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Switching the Interior Hydrophobicity of a Self-Assembled Spherical Complex through the Photoisomerization of Confined Azobenzene Chromophores**

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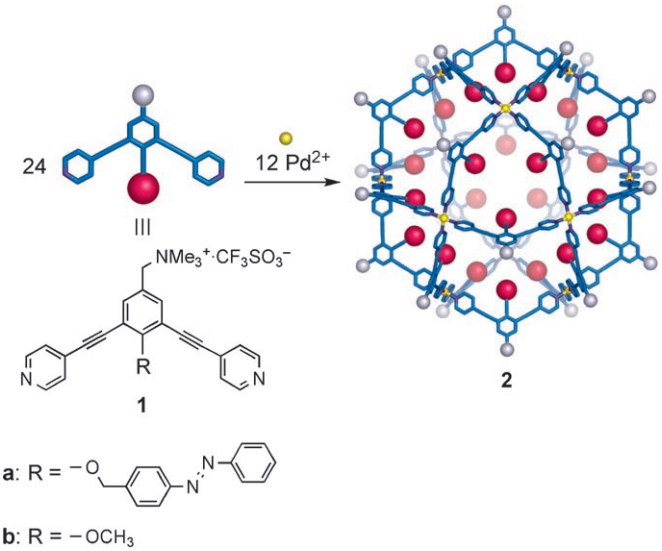
Control of restricted nanosized space by external stimuli that accompany changes of local structures and properties has attracted a great deal of attention.[1] Light is a particularly useful and efficient stimulus to cause reversible structural changes in molecular and supramolecular systems. Azobenzene is a well-known chromophore that responds to light and undergoes *cis–trans* isomerization, resulting in large changes in its size and polarity.[2] The micellization of azobenzene-containing copolymers has been, for example, reversibly switched by light because the *trans*-to-*cis* isomerization of the chromophore increases the dipole moment, dramatically changing the hydrophilic/hydrophobic balance of the core.[3] Although dendrimers with azobenzene functionalities around the peripheries[4] have also been well studied, the assembly of many azobenzene moieties at the interior[5,6] of dendrimers is synthetically troublesome. Therefore, it is an intriguing task to confine a restricted number of azobenzene chromophores in the well-defined core regions of nanosized molecules with ease. Such structures make it possible to reversibly change the properties of the interior environment by photoisomerization.

We have previously shown that upon complexation with 12 metal ions, 24 pyridine-based bent bridging ligands spontaneously assemble in solution into a spherical complex with a precise chemical structure and uniform diameter (Scheme 1).[7] Attaching a functional group to the convex[7a] or concave[7b–d] side of each ligand leads to the 24-fold surface or endohedral functionalization of the sphere, respectively. We herein describe a highly cationic spherical complex bearing azobenzene groups that face inwards.[8] The core of the complex features the dense array of 24 azobenzenes. This spherical complex can be regarded as an azobenzene-functionalized "inverse dendrimer"[9] with branches in the converging region of the space. We show that hydrophobicity in the complex can be switched by the photoisomerization of the azobenzene moieties.



Scheme 1. Self-assembly of $M_{12}L_{24}$ spherical complexes **2** with 24 endohedral azobenzene groups (**2a**) and 24 methoxy groups (**2b**).

Ligand **1a** was prepared in a relatively high yield from 3,5-dibromo-4-hydroxybenzyl alcohol in five steps: 1) phenolic O-alkylation with 4-(bromomethyl)azobenzene; 2) the Sonogashira coupling with 4-ethynylpyridine; 3) CBr_4/PPh_3 bromination, 4) quaternary ammonium salt formation with a large excess of trimethylamine; and 5) counteranion exchange to triflate ions (see the Supporting Information). Nontethered ligand **1b** was also prepared in a similar way. When ligand **1a** (17.7 μmol) was treated with $Pd(OSO_2CF_3)_2$[10] (8.9 μmol) in CD_3CN (1.8 mL) for 4 h at 50 °C, the azobenzene-containing $M_{12}L_{24}$ complex **2a** was quantitatively obtained, as indicated by ^1H NMR spectroscopy. Complex **2b** was also prepared in a similar way to **2a**. Cold-spray ionization mass spectrometry (CSI-MS)[11] of the complexes **2a** and **2b** clearly confirmed an $M_{12}L_{24}$ composition with molecular weights of 21987 and 17612 Da, respectively.

Single crystals of **2a** were obtained and subjected to a synchrotron X-ray diffraction study. Despite the extremely high flux and low divergence of the synchrotron X-ray radiation, only the spherical shell framework of **2a** was confirmed by the crystal-structure analysis because the azobenzene moieties in the sphere were highly disordered (see the Supporting Information). Therefore, after modeling

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the azobenzene units, the low-quality crystal structure of **2a** was optimized by a force-field calculation on the Cerius[2] program. The optimized structure showed that all of the *trans* form of the azobenzene moieties aligned with the terminal ends heading towards the core of the complex (Figure 1a). The outer diameter of the complex was approximately 5.2 nm. At the triangular and square windows of the spherical shell were located 24 closely packed azobenzene moieties that serve as "partition walls" (Figure 1b,c).

The *trans*-to-*cis* photoisomerizations of the azobenzene moieties in ligand **1a** and complex **2a** on irradiating with UV light at 365 nm were monitored by UV/Vis and ^{1}H NMR spectroscopies (Figure 2a). The ^{1}H NMR spectral changes indicated that 67% of the *trans*-azobenzene moiety in ligand **1a** was converted to the *cis* isomer at the photostationary state (PSS), whereas, in complex **2a**, only 17% of the *trans*-azobenzene moieties were converted.[12,13] The rapid attainment of the PSS in complex **2a** is partly due to the suppression of *trans*–*cis* isomerization by the absorption around 300–370 nm (Figure 2b), which is ascribed to Pd^{II}–pyridine metal-to-ligand charge-transfer (MLCT).

Upon irradiation at 436 nm (50–90 min region in Figure 2a), the azobenzene moieties of both **1a** and **2a** reached the PSS (approximately 20% *cis* isomer) because both *trans*- and *cis*-azobenzenes have azo n–π* absorption at this wavelength (Figure 2b, inset). On heating the solution at 50°C for 12 h, the thermally unstable *cis* form of azobenzene moieties in complex **2a** completely returned to the initial *trans* forms. Thus, we confirmed the reversible conversion between the *trans* and *cis* forms of complex **2a** by utilizing UV-light irradiation and heating, although the *cis* content upon irradiation is not very high.

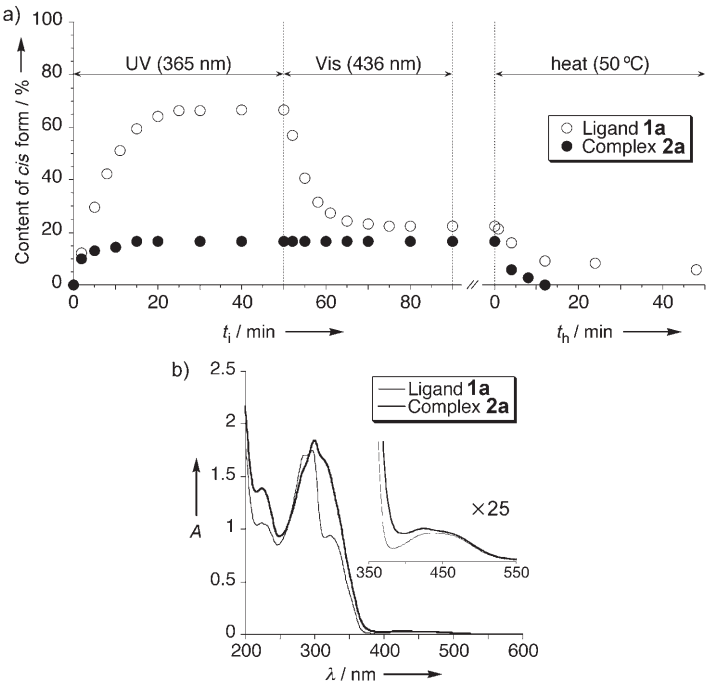

Figure 2. a) Changes in the content of the *cis* form in ligand **1a** and complex **2a** as a function of time under irradiation of UV light (365 nm), Vis light (436 nm), and heating (50°C). b) UV/Vis spectra of ligand **1a** and complex **2a** before UV-light irradiation. t_i = irradiation time, t_h = heating time.

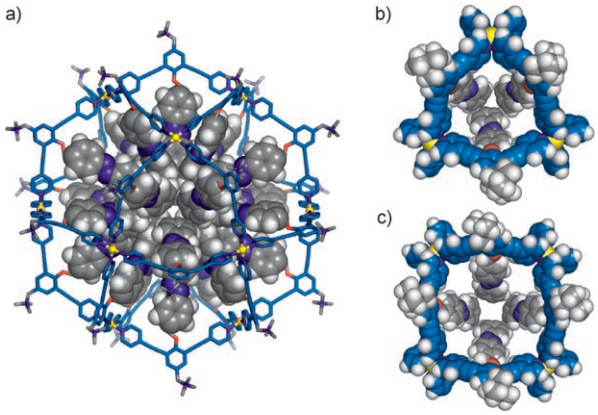

Figure 1. a) Molecular model of **2a**. Azobenzene units were modeled within the shell framework, which was determined by the X-ray crystal structure analysis. The whole was then optimized by a force-field calculation on the Cerius[2] program. Azobenzene units are shown in the Corey–Pauling–Koltun (CPK) representation (aromatic shell: blue, N: dark blue, Pd: yellow, O: red, C: gray, H: white). Top views of b) triangular and c) square cavities of **2a** (the CPK full representation).

When complex **2a** was mixed with a hydrophobic guest, pyrene (19-fold molar excess to **2a** at saturation) in $CH_3CN/H_2O = 1:1$, upfield shifting of the signals of the guest was observed in the ^{1}H NMR spectrum (e.g., $\Delta\delta_{H_2} = -0.28$ ppm; Figure 3b), indicating the uptake of pyrene guest into the core of **2a**. Hydrophobic accumulation of *trans*-azobenzene units in the sphere is essential to the guest uptake because neither free ligand **1a** nor empty spherical complex **2b** showed such an effect (Figure 3c,d). Molecular modeling suggests that triangular and square cavities constructed by the assembled azobenzene units serve as hydrophobic pockets or portals (Figure 1b,c). In a more polar solvent ($CH_3CN/H_2O = 1:3$), the guest was more shielded ($\Delta\delta_{H_2} = -0.51$ ppm) because the guest uptake is driven by hydrophobic interaction.[14]

The hydrophobicity of the interior of complex **2a** can be switched by the reversible isomerization of the azobenzene moieties, as evident in ^{1}H NMR spectra. A hydrophobic guest, 1-pyrenecarboxaldehyde (**3**), was used as a probe. In CH_3CN/H_2O (1:1) solvent, the probe guest **3** was shielded in complex **2a** ($\Delta\delta_{CHO} = -0.36$ ppm). Upon irradiation with UV light, the *trans*-azobenzene moieties in complex **2a** were converted to the *cis* isomers (around 20% conversion at PSS). Because *cis*-azobenzene is more polar than the *trans* isomer, the interior of complex **2a** is expected to become less hydrophobic. In fact, the formyl proton of **3** was less shielded, indicating that the interaction between complex **2a** and guest **3** was weakened (Figure 4b). The signal of the pyridine α protons of complex **2a** was split because the symmetry of the complex was reduced by the partial *trans*-to-*cis* isomerization.

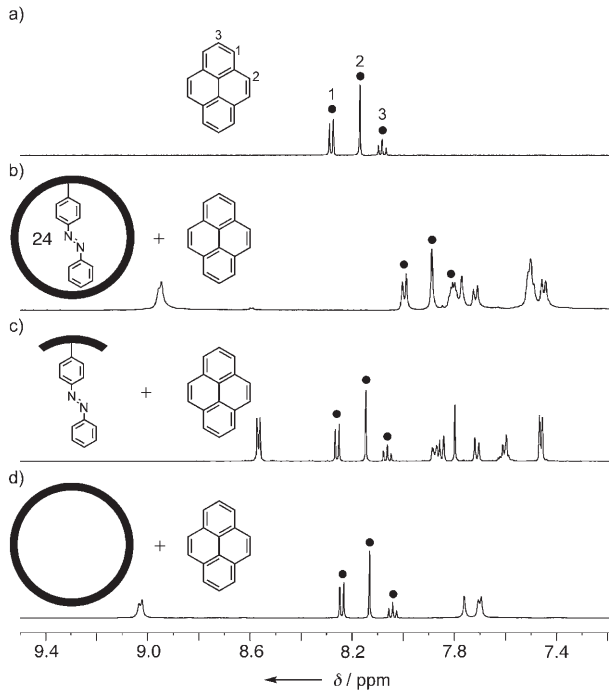

Figure 3. ^{1}H NMR spectra (aromatic region) of pyrenes in the presence of a) no additive, b) complex **2a**, c) ligand **1a**, and d) complex **2b** (500 MHz, CD_3CN/D_2O = 1:1, 300 K, tetramethylsilane (TMS)).

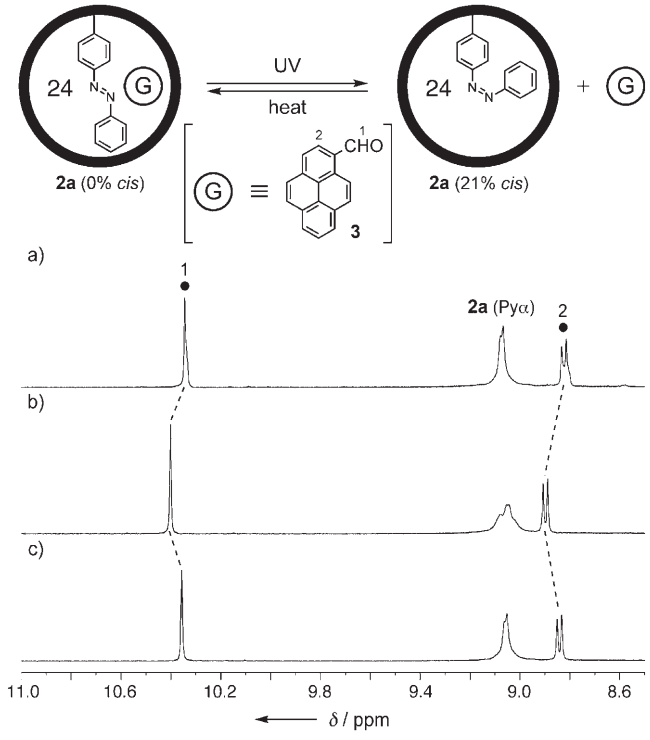

Figure 4. Changes in the ^{1}H NMR spectra of **3** in the presence of complex **2a**: a) initial state; b) after irradiation with UV light (365 nm); c) after heating at 50 °C (500 MHz, CD_3CN/D_2O = 1:1, 300 K, TMS).

After heating at 50 °C for 12 h, all the azobenzene moieties in complex **2a** returned to the *trans* forms. Thus, guest **3** was again taken up by **2a** and the signal of the formyl proton of **3** was shifted upfield to the same degree as in the initial state (Figure 4c). These observations indicate that the hydrophobic environment in complex **2a** is reversibly changed by the isomerization of the azobenzene moieties.

In summary, we have prepared a spherical complex with 24 azobenzene moieties concentrated at the interior of the sphere. The photoisomerization of the azobenzene chromophores in the complex switches the hydrophobicity relayed to reversible guest uptake into the spherical complex. The successful affinity control through the photoisomerization of the chromophore promises the preparation of a variety of photoresponsive "molecular nanoparticles" whose interior environments are dramatically changed by light.

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[12] It is known that in dendrimers with azobenzene units throughout their architecture, significantly lower conversions from the *trans* to the *cis* isomers are observed. See reference [6d, f].

[13] When a heterocomplex assembled from a mixture of ligand **1a** and ligand **1b** (4:20) was irradiated, the *trans*-to-*cis* conversion was also approximately 20%. This result indicates that the low conversion to the *cis* form was not ascribed to the dense packing of the azobenzene moieties in the complex. For the details on the heterocomplex, see the Supporting Information.

[14] It was estimated by examination of the ^{1}H NMR spectrum that approximately 16 pyrene molecules were interacting with complex **2a** in $CH_3CN/H_2O = 1:3$.

