Molecular Capsules

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Micelle-like Molecular Capsules with Anthracene Shells as Photoactive Hosts**

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Micelles are spherical assemblies of amphiphilic molecules and one of the oldest classes of supramolecules. They are used in a wide range of practical applications, such as dissolution, separation, preservation, and as reaction vessels.[1–3] The amphiphiles are typically linear molecules with hydrophilic "heads" and hydrophobic "tails", so that *hydrophobic interactions* in water induce the spontaneous formation of spherical aggregates (Figure 1a). Inspired by the assembly

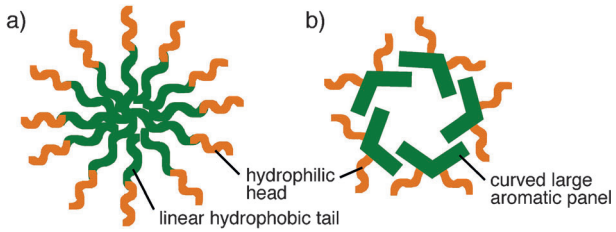

Figure 1. Schematic representation of spherical assemblies of amphiphilic molecules. a) A standard micelle composed of linear amphiphiles. b) A molecular capsule with an aromatic shell composed of rigid bent amphiphiles.

of micelle structures, we envisaged that *aromatic–aromatic interactions* between large aromatic rings could replace the requisite long hydrophobic tail and favor the assembly of a new class of nanometer-sized molecular capsules (Figure 1b) with potential applications as functional containers[4–9] and reactors.[10–12] Large aromatic compounds have received much attention as planar and photo-/electrochemically active mesogens; derivatives decorated with flexible hydrophilic or hydrophobic side chains can generate infinite columnar assemblies that exhibit extensive aromatic–aromatic interactions.[13,14] However, discrete capsule-like micellar assemblies cannot readily form from such rigidly planar aromatic compounds. Although molecular capsules formed through noncovalent hydrogen-bonding,[5,6] coordinative metal–ligand,[7,15] hydrophobic,[16] and van der Waals/CH–π interactions[17] have been studied,[18] the majority of these capsules, and known micelles, do not contain extended aromatic frameworks and are typically not photoactive.[19] Thus, systems capable of efficient energy transfer between a host and a guest are needed to enrich the photofunctionality of the molecular capsules.[20]

Herein, we report the preparation of micelle-like molecular capsules from amphiphilic molecules by the use of curved large aromatic panels instead of the usual linear hydrophobic tails (Figure 1b). The self-assembly of these capsules is promoted by a combination of hydrophobic forces and π-stacking interactions. Amphiphile **1** contains two anthracene moieties connected through an *m*-phenylene spacer functionalized with two hydrophilic ammonium or sulfobetaine groups (Figure 2a). Steric repulsion between the bulky

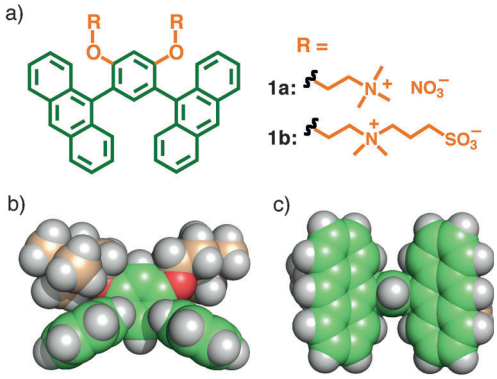

Figure 2. Bent amphiphilic molecules **1**. a) Amphiphilic molecules **1a** and **1b** designed to form hydrophobic aromatic frameworks substituted with hydrophilic groups. b,c) Side and front views of the structure of **1a** as optimized by DFT calculations (B3LYP/6-31G* level) without the counterions.

ortho substituents forces the anthracene moieties and the phenylene spacer into an orthogonal conformation and thus leads to a bent aromatic panel (Figure 2b,c).[21,22] The pendant ammonium groups of **1a** provide a hydrophilic surface on the *exo*-cyclic face of the rigid hydrophobic panel. Accordingly, in an aqueous medium, the bent amphiphile **1a** quantitatively assembles into the spherical capsule **2a** through π-stacking and hydrophobic interactions. This new capsule has the following remarkable features: 1) the diameter of the core

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framework is approximately 1 nm with a narrow size distribution; 2) the critical micelle concentration (CMC) is approximately 1.0 mM; 3) the anthracene shell emits pale-green fluorescence; 4) selective encapsulation is found for hydrophobic fluorescent dyes; 5) efficient fluorescence resonance energy transfer (FRET) emission is observed from the encapsulated guests upon the irradiation of the host framework.

Amphiphile **1a**, in which hydrophilicity is provided by two quaternary ammonium substituents, was synthesized in good yield (ca. 60% yield over six steps) from 1,3-dimethoxybenzene.[23] The concise synthesis and simple isolation procedures facilitated the gram-scale preparation of **1a**. The heating of a suspension of **1a** (2.0 μmol) in D_2O (1.0 mL) at 80°C for 1 min resulted in a clear colorless solution, which indicated the quantitative formation of **2a**. NMR spectroscopy, particle-size analysis, and atomic force microscopy (AFM) of **2a** confirmed the formation of a micellar structure with a core diameter of approximately 1 nm.

The formation of **2a** from **1a** was readily observed by ^{1}H NMR spectroscopic analysis (Figure 3). The spectrum of

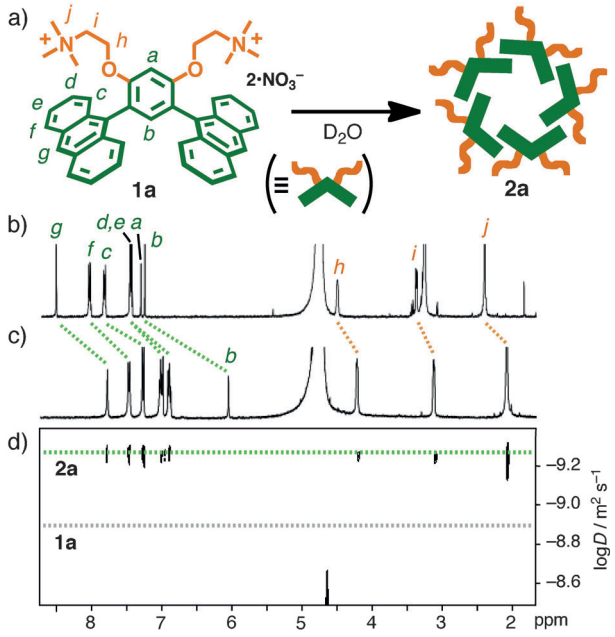

Figure 3. Formation of the molecular capsule **2a** from bent amphiphiles **1a** in an aqueous solution. a) Schematic representation of the self-assembly of **2a** from **1a** in D_2O. b) ^{1}H NMR spectrum (400 MHz, room temperature) of a solution of **1a** in CD_3OD. c) ^{1}H NMR and d) DOSY spectrum (400 MHz, tetramethylsilane as an external standard) of a solution of **2a** in D_2O (2.0 mM as based on **1a**) at 30°C.

1a in CD_3OD showed the seven aromatic signals of the anthryl (H_{c-g}) and *m*-phenylene ($H_{a,b}$) groups in the range of $\delta = 7.31$–8.59 ppm (Figure 3b). After the formation of **2a** in D_2O (2.0 mM as based on the quantity of **1a** used), these signals were significantly shifted upfield (Figure 3c). The pendant hydrophilic groups (H_{h-j}) appeared at $\delta = 2.46$–4.57 ppm and experienced small upfield shifts upon the formation of **2a**. The large upfield shifts of the anthracene signals ($\Delta\delta_{max} = -0.74$ ppm) as well as the results of NOESY analysis[23] suggest intermolecular aromatic interaction of the rings and thus support the formation of **2a**. Moreover, the huge upfield shift of the signal for H_b on the central *m*-phenylene ring ($\Delta\delta = -1.20$ ppm) is indicative of a capsular structure owing to the efficient shielding effect of neighboring anthracene rings in the assemblies $(\mathbf{1a})_n$ (Figure 3c).[21,22] The diffusion-ordered spectroscopy (DOSY) NMR spectrum of **2a** in D_2O showed a single band at a diffusion coefficient (D) of 5.1×10^{-10} m^{2}s^{-1} (Figure 3d), which is significantly smaller than that of **1a** in CD_3OD (1.3×10^{-9} m^{2}s^{-1}). The hydrodynamic diameter of **2a** was estimated to be approximately 1.0 nm on the basis of the diffusion coefficient and the Stokes–Einstein equation. Dynamic light scattering (DLS) and the induced grating (IG) method[23,24] confirmed the presence of small assemblies with a diameter of approximately 1 nm and a narrow size distribution (±0.5 nm; see Figures S29 and S30 in the Supporting Information) and also revealed the absence of large aggregates (of 10–100 nm in diameter). In sharp contrast, usual micelles are prone to form larger aggregates with large size distributions (see Figure S29D).

AFM analysis of **2a** was carried out under both wet and dry conditions. An aqueous solution of **2a** (2.0 mM as based on **1a**) was cast on a freshly cleaved mica surface. Wet-state AFM analysis provided clear images of small spherical particles with an average diameter of (2.3 ± 1.0) nm (Figure 4a–c), which is comparable to the average diameters,

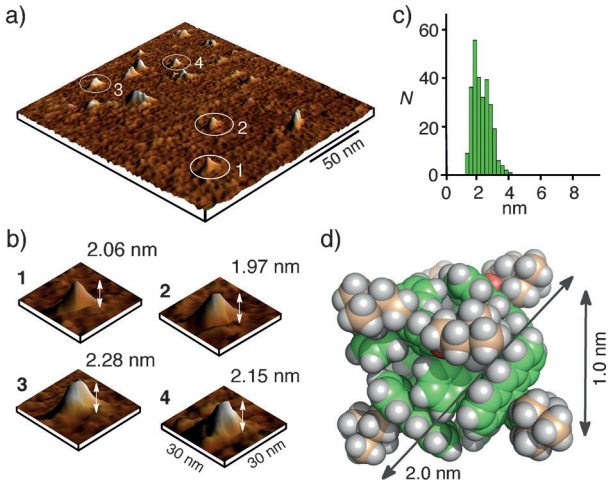

Figure 4. Structural analysis of the spherical capsule **2a** by AFM. a) AFM image of a solution of **2a** in H_2O (2.0 mM as based on **1a**) on mica. b) Height profiles of selected features (highlighted in (a)) of the AFM image of **2a**. c) Size and number (N) distribution of the AFM image of **2a**. d) Molecular modeling of capsule **2a** composed of four molecules of **1a**.

including the peripheral bulky ammonium groups, of the structures predicted by molecular modeling for spherical assemblies $(\mathbf{1a})_n$ with $n = 4$–6. For example, the external diameter of a tetrameric assembly of **1a** is approximately 2.0 nm (Figure 4d), and the core framework (ca. 1 nm in diameter) has an inner cavity expected to accommodate

planar guest molecules. The assemblies are robust even after the complete evaporation of water. Dry-state AFM images showed large spherical particles of uniform dimensions (height) of approximately 2.0 nm (see Figure S31).[23]

Like micellar assemblies, the capsule **2a** is sensitive to concentration. Concentration-dependent NMR spectroscopic studies (at 0.25–4.0 mM as based on **1a**) demonstrated that the CMC value of **2a** is ≤ 1.0 mM and thus approximately 10 times smaller than that of sodium dodecyl sulfate (SDS) micelles. At a lower concentration (< 0.25 mM), the aromatic signals of **2a** in the ^{1}H NMR spectrum shifted back downfield, and the DOSY spectrum showed a broadened band around $D = 7.6 \times 10^{-10}$ m^2 s^{-1}. However, in stark contrast to typical micelles, **2a** is insensitive to both temperature and the pH value. The proton signals of **2a** (2.0 mM) in the ^{1}H NMR spectrum remained almost unchanged up to 70 °C and in the pH range 1–13 (see Figures S27 and S28).[23,25] We believe the higher stability of **2a** stems from intermolecular *aromatic–aromatic interactions* of the anthracene frameworks.

Micelle **2a** is effectively a dense molecular cluster of anthracene fluorophores and exhibited unusual emission behavior. The UV/Vis spectra of **1a** and **2a** were quite similar and exhibited absorption bands at 320–420 nm, which were assigned to the π–π* transitions of the anthracene moieties (Figure 5a).[21] There were significant differences,

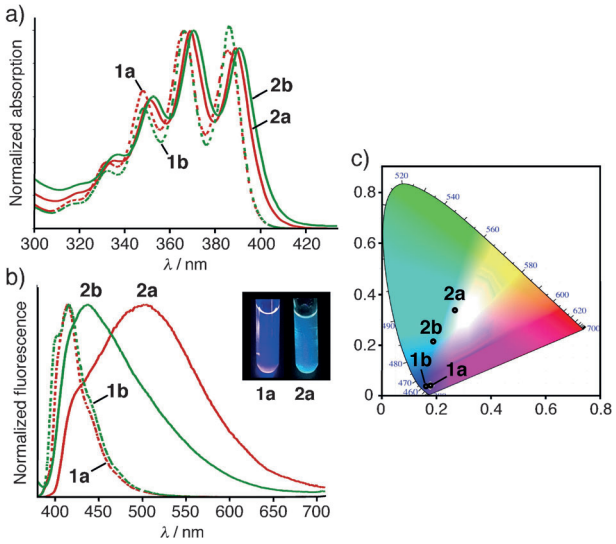

Figure 5. Spectroscopic properties of capsules **2a** and **2b** as compared with **1a** and **1b**. a) Normalized absorption spectra and b) normalized fluorescence spectra ($\lambda_{ex} = 370$ nm) of **1a** (red dotted line) and **1b** (green dotted line) in MeOH and **2a** (red line) and **2b** (green line) in H_2O at room temperature. c) CIE coordinate diagram of the fluorescence color of **1a** and **1b** in MeOH and **2a** and **2b** in H_2O.

however, in the emission behavior of **1a** and **2a**. A typical blue anthracene-like emission ($\lambda_{max} = 415$ nm) was observed for a solution of **1a** in methanol upon irradiation at 370 nm. In contrast, the irradiation of an aqueous solution of **2a** at 370 nm resulted in a pale-green emission due to a broad fluorescent band from 400 to 700 nm ($\lambda_{max} = 505$ nm, $\Phi_F = 0.07$), which most likely arises from anthracene excimer aggregates (Figure 5b).[26] The excitation spectrum of **2a** resembles the absorption band of **1a** and **2a** (Figure 5a) and indicates that the emission results from the excitation of orthogonal and thus decoupled anthracene moieties. The CIE chromaticity diagram (CIE = International Commission on Illumination) of **1a** and **2a** was used to quantify the total emission color ((0.16, 0.04) and (0.25, 0.34), respectively; Figure 5c). The color of **2a** approaches pure white (0.31, 0.34), unlike that of most anthracene derivatives or their assemblies.

Simple modification of the hydrophilic groups on the *exo*-cyclic surface of amphiphile **1** gave improved micelle behavior. Amphiphile **1b**, obtained in one step from the precursor to **1a**, has pendant zwitterionic sulfobetaine hydrophilic groups and gave rise to spherical assemblies **2b** in H_2O. AFM analysis revealed that the average diameter of **2b** is 3.9 nm, although the modeled aromatic shell of **2b** is comparable to that of **2a** (see Figure S40). Notably, **2b** showed a lower CMC value (0.03 mM), which indicates that the micellar structure of **2b** is more stable than that of **2a**.[23] The large hydrophilic sulfobetaine groups cover the *exo*-cyclic surface of **1b**, as revealed in detail by the X-ray crystal structure (see Figure S41). The pale-blue fluorescence of **2b** is different from that of **2a** and indicates that the large sulfobetaine groups alter the intermolecular anthracene–anthracene interactions of **2b** (Figure 5b,c).

The hydrophobic cavity of capsule **2**, defined by the fluorescent anthracene shell, successfully encapsulated Nile red (**3**) and 4-(dicyanomethylene)-2-methyl-6-(4-dimethylaminostyryl)-4*H*-pyran (**4**), well-known hydrophobic fluorescent dyes, to produce photoactive host–guest complexes (Figure 6a). A slight excess of water-insoluble **3** was added to an aqueous solution of **2a** (2.0 mM as based on **1a**), and the resulting suspension was stirred at room temperature for 1 h. A clear blue solution of **2a** containing **3** (denoted **2a**⊃**3**) was obtained after the removal of the remaining free **3** by filtration (Figure 6b).[27] The UV/Vis spectrum of the solution showed a new absorption band at $\lambda_{max} = 610$ nm due to encapsulated **3**. Dye **4** was enclathrated under similar conditions to give a red solution of **2a**⊃**4** with a UV/Vis absorption band at $\lambda_{max} = 508$ nm (Figure 6b). The host–guest complex **2a**⊃**3** exhibited blue emission upon irradiation of the host anthracene absorption band at 370 nm. Two weak, broad emission bands were present in the emission spectrum at $\lambda =$ 420–570 and 640–760 nm (Figure 6c) and were assigned to the anthracene moieties of **2a** and enclathrated **3**, respectively. These bands indicate that FRET efficiency from host **2a** to guest **3** is moderate (66% as calculated from the fluorescence-quenching data). The aqueous solution of **2a**⊃**4** displayed efficient FRET, and only red emission was observed (Figure 6c). The absorption band ($\lambda_{max} = 508$ nm) of **4** overlaps greatly with the emission band of **2a**; accordingly, strong red emission ($\lambda_{max} = 642$ nm, $\Phi = 0.23$) from guest **4** was observed upon irradiation of the anthracene bands of **2a**⊃**4** at 370 nm. The apparent efficiency of the energy transfer was estimated to be 97% from the fluorescence-quenching profile of the anthracene moieties. Interestingly, the red emission of **2a**⊃**4** was enhanced by a factor of 1.3 when the host–guest complex

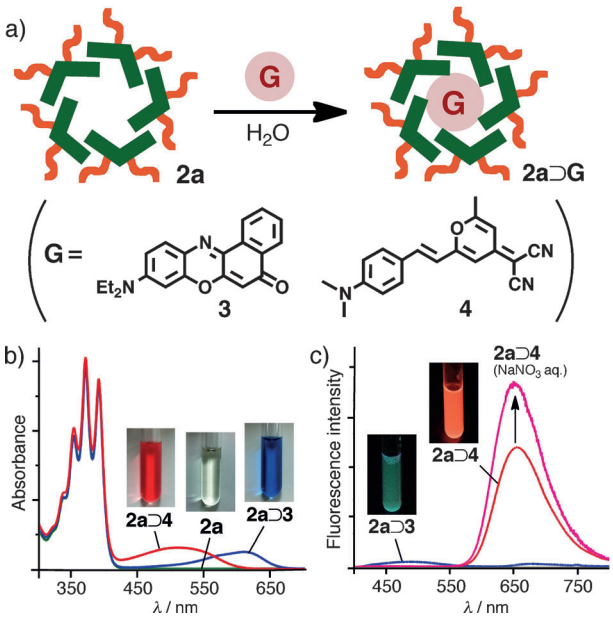

Figure 6. Encapsulation of the fluorescent guests **3** and **4** by **2a** in an aqueous solution. a) Schematic representation of the encapsulation of the guests by **2a**. b) Absorption spectra (H_2O, 2.0 mM as based on **1a**, room temperature) of **2a**, **2a⊃3**, and **2a⊃4** with photographs of the solutions. c) Fluorescence spectra (H_2O, 2.0 mM as based on **1a**, λ_{ex} = 370 nm, room temperature) of **2a⊃3** and **2a⊃4** with/without $NaNO_3$ (5 mM) with photographs of the solutions (λ_{ex} = 365 nm).

was prepared in an aqueous solution containing $NaNO_3$ (5.0 mM; Figure 6c).[28]

The capsular structure of **2** is essential to both the encapsulation of hydrophobic fluorescent guests in water and the strong fluorescence of encapsulated guests through efficient energy transfer from the host shells. When isolated **2a⊃4** and **2a⊃3** were dissolved in MeOH, the host–guest complexes disassembled, and only blue emission from free **1a** at 417 nm was observed upon irradiation at 370 nm (see Figure S50). The control of energy transfer from self-assembled donors to acceptor chromophores has been demonstrated in the gel state.[20] However, efficient FRET emission from guests within discrete self-assembled hosts has not been reported previously.[19]

In summary, we have successfully prepared novel molecular capsules reminiscent of micelles through both aromatic–aromatic and hydrophobic interactions of amphiphiles providing bent aromatic frameworks. The straightforward synthesis, high stability, and efficient FRET emission properties of this new class of self-assembled molecular capsules with spherical aromatic shells and their aqueous green chemistry reinforce our expectation that these capsules, which can be described as "aromatic micelles" as contrasted with previous "hydrocarbon micelles", will expand the application of molecular flasks, since the majority of previous self-assembled hosts were not photoactive.[19] The present nanocapsules might be suitable for potential applications in the fields of photofunctional dyes, sensors, and materials owing to their ability to accommodate guest molecules and their efficient host–guest energy transfer in aqueous media. We expect that the functionalization of the aromatic shells as well as the use of other extended aromatic panels will lead to new molecular capsules with a wide range of fluorescent properties. Studies along these lines are currently in progress in our research group.

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[23] See the Supporting Information. In the NOESY spectrum of **2a**, two sets of correlation signals (H_e–H_g and H_b–H_d) were observed between different amphiphilic molecules (see Figure S55).

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[26] The emission lifetime (τ) of **2a** (23 ns) is longer than that of **1a** (11 ns).

[27] ^{1}H NMR spectra of **2a**⊃**3** and **2a**⊃**4** in D_2O revealed that the aromatic signals from the shells of **2a** were hardly altered by the encapsulation of guest **3** or **4**. This result indicates that the shape and size of the capsule framework are retained, as also evidenced by DOSY NMR spectroscopic analysis (see Figure S44 and S46). In contrast, the proton signals of the encapsulated guests were significantly broadened owing to restriction of the molecular motion by the limited cavity of **2a** (see Figures S42 and S45). Thus, the NOESY and DOSY spectra exhibited only signals derived from the host framework. When CD_3OD (20–80% v/v) was added to solutions of the host–guest complexes in D_2O, the guest signals in the ^{1}H NMR spectra were observed with large upfield shifts (see Figures S53 and S54).

[28] The absorption spectrum of **2a**⊃**4** in methanol revealed that the ratio of **1a** to **4** is 20:1, which indicates that approximately 20% of capsule **2a** binds one molecule of **4**. The increase in solvent polarity upon the addition of the salt $NaNO_3$ promotes the enclathration of dye **4** by capsule **2a**.