Self-Assembly

DOI: 10.1002/anie.201104670

A Sphere-in-Sphere Complex by Orthogonal Self-Assembly**

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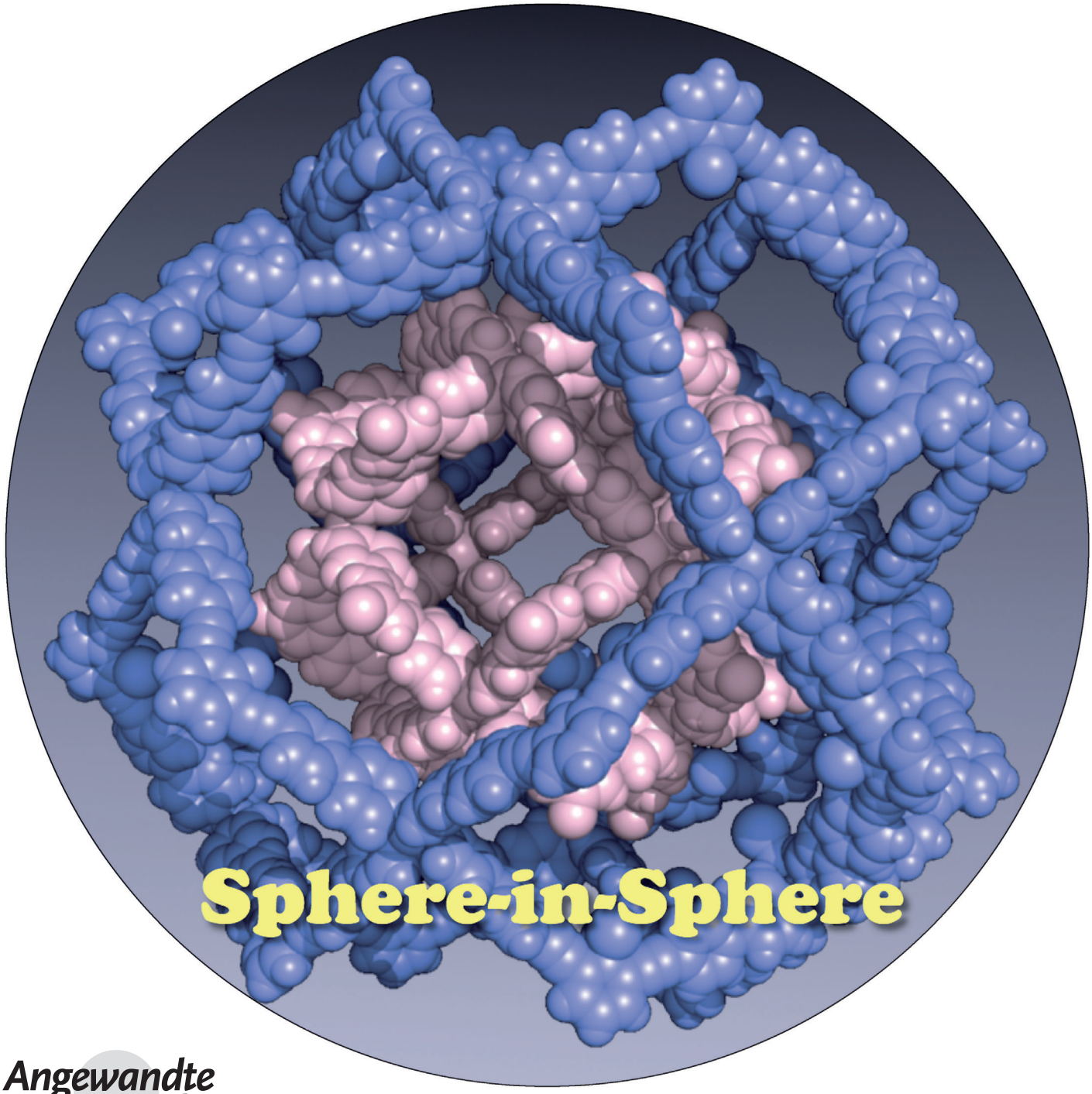
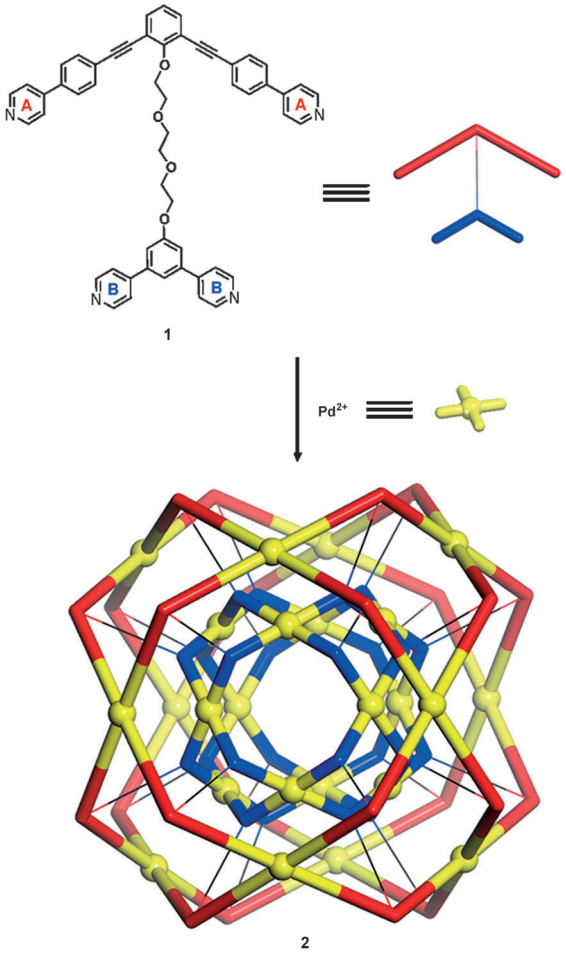


Sphere-shaped viral capsids often possess double-shell structures with independent inner and outer shells formed from different subunits.[1] The self-assembly processes of the two shells are orthogonal, that is, they do not interfere with each other. Structural orthogonality greatly facilitates the highly essential functional subdivision in complex biological assembly systems.[2,3] We and others have previously reported several artificial spherical molecules that have a structural resemblance to the hollow-shell virus capsids,[4–18] but the formation of a subdivided complex structure such as a double-shell virus capsid by orthogonal self-assembly has never been reported.[19]

The simple model compound **1** was synthesized to examine orthogonal self-assembly. The dual, linked bispyridinyl ligand **1** displays two, effectively identical, coordination sites **A** and **B**. Thus, when treated with metal ions, a random assortment of various heteroleptic, oligomeric complexes would be expected. However, we now report that simple treatment of ligand **1** with Pd^{II} ions results in the giant sphere-in-sphere complex **2** consisting of 24 Pd^{II} ions and 24 ligands assembled into two spherical shells (Scheme 1). The orthogonal self-assembly of **2** is analogous to the high fidelity of protein assembly, where individual subunits unfailingly locate their predetermined positions.

The synthesis of **1** was achieved in two high-yielding steps based on the Mitsunobu reaction of bidentate pyridinyl units of two different lengths, which were synthesized by procedures similar to those previously reported by our research group (for details, see the Supporting Information).[17–21] The triethylene glycol (TEG) chain was chosen as a linker, as it not only provides the required spacer length but also improves the overall flexibility and solubility of the ligand.

Ligand **1** was treated with an equimolar amount of $Pd(NO_3)_2$ (both 5 mM) in [D_6]dimethyl sulfoxide ([D_6]DMSO) at 80 °C for 6 h. All the signals became broadened in the ^{1}H NMR spectrum (Figure 1a), thus suggesting the formation of a giant structure whose tumbling motions are slow on the NMR time scale. Moreover, the number of signals in the aromatic region remained unchanged, which indicates that the complex has a highly symmetrical structure. All the PyH_α and PyH_β (Py = pyridyl) signals shifted clearly downfield as a result of coordination to the Pd^{II} centers. Diffusion-ordered NMR spectroscopy (DOSY) showed a single band at $D = 3.16 \times 10^{-11}\ m^2 s^{-1}$ ($\log D = -10.50$), which is much smaller than that of the free ligand **1** at $D = 1.58 \times 10^{-10}\ m^2 s^{-1}$ ($\log D = -9.80$) in [D_6]DMSO (Figure 1b). These observations were consistent with the formation of the sphere-in-sphere complex **2**.



Scheme 1. Self-assembly of sphere-in-sphere complex **2**.

The composition of **2** was confirmed as [Pd_{24}(**1**)$_{24}$] by cold-spray ionization time-of-flight mass spectrometry (CSI-TOF-MS).[22] Mass analysis of the complex was immensely difficult because of its very high molecular weight and the relatively weak Pd^{II}–N interactions. Nevertheless, after optimizing the conditions and examining several counterions, the triflate (TfO^-) salt of **2** was found to afford a series of signals corresponding to [**2**(TfO^-)$_m$]$^{m+}$ (m = 20–12), thus confirming the molecular weight of **2** ([$Pd_{24}(C_{54}H_{42}N_4O_4)_{24}$]$^{48+}$·48($TfO^-$)) as 29172.31 Da. Notably, the finely resolved isotopic distribution observed at each MS signal was also in perfect agreement with the simulated pattern (Figure 2).

Ultimately, the giant, sphere-in-sphere structure of **2** was unambiguously determined by single-crystal X-ray analysis (Figure 3).[23] Suitable single crystals were obtained by slow diffusion of ethyl acetate vapor into a solution of **2** (TfO^- salt) in DMSO over about 2 months. A small yellowish block crystal was sealed in a capillary for data collection. The poor scattering nature of this kind of complex meant that high-flux synchrotron diffraction was essential to obtain high quality data to solve the structure.

In the crystal state, the two independent spherical frameworks of **2**, with diameters of 6.3 and 3.5 nm, were clearly

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[**] This research was supported by the CREST project of the Japan Science and Technology Agency (JST), for which M.F. is the principal investigator, and also in part by KAKENHI and MEXT. Synchrotron X-ray diffraction studies were performed at KEK and SPring-8.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201104670.

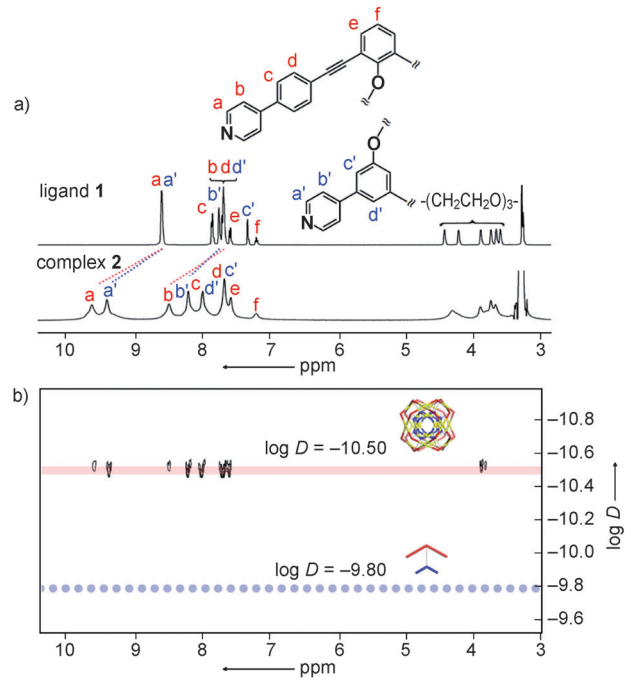

Figure 1. a) ^{1}H NMR (500 MHz, [D$_6$]DMSO, 300 K) spectra of ligand **1** and complex **2** (NO_3^- salt). b) ^{1}H DOSY (500 MHz, [D$_6$]DMSO, 300 K) spectrum of complex **2** (the region for ligand **1** is also indicated by a blue dotted line).

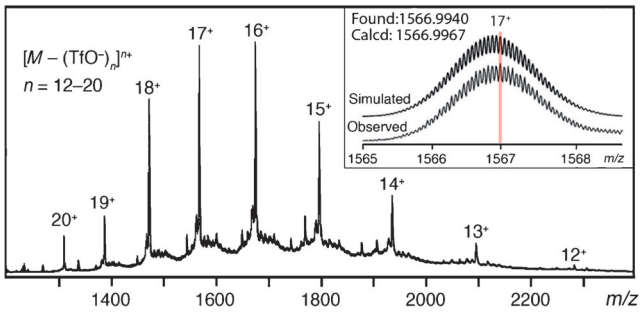

Figure 2. CSI-TOF mass spectrum of complex **2** (TfO^- salt), with an inset showing the observed and simulated isotopic patterns of the 17^+ signal.

visible, but the majority of the triethylene glycol tethers and counterions were severely disordered and could not be resolved. The inner sphere remained highly spherical whereas the outer sphere exhibited oval distortion, presumably because of packing effects. The inner sphere is held in place by 24 linkers, in particular by 8 linkers that are distributed symmetrically around the core and exhibit a relatively extended conformation.[24]

In the early stages of self-assembly, numerous oligomeric complexes are generated by the random coordination of sites **A** and **B** at every Pd^{II} center. We anticipated that the formation of numerous oligomers would make it extremely difficult to find the right pathway to assemble the sphere-in-sphere structure; furthermore, as the degree of oligomerization increases, the unfavorable kinetic trap of oligomeric

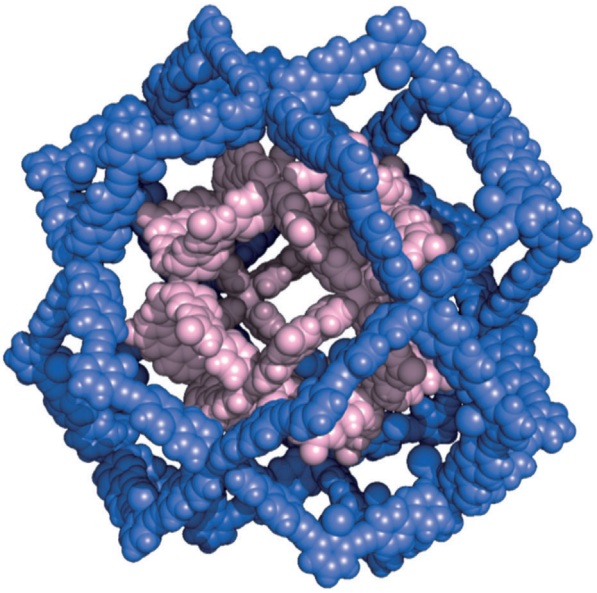

Figure 3. Crystal structure of the sphere-in-sphere complex **2**. All atoms are depicted as sphere models. Atoms of the interior sphere are in pink, and the exterior sphere are in blue. Counterions (TfO^-) and the TEG linkers are omitted for clarity.

intermediates predominates over self-assembly. In fact, we had previously observed a significant kinetic trap in the self-assembly of multicomponent $[M_{12}L_{24}]$ spheres.[25] To our surprise, despite the formation of numerous oligomers, all of them still remain in equilibrium, roaming around indefinitely on the potential surface. A highly symmetric $[M_{12}L_{24}]$ cuboctahedral framework[17] is the only stable structure and thus ligand **1** eventually finds pathways where sites **A** and **B** form the homoleptic complexes that lead to orthogonal, sphere-in-sphere $[M_{12}L_{24}]$ shells.

We also observed that the formation of the inner and the outer shells is simultaneous and at no stage in the self-assembly were detectable, resolved intermediary structures, such as a preformed inner or outer shell, observed. When, for example, 0.5 equivalents of $Pd(NO_3)_2$ were used for complexation with ligand **1**, the ^{1}H NMR spectra revealed the formation of only **2** (ca. 50%), concomitant with remaining free ligand **1** (ca. 50%), but no intermediary structures were observed (see Figure S7 in the Supporting Information). ^{1}H DOSY experiments also confirmed the formation of the sphere-in-sphere complex (see Figure S8 in the Supporting Information).

In summary, we have succeeded in the self-assembly of the first artificial sphere-in-sphere molecule. Previously, we demonstrated that giant, multicomponent discrete aggregates can act as kinetic traps, which endow stability,[25] and that $[M_nL_{2n}]$ spherical complexes are subject to geometrical constraints that favor unique n values.[18] Here, we used two tethered ligands to enforce structural subdivisions that necessitated self-assembly in an orthogonal fashion with high fidelity. We believe that our synthetically simple systems can help deepen the mechanistic understanding of the hidden mechanisms and emergent behavior that generates the beautiful and highly complex structures found in biology.

Experimental Section

Synthesis of **2** (NO_3^- salt): Ligand **1** (2.97 mg, 3.66 μmol) was treated with $Pd(NO_3)_2$ (0.85 mg, 3.7 μmol) in DMSO (0.730 mL) at 80 °C for 6 h. ^{1}H NMR spectroscopy confirmed the quantitative formation of **2**. An excess amount of a mixture of ethyl acetate and diethyl ether (1:1 in volume) was added to the solution of sphere **2** and the precipitate was collected by centrifugation and dried in vacuo to give **2** as a yellow solid (71% yield). M.p. > 300 °C (decomp). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 300 K): $\delta = 9.63$ (br, 96H), 9.41 (br, 96H), 8.50 (br, 96H), 8.21 (br, 96H), 8.01 (br, 120H), 7.69 (br, 144H), 7.59 (br, 48H), 7.22 (br, 24H), 4.34 (br, 96H), 3.93 (br, 96H), 3.78 (br, 48H), 3.71 ppm (br, 48H). Diffusion coefficient ([D$_6$]DMSO, 300 K): $D = 3.16 \times 10^{-11}$ m^2 s^{-1}. ^{13}C NMR (150 MHz, [D$_6$]DMSO, 300 K): $\delta =$ 161.2 (C), 160.6 (C), 151.9 (CH + CH), 149.8 (C + C), 136.9 (C), 134.9 (CH + C), 132.7 (CH), 128.2 (CH), 124.8 (CH + CH + CH + C), 118.9 (CH), 117.3 (C), 115.7 (CH), 93.6 (C), 88.0 (C), 74.0 (CH_2), 67.0 ($CH_2 + CH_2 + CH_2 + CH_2$), 68.4 ($CH_2$). IR (KBr): $\tilde{\nu} = 3425$, 3095, 2916, 2879, 2362, 2341, 1673, 1611, 1551, 1491, 1407, 1379, 1215, 1114, 1074, 1025, 952, 825, 770, 698, 643, 523 cm^{-1}. Elemental analysis calcd for $C_{1296}H_{1008}N_{144}O_{240}Pd_{24}$·120 DMSO: C 53.68%, H 5.07%, N 5.87%; found: C 53.74%, H 4.88%, N 6.05%.

Synthesis of complex **2** (TfO^- salt): Complexation was carried out as above, but using $Pd(TfO)_2$ as the metal source. ^{1}H NMR spectroscopy and CSI-TOF-MS confirmed the quantitative formation of **2**. ^{1}H NMR (500 MHz, [D$_6$]DMSO, 300 K): $\delta = 9.59$ (br, 96H), 9.39 (br, 96H), 8.48 (br, 96H), 8.21 (br, 96H), 8.00 (br, 120H), 7.68 (br, 144H), 7.60 (br, 48H), 7.21 (br, 24H), 4.35 (br, 96H), 3.93 (br, 96H), 3.77 (br, 48H), 3.71 ppm (br, 48H). CSI-TOF-MS (TfO^- salt, CH_3CN): m/z calcd for $[M-17\,TfO^-]^{17+}$ 1566.9967, found 1566.9940; these signals are those with the highest intensities.

Crystal data of **2** (TfO^- salt): Space group $I4/m$, $a = b = 46.292(7)$, $c = 72.767(15)$ Å, $V = 155936(44)$ Å^3, $Z = 2$, $T = 293$ K. Anisotropic least-squares refinement for all atoms on two spherical frameworks and isotropic refinement for the other atoms on 11821 independent merged reflections ($R_{int} = 0.0914$) converged at residual $wR_2 = 0.5848$ for all data; residual $R_1 = 0.2487$ for 7095 observed data [$I > 2\sigma(I)$], and GOF = 2.417. Full experimental details and crystallographic analysis are given in the Supporting Information.

Received: July 6, 2011
Revised: August 8, 2011
Published online: September 8, 2011

Keywords: coordination modes · entropic effects · N ligands · palladium · self-assembly

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