Behavior of Spiropyrans 1a and 2a



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assumption is also supported by **2a** being protonated (λ_{max} ~ 402 nm) upon lowering the pH of the solution from 8.9 to 6.5 and the protonated form reversing to **2a** upon increasing the pH of the solution from 6.5 to 8.9 (Figures S9–S11, SI). In the absence of ^{1}H NMR spectra we are unable to unequivocally state which one of the structures in Scheme 2 represents the **2a**–OA complex.

On the basis of the known behavior of merocyanine derivatives in water, organic solvents, and organized assemblies, several questions come to mind: (a) How stable is **2a**@OA in water? (b) Will it revert to spiropyran upon irradiation with visible light? (c) Would **1a**@OA_2–**2a**@OA exhibit photochromic behavior in water similar to uncomplexed **1a**–**2a** in isotropic solution? (d) Would this photochromic process result in reversible capsular disassembly–assembly? (e) How would OA, as it does with the various other excited state reactions, affect the various excited state decay processes of **2a** and **1a**?

Remarkably, upon irradiation of **2a**@OA with 420 ± 20 nm light the red color disappeared with the formation of **1a**@OA_2 as confirmed by UV absorption spectra (Figure S12, SI). If the reformed **1a** molecule had remained in solution, it would have precipitated, especially after several cycles. Even after 10 cycles there was no evidence of turbidity due to free **1a**. Thus, **1a**@OA_2–**2a**@OA interconversion is not only photochromic but also triggers disassembly assembly of the capsule. This is a much welcomed result from our previous finding of the possibility of the disassembly of the OA capsule by a phototriggering reaction.[19,20] In this case, the capsule was not reassembled.

The photochromic process could be repeated for at least 10 cycles at pH 7 and 9 with ~25% loss of **1a** and/or **2a** (Figure S12 and S13, SI). The thermal stability of **2a**@OA was monitored by its absorption at 511 nm. It took almost 20 h for the merocyanine to thermally reverse to spiropyran (Figure 3)

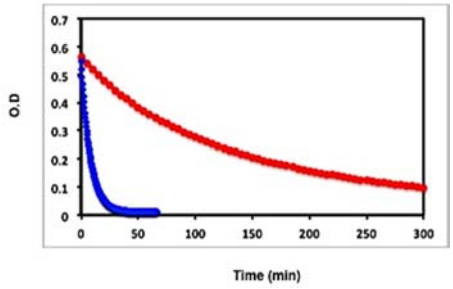


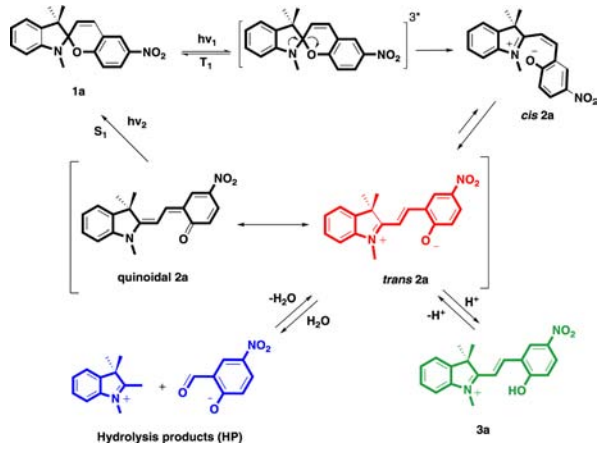
Figure 3. Decay of the absorption at 511 nm due to **2a**@OA (red) and **2a** in acetonitrile (blue). Reisomerization rate constants for **2a** in acetonitrile and OA are 2×10^{-3} s^{-1} and 1.1×10^{-4} s^{-1}, respectively.

while in acetonitrile the solution became colorless in less than 30 min. The rate of return was about 19 times slower than in acetonitrile. Although in methanol–water mixture **2a** is known to decompose to the products shown in Scheme 3,[21,22] there was no evidence of such decomposition in the case of **2a**@OA even after 20 h.

The above observations suggest that OA provides extraordinary stability for **1a** and **2a** in water while preserving their photochromic property. This capability of OA is distinctly different from cyclodextrins, cucurbiturils, and calixarenes, each of which has its own limitation as mentioned above.

The ring opening of **1a** and closing of **2a** have been established to proceed from the excited triplet and singlet state,

Scheme 3. Mechanism of Photointerconversion between 1a and 2a and Further Reactions of 2a



respectively,[23–25] and reported to have sub-nanosecond lifetimes in isotropic solution.[25–27] As illustrated in Scheme 3, formation of **2a** and the reverse process involve at least two steps, ring-opening/closing and *cis*–*trans* isomerization. Having established previously the slow *cis*–*trans* isomerization of stilbene and GFP chromophore derivatives within OA,[14] we wished to examine the excited-state behavior of **2a** involving *cis*–*trans* isomerization as the primary step.

As expected, **2a**@OA showed fluorescence (Figure S8, SI).[28] Interestingly, the lifetime of **2a**@OA as monitored by the decay of fluorescence was 10 times longer within OA (biexponential: 3.3 ns (83%); 0.8 ns (17%); Figure 4) than in organic solvents.

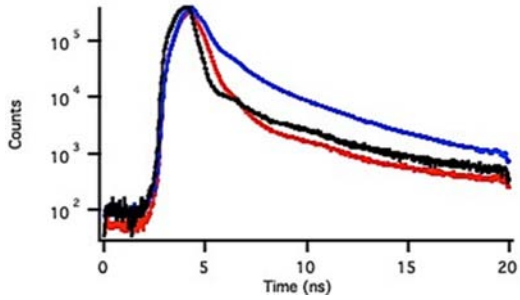


Figure 4. Decay of the fluorescence of **2a**@OA (blue), **2a** in ethanol (red), and instrument response function (IRF) (black). The decay in the case of **2a**@OA is biexponential with lifetimes 3.3 ns (83%) and 0.8 ns (17%). Emission decay was monitored at 625 ± 5 nm, and the sample was excited using LED at 405 ± 10 nm.

Such a remarkable influence of a supramolecular assembly on the photochromic behavior of spiropyrans, to our knowledge, has no precedence in solution and is only known in solid polymer matrix.[28] Evidence in favor of **2a** existing as several conformers in toluene solution has been obtained by recording the excitation spectra by monitoring **2a** fluorescence at different wavelengths.[27] Within OA, regardless of the monitoring and exciting wavelengths, both the emission and the excitation spectra remained the same (Figure S14 and S15, SI), suggesting that the majority of **2a** molecules remain in a single conformation within OA. Ultrafast time-resolved studies can further our knowledge on the extraordinary influence of OA on the excited-state dynamics of the photochromic process.

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In this paper, we have demonstrated the possibility of reversible disassembly and assembly of the OA capsule by a photochromic reaction. The influence of OA on the excited-state behavior and ground-state stability of a well-known spiropyran system is far superior to those of other organized supramolecular assemblies. The process described here could be useful in transporting and releasing small hydrophobic molecules in a spatially and temporally controlled manner in an aqueous environment. The concept expounded here could also be translated to other larger water-soluble cavitands and capsules. We propose to pursue such studies as well as monitor molecular dynamics of photochromic systems within OA through time-resolved ultrafast experiments.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00405.

Experimental procedure, ^{1}H NMR, DOSY, and NOESY spectra of host−guest complexes, absorption and fluorescence spectra of the photochromic solution of host−guest complexes, and experimental data on **1b** and **1c** (PDF)

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Notes

The authors declare no competing financial interest.

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