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Solution structure of copper-seamed C-alkylpyrogallol[4]arene nanocapsules with varying chain lengths†

Harshita Kumari,^a Steven R. Kline,^{*b} Nathaniel J. Schuster^a and Jerry L. Atwood^{*a}

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The stability of copper-seamed C-alkylpyrogallol[4]arene hexamers with varying chain lengths in solution has been studied using small-angle neutron scattering (SANS). The progression in diameter of spherical capsules with increasing alkyl chain lengths of copper-seamed hexamers in solution suggests both robustness as well as a close correlation between the solid phase and solution phase structures.

Naturally occurring macromolecules like DNA serve as excellent examples of self-assembled molecular superstructures.¹ Their self-assembly process can be described as bringing together complementary molecular entities that have the propensity to self-orient into functional molecular devices. Self-assembled hosts are an especially important class of molecular superstructures. They include bilayers,² molecular channels,³ cylindrical tubes⁴ and spherical nanocapsules and have the capacity to mimic viral geometries.⁵ Amongst these hosts, metal–organic nanocapsules (MONCs) capture extensive attention owing to their potential to accommodate guests,⁶ show magnetic interactions,⁷ and self-assemble into various conformations.⁵

The spontaneous formation of a spherical molecular assembly from six C-methylresorcin[4]arene macrocycles and eight water molecules focused attention on nanocapsule research. This assembly is seamed together by 60 hydrogen bonds and possesses a cavity of approximately 1375 Å³.⁸ Similar to C-alkylresorcin[4]arenes, C-alkylpyrogallol[4]arenes (PgC_n, where *n* = alkyl chain length) self-assemble into hexameric nanocapsules. Seamed together by 72 hydrogen bonds, pyrogallol[4]arene hexamers are more robust than their resorcin[4]arene counterparts. Indeed, the incorporation of water molecules into their hydrogen-bonded frameworks has not been reported. The cavities of the PgC_n hexameric nanocapsules are large enough to accommodate fluorescent molecular probes.^{6,9–12} Crystallographic studies later revealed that the replacement of hydrogen ions in the hydrogen-bonded framework of the PgC_n nanocapsules with metal ions

produced especially robust nanocapsules with dimensions similar to hydrogen-bonded hexamers.^{13–16} In the formation of these metal–organic assemblies, both metal ions and solvent molecules were observed to direct the shape and size of the MONCs. For example, the pyridine solvent favours the formation of dimeric zinc- or nickel-seamed nanocapsules while methanol or acetone provide solvent environment preferable for the self-assembly of copper- or gallium-seamed hexamers.^{13–20} However, the rationale for the preferred metal–solvent selectivity, their mechanisms of formation and the parameters governing their architectures are yet to be determined. Our initial investigations explored the stability, shape, and size of MONCs in solution. It is clear that knowledge of MONC cavity volume and stability are key for the use of MONCs for applications such as drug delivery or guest entrapment.²¹ In this contribution, we investigate the shape and size of copper-seamed C-alkylpyrogallol[4]arene nanocapsules PgC_nCu (*n* = 3, 6, 9) upon change of the alkyl chain lengths using small-angle neutron scattering (SANS). Unlike diffusion NMR or DLS, SANS, without assumption, can measure the size, shape, and internal arrangement of nanostructures.

PgC_nCu MONCs were prepared by adding a methanol solution of PgC_n (0.01 mol L^{−1}) to a methanol solution of

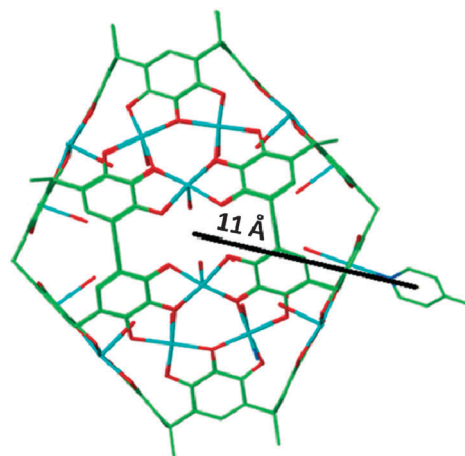


Fig. 1 Single crystal XRD structure for C-propylpyrogallol[4]arene metal-seamed hexamer illustrating the approximate radius of the capsule. For clarity only one of the pyridine ligands attached to metal ion framework is shown. O: red, M (metal): turquoise, C: green, N: blue.

^a Department of Chemistry, University of Missouri–Columbia, 601 S. College Avenue, Columbia, MO 65211, USA. E-mail: AtwoodJ@missouri.edu

^b NIST Center for Neutron Research, Gaithersburg, MD 20899-6102, USA. E-mail: Steven.kline@nist.gov; Fax: +1 573 882 2754; Tel: +1 573 882 8374

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copper(II) nitrate (0.04 mol L^{-1}), which yielded a brown precipitate of the copper hexamer.[‡] These hexamers were collected, dried, and then dissolved in deuterated acetone at mass fractions of 1% and 5% to obtain sufficient scattering in SANS. The samples were left overnight to ensure saturation without precipitation. About 0.6 mL of sample was then pipetted into demountable titanium cells of 2 mm path length which were mounted in the SANS sample chamber and maintained at a temperature of 25 °C. All measurements were performed on the NG3 30 m SANS instrument at the **NIST Center for Neutron Research** in Gaithersburg, MD.²² For the measurements, neutrons of wavelength $\lambda = 6 \text{ Å}$ with a full width half-maximum of $\Delta\lambda/\lambda = 15\%$ were used. Two different sample to detector distances, 1.3 m and 4.5 m, were used to cover the overall q range of $0.012 \text{ Å}^{-1} < q < 0.52 \text{ Å}^{-1}$. The measured raw data were corrected for the background and empty cell scattering, followed by calibration with the normalized detector sensitivity. The corrected data sets were placed on an absolute scale using the direct beam flux method before averaging the 2-D data to 1-D, corrected $I(q)$ data. To obtain the structure of the species in solution, the reduced data were modelled with NCNR-supplied software²³ incorporating the instrumental q -resolution function.

Each nanocapsule was measured at mass fractions of 1% and 5% to ensure sufficient scattering and to test that the capsule structure does not change with concentration. For PgC_3Cu , the SANS intensity from a sample of mass fraction of 1% was too weak, but using a mass fraction of 5% provided sufficient scattering. For PgC_6Cu and PgC_9Cu , mass fractions of 1% and 5% both provided good data. The SANS data for PgC_nCu hexamers is given in Fig. 2 ($n = 3$), Fig. 3 ($n = 6$), and Fig. 4 ($n = 9$). For PgC_6Cu and PgC_9Cu , the SANS curves at different concentrations were the same shape, scaling with concentration, indicating that the structures do not change shape or size. So these data were fitted simultaneously to a single structural model to better determine the structural parameters of the nanocapsules.

For data analysis, the coherent scattering length density (SLD) of both the solute and solvent were calculated and held

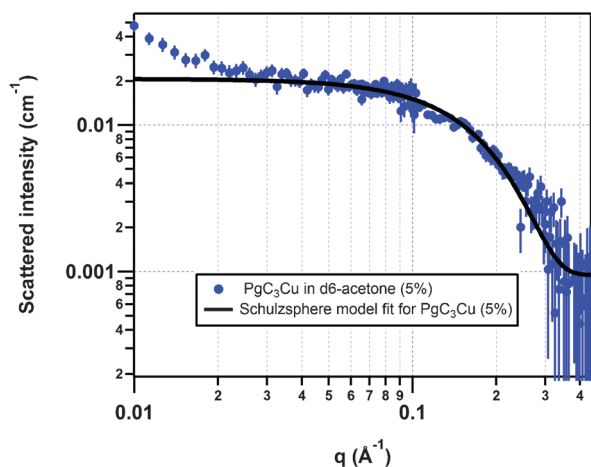


Fig. 2 SANS intensity from C-propylpyrogallol[4]arene copper hexamer at a mass fraction of 5%. The solid line is the model fit with a polydisperse sphere model. The error bars on the SANS data points represent one standard deviation in the measured intensity.

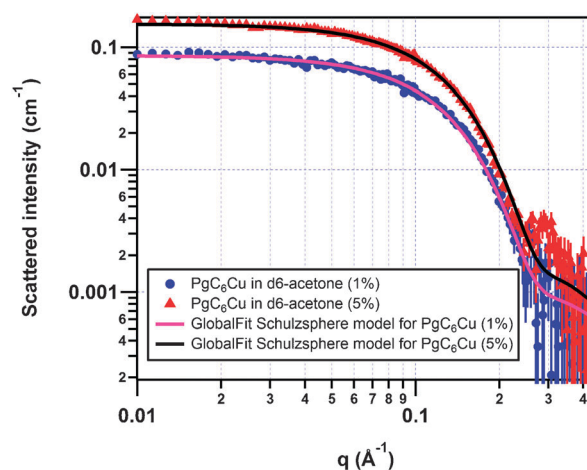


Fig. 3 SANS intensity from C-hexylpyrogallol[4]arene copper hexamer at mass fractions of 1% and 5%. The solid lines are the global polydisperse sphere model fit with radius and polydispersity common to both data sets.

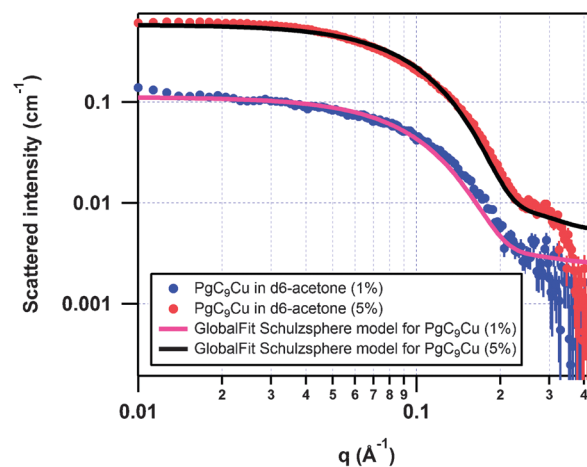


Fig. 4 SANS intensity from C-nonylpyrogallol[4]arene copper hexamer at mass fractions of 1% and 5%. The solid lines are the global polydisperse sphere model fit with radius and polydispersity common to both data sets.

fixed. Since the capsules are largely hydrogenated, we preferentially used deuterated solvents to enhance the coherent scattering contrast and reduce the incoherent scattering in the SANS measurements. Thus, we employed d_6 -acetone as a solvent with a calculated SLD of $5.39 \times 10^{-6} \text{ Å}^{-2}$. Likewise, SLDs for PgC_3Cu , PgC_6Cu and PgC_9Cu were calculated to give $1.74 \times 10^{-6} \text{ Å}^{-2}$, $1.42 \times 10^{-6} \text{ Å}^{-2}$ and $1.18 \times 10^{-6} \text{ Å}^{-2}$, respectively.

To determine the best representation of the solution structure of the nanocapsules, the reduced SANS data was analyzed by fitting to a number of possible shapes, then judging which was the most likely shape for the nanocapsule. The shapes used were: polydisperse sphere, polydisperse core-shell sphere, core-shell sphere, ellipsoid, and hollow tube. Elongated structures in general gave a very poor quality fit and were quickly ruled out. In other spherical models such as core-shell sphere and polydisperse core-shell structural models, the shell thickness tended to zero and hence reverted to a uniform spherical

Table 1 Summary of dimensions of pyrogallol[4]arene copper hexamer in solution phase (SANS) and solid phase (XRD)^a

Sample	SANS radius (Å)	Sqrt (χ^2/N)	XRD radius (Å) ^a
PgC ₃ M ^b	11.12 ± 0.02	1.42	11.1
PgC ₆ Cu	14.89 ± 0.15	1.29	16.6
PgC ₉ Cu	17.59 ± 0.02	4.78	18.6

^a Orientation of the different chain lengths in 3-D varies slightly (± 1.5 Å) for a given XRD structure. The XRD radius reported is the longest radial distance from the centroid of hexamer to the last carbon of the longest alkyl chain. ^b Here M is nickel. Ni and Cu hexamers are isostructural; (PgC₃Cu is difficult to crystallize). Uncertainties reported are one standard deviation.

structure. Therefore, based on the statistical quality of the fits and requiring that the length scales be physically reasonable, the scattering data for hexamers of chain lengths $n = 3, 6$, and 9 in solution fitted best to a polydisperse Schulz sphere model.^{24,25} While the single PgC₃Cu data set was fitted by itself to the polydisperse sphere model, the two PgC₆Cu and two PgC₉Cu data sets were fitted simultaneously. During the simultaneous (global) fitting, the radius and polydispersity are common to both concentrations, while the concentration and incoherent background are individual to each data set, and the SLDs are held fixed at the calculated values. This procedure provides the best refinement of the structural parameters from analysis of the SANS data (Fig. 2–5; See supporting information).

In lieu of a full crystallographic analysis,²⁶ the radius of the capsule in the solid state can be estimated as the distance from the centre of the capsule to the last carbon of the alkyl chain. However, for the PgC₃M (where M is metal) hexamer, the distances between the capsule centroid–ligand (pyridine) centroid and the capsule centroid–C₃ (last carbon of alkyl chain) are about equal. Fig. 1 shows the structure of the PgC₃M hexamer (with pyridine ligand) in the solid-state and the radius of the sphere. XRD data from all three PgC_nCu samples yields estimates that are comparable to the orientationally averaged solution structure from SANS, and the results are shown in Table 1. The geometric dimensions (shape and size) obtained for the hexamers in the solution phase are nearly identical to those from the solid-state. Thus, SANS data analysis for the solvent-solubilized PgC_nCu hexamers not only confirms their spherical shape in solution but also reveals the expected progressive increase in capsule radius with increase in alkyl chain length.

In summary, the current study has revealed the stability of PgC_nCu hexamers in solution, their progression in size with increased chain length, and the uniform distribution of spherical hexamers in solution. This detailed structural characterization will help in understanding the limits of guest inclusion²⁷ and the mechanisms of MONC formation. SANS measurements also are useful to determine the structures of species that are difficult to crystallize²⁸ due to the close relation between the solution phase (neutron scattering measurements) and solid state (X-ray crystallographic data) structures of MONCs. However, one can expect to see some structural variation as a result of packing arrangements in the solid state where there is no solvent present.

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Notes and references

† C-alkylpyrogallol[4]arenes were synthesized using literature procedures. In a general experiment, methanolic solution of C-alkylpyrogallol (1 equiv.) was added to a methanolic solution of copper nitrate to yield brown precipitate.

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