JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
COMMUNICATION
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Exploring the Ellipsoidal and Core−Shell Geometries of Copper-Seamed *C*-Alkylpyrogallol[4]arene Nanocapsules in Solution

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S *Supporting Information*

ABSTRACT: Small-angle neutron scattering (SANS) studies were used to probe the stability and geometry of copper-seamed *C*-alkylpyrogallol[4]arene (PgC_nCu; $n = 11, 13, 17$) hexamers in solution. Novel structural features are observed at chain lengths greater than 10 in both solid and solution phase. Scattering data for the $PgC_{11}Cu$ and $PgC_{13}Cu$ in chloroform fitted as core−shell spheres with a total spherical radius of about 22.7 and 22.9 Å respectively. On the other hand, the scattering curve for the $PgC_{17}Cu$ hexamer at both 1% and 5% mass fractions in *o*-xylene did not fit as a discrete sphere but rather as a uniform ellipsoid. The geometric dimensions of the ellipsoid radii are 24 Å along the minor axis and 115 Å along the major axis. It is expected that an individual hexamer with heptadecyl chains would exhibit a uniform radius of *ca.* 24 Å. However, an approximate ratio of 1:5 between radii lengths for the minor axis and major axis is consistent with interpenetration of the heptadceyl chains of adjacent hexamers to form a single ellipsoidal assembly.

The study of supramolecular nanoassemblies in solution is an exciting new area of endeavor. Among the few reported examples of nanoassemblies in solution are the studies of self-assembly of copolymers into nanotubes[1] or the rigid-rod behavior of functionalized single-walled carbon nanotubes.[2] The supramolecular assemblies have evolved from calix[*n*]arenes ($n = 4, 5, 6, 8$) that form Russian dolls and 2-D and 3-D polymers, to resorcin[4]arenes yielding H-bonded hexamers,[3−5] and more recently to metal-seamed capsules involving pyrogallol[4]arenes.[6−10] However, it was only in the past decade that calixarene-based assemblies were explored in solution.[11,12]

Structurally similar to rescorin[4]arenes, with four additional hydroxyl groups, pyrogallol[4]arenes (PgC_n, where n = alkyl chain length) yield more robust nanocapsular frameworks. The stability may be attributed to the presence of 12 additional H-bonds.[6,7,9,13] Several arrangements of metal−organic nanocapsules (MONCs) have been distinguished on the basis of the orientation of the metals around the PgC_n macrocycle. The formation of MONCs first involved the rapid formation of copper-coordinated PgC_n hexamers that involved insertion of 24 Cu^{2+} ions into a H-bonded framework.[6] Later, Zn-seamed dimers,[8,9] Ga-seamed rugby ball shaped hexamers, and mixed-metal seamed hexamers were shown to self-assemble as MONCs.[10]

The dimensions of both single-metal (copper) and mixed-metal (gallium−zinc/gallium−copper/gallium−nickel/gallium−cobalt) seamed hexameric MONCs are similar to that of the H-bonded hexamer. This close structural similarity between the metal-seamed and nonmetal-seamed/H-bonded hexamers in the solid state has led to interest in comparing their geometric dimensions in solution. Our interest in metal-seamed hexamers bearing long alkyl chains stems from the previously reported ellipsoidal assembly of *C*-undecylpyrogallol[4]arene H-bonded (PgC_{11}) hexamers (Figure 1b).[14] The solid-state structure of the PgC_{11} hexamer was obtained by a single crystal XRD study in which it was found that the C_{11} alkyl chains were interdigitated in two, not three, dimensions. This deviation from a rather spherical arrangement of the alkyl chains for $n < 11$ to a 2-D focus of the $n > 11$ alkyl chains led us to consider the possibility of using such longer alkyl chain H-bonded hexamers as building blocks for even larger supramolecular assemblies.[15] However, use of the single crystal X-ray diffraction method for structure elucidation of nanocapsules with longer alkyl chains ($n > 11$) has proven difficult due to complexities in refining the long hydrocarbon chains. Thus, beyond the *C*-undecylpyrogallol[4]arene (PgC_{11}) H-bonded hexamer, no long chain hexamer has been characterized in the solid state (Table 1).[14]

Given the difficulties in crystallization of long alkyl chain nanocapsules and their structural analogy to the related metal-seamed hexameric MONCs, we investigated the more robust copper-seamed *C*-alkylpyrogallol[4]arene hexamers in solution.[16] We expected to probe both the stability and geometric dimensions of these MONCs in solution.

Herein, we report a solution phase study of the *C*-heptadecylpyrogallol[4]arene copper ($PgC_{17}Cu$) hexamer (**1**) with an ellipsoidal shape and $PgC_{11}Cu$ (**2**) and $PgC_{13}Cu$ (**3**) with a spherical core−shell shape. Our study sought, in part, to understand the shape and size of long alkyl chain hexamers in solution. Given the possibilities for rearrangement of the building blocks of the capsules in solution, one would expect either an unstable nanocapsule or a stable uniform arrangement for the nanocapsule. Hence, we employed small-angle neutron scattering (SANS) as a characterization technique to discern the size and shape of solvent-solubilized **1** ($PgC_{17}Cu$), **2** ($PgC_{11}Cu$), and **3** ($PgC_{13}Cu$). Two factors make SANS an ideal technique for the analysis of nanocapsules. First, SANS measurements are ideal for quantifying length scales from 1 to 1000 nm. Second, SANS is a nondestructive technique, capable of measuring bulk samples.

Received: September 8, 2011
Published: October 04, 2011

dx.doi.org/10.1021/ja208195t | *J. Am. Chem. Soc.* 2011, 133, 18102–18105

1, **2**, and **3** were prepared by dissolving 1 mol of PgC_n (n = 11, 13 or 17) and 4 mol of copper(II) nitrate solution in acetone to yield a brown precipitate. The prepared solid-state samples **2** and **3** were dissolved in $\mathrm{CDCl_3}$ at a mass fraction of 3% for SANS. The solvent $\mathrm{CDCl_3}$ was used for these measurements ($\mathrm{PgC_{11}Cu}$ and $\mathrm{PgC_{13}Cu}$) as it favored the solubilization of the long alkyl chain length hexamers. On the other hand, **1** was dissolved in deuterated *o*-xylene at 1% and 5% mass fractions for SANS. The two concentrations/mass fractions of **1** were used to ensure sufficient scattering statistics and to investigate the effects of solution concentration on the structures present in solution. The solutions were left overnight to stabilize and were measured at 25 °C in demountable titanium cells (2 mm path length).

SANS measurements were performed on the NG3 30 m SANS instrument at the NIST Center for Neutron Research.[17] For the measurements, neutrons of wavelength λ = 6 Å with a full width half-maximum $\Delta\lambda/\lambda$ = 15% were used, and sample to detector distances of 1.3 and 4.5 m covered the overall q range of $0.012\ \text{Å}^{-1} < q < 0.52\ \text{Å}^{-1}$. Here $q = (4\pi/\lambda)\sin(\theta/2)$ is the magnitude of the scattering vector and θ is the scattering angle. The sample scattering was corrected for the background, the empty cell scattering, and the sensitivity of the individual detector pixels. The corrected data sets were placed on an absolute scale, and the structure was modeled using Igor Pro software.[18]

The neutron scattering data of nanocapsules **1**, **2**, and **3** were analyzed by fitting to a variety of spherical and elongated structural models. Instrument resolution was included in the model fits to account for resolution smearing. In the ellipsoid model, we calculate the form factor, $P(q)$, for a monodisperse ellipsoid (ellipsoid of revolution) with uniform scattering length density whereas the spherical core–shell model describes a monodisperse spherical particle with a core–shell structure. In all cases, the nanocapsules are dilute enough that interparticle interactions are not significant.

In our initial investigation, SANS data analysis of chain lengths of n = 11 (**2**) and 13 (**3**) were conducted. The scattering data for these chains did not fit to a simple spherical or polydisperse spherical shape; however, for both **2** and **3** the scattering data was best fitted to a core–shell sphere[19] model.[20] This was an important observation as three scattering length densities (SLDs), for the core ($\mathrm{PgC_0Cu}$; SLD = 2.53×10^{-6} Å^{-2}), shell (alkyl chain: $\mathrm{C_{11}}$ SLD = -5.3×10^{-7} Å^{-2}; $\mathrm{C_{13}}$ SLD = -6.5×10^{-7} Å^{-2}), and the solvent ($\mathrm{CDCl_3}$ [SLD = 3.16×10^{-6} Å^{-2}]), are calculated separately and held fixed when fitting the core–shell sphere model, yielding a good fit. Fitting using a model of a polydisperse core–shell structure resulted in a best-fit polydispersity of zero, confirming that the monodisperse core–shell structure is correct.

The fitting reveals a core radius of 10.0 ± 0.41 Å and a shell thickness of 12.0 ± 0.53 Å for the $\mathrm{PgC_{13}Cu}$ hexamer. The total

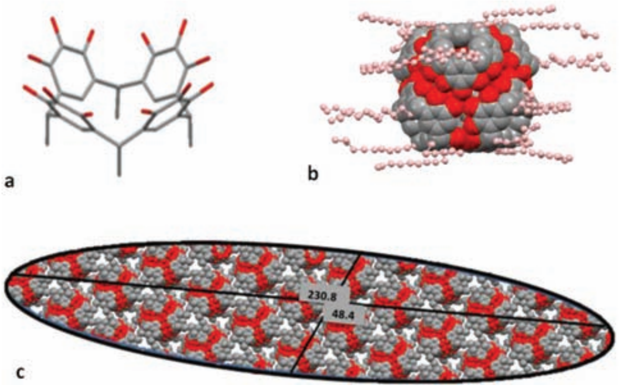

Figure 1. (a) Structure of pyrogallol[4]arene. (b) H-bonded nanocapsule composed of a single C-undecylpyrogallol[4]arene ($\mathrm{PgC_{11}}$) hexamer in the solid state and (c) model of C-heptadecylpyrogallol[4]arene ($\mathrm{PgC_{17}Cu}$, **1**) hexameric nanocapsules assembled as an ellipsoid in solution. In (b), the solid-state structure shows that the $\mathrm{C_{11}}$ alkyl chains radiate in a 2-D fashion into an ellipse-like arrangement. In (c), the model of the ellipsoidal nanocapsules in solution shows interdigitation into an ellipsoidal assembly.

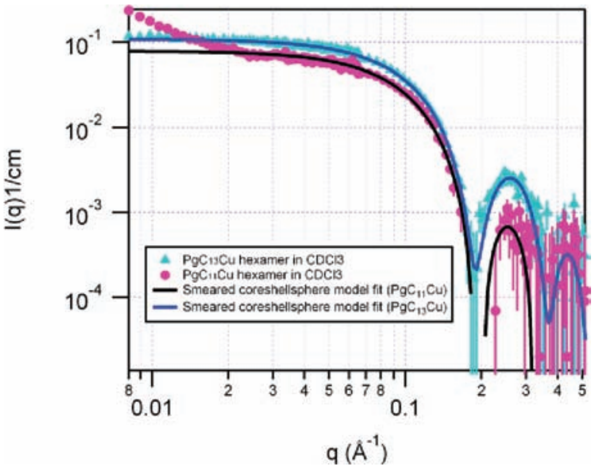

Figure 2. SANS core–shell sphere data and model fits for copper-seamed C-undecylpyrogallol[4]arene ($\mathrm{PgC_{11}Cu}$ or **2**; pink circles) and copper-seamed C-tridecylpyrogallol[4]arene ($\mathrm{PgC_{13}Cu}$ or **3**; turquoise/blue triangles) hexamers in $\mathrm{CDCl_3}$. The error bars on the SANS data represent one standard deviation.

Table 1. Summary of Shape and Alkyl Chain Lengths of H-Bonded and Cu-Seamed Pyrogallol[4]arene Hexamers

PgC_n H-bonded hexamer (Solid-state)[14]		PgC_n Cu-seamed hexamer (Solid-state)[6]		PgC_n Cu-seamed hexamer (Solution-phase)	
Alkyl Chain	Shape	Alkyl Chain	Shape	Alkyl Chain	Shape
n = 1–9	Sphere	n = 1–9	Sphere	n = 1–9	Sphere
n = 11	Ellipsoid	n > 9	Not available	n = 11	Core–Shell Sphere
				n = 13	Core–Shell Sphere
				n = 17	Ellipsoid

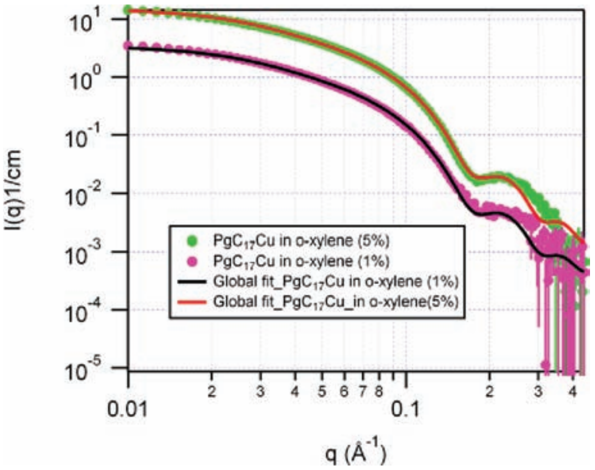

Figure 3. SANS data and the Smeared Uniform Ellipsoid model global fit for *C*-heptadecylpyrogallol[4]arene in *o*-xylene (both 1% and 5% mass fractions).

radius of this species in solution was therefore 22.0 ± 0.64 Å. Similarly, for the $n = 11$ chain length, the hexamer fitted to a core−shell sphere with a core radius of 8.4 ± 0.63 Å and shell thickness of 13.7 ± 0.78 Å, for a total radius of 22.1 ± 1.0 Å (Figure 2; see Supporting Information (SI)). The different core and shell dimensions may be a result of different levels of solvation of the alkyl chain shell. This would alter the scattering contrast, which was not taken into account in this structural model. However, the overall radius of the $PgC_{11}Cu$ and $PgC_{13}Cu$ core−shell spheres are nearly identical, which is as expected since the length of the alkyl chains is not much different.

For the data analysis of **1**, the neutron scattering length density (SLD) of **1** was calculated from the overall molecular formula $C_{576}H_{888}O_{72}Cu_{24}$ and a mass density of 1.4 g/mL, giving an SLD of 8.97×10^{-7} Å^{-2}. The SLD of deuterated *o*-xylene was calculated to be 5.92×10^{-6} Å^{-2}. The data at mass fractions of 1% and 5% were fitted simultaneously to a variety of structural models, keeping the SLDs fixed at their calculated values. Spherical structures provided a poor fit for **1** at the low *q*-values indicating the presence of an elongated structure in solution. Thus, uniform ellipsoid, triaxial ellipsoid, sphere, cylinder, elliptical cylinder, and prolate core−shell model fits were attempted (see SI).

The scattering data for both the 1% and 5% mass fraction data sets fit poorly as a cylinder, elliptical cylinder, and prolate core shell model, with either a high χ^2 value or high standard deviation of fitted length scales (see SI). However, the data fitted well with a uniform ellipsoid model for hexamer **1**. The fitted ellipsoidal dimensions of **1** are 115.4 ± 0.2 Å (half length of the axis of rotation) and 24.2 ± 0.02 Å (half length of the minor axis). Since the rotation axis is greater than the minor axis, the shape is a prolate ellipsoid displaying a limiting power-law slope approaching q^{-1} at low q (Figure 3; see SI).

The ellipsoidal shape of **1** or $PgC_{17}Cu$ in solution is analogous to the earlier reported solid-state structure of the H-bonded PgC_{11} hexamer (Table 1).[14] In the solid-state study, the H-bonded hexamers with alkyl chain length $n \geq 9$ were reported to have chains radiating in a disk-like arrangement, rather than uniformly, exposing two of the H-bonded faces.[14] Note, however, that the framework of the H-bonded capsule itself remains spherical (Figure 1).[14] Analogous to the H-bonded capsules with $n < 11$, the copper-seamed PgC*n* hexamers of similar alkyl chain lengths ($n = 3, 6, 9$) have been revealed to exist as spheres both in solution (for alkyl lengths $n = 3, 6, 9$) and in the solid state ($n = 3, 6, 9$).[16] Single crystals suitable for diffraction of copper-seamed hexamers with chain lengths $n > 9$ were difficult to obtain (Table 1).

The fact that the dimensions of the H-bonded and the Cu-seamed hexamers are equivalent suggests the capsule itself, disregarding the chain length, is spherical in both solid[6] and solution phase (from SANS data analysis).

With respect to the overall structure, for similar reasons, it is likely that the copper MONCs with $n > 9$ have ellipsoidal dimensions in the solid state. However, in the case of Cu MONCs with $n = 11$ and 13 the SANS data indicate that the overall structures in the solution phase are spherical. It is not until $n = 17$ that ellipsoidal dimensions are found in solution. Retention of spherical shape in solution at larger n can be attributed to the absence of a lattice allowing uniform distribution of alkyl chains at larger lengths. The SANS study of previously reported PgC_nCu hexamers for alkyl lengths $n = 3$, 6, and 9[16] as well as the current core−shell spherical structures for $n = 11$, 13 indicates a progressive increase in spherical size with an increase in alkyl chain length.[16] The presence of discrete spherical entities in solution confirms the robustness of MONCs in solution (Table 1).

For **1** in *o*-xylene, the SANS measurements show a shorter axis of 48 Å diameter in solution, which is in proportion with the 44 Å diameter of the spherical PgC_{13} copper-seamed hexamer. These values suggest either (a) the alkyl chains radiate uniformly in solution for the individual **1** nanocapsules in a spherical arrangement or (b) no alkyl chains lie along the shorter axis and instead a group of nanocapsules are packed with H-bonded faces exposed to one another. It indicates the presence of one nanocapsule in sphere fashion or more than one in disk-like fashion along the minor axis. In either case the major axis (231 Å or 23.1 nm diameter) of the ellipsoid is enabled by the interdigitation of alkyl chains in this direction. Such a solution phase ellipsoidal nanocapsular assembly is modeled in Figure 1c from the data in Figure 3.

Comparing the radii of the major and minor axes gives an approximate ratio of 1:5 (more precisely 1:4.8). This indicates an approximate volume (number) ratio of hexamers along the two axes of 1:5. The ellipsoidal shape of **1** does not change with 1% or 5% mass fractions, indicating equilibrium between the soluble ellipsoidal nanocapsule and the solvent rather than just aggregation or incomplete dissolution of the precipitated material. The absence of aggregation is further confirmed by the observed neutron scattering data at low q fitting well to an ellipsoidal geometry. These results reveal, to some extent, the limits to which self-assembled entities can stabilize in solution without aggregation, although it is reasonable to expect more complex assemblies to crystallize out.

The current solution-phase study emphasizes the robust intactness of these MONCs at long chain lengths. In addition, the ellipsoidal self-assembly (**1**) also mimics the structures of cell-adhesion-like desmosomes. That is, the interspersion of the heptadecyl chain along the major axis of the ellipsoid between adjacent nanocapsules yields self-assembled hexamers in solution that in part adhere to each other like cell desmosomes (Figure 1c). Long alkyl chains also add a new dimension to nanocapsules by providing structural variables that give access to functions like ion channels.[21,22]

In conclusion, SANS reveals the presence of stable core−shell spherical structures of $PgC_{11}Cu$ (**2**) and $PgC_{13}Cu$ (**3**) in chloroform and formation of an ellipsoidal assembly for $PgC_{17}Cu$ in *o*-xylene. The ellipsoidal shape of **1** is consistent with both the progression in size of the hexamer and interdigitation of alkyl chains along the long axis of the hexamers. Such interlocking facilitates the formation of strong hydrophobic bilayers that mimic biological membranes connecting two adjacent cells or nanocapsules. Future studies will focus on exploring the biological properties of long-chained hexamers and studying parameters in solution that could assist favorable crystallization. It is likely that SANS studies of MONCs in solution will provide insight into the mechanism of formation of these MONCs,[23] eventually allowing synthesis directed toward specific practical applications (e.g., drug encapsulation).[24]

ASSOCIATED CONTENT

Ⓢ **Supporting Information.** Description of materials and methods; form factor analysis of measured SANS data. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

We thank the NSF for support of this research (J.L.A.). This work utilized facilities supported in part by the NSF under Agreement No. DMR-0944772 (S.R.K.). We also thank Dr. Carol A. Deakyne for inspiring discussions.

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