Host-Guest Chemistry

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Discrete and Well-Defined Hydrophobic Phases Confined in Self-Assembled Spherical Complexes**

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Long alkyl chains have a tendency to spontaneously aggregate and form localized hydrophobic environments in polar media.[1] This tendency has been exploited to prepare a variety of micelles,[2] vesicles,[3] tubes,[4] core-shell structured polymers,[5] and dendrimers[6] in which the localized hydrophobic environments show interesting properties. These artificial long alkyl chain systems, as well as biomembranes,[7] which are bilayered aggregates of long organic phosphates, are typically structurally dispersed. The structural disparities result in a distribution of properties. Here we report discrete and well-defined structures of alkyl chains confined within a 5 nm spherical coordination shell (Figure 1). The shell framework quantitatively assembles from 12 Pd^{2+} ions and 24 nonlinear ligands[8,9] and sharply defines the boundary of the interior hydrophobic region of the long alkyl chains. Furthermore, the nature of hydrophobic interior can be simply tuned by varying the length of the pendant alkyl chains.

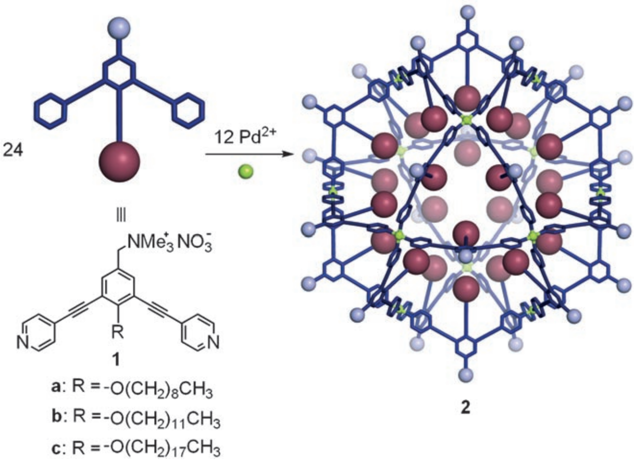

Figure 1. Self-assembly of *endo*-hydrophobic $[M_{12}L_{24}]$ spherical complexes **2a**–**c**.

Amphiphilic ligands **1a**–**c** bearing inner alkyl chains and outer quaternary ammonium groups were designed with the expectation that, after self-assembly into spheres **2a**–**c**, the alkyl chains would form a localized hydrophobic phase and the outer ammonium groups would increase the solubility of the spheres in polar media, namely DMSO or DMSO/H_2O mixtures. Ligands **1a**–**c** were prepared in six steps from 3,5-dibromo-4-hydroxybenzene carbaldehyde (see the Supporting Information). When ligand **1a** (10 μmol) was treated with $Pd(NO_3)_2$ (6 μmol) in deuterated dimethyl sulfoxide for one hour at 70 °C, the formation of the $[M_{12}L_{24}]$ spherical complex **2a** as a single product was observed by ^1H NMR spectroscopy. The large downfield shifts of the pyridine α and β protons ($\Delta\delta = 0.66$ and 0.29 ppm, respectively) are ascribed to metal–pyridine coordination (Figure 2). Spheres **2b** and **2c** were also prepared in the same fashion. After anion exchange of nitrate (NO_3^-) for triflate ions ($CF_3SO_3^-$), cold-spray ionization mass spectrometry (CSIMS)[10] clearly confirmed the $[M_{12}L_{24}]$ composition of **2a**–**c** with molecular weights of 20304, 21313, and 23337 Da, respectively.

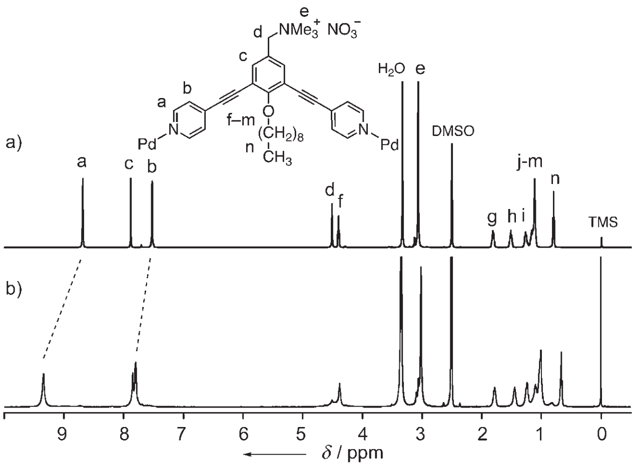

Figure 2. ^1H NMR spectra of a) **1a** and b) **2a** (500 MHz, $[D_6]DMSO$, 300 K). TMS = tetramethylsilane.

The rigid shell framework of the $[M_{12}L_{24}]$ complexes was revealed by X-ray crystallographic analysis of complex **2b**. Single crystals of **2b** were obtained by slow vapor diffusion of ethyl acetate into a solution of **2b** in DMSO. Synchrotron X-ray irradiation with high flux and low divergence provided high quality data from which the structure of the exterior shell, with a diameter of 4.7 nm and peripheral cationic groups (Figure 3a), was clearly identifiable. Only the initial $-OCH_2CH_2-$ segment of the alkyl chains could be definitively

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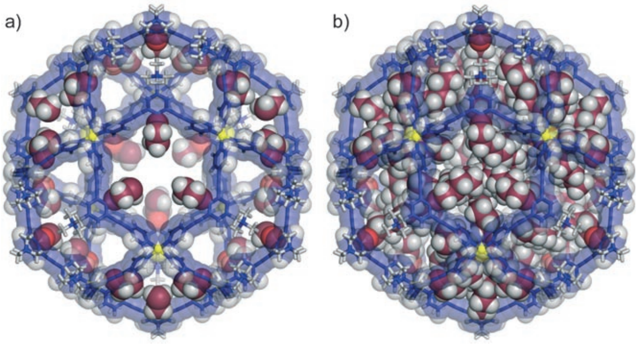

Figure 3. Molecular structure of complex **2b**. a) The crystal structure of the shell framework, outer cationic groups, and first -OCH_2CH_2-segment of the alkyl chain. The remaining alkyl chains are severely disordered. b) The combined crystal structure and MD simulation of disordered side chains.

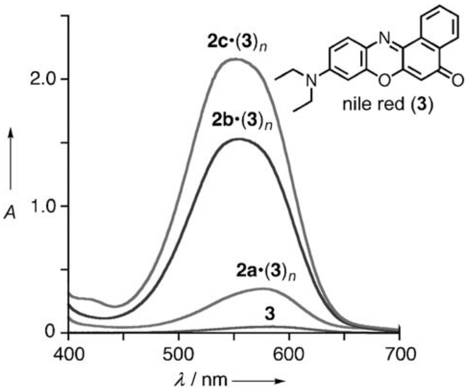

Figure 4. UV/Vis absorption spectra of nile red (**3**) dissolved in the hydrophobic cores of **2a–c** (84 μM) in DMSO/H_2O (1:1).

located because of severe disorder of the remainder of the alkyl side chains. Therefore, the disordered alkyl chain segments were modeled separately and attached to the crystal structure of the shell. Simulated annealing by molecular dynamics (MD) calculations (100 iterations from 2000 K to 300 K) gave an optimized structure. The combined crystal structure and MD simulation show that the cavity of the spherical complex is filled with 24 flexible $C_{12}H_{25}$ chains, thereby forming a localized hydrophobic pocket with a uniform shape and size (Figure 2b).[11]

Complexes **2a–c** provide a 5 nm hydrophobic phase localized and isolated from the polar solvent that should be able to solubilize hydrophobic guests. The well-known hydrophobic dye, nile red (**3**),[12,13] was examined as a guest because its poor solubility in aqueous solvents and its solvatochromatic nature make it suitable for estimating the polarity and hydrophobicity of the local environment.[14] An excess of **3** was suspended in solutions of **2a–c** in DMSO and the resulting solutions were then diluted with water to increase the solvent polarity (DMSO/H_2O 1:1).[15] Residual **3** was removed by filtration. Free **3** is sparingly soluble in DMSO/H_2O (1:1) and thus solutions of **3** showed only a very weak UV/Vis absorption. In contrast, **3** shows enhanced solubility in solutions of **2a–c** in DMSO/H_2O (1:1; Figure 4).

The solubility and solvatochromatic behavior of **3** clearly show that the properties of the hydrophobic interiors of **2a–c** vary with the length of the alkyl chains. The solubility of **3** is enhanced in the order **2a** < **2b** < **2c**, which indicates that more molecules of **3** are trapped in hosts that have a greater hydrocarbon density. The solvatochromism of **3**, which shows bathochromic shifts in nonpolar media, also directly reflects the concurrent reduction in the polarity of the complexes. The maximum absorption wavelength (λ_{max}) of included **3** underwent a bathochromic shift in the order of **2a** < **2b** < **2c** (576, 555, and 552 nm, respectively), in good agreement with the expected solvatochromism of **3**.

Trapped **3** is expelled from the core of **2a–c** into the bulk solvent when the polarity of the solvent is reduced by diluting with CH_3CN, a less polar solvent. In a CH_3CN/DMSO/H_2O mixture (38:1:1), only free **3** is observed by UV/Vis spectroscopy (538 nm, see the Supporting Information). The concentrations of displaced **3** were calculated, and it was estimated that spheres **2a–c** contained 2, 10, and 12 molecules of **3** per complex, respectively.

In summary, we have prepared well-defined spherical complexes containing 24 interior alkyl chains. The aggregated alkyl chains form approximately 5 nm sized "hydrocarbon droplets" that provide a localized hydrophobic environment. These discrete hydrophobic phases completely differ from previously studied, ill-defined long alkyl chain aggregates in that 1) the shape and size are uniform and can be analyzed by crystallographic methods and 2) the hydrophobic nature can be precisely tuned by simply changing the length of the alkyl chains. New properties and functions of solutes can be developed within such "designer" hydrophobic environments.

Experimental Section

Inclusion of **3** in spheres **2a–c**: A solution of **3** in DMSO (16 mM, 0.19 mL) was added to solutions of **2a** in DMSO (0.23 mM, 0.56 mL). The resulting DMSO solutions (0.75 mL) were diluted with water (0.75 mL) to increase the solvent polarity, and stirred for 1 h at 4 °C. After excess **3** was removed by filtration, the filtrates were analyzed by UV/Vis absorption (Figure 3). The same procedure was performed for **2b** and **2c**.

Calculation of the number of molecules of **3** within the spheres **2a–c**: The solutions of **3** with **2a–c** (DMSO/H_2O 1:1, 0.1 mL) were diluted 20-fold with CH_3CN (1.9 mL). As **3** was observed at the same maximum absorption wavelength as that of free **3** (538 nm; see Figure S8 in the Supporting Information), **3** appeared to have been expelled from the spheres into the bulk solvent. The concentration of expelled **3** was calculated from the absorbance at 538 nm by using the calibration curve of **3** (see Figure S9 in the Supporting Information), and calculated to be 0.82 (**3**), 6.6 (**3** + **2a**), 43 (**3** + **2b**), and 52 μM (**3** + **2c**). From the concentration of **2a–c** (4.2 μM), the number of molecules of **3** encapsulated in **2a–c** was estimated to be 2, 10, and 12 molecules per sphere, respectively.

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[11] Crystallographic analysis of **2b**: The diffraction data were measured at the Photon Factory Advanced Ring for Pulse X-rays (PF-AR) of the High Energy Accelerator Research Organization (KEK). $C_{720}H_{552}N_{120}O_{346}Pd_{12}S_{60}$, pale yellow block ($0.20 \times 0.20 \times 0.20$ mm^3), cubic, space group $Fm\bar{3}m$, $a = b = c = 59.475(7)$ Å, $V = 210379(42)$ Å^3, $T = 90$ K, $Z = 4$, $\rho_{\text{calcd}} = 0.619$, 1432 unique reflections out of 2606 with $I > 2\sigma(I)$. The structure was solved by direct methods (SHELXL-97) and refined by full-matrix least-squares methods on F^2 with 186 parameters, R_1-($I>2\sigma(I)$) = 0.2331, $wR_2 = 0.5202$, GOF = 2.130, max./min. residual electron density 0.805/−1.046 e Å^3. The R_1 value of 0.2331 is very large, because of the large cavity size and a large number of severely disordered alkyl chains, solvent molecules, and nitrate anions that lead to a very large void ratio of 83 % of the unit cell. CCDC 684137 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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[15] In this highly polar solvent mixture (DMSO/H_2O = 1:1), the high stability and the uniform structure of complexes **2a–c** were confirmed by NMR spectroscopy. See the Supporting Information.