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Molecular Capsules

# Controlling the Self-Assembly of Metal-Seamed Organic Nanocapsules**

*Harshita Kumari, Andrew V. Mossine, Steven R. Kline, Cindi L. Dennis, Drew A. Fowler, Simon J. Teat, Charles L. Barnes, Carol A. Deakyne,* and Jerry L. Atwood**

The advent of modern molecular characterization techniques in the mid 20th century brought about a renaissance in our understanding of life's many processes. Notably, the structural determination of large biomolecules through the development of techniques such as NMR spectroscopy and X-ray diffraction (XRD) has given scientists valuable insight into the inner workings of cells.[1] Many of these molecules are highly symmetrical, multicomponent entities, though determining the processes by which they assemble has been a difficult task. The biosynthesis of DNA, for example, came much later than its structural characterization by Watson and Crick.[2] It is exactly this knowledge, however, that allows one to control the system. Supramolecular chemists have likewise endeavored to control the self-assembly processes in multicomponent entities.[3–5] Although simpler than many biomolecules, the size and complexity of the macromolecules that embody this field largely preclude the use of standard mechanistic analyses that are applicable to smaller compounds.

Our work has focused on metal-seamed pyrogallol[4]arene (PgC) nanocapsules.[6] Forming rapidly through self-assembly, these large entities are composed of 2 or 6 macrocyclic units that act as chelates through their upper rims for 8, 12, or 24 metal ions (Figure 1).[7] It is important to note that the 6-macrocycle, 24-metal ion hexameric nanocapsule results from the remarkable self-assembly of 30 entities. The dimeric or hexameric capsules are highly symmetrical, relatively stable under standard conditions, and have interior voids and interesting coordination environments that make them appealing for potential magnetic and biomedical applications such as formation of nanowires, tagging of agents for biomedical assays or drug encapsulation. Although the synthesis of these entities is relatively straightforward and inexpensive, one major problem has previously hindered our progress in this field: product control. A mixture of both dimeric and hexameric products almost always forms, and purification is, at best, difficult. Compounding the issue is the fact that the two entities are stoichiometrically identical and often paramagnetic, preventing techniques such as atomic absorption and NMR spectroscopy, respectively, from providing useful mechanistic insight. Morphological control is key in the manipulation of any macromolecule destined for practical application. Thus, elucidating the parameters that control the formation of one entity over another is generally an important step in the growth of nanoscience.

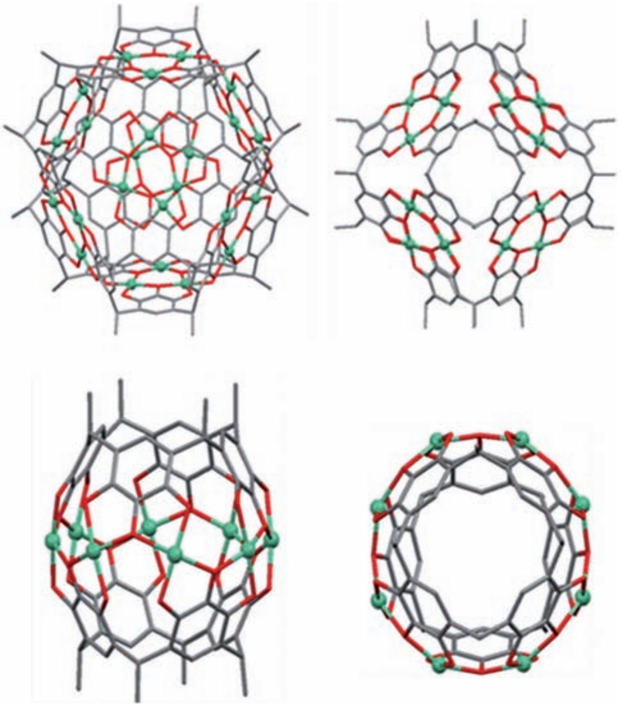

***Figure 1.*** Top: Two different side views of the *C*-alkylpyrogallol[4]arene nickel hexamer. Bottom: Side (left) and top views (right) of the nickel dimer. Green atoms are nickel "seams".

In order to gain insight into this critical problem, small-angle neutron scattering (SANS) data has been used to elucidate the effect of temperature, solvent, and metal

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[*] Dr. H. Kumari, A. V. Mossine, Dr. D. A. Fowler, Dr. C. L. Barnes, Prof. C. A. Deakyne, Prof. J. L. Atwood
Department of Chemistry, University of Missouri-Columbia
601 S. College Avenue, Columbia, MO 65211 (USA)
E-mail: deakynec@missouri.edu
atwoodj@missouri.edu

Dr. S. R. Kline
NIST Center for Neutron Research, National Institute of Standards and Technology, Gaithersburg (USA)

Dr. C. L. Dennis
Material Measurement Laboratory, National Institute of Standards and Technology, Gaithersburg (USA)

Dr. S. J. Teat
Advanced Light Source, Lawrence Berkeley National Laboratory, Berkeley (USA)

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identity on the ratio of capsular products. Crystallization of these entities and their analysis by single-crystal XRD also served an important function in this study, not only in establishing the existence of both capsular species for the two metals investigated (Ni and Cu) but also as a method to verify purity. Although recrystallization of the hexameric moiety proved difficult, several reproducible methods have been developed for the isolation of crystalline Ni and Cu capsules of both the hexamers and their dimeric counterparts.

Dimeric (hexameric) products for both metals were produced in a rather simple fashion: addition of 4 equivalents $M(NO_3)_2$ and 14 equivalents pyridine to a warm (cold) 0.1 M MeCN (or MeOH for Ni) solution of $PgC_3$ led to yellow (dark green) and reddish-brown precipitates for Ni and Cu, respectively. The dimer precipitates were dissolved in a minimal amount of boiling dimethylsulfoxide (DMSO) and crystals of the dimeric products formed on cooling. Alternatively, a similar ratio of reactants was added directly to a boiling 0.1 M DMSO solution of $PgC_3$, with crystalline products forming upon cooling. Regardless of synthesis protocol or metal identity, the dimeric capsule features two PgC hemispheres seamed together by a belt-like arrangement of the eight metal ions along the "equator" (Figure 1). All dimers produced following the techniques presented herein contain a single entrapped guest and eight *exo*-ligands coordinated to the metals along the periphery. In all cases, the guests/ligands were pyridine or DMSO, depending on the synthesis protocol.[8,9]

Hexameric moieties of Cu and Ni (Figure 1) were much more difficult to crystallize; thus, for both the $PgC_3Cu$ and $PgC_3Ni$ hexamers microcrystalline powder was used for the control SANS experiment.[8] Single crystals were, however, easily obtained with $PgC_1$. Addition of copper nitrate to an acetone solution of $PgC_1$ led to the formation of very well diffracting crystals. Interestingly, two types of crystals formed in $Cu(OAc)_2$/DMSO/MeCN solution, identified as hexamers and dimers, aptly exemplifying the dilemma. Although crystals of $PgC_3NiPy$ hexamer in MeOH at room temperature formed following the same protocol used for the dimer, these crystals diffracted poorly affording only a unit cell determination. However, the analogous synthesis using $PgC_6$ or $PgC_3$, with 4-picoline instead of pyridine, led to crystals suitable for X-ray analysis.[8] Unlike the Cu hexamer, which typically exhibits a square planar ligand field about the metal centers, each Ni center accommodated both an external pyridine ligand and an internal ligand (likely water), making its ligand field octahedral. Both Ni and Cu hexamers are, nevertheless, arranged similarly in terms of the metals, with eight 3-metal clusters arranged symmetrically along the periphery (Figure 1).[9]

The solution-phase nature of assembled supramolecular structures is relatively unexplored.[10–12] Here, in addition to the solid-state studies, SANS (NG7 30 m SANS, NIST Center for Neutron Research) analyses were performed to investigate the geometric size and shape of both dimeric and hexameric metal-seamed organic nanocapsules (MONCs) in solution.[13,14] Control experiments involving SANS were run at room temperature 2 h after dissolving pure dimer or pure hexamer in deuterated solvent. The radii obtained for the dimer (ca. 7 Å) and the hexamer (ca. 10 Å) remained constant, within experimental error, in all subsequent experiments (Figure 2). To assess the effect of temperature, time, metal, and solvent in controlling nanocapsule formation, scattering measurements were performed at both 0 and 3 days on samples prepared by combining separate dilute solutions of *C*-propylpyrogallol[4]arene ($PgC_3$), nickel(II) nitrate or copper(II) nitrate, and pyridine in either methanol or acetone solvent.[15,16]

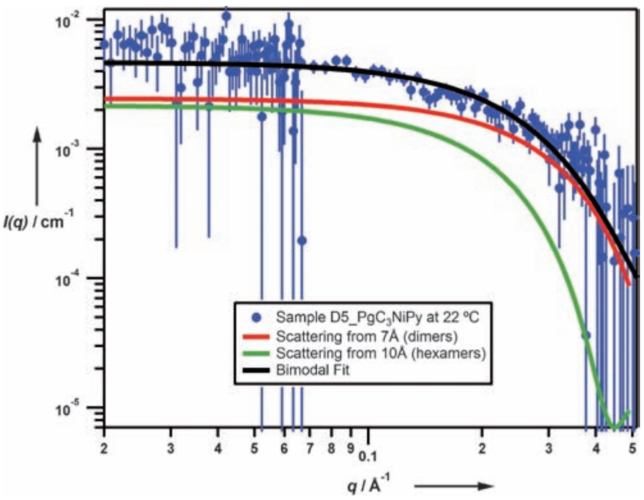

***Figure 2.*** Schulz sphere fits for a pure dimer (red) or a pure hexamer (green) and a bimodal Schulz sphere fit for a mixture of the two species (black). Error bars represent one standard deviation of the intensity. Scattering data obtained from SANS measurements is corrected for the background and empty cell scattering, then calibrated and reduced. Various spherical, cylindrical, or ellipsoidal models are then fitted to the data to determine the shape. The large error bars in the graph at either end of the plot are indicative of decreased scattering at the edge of the detector and do not affect the overall interpretation of the species in solution.

In these experiments, the 1:4:14 $PgC_3$:metal:Py concentration ratio was kept constant for all measurements. Samples were prepared at temperatures of −40 °C, room temperature and 50 °C and then maintained at room temperature on the beamline for scattering measurements. Spherical, ellipsoidal and cylindrical models were fitted to each data set to determine the type, shape and volume fraction of the species formed in solution.[17] In all cases, the best fit to the data was obtained with either a unimodal or bimodal Schulz sphere model (Figure 2).[18,19]

For $PgC_3Ni$ in methanol the scattering data analysis at day 0 reveals an increase in the dimer volume fraction with respect to temperature, with ratios of 1.0 at −40 °C, 1.9 at room temperature, and 2.5 at 50 °C. On the other hand, the relative hexamer volume fractions decrease from about 4.2 at −40 °C and room temperature to 1.0 at 50 °C. From day 0 to day 2 (50 °C) or 3 (room temperature), there is an increase in dimer volume fraction and a decrease in hexamer volume fraction such that the dimer dominates by about an order of magnitude. Surprisingly, the hexamer concentration goes to zero at day 3 for the −40 °C sample, indicating conversion of hexamer to dimer (Supporting Information, Table S2).[17]

Two related 3 day stability studies were also conducted. In the first, the initial synthesis temperature was maintained in the beamline (−20 °C, room temperature, or 50 °C). In the second, the synthesis was carried out at room temperature and the temperature was changed in the beamline. Similar results were obtained from all three sets of experiments, including the loss of hexamer at the lowest temperature (Table S2).[17]

Shifting our attention to the acetone-solubilized samples, both Cu- and Ni-seamed nanocapsules were studied following the original protocol. The day 0 scattering data for the $PgC_3Cu$ samples give relative dimer volume fractions of 1.0 at −40 °C, 2.9 at room temperature, and 4.0 at 50 °C. In contrast, the relative hexamer volume fractions vary from 2.1 at −40 °C to 1.0 at both room temperature and 50 °C. The 3 day stability measurements demonstrate that the dimer volume fraction not only increases but also reaches the same magnitude regardless of the initial synthesis temperature. Again, the hexamer volume fractions are lower than those for the dimer. The acetone solubilized $PgC_3Ni$ samples also show higher formation of hexamers at low temperature (day 0) with subsequent predominance of the dimer (day 3).[17]

The SANS measurements help to elucidate the role of temperature, solvent and metal in controlling the formation of these MONCs. The results suggest that the hexamers are kinetically favored at low temperatures but that the dimers are thermodynamically favored at all temperatures (Figure 3). When the temperature of the solution is held constant for three days, the major entity is the dimer. However, at day 0 the relative hexamer volume fractions are largest at low temperature, regardless of the identity of the solvent or metal. Nevertheless, the effect of temperature on the drop in production of hexamers is more pronounced in methanol than in acetone. Changing the solvent also affects the overall production of both types of capsules, as acetone appears to yield higher volume fractions of both dimers and hexamers at lower temperature. The decrease in hexamer population with temperature is slightly larger for the copper–acetone capsules than for the analogous nickel capsules.

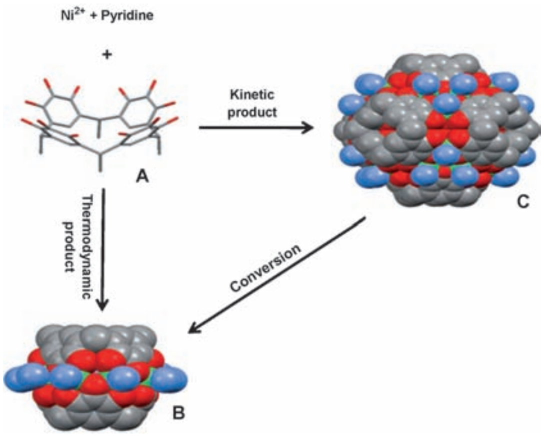

**Figure 3.** The temperature-dependent synthesis of dimeric (**B**) and hexameric (**C**) nickel/copper capsules from pyrogallol[4]arene (**A**). Addition of Ni/Cu and pyridine to **A** yields preferentially **B** or **C** depending on temperature, metal, and solvent. Propyl groups and pyridine rings are omitted for clarity.

In conclusion, factors that can be manipulated towards directed syntheses of metal-seamed organic nanocapsules have been identified. Specifically, preferential formation of dimers occurs at higher temperatures, in methanol solutions and with nickel metal. In addition, we have found conditions under which the nickel-seamed hexamer converts to the dimer. Overall, we have demonstrated that supramolecular self-assembly can indeed be both understood and utilized to selectively control the formation of MONCs.

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