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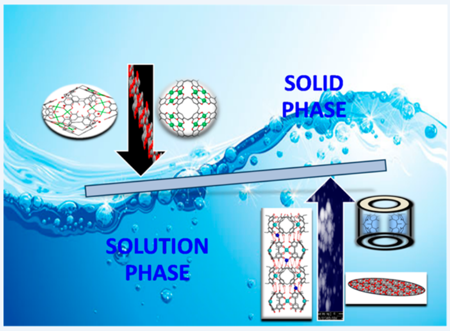
Solution Structures of Nanoassemblies Based on Pyrogallol[4]arenes

Harshita Kumari, Carol A. Deakyne, and Jerry L. Atwood*

Department of Chemistry, University of Missouri—Columbia, 601 S. College Avenue, Columbia, Missouri 65211-7600, United States



CONSPECTUS: Nanoassemblies of hydrogen-bonded and metal-seamed pyrogallol[4]arenes have been shown to possess novel solution-phase geometries. Further, we have demonstrated that both guest encapsulation and structural rearrangements may be studied by solution-phase techniques such as small-angle neutron scattering (SANS) and diffusion NMR. Application of these techniques to pyrogallol[4]arene-based nanoassemblies has allowed (1) differentiation among spherical, ellipsoidal, toroidal, and tubular structures in solution, (2) determination of factors that control the preferred geometrical shape and size of the nanoassemblies, and (3) detection of small variations in metric dimensions distinguishing similarly and differently shaped nanoassemblies in a given solution. Indeed, we have shown that the solution-phase structure of such nanoassemblies is often quite different from what one would predict based on solid-state studies, a result in disagreement with the frequently made assumption that these assemblies have similar structures in the two phases. We instead have predicted solid-state architectures from solution-phase structures by combining the solution-phase analysis with solid-state magnetic and elemental analyses.

Specifically, the iron-seamed *C*-methylpyrogallol[4]arene nanoassembly was found to be tubular in solution and predicted to be tubular in the solid state, but it was found to undergo a rearrangement from a tubular to spherical geometry in solution as a function of base concentration. The absence of metal within a tubular framework affects its stability in both solution and the solid state; however, this instability is not necessarily characteristic of hydrogen-bonded capsular entities. Even metal seaming of the capsules does not guarantee similar solid-state and solution-phase architectures. The rugby ball-shaped gallium-seamed *C*-butylpyrogallol[4]arene hexamer becomes toroidal on dissolution, as does the spherically shaped gallium/zinc-seamed *C*-butylpyrogallol[4]arene hexamer. However, the arenes are arranged differently in the two toroids, a variation that accounts for the differences in their sizes and guest encapsulation.

Guest encapsulation of biotemplates, such as insulin, has demonstrated the feasibility of synthesizing nanocapsules with a volume three times that of a hexamer. The solution-phase studies have also demonstrated that the self-assembly of dimers versus hexamers can be controlled by the choice of metal, solvent, and temperature. Controlling the size of the host, nature of the metal, and identity of the guest will allow construction of targeted host−guest assemblies having potential uses as drug delivery agents, nanoscale reaction vessels, and radioimaging/radiotherapy agents. Overall, the present series of solid- and solution-phase studies has begun to pave the way toward a more complete understanding of the properties and behavior of complex supramolecular nanoassemblies.

1. INTRODUCTION

In order to understand reactivity, it is generally necessary to have a detailed understanding of the structure of the reactants. Nucleation, for example, may be viewed as a complex supramolecular reaction, and thus one naturally begins the study of such phenomena by carefully characterizing the various component species. Therein lies the difficulty, of course. Although there is significant interest in solid-state reactions, including solid-state nucleation,[1,2] most investigations still focus on chemical processes occurring in solution. Yet for complex supramolecular assemblies, little is known about solution structure. Indeed, the conventional operating principle is that solid-state structure is reflected in solution-phase structure. The validity of this assumption is not guaranteed, however, and warrants thorough testing. In this Account, we discuss results derived from analyses of solution structure based on small-angle neutron scattering (SANS) and diffusion NMR that yield insight into this question. In addition, magnetism measurements provide a different way of viewing structure, and such studies usefully supplement the SANS technique.

2. SOLUTION-PHASE BEHAVIOR OF PYROGALLOL[4]ARENE- AND RESORCIN[4]ARENE-BASED NANOASSEMBLIES

It is only recently that supramolecular chemists have begun to focus on solution-phase properties of complex architectures. Orthogonal self-assembly occurs in solution and is a process wherein different components of a given system self-sort on different time scales. Understanding the steps or processes involved in the self-assembly phenomenon in the solid and solution phases and the parameters that allow control over product formation are not only fundamentally relevant but also of great interest to the scientific community. Distinguishing

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solution structures from solid-state geometries has assisted in connecting the steps involved in self-assembly and provided insight into the transition from the solution to the solid phase.

Recent articles on nanoassemblies derived from pyrogallol[4]arenes and resorcin[4]arenes have addressed the solution stability,[3−8] host−guest interactions,[9] and mechanisms of formation of the supramolecular cages, including the effect of guest templation.[10,11] *C*-alkylpyrogallol[4]arenes (PgC_n, where *n* is the alkyl tail length) and *C*-alkylresorcin[4]arenes (RsC_n), structurally related to calix[4]arenes, are bowl-shaped cyclic oligomers with 12 and eight hydroxyl groups, respectively, at their upper rims. These hydroxyl groups provide hydrogen-bonding sites and, by virtue of deprotonation, metal interaction sites to allow formation of hydrogen-bonded (PgC_n/RsC_n) and metal-seamed (PgC_n) hexameric and dimeric nanocapsules, respectively (Figure 1).[11−14]

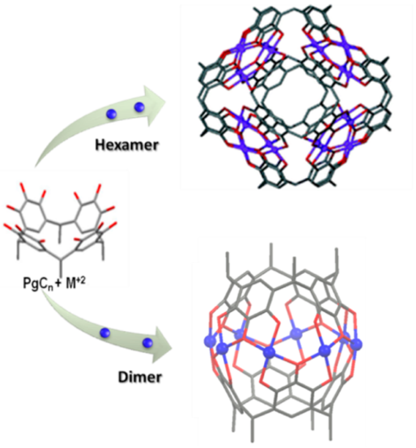

Figure 1. Stick form representation of a pyrogallol[4]arene bowl (left). The figure shows the self-assembly of pyrogallol[4]arenes into metal-seamed hexamers and dimers. Carbon atoms are shown in gray, oxygen atoms are shown in red, and the metal centers are shown in purple. For clarity, the hydrogen atoms are not shown.

Although nanoassemblies have now been synthesized with a range of alkyl groups, metals, guests, and axial ligands, only a few assemblies have been studied in solution. In many of these studies, insight into solution behavior was obtained through the application of well-established characterization techniques, such as light scattering, fluorescence spectroscopy, spinning disc processing, and diffusion NMR.[9,15−17] For example, Cohen and co-workers have effectively utilized diffusion NMR to investigate the formation of calixarene-based nanoassemblies,[18] whereas Rebek and co-workers[19,20] have studied host−guest and host−host equilibria of such nanoassembies. Moreover, Gokel and co-workers[21,22] have examined the dynamics of pyrogallol[4]arene self-assembly processes at the air−water interface via Langmuir trough and Brewster angle microscopy (BAM) measurements.

2.1. Self-Assembly and Molecular Recognition of Hydrogen-Bonded Pyrogallol[4]arene- and Resorcin[4]arene-Based Nanoassemblies

The air−water interface studies conducted by Gokel and co-workers focused on the pore formation and dynamics of self-assembly of pyrogallol[4]arenes. Similar results were obtained regardless of whether the macrocycles are organized as bilayers, nanotubes, or nanocapsules in the solid state.[21] The surface-pressure isotherms and high collapse pressures for pyrogallol[4]arenes with 3-pentyl and *n*-hexyl side chains revealed the formation of stable monolayers at the air−water interface.[21] In fact, the branched chain 3-pentylpyrogallol[4]-arene is highly organized even in the absence of compression.[21] The nonpolymeric, amphiphilic nature of straight and branched short-chain pyrogallol[4]arenes was further demonstrated.[22] Unexpectedly, the behavior of the straight-chain PgC_3 macrocycle at the air−water interface was indistinguishable from that of PgC_6, PgC_9, and PgC_{12}.[22] In a separate study, planar conductance measurements revealed pore formation by 2-ethylpropyl- and 2-propylbutylpyrogallol[4]arene.[23] Interestingly, the two systems have different pore sizes and, most likely, different mechanisms of formation.[23] Perhaps most importantly, an HPLC study of an equimolar ratio of PgC_{10} bilayer and PgC_{10} capsule in EtOAc indicated an equilibrium between aggregated and separated macrocyles in solution, suggesting that the self-assembly process of pyrogallol[4]arene is dynamic and that solvent is critical in the subsequent crystallization of preferred moieties.[24]

Rebek and co-workers have investigated the molecular recognition process of resorcin[4]arenes with respect to formation of hydrogen-bonded molecular capsules[19] and cavitands.[20] The 1-D and 2-D NMR studies of resorcin[4]arene with $Hex_4N^+Br^-$ revealed the existence of signals for free and bound ammonium salt in solution. The two separate signals indicate the presence of energy barriers, resulting from the hydrogen-bonds of the nanoassembly, which disallow exchange of guests from the cavity to the capsule exterior. However, the transport of neutral aromatic guests into the capsule interior was found to be reversible.[25] In another study, ^1H NMR spectroscopy was performed to investigate the disproportionation equilibria of carboxylic acid and primary carboxamide homo- and heterodimers in different capsular environments.[26] The importance of molecular recognition was emphasized by the preferential formation of hetero- versus homodimers and the adaptability of the guests to the enclosed chemical spaces within the host environments.[26]

The diffusion NMR studies by Avram and Cohen have shown the formation of hydrogen-bonded resorcin[4]arene-based hexamers in chloroform, wherein spontaneous self-assembly is enabled without the aid of a separate guest molecule.[15] The upfield NMR peaks of chloroform had a diffusion coefficient similar to that of the nanocapsule, indicating the entrapment of chloroform within the hexamer. The encapsulated neutral chloroform was subsequently exchanged with a tetrahexylammonium cation. Cohen and co-workers have also demonstrated the formation of hydrogen-bonded pyrogallol[4]arene hexamers in chloroform, the role of water in the construction of resorcin[4]arene hexamers in chloroform, and hence the greater stability of hydrogen-bonded pyrogallol[4]arene hexamers than resorcin[4]arene hexamers.[9,16] Later, it was shown that octahydroxypyridine[4]arene self-assembles into hexameric and dimeric entities in chloroform, again with encapsulated solvent.[27] Unlike the resorcin[4]-arene hexamers, the addition of trifluoroacetic acid led to the disassembly of both the octahydroxypyridine[4]arene hexamer and dimer into monomers.[27] In a mixture of pyrogallol[4]arene, resorcin[4]arene, and octahydroxypyridine[4]arene macrocycles, self-sorting occurs and hence no heterohexamers are obtained.[16] This study also demonstrated that the hexamers are much more abundant in nonpolar solvents than was previously thought.[16] More recently, the diffusion NMR studies conducted by Cohen and co-workers revealed the formation of lipophilic calix[4]pyrrole−resorcinarene⊂trialkylamine hexamers in chloroform.[28] In these complexes, the trialkylamine guests interact with the external walls of the hexamers.

The internal structure of large supramolecular nanoassemblies is yet another property that is difficult to discern. Atwood et al. have used fluorescent probe guest molecules, such as pyrene butyric acid (PBA) and 4-[3-(9-anthryl)propyl]-*N,N*-dimethylaniline (ADMA), to investigate this property for *C*-hexylpyrogallol[4]arene (PgC_6) hexamers.[29,30] Combined single-crystal X-ray diffraction and spectroscopic studies revealed the presence of two PBA molecules (Figure 2) versus one ADMA molecule within the host nanocapsule in both the solid and solution phases.[29,30] In the first host−guest assembly, the two *endo*-PBA molecules were separated by about 8 Å within the host cavity and were shown to interact with the inner PgC_6 capsular wall. In the second host−guest assembly, the *exo*-ADMA molecule is associated with the outer PgC_6 capsular wall.[30] The preferred location of the PBA versus ADMA guest induced investigation of the limits for guest encapsulation within the PgC_6 hexamers. The ^1H NMR study of PgC_6⊂benzo[α]pyrene and PgC_6⊂pentacene in chloroform indicated that for both guests the capsules are partially occupied in the solid state and the guest is released upon dissolution of the crystals.[31] The guest-to-host occupancies were 1:14 and 1:40 per nanocapsule for benzo[α]pyrene and pentacene, respectively, in the solid state.[31] Electronic structure calculations on a half capsule or PgC_0 trimer with benzo[α]pyrene demonstrated that the benzo[α]pyrene is too large to fit along the wall.[31] In contrast, the molecular modeling of pyrene and benzene within the PgC_0 trimer resulted in edge-on and face-to-face CH···O and $\pi\cdots\pi$ guest−host interactions, respectively, consistent with the experimental results.[29]

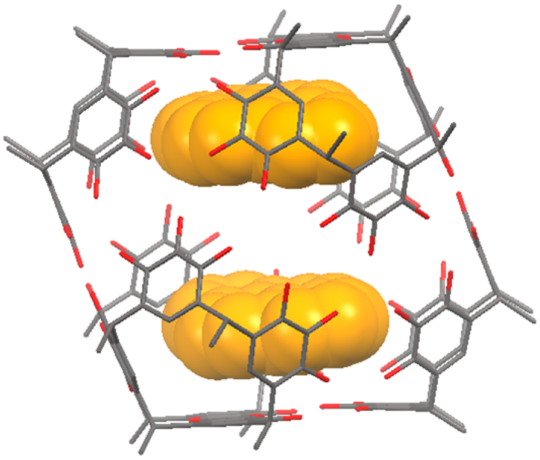

Figure 2. Entrapment of pyrene butyric acid guests within the hydrogen-bonded *C*-hexylpyrogallol[4]arene [$(PgC_6)_6$] hexameric nanocapsule. Hydrogen atoms and alkyl tails have been removed for clarity.

In 2008, Raston and co-workers[17] investigated the use of shear in disassembling and reassembling hydrogen-bonded *C*-alkylpyrogallol[4]arene hexameric nanocapsules using spinning disc processing (SDP) in solution. The hydrodynamic diameters of the hexamers formed pre- and post-SDP were analyzed using dynamic light scattering. The application of SDP to the nanocapsules provided a method to control their self-assembly in solution and to incorporate nonsolvent guest molecules within the nanocapsules; however, presumption of the spherical shape of the nanoassembly in solution persisted.

Although diffusion NMR, dynamic light scattering, and other types of spectroscopy are clearly powerful techniques, they often fail to reveal structural details of complex assemblies in solution. These techniques may provide only partial structural information because of limitations such as paramagnetism or presumption about the spherical architecture of species in solution. Small-angle neutron scattering (SANS), on the other hand, is capable of providing geometric insight into the species present in solution, regardless of paramagnetism. SANS can yield information about not only the shape and size of nanoassemblies in solution but also the factors controlling their formation. In the next section, we discuss SANS studies that have been interwoven with magnetic measurements to explore the architecture and magnetic properties of hydrogen-bonded and metal-seamed resorcin[4]- and pyrogallol[4]arenes in the solid and solution phases. *In situ* neutron scattering and magnetic measurements give insight into the similarities as well as differences between solid-state and solution structures of these nanoassemblies.[32] The effective combination of these methods has provided a more complete understanding of the self-assembly of noncovalently bonded supramolecular architectures in solution.

2.2. Solution-Phase Structures of Pyrogallol[4]arene- and Resorcin[4]arene-Based Nanoassemblies

2.2.1. Dimeric and Hexameric Spheres. Solid-state analyses often aid in our understanding of solution-phase behavior; however, using solution-phase analyses to understand solid-state behavior is not generally implemented.[33] Atwood and co-workers have applied this reverse approach to further the understanding of the structural dependence of pyrogallol[4]arenes and metal-seamed pyrogallol[4]arenes (PgC_nM) on tail length. *C*-Alkylpyrogallol[4]arenes can self-assemble as hydrogen-bonded capsules, tubes, and bilayers or as metal-seamed dimeric and hexameric nanocapsules, depending upon the nature of the solvent and the alkyl groups. For example, solid-state studies reveal that the hydrogen-bonded PgC_n hexamers with $n \leq 9$ are spherical, whereas the hexamer with $n = 11$ is ellipsoidal in structure.[34] The change in the structure of the hydrogen-bonded hexamers led to the investigation of the structure of metal-seamed hexamers with longer alkyl tails.[35] Obtaining structural information with the use of single-crystal X-ray diffraction (XRD) was difficult due to complexities caused by the disorder associated with longer chain lengths. Thus, these species were studied in solution. To establish a correlation between solid-state (XRD) and solution-phase (SANS) geometries, we first studied copper-seamed *C*-alkylpyrogallol[4]arene hexamers (PgC_nCu) with shorter alkyl chain lengths. The solid-state spherical geometries of the PgC_nCu nanoassemblies with n = 3, 6, or 9 were retained in acetone solution.[3] Moreover, the dimensions of the solution-phase structures closely match their single-crystal XRD dimensions, further demonstrating the similarity in dimensions of hydrogen-bonded and metal-seamed PgC_n hexamers. Unexpectedly, the SANS data for $PgC_{11}Cu$, $PgC_{13}Cu$, and $PgC_{17}Cu$ were best fitted to core−shell, core−shell, and ellipsoidal geometries, respectively, in solution (Figure 3, Figure 4).[5] Despite starting with different mass fractions (1 and 5 wt %) of $PgC_{17}Cu$, the resulting ellipse had identical dimensions suggesting formation of a discrete supramolecular entity rather than mere aggregation.[5] The discrete architectures

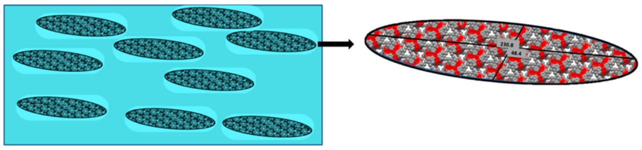

Figure 3. An ellipsoidal model of the copper-seamed C-heptadecylpyrogallol[4]arene nanoassembly ($PgC_{17}Cu$) with a minor rotation axis of ~48 Å (radius) and major rotation axis of ~230 Å.

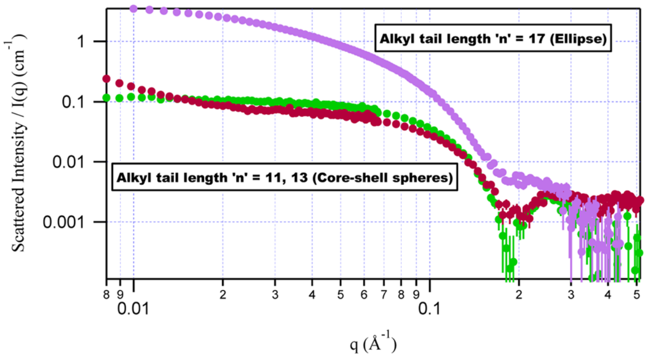

Figure 4. An overlay of SANS curves (scattered intensity, $I(q)$, versus scattering vector, q) showing the difference in curve shape for core−shell versus ellipsoidal geometries.

found for the assemblies with longer alkyl tails reveal the limits to which self-assembled entities can be stabilized in solution.[5]

Although the synthesis of dimeric and hexameric pyrogallol[4]arene-based metal-seamed nanocapsules is relatively straightforward, discerning the parameters governing the self-assembly process is not.[11] A mixture of both dimeric and hexameric products almost always forms during the synthesis because of the identical stochiometric ratios for the two entities, and product control and purification have been a challenge. The SANS measurements of the copper- and nickel-seamed C-propylpyrogallol[4]arene-based nanocapsules, however, have delineated the roles of temperature, solvent, and metal in controlling the formation of these nanocapsules. Both high temperature synthesis and three-day temperature SANS studies (temperature held at 50 °C, RT, and −20 °C for 3 days) indicate that the dimers are the major products under such conditions. In contrast, low temperature synthesis (−20 to −40 °C) shifts the equilibrium toward the hexamers, indicating that the dimers are thermodynamically favored at all temperatures but the hexamers are kinetically favored at low temperatures (Figure 5).[11] The effect of temperature on the production of dimers vs hexamers is more evident in methanol than in acetone. In fact, use of acetone enhances overall product yield because the volume fractions of both dimers and hexamers are larger at low temperature in acetone than in methanol. Also, copper nanocapsules show a slightly larger decrease in hexamer population in acetone than do nickel nanocapsules in acetone.[11] Overall, this study demonstrates that the self-assembly of pyrogallol[4]arenes can be understood and controlled with respect to the formation of metal-seamed organic nanocapsules.[11]

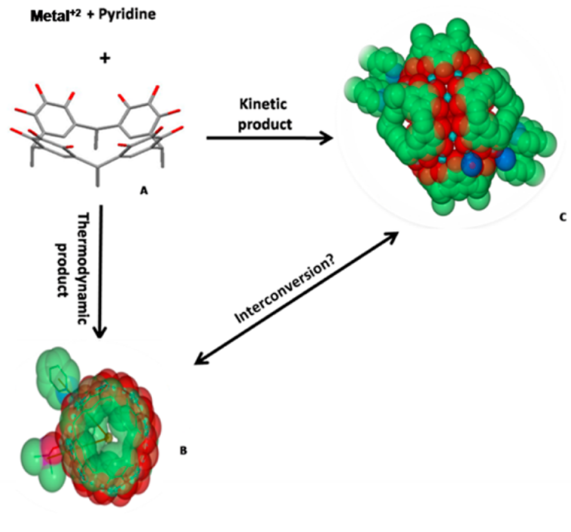

Figure 5. Schematic for the temperature-dependent synthesis of metal-seamed organic dimers (B) and hexamers (C) from pyrogallol[4]arene (A). Addition of metal^{2+} and pyridine to A yields B or C depending on the temperature, metal, and solvent employed.

2.2.2. Toroidal Structures. Unlike the spherical copper- and nickel-seamed hexamers,[11,36] gallium-seamed hexamers exist as a "rugby-ball" or distorted sphere in the solid state.[37,38] Although novel ellipsoidal and core−shell solution structures were found for the $PgC_{17}Cu$ and $PgC_{11}Cu/PgC_{13}Cu$ hexamers, respectively,[5] a transition in structure upon dissolution was not reported. Solution-phase studies (diffusion NMR-DOSY, NMR exchange spectroscopy (EXPY), and SANS) on the gallium hexamers revealed their rearrangement to toroidal assemblies, which disclosed the unique "fluxional nature" of gallium-seamed nanocapsules (Figure 6).[4] Similarly, the gallium−zinc mixed-metal nanoassembly (XRD) rearranges from a spherical architecture in the solid state to that of a toroid in solution.[4,39] Interestingly, the two toroids are different in metric dimensions; thus, the structures of PgC_4Ga and PgC_4GaZn are different in both the solid and solution phases (Figure 6).

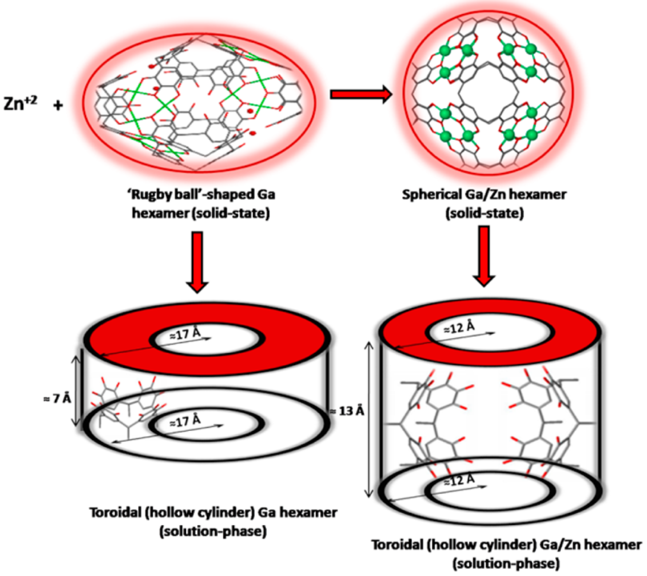

Figure 6. Graphical representations of the geometries of gallium-seamed and gallium/zinc-seamed pyrogallol[4]arene nanoassemblies as a function of change in phase (solid to solution or solid to solid).

A ^{71}Ga NMR study of the two nanoassemblies indicated the presence of metal in the toroidal frameworks and diffusion NMR studies indicated that a guest is encapsulated only within the PgC_4GaZn toroids in acetone. Prompt γ activation analysis (PGAA) studies of a series of gallium−transition metal

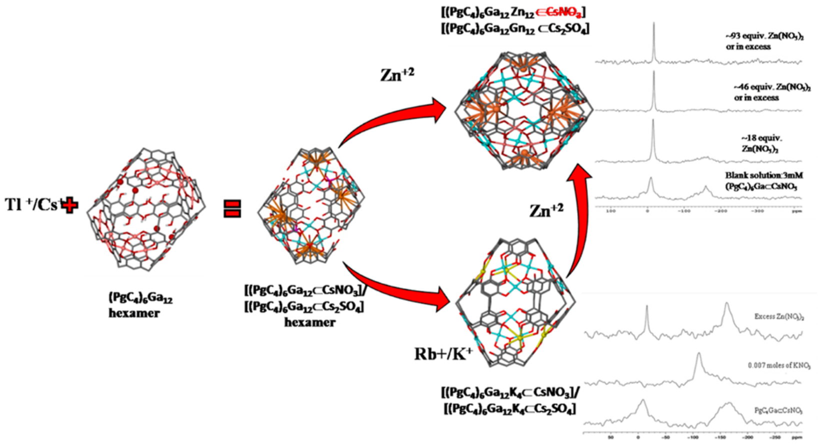

Figure 7. Schematic showing the transport of Cs/Tl ions into a gallium hexamer and the subsequent change in geometry resulting from the closing of the gates by the tertiary (Rb/K/Zn) ions. The effect of the addition of the tertiary ions on the amount of free and bound Cs/Tl ions is indicated by the shifts in the relevant peaks of the NMR spectra.

hexamers PgC_4GaM demonstrated that the Ga^{3+}/M^{2+} ratio in the hexamers varies with M, decreasing from Co^{2+} to Zn^{2+}. This trend among the late 3d transition metals directs the self-assembly of mixed-metal (Ga/M) pyrogallol[4]arene complexes. Overall, combined SANS and NMR analyses helped elucidate the structural rearrangements, metal coordination environment, and arrangement of macrocyles in solution-phase frameworks.[4]

In addition to the SANS studies, ion-transport studies have been conducted on gallium-seamed pyrogallol[4]arene-based nanoassemblies.[40] Specifically, the transport of CsOH, Cs_2SO_4, $CsNO_3$, $AgNO_3$, $Tl_2(SO_4)$, and $TlNO_3$ into gallium-seamed C-butylpyrogallol[4]arene (PgC_4Ga) hexamers has been examined. With respect to cation transport, $AgNO_3$ and CsOH were first studied in the solid state.[41] Unlike the previously reported cesium(I) dimer of pyrogallol wherein the metal centers are located at the upper rim of the pyrogallol,[42] the cesium(I)/silver(I) centers in the PgC_4Ga hexamer are not observed in the framework.[41] Rather, both cations are located inside the nanocapsule but close to the capsular wall. The Ag(I) ions are positioned close to the Ga_3O_3 triads, whereas the Cs(I) ions are positioned close to the water gates of the nanoassembly. The transport of cesium nitrate and sulfate complexes into PgC_4Ga was then investigated to deduce the effect of the anion on ion transport.[43] The combined ^{133}Cs NMR, elemental, and solid-state studies showed higher entrapment of Cs ions within PgC_4Ga when the counterion is sulfate than when it is nitrate. The placement of the anion with respect to the host framework plays an important role in anchoring the cation within the nanoassembly: sulfate is located inside the capsule, whereas nitrate is located outside the capsule. The positioning of the sulfate anion in the capsule interior not only facilitates the anchoring of cesium ions within the framework but also prevents subsequent expulsion of cesium on addition of a third metal or zinc (Figure 7).[43]

The addition of zinc(II) causes stitching of the capsular walls and a concomitant geometric rearrangement (Figure 7). Thus, the Cs and sulfate ions are retained despite the rearrangement from solid-state rugby-ball (PgC_4Ga) to solution-phase toroid (PgC_4Ga) to solution-phase toroid (PgC_4GaZn) to solid-state sphere (PgC_4GaZn). In contrast, with the nitrate anions positioned outside the Ga_3O_3 triads or capsular wall, full expulsion of the Cs ions occurs.

Addition of K^+/Rb^+ to the $PgC_4Ga\text{-}CsNO_3/Cs_2SO_4$ complexes produced a second set of trimetallic PgC_n-based nanoassemblies (Figure 7), Ga/K/Cs- and Ga/Rb/Cs-PgC_4, in which the water gates are replaced with K/Rb gates. Regardless of the nature of the anion, the strong $K^+/Rb^+\cdots\pi$ interactions cause a decrease in the peaks in the ^{133}Cs NMR spectra associated with the free cesium and an increase in the peaks associated with the bound cesium, indicating a shift in chemical equilibrium.[43]

Finally, the transport of thallium(I) nitrate and thallium(I) sulfate into PgC_4 was investigated via single-crystal XRD and ^{205}Tl NMR.[44] Again, the sulfate ions of $PgC_4Ga\subset Tl_2(SO_4)$ are positioned inside the nanoassembly, whereas the nitrate ions of $PgC_4Ga\subset TlNO_3$, are positioned outside the nanoassembly.[44] Interestingly, unlike the cesium complexes, the position of the anion with respect to the PgC_4Ga framework does not affect the entrapment or escape of thallium ions from the cavity. The Tl^+ ions are retained regardless of the identity of the anion, indicating that the $Tl^+\cdots\pi$ interactions are sufficiently strong that thallium does not require an anchoring anion (sulfate or nitrate). Also, for both the sulfate and nitrate complexes, replacement of the water gates of the PgC_4Ga nanoassembly with Rb/K gates and replacement of the Rb/K gates with Zn ions does not alter the occupancy of the thallium ions within the cavity. That is, the trimetallic nanoassemblies $PgC_4GaK\subset Tl$, $PgC_4GaRb\subset Tl$, and $PgC_4GaZn\subset Tl$ are formed.[37,44,45] Overall, this work demonstrates that the strength of the cation$\cdots\pi$ interactions and, secondarily, the placement of the anion with respect to the capsular framework play important roles in the stability of these inclusion complexes.[45]

2.2.3. Tubular Structures.

In addition to forming spheres and toroids, pyrogallol[4]arenes self-assemble into bilayers[42] and nanotubes. For example, Dalgarno and co-workers have synthesized pyrene-containing hydrogen-bonded PgC_6 nanotubes.[46] The tubular framework of PgC_6-pyrene consists of four PgC_6 units associated with four pyrene molecules located exo to the tubular framework. The tubular framework has a hydrophilic interior composed of the upper rim pyrogallol[4]arene hydroxyl groups.[46] The dissolution of these hydrogen-bonded nanotubes in acetone, acetonitrile/water (5:2), or methanol results in a rearrangement to a dimeric hydrogen-bonded nanocapsule, as evidenced by the analysis of SANS data

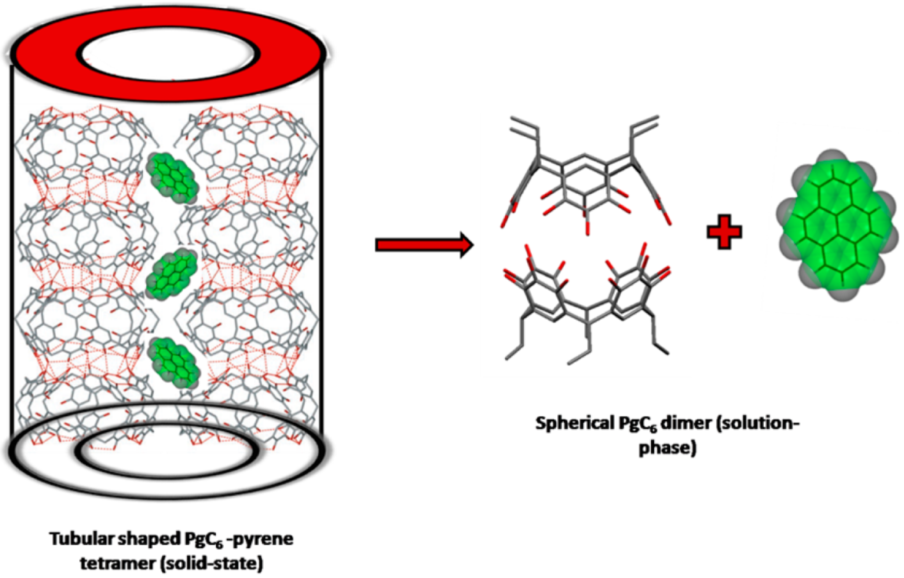

Figure 8. Structural rearrangement of PgC_6−pyrene from a tubular (solid state) to a spherical (solution phase) architecture.

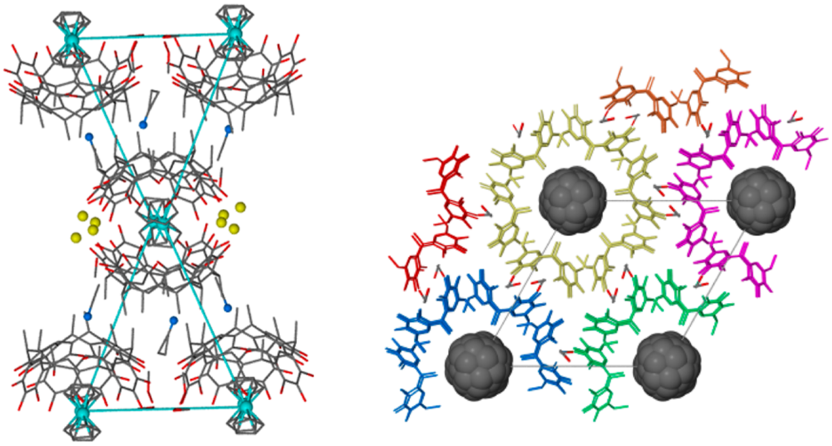

Figure 9. (left) Side views of the ferrocene-enclosing dimers showing the diagonal (1.5 nm) and perpendicular distances (1.2 nm) between iron atoms (shown in turquoise). (right) Top view of the ferrocene-enclosing nanotubes showing the distance (2.1 nm) between adjacent iron centers (gray, space-filled). The pyrogallol[4]arenes are shown in stick form. A total of six PgCs comprise a given tubular section (see the yellow tube).

(Figure 8). This is the first example of a rearrangement from a tube to a sphere in solution.

Morelos-Gomez and co-workers have designed metal-containing organic frameworks with magnetic properties, for example, molecular magnets and nanowires.[47] Building on this earlier work, hydrogen-bonded ferrocene-enclosing dimers and nanotubes (Figure 9) were constructed that could serve as potential supramolecular hosts with desired functionality.[7,8,48] Unlike the PgC_6−pyrene nanotube, the framework of the $PgC_1 \subset$ferrocene tube comprises alternating units of three PgC_1 molecules and one ferrocene, with the guest positioned endo with respect to the tubular framework.[8,33] An overlay of the two layers of $PgC_1 \subset$ferrocene along the tubular length of three PgC_1 units forms a hexameric tubular arrangement in which the upper rim hydroxyl groups form the hydrophilic exterior of the tube.[8,33] The PgC_6−pyrene[46] and $PgC_1 \subset$ferrocene[8,33] solid-state structures demonstrate the ability of pyrogallol[4]arenes to host and selectively interact with guest moieties. SANS studies of these species revealed that only the ferrocene-enclosed dimers[7] are stable in solution. That is, the ferrocene-enclosed nanotubes rearrange to hydrogen-bonded dimers,[8] a result that is again consistent with the thermodynamic preference of hydrogen-bonded dimers over hydrogen-bonded tubes in solution.

The differences in the magnetic properties of nanomeric assemblies containing the same metal can be due to host−guest interactions and structural differences (tube vs sphere and dimer vs hexamer). For pyrogallol[4]arene nanoassemblies, metal−metal distances, overall structural architecture, and placement of the metal center as a guest or as part of the host framework were used to elucidate the solid-state magnetic properties of the PgC_1−ferrocene dimer, the PgC_1−ferrocene ($PgC_1 \subset Fc$) nanotube, the PgC_3Ni dimer, and the PgC_3Ni hexamer.[32,48] Magnetic measurements on these nanoassemblies revealed paramagnetic behavior and a weak antiferromagnetic alignment, both of which suggest weak dipolar interactions between the metal centers. The combined magnetic and solid-state data allowed Kumari et al. to differentiate between magnetic atom occupancy within the framework wall (PgC_3Ni hexamer/dimer) as opposed to magnetic atom occupancy within an encapsulated guest ($PgC_1 \subset Fc$ tube/dimer).[32,48] These solid-state magnetic analyses of the $PgC_1 \subset Fc$ and

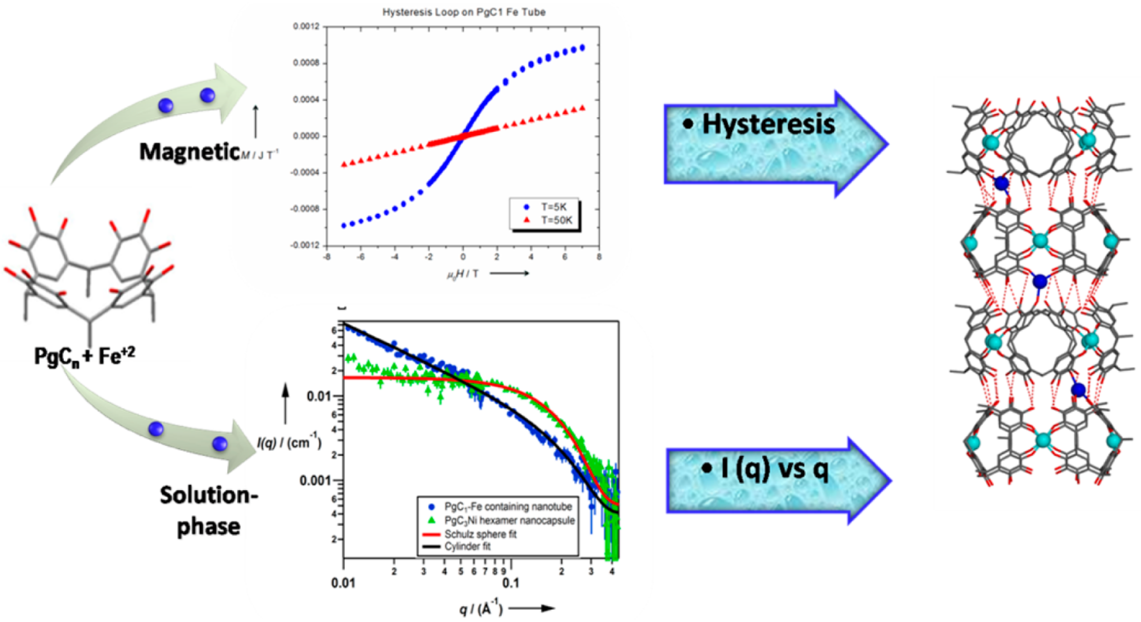

Figure 10. Front view of the proposed model of the PgC_1Fe framework (right) deduced from combined SANS and solid-state magnetic studies. Gray sticks, C; red sticks, O; turquoise solid circles, Fe within a PgC; dark blue solid circles, Fe between two PgC units.

PgC_3Ni nanoassemblies aided in interpreting the magnetic properties and predicting the geometry of a PgC_1Fe assembly.[49] Overall, the SANS, solid-state magnetic, and elemental analyses revealed that PgC_1Fe has a tubular architecture that is held together via Fe atoms in both solution and the solid state (Figure 10). Hence, PgC_1Fe is the first example of a metal-containing pyrogallol[4]arene-based tube in solution. The shape and length of the PgC_1Fe nanoassembly were controlled via C_5H_5N concentration and centrifugation time, respectively,[49] identifying two additional factors in controlling the self-assembly of pyrogallol[4]arene based nanoassemblies.[11,49]

2.2.4. Biotemplated Structures. Besides the nanomagnetic studies of pyrogallol[4]arene-based assemblies, an additional nanofluidic study was performed to develop a biotemplate (insulin) driven construction of larger supramolecular hosts from resorcin[4]arenes.[10] The primary SANS studies involved contrast variation methods that utilized inhomogeneties between the solvent and solute (resorcin[4]-arene–insulin) systems. The results indicate the encapsulation of an insulin monomer within a *C*-methylresorcin[4]arene (RsC_1) nanocapsule. The RsC_1⊂insulin nanoassembly has a total radius of ~16 Å (Figure 11)[10] and a volume that is three times that of the metal-seamed pyrogallol[4]arene hexamers. The shell (thickness = 7 Å) consists of a monolayer of RsC_1, and the core (radius = ~9 Å) consists of the insulin monomer. The cone-shaped RsC_1, confirmed by ^1H NMR studies, provides interaction sites between the insulin and upper-rim hydroxyl groups. This host–guest complex of RsC_1 with insulin demonstrates that cavity sizes can be modulated when supramolecular complexes self-assemble in solution.[10]

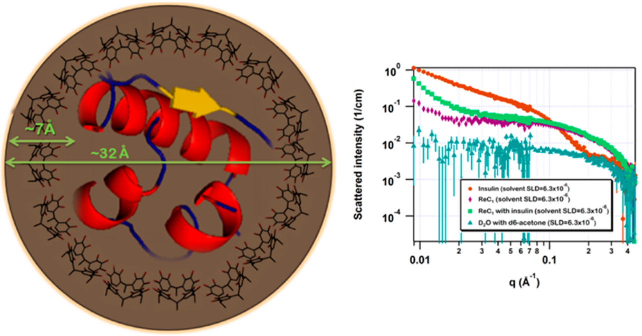

Figure 11. A structural model of an insulin monomer within a resorcin[4]arene nanocapsule (left); contrast variation SANS graphs for the control, resorcin[4]arene, insulin, and resorcin[4]-arene⊂insulin entities.

To summarize, solution-phase studies have provided insight into the factors that affect the self-assembly process of supramolecular complexes. Controlling parameters, such as temperature, pH (C_5H_5N concentration), solvent, metal, and centrifugation time, have been identified and should allow the synthesis of host assemblies with desired functionality.[4,11,49] These studies not only enabled the discernment of stable versus fluxional architectures in solution[4,43,44] but also afforded the structural insight needed to identify and model novel nanoassemblies[49] that are difficult to crystallize. Overall, the synergistic interplay of solution-phase, solid-state, and magnetic studies assisted in manipulating the synthesis and properties of supramolecular hosts.

3. CONCLUDING REMARKS

The study of solution-phase supramolecular nanoassemblies is an important area of soft materials and efforts dedicated to elucidating the properties of these intriguing entities in solution are rapidly increasing due to the potential application of these entities in medicine and radiology. Indeed, the better the mechanism of formation and other properties of supramolecular nanoassemblies are understood in solution, the more innovatively supramolecular architectures can be designed. The dynamic nature of soft matter makes characterization of such noncovalently bonded nanoassemblies in solution a challenge. It is clear that small-angle neutron scattering can be used singly or combined cooperatively with diffusion NMR and other types of spectroscopy to characterize supramolecular nanoassemblies in solution. Such novel approaches can now be extended to the investigation of supramolecular gels, polymers, and other complex fluids.

AUTHOR INFORMATION

Corresponding Author

*Prof. Jerry L. Atwood. E-mail: AtwoodJ@missouri.edu.

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Biographies

Harshita Kumari was born in Bareilly, U.P., India in 1982. She obtained her B.S. from Nagpur University in 2005 and her Ph.D. from University of Missouri—Columbia in 2011 under the supervision of Prof. Jerry L. Atwood. From 2009–2011, she was a foreign guest researcher at NIST Center for Neutron Research at National Research of Standards and Technology (NCNR-NIST). In 2011, she joined Prof. Carol A. Deakyne as a postdoctoral fellow, wherein she focused on theoretical studies. During her postdoctoral term, she continued her experimental studies at NCNR-NIST. In 2012, she received RSC Journals Grant for International Authors and visited Stellenbosch University as a visiting scientist. Since 2013, she has been a research associate with Prof. Carol A. Deakyne and Prof. Jerry L. Atwood. Her research interests are complex fluids, solution structures, and magnetic properties of supramolecular nanoassemblies, host−guest interactions, and gas sorption.

Carol A. Deakyne was born in Patuxent River, Maryland, USA, in 1949. She obtained her B.S. degree from Rider College in 1971 and her M.S. degree from Carnegie Mellon University in 1972. She obtained her Ph.D. from Princeton University in 1976 under the supervision of Leland C. Allen. After a postdoctoral appointment with Arieh Warshel at the University of Southern California, she began an appointment in 1978 as an Assistant Professor at College of the Holy Cross, which was followed by an appointment in 1984 as a contractor at the Air Force Geophysics Laboratory. She moved to Illinois in 1990 to take up a position as Associate Professor at Eastern Illinois University and was promoted to Professor in 1994. In 2003, she joined the University of Missouri as Associate Professor, where she rose to a full Professor in 2013. Her research interests currently focus on the areas of nanocapsular assemblies and radiopharmaceuticals. In particular, she is using computational techniques to elucidate and predict the structures, properties, and behavior of resorcin[4]arene- and pyrogallol[4]arene-based host−guest complexes and of metal-cyclized somatostatin peptide analogues.

Jerry L. Atwood was born in Springfield, Missouri, USA, in 1942. He attended Southwest Missouri State University, where he obtained his B.S. degree in 1964. He carried out graduate research with Galen Stucky at the University of Illinois, where he obtained his Ph.D. in 1968. He was immediately appointed as an Assistant Professor at the University of Alabama, where he rose through Associate Professor (1972) to full Professor in 1978. In 1994, he was appointed Professor and Chair at the University of Missouri-Columbia. In 1999, he was appointed Curators' Professor. His research interests revolve around a number of themes in supramolecular chemistry, with his most recent focus being on the self-assembly of large noncovalent nanocapsules and the control of encapsulated space, gas sorption, and separation.

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ABBREVIATIONS

SANS, Small-angle neutron scattering; XRD, X-ray diffraction; NMR, nuclear magnetic resonance

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