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Review

Mixed metal-organic nanocapsules

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ABSTRACT

The formation of hydrogen-bonded nanometer scale capsules from *C*-methylresorcin[4]arene represented a new area of research within the broad field of supramolecular chemistry. The related pyrogallol[4]arenes form nanocapsules of similar dimensions and this research now extends into the formation of novel metal-organic nanocapsules (MONCs). These relatively new systems are described here, with particular focus on recent advances in the formation of MONCs that are seamed together by more than one type of metal ion. This chemistry holds great potential for the isolation of designer materials that allow for enhanced control over the ratios of metal ions within these supramolecular assemblies.

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1. Introduction

The controlled assembly of multi-component systems into large nanometer scale entities is a fundamental and challenging goal of supramolecular chemistry. In the solid state, advances in (and understanding of) crystal engineering has played a key role in the assembly of these challenging superstructures. Covalent synthesis, hydrogen bonding and directed metal coordination constitute three main approaches that have been employed in the construction of large multi-component molecular architectures from comparatively small synthetic building blocks [1]. These architectures are often inherently of nanometer dimensions and can possess large internal cavities that have potential for exploitation as nano-reactors, host-guest frameworks, or as platforms for the design of materials with tailored properties (such as magnetism) [2–4]. We recently reviewed progress in metallo-supramolecular assemblies, with a particular focus on the formation of capsule-like structures, and the use of calixarenes in the assembly of nanometer scale metal-organic nanocapsules (MONCs) [5]. This related review updates developments in the formation of MONCs, and will summarize very recent work on the formation of such nanocapsules seamed together by more than

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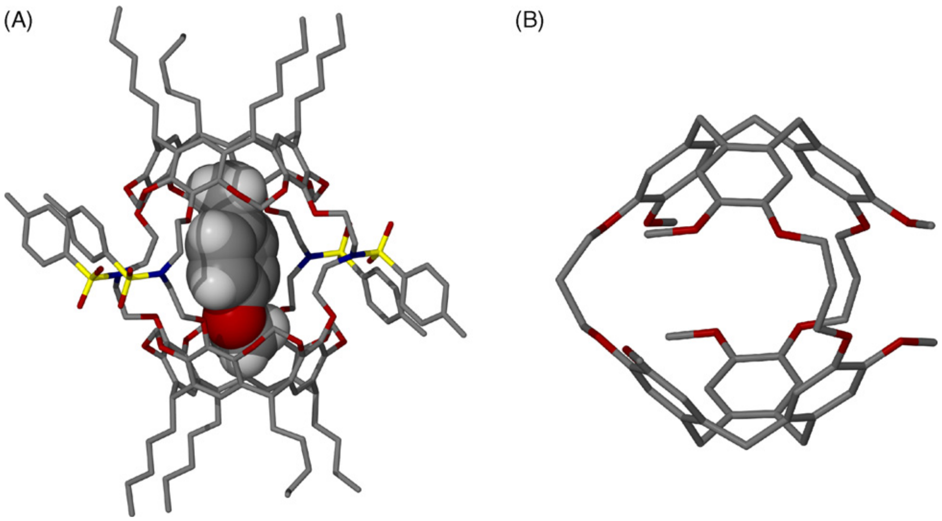

Fig. 1. (A) A carceplex containing a suitably sized guest molecule [8]. (B) Flexible organic capsule composed of two covalently linked cyclotriveratrylene molecules [9]. Figures not to scale.

one type of metal ion. In order to place these results in a relevant context, a short summary of covalent organic cages, and metal-organic polyhedra, boxes and cages follows. These areas of research are expansive and the examples shown are only representative of a small portion of the excellent work carried out in these areas. In selecting articles for inclusion in this discussion no particular preference has been given to the chosen authors. Rather we have chosen to include examples that show some relevant advances in particular areas that relate to the discussion of MONCs.

1.1. *Covalently bonded organic (nano)capsules*

A rich series of organic (nano)capsules has been realized through the use of covalent synthesis. Importantly, these covalently linked host molecules can offer greater structural stability, facile structural variation, functional group tolerance, and solubility in organic solvents. Cram and Collet made important early contributions to this area of endeavor. Cram et al. synthesized a series of carceplexes based on bowl-shaped cavitands [6–8]. These studies led into exploration of various aspects of what was termed the ‘inner phase’, and due to the presence of strong covalent bonds locking the hemispheres together, small guest molecules could be trapped and confined within this encapsulated space (Fig. 1A). This pioneering work witnessed the development of many novel host-guest arrangements that exist as carceplexes and hemi-carceplexes. Collet succeeded in covalently linking two cyclotriveratrylene molecules together to form flexible host capsules (Fig. 1B). Again, small molecules were trapped and held on the capsule interior to varying degrees [9].

The covalent synthesis of very large molecular containers has been predominantly pioneered by the Sherburn [10], Sherman [11] and Warmuth groups [12,13]. Sherburn and co-workers covalently synthesized a non-collapsible ‘tureen-shaped’ container (or ‘superbowl’) by means of multiple-step chemical reactions [10]. Since this ‘tureen-shaped’ container only consists of five cavitand bowls linked by eight covalent bonds (Fig. 2), small guest molecules may enter and exit this molecular cavity with relative ease. A similar six-bowl container molecule was successfully synthesized by Sherman and co-workers, and this rigid capsule possesses only small pores [11]. The presence of these small pores allows for the permanent encapsulation of guest species in much the same way as the carceplexes reported by Cram [8].

Warmuth et al. have developed a facile one-pot route to a similar six-bowl container through the condensation reaction between a tetra-formylcavitand and ethylendiamine [12]. In this remarkable reaction, eighteen small components react/self-assemble into this giant supermolecule which contains a cavity of *ca.* 1700 Å^3. Accompanying computational studies show that the assembly contains large pores that would allow for the transport of guest species to the interior of the assembly. Notably, solvent effects are particularly important for the control of this condensation reaction [13].

These developments show that covalently linked organic (nano)capsules have much to offer with respect to host-guest chemistry and the design of desirable materials. These underpinning discoveries will inform future reaction design and utilization of these supermolecules.

1.2. *Hydrogen-bonded organic capsules*

Hydrogen bonds and van der Waals forces have also been used to assemble various types of nanometer scale molecular container. There are advantages, such as reversibility, in the use of rather weak forces for the formation of nanocapsules [1].

Rebek et al. have reported a series of non-covalent dimeric nanocapsules [14,15]. For example, by means of an elegant synthetic approach, utilizing one self-complementary subunit having hydrogen-bonded acceptors in the central portion and hydrogen-

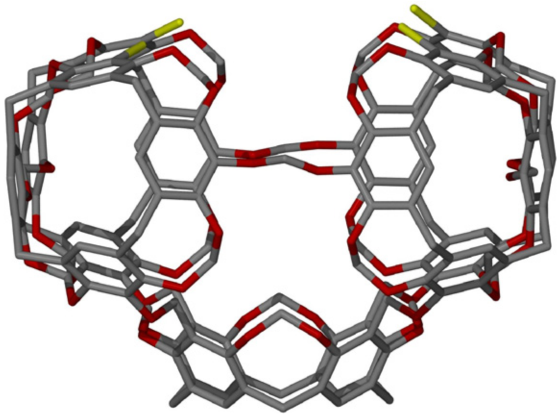

Fig. 2. Partial structure of the ‘tureen-shaped’ container molecule synthesized from five cavitand sub-units [10].

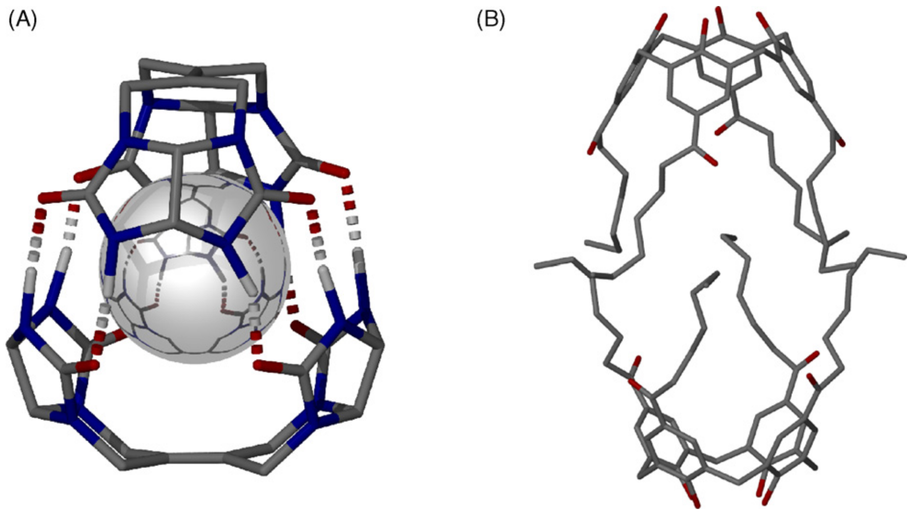

Fig. 3. (A) Hydrogen-bonded 'tennis-ball' container formed by complementary hydrogen bonding interactions [13,14]. Encapsulated space is represented by a spheroid. (B) van der Waals capsule formed by two *p*-acylcalix[4]arenes, showing interdigitation of the hydrophobic alkyl chains [19,20].

bonded donors on the terminal portion, two such subunits can self-assemble into 'tennis ball' or 'softball'-shaped pseudospherical capsules, stabilized by hydrogen bonds (Fig. 3A). Due to the relatively small interior cavity, these dimeric capsules only encapsulate small guest molecules but serve as excellent examples for the programmed assembly of small molecular subunits into larger capsule species.

Resorcin[4]arenes have both functional hydroxyl groups on their rims and concave bowl-shaped cavities. Due to this character, they are reported to form a range of capsule architectures through hydrogen bonding to their hydroxyl groups. Atwood et al. showed that two resorcin[4]arenes may be seamed together using hydrogen bonding to propan-2-ol [16]. In addition, water molecules have also been used to bridge two resorcin[4]arenes together by means of complementary hydrogen bonding [17,18].

van der Waals forces have also be used to good effect in the formation of molecular capsules. For example, Ripmeester and Coleman et al. have reported the synthesis of calixarenes with acyl groups with hydrophobic tails at the upper-rim of the molecular framework [19,20]. Two desired *p*-acylcalix[4]arenes were then assembled into dimeric van der Waals capsules (Fig. 3B). These assemblies show very interesting host-guest behavior and the ability to allow guest transport to the capsule interior through the crystal lattice.

1.3. Hydrogen-bonded C-alkylresorcin[4]arene and C-alkylpyrogallol[4]arene nanocapsules

In 1997 Atwood and MacGillivray reported a voluminous spherical nanocapsule with an internal volume of ca. 1500 Å^3, in which six *C*-alkylresorcin[4]arenes and eight water molecules were combined together through 60 hydrogen bonds (Fig. 4A) [21]. This report has spurred numerous explorations into large spherical nanocapsules. Ugono and Holman obtained a similar, but achiral, capsule in which six 2-ethylhexanol molecules took the place of six out of eight structural hydrogen-bonded water molecules in the capsule seam [22].

C-Alkylpyrogallol[4]arenes also self-assemble into a similar hexameric nanocapsule with an internal volume of *ca.* 1250 Å^3 [23,24]. Compared with the *C*-alkylresorcin[4]arene hexameric nanocapsule, no water molecules are required due to the presence of additional upper-rim hydroxyl groups of pyrogallol relative to resorcinol. Structural studies show that the [*C*-alkylpyrogallol[4]arene]$_6$ nanocapsule is bonded together by eight hydrogen bonds per unit, as compared with the 2.6 hydrogen bonds per unit of the [*C*-alkylresorcin[4]arene)$_6$(H_2O)$_8$] nanocapsule. This nanocapsule motif is relatively tolerant towards the presence of polar species that can interfere with the hydrogen-bonded capsule seam, and the existence of both nanocapsule motifs in the solution phase has been confirmed in extensive studies by the groups of Rebek and Cohen [25–31].

Some of our own work has focused on the solid state characterization of these nanocapsule motifs, and the associated host-guest chemistry on the voluminous capsule interiors. Ethyl acetate is the solvent of choice in harvesting single crystals of the *C*-alkylpyrogallol[4]arene hydrogen-bonded nanocapsules, through which even the quantitative conversion from monomers into nanocapsules has been attained [32]. Acetonitrile has also been a good solvent for both nanocapsule formation, and the co-crystallization of probe molecules on the capsule interior (Fig. 4B) [33]. Notably, the stability of these [*C*-alkylpyrogallol[4]arene]$_6$ nanocapsules allows one to probe the encapsulated chemical environment in solution by means of fluorescence spectroscopy.

In addition to the [*C*-alkylresorcin[4]arene)$_6$(H_2O)$_8$] and [*C*-alkylpyrogallol[4]arene]$_6$ motifs described above, Atwood et al. also obtained and structurally characterized a hydrogen-bonded hexameric nanocapsule from the self-assembly of six mixed pyrogallol/resorcinol macrocycles [34]. The macrocycle in question is simply synthesized by routine methods, but with the use of both resorcinol and pyrogallol as starting materials. This hexameric capsule has the geometry of a trigonal anti-prism and contains *ca.* 800 Å^3 internal free volume (housing six diethyl ether molecules).

1.4. Metal-organic polyhedra, boxes, cages and capsules

Various approaches have been taken towards the combination of designer ligands and metal ions to produce a large library of metal-organic superstructures. These can be described as metal-organic polyhedra, boxes, cages and capsules. A non-comprehensive, brief overview of work in this area by different research groups follows, prior to our discussion of metal-organic pyrogallol[4]arene (nano)capsules.

Fujita et al. have blocked coordination sites on metal centers to great effect to generate a novel series of metal-organic structures with desirable topologies [35–37]. For example, these authors have synthesized a close-shelled nanocapsule based on six 1,3,5-tris(3,5-pyrimidyl)benzene molecules and 18 Pd^{2+} metal ions. X-ray structural analysis showed this hexahedral nanocap-

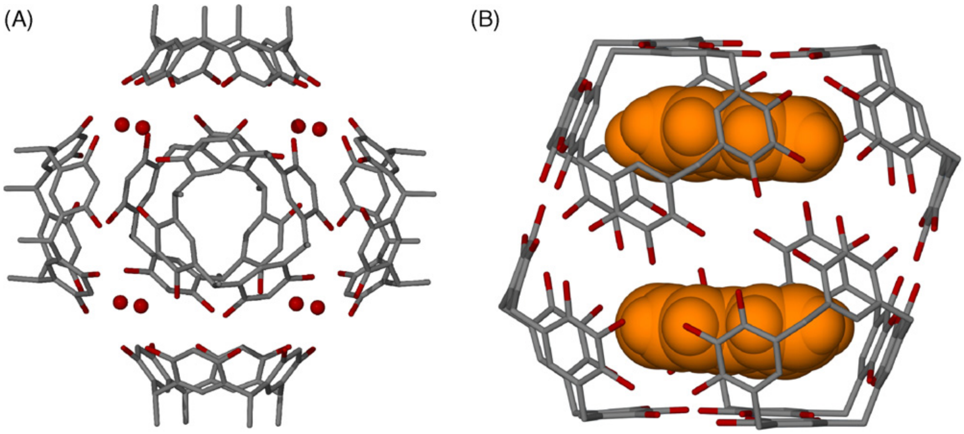

Fig. 4. (A) The [*C*-alkylresorcin[4]arene$)_6(H_2O)_8$] nanocapsule [21]. (B) A [*C*-alkylpyrogallol[4]arene$]_6$ nanocapsule playing host to probe guest molecules (pyrene butyric acid) [33]. Figures not to scale. Hydrogen atoms and pyrogallol[4]arene alkyl chains omitted for clarity.

sule contains *ca.* 900 Å^3 of internal volume. Only small molecules such as water enter and exit freely [35]. In order to create more open clefts to allow small molecules to transport more efficiently into and out of this type of nanocapsule, ligand modifications were effected (Fig. 5A). Molecules such as CBr_4, CH_2Br_2, and $CHCl_3$ subsequently enter and exit the framework interior [36]. These authors also demonstrated that a similar strategy involving different solvents could provide other structures. For example, Pd^{2+} ions react with 1,2-bis[2-(pyridine-4-yl)ethynyl]benzene to assemble into a M_4L_8 box-shaped structure in DMSO while a M_3L_6 complex is formed in MeCN (Fig. 5B) [37].

Stang et al. have employed alternative protection methods for coordination sites to effect the formation of various supramolecular structures. For example, the nanometer scale supramolecular cage shown in Fig. 5C is formed from the tritopic pyridyl ligand and pre-constructed Pt^{2+} molecular clips [38]. One nitrate occupies the cavity of this positively charged cage structure. These authors have also synthesized a truncated tetrahedron nanometer scale cage based on six *cis*-$Pt(PMe_3)_2(OTf)_2$ metal complexes and four 1,3,5-tris(4-pyridylethynyl)benzene building blocks [39]. The assembly has a diameter of *ca.* 25 Å.

Raymond et al. showed that the reaction of 2,6-diaminoanthracene with $TiO(acac)_2$ affords a M_2L_3 helicate in the absence of an Me_4N^+ guest [40]. The presence of a Me_4N^+ guest results in the formation of a M_4L_6 tetrahedron, and remarkably the two structures can be inter-converted by the addition or removal of Me_4N^+. These authors also showed that a racemic mixture of chiral tetrahedral M_4L_6 supramolecular clusters was synthesized based on a similar ligand with Ga^{3+} or Fe^{3+} ions [41]. This nano-cluster shows an apparent preference in encapsulating the Et_4N^+ over the smaller Me_4N^+ and the larger Pr_4N^+.

Saalfrank et al. synthesized a tetrahedral structure by the reaction of di-*tert*-butyl-malonate and iron(II) chloride [42]. By changing the malonate to a tolyl derivative, this preferentially affords a M_6L_6 trigonal antiprismatic cluster.

Ward et al. employed a similar approach in the synthesis of cage structures through the action of *N*,*N*-bidentate chelating ligands with various transition metals [43,44]. In addition, through the

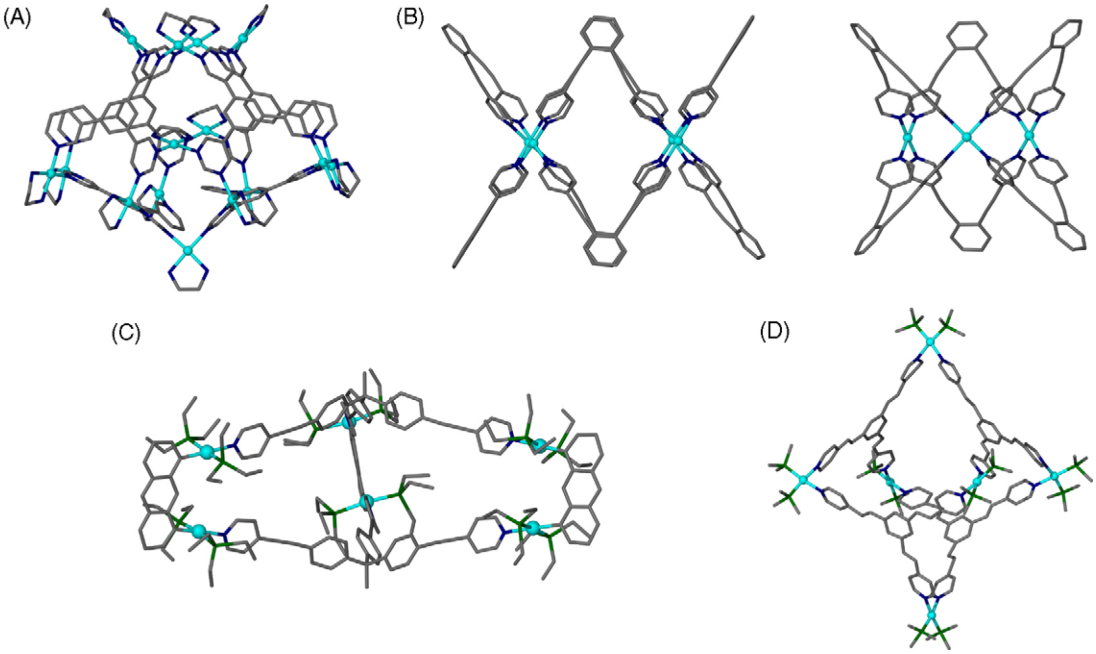

Fig. 5. (A) A metal-organic cage with induced designer pores by ligand alteration [36]. (B) M_4L_8 and M_3L_6 structures formed from the same components in the presence of different solvents [37]. (C) A nanometer scale cage formed from tripodal linkers and pre-formed molecular clips [38]. (D) A nanometer scale truncated tetrahedral cage structure [39]. Figures not to scale.

modification of ligand length, control of cavity size was attained. For example, a M_8L_{12} molecular cube was formed in which a metal ion resides at each vertex and a bridging ligand spans each edge [45]. One BF_4-anion stays within the cavity of this cube.

Severin et al. reported a neutral half-sandwich metal complex, which was synthesized from the reaction of $[(cymene)Ru(NO_3)_2]$ with 3,5-pyridinedicarboxylic acid [46,47]. This neutral cage nanocapsule can further act as an exo-receptor for alkali metal ions. For example, K^+ can coordinate with the nanocapsule and force rearrangement to a dodecanuclear cage with the same molecular components.

Calixarenes have also been used in the programmed metal-assisted assembly of discrete metal-organic structures. Harrison et al. have synthesized a series of capsule-like architectures by means of various combinations of metal ions such as copper, iron, or cobalt with functional resorcin[4]arenes (Fig. 6A) [48,49]. One common character of these resorcin[4]arenes is that they possess "upper-rim" functionalities which may be used to coordinate metal ions by means of appropriate synthetic modification.

Hardie et al. reported the use of modified cyclotriveratrylenes (CTVs) in the synthesis of several capsule-like architectures [50,51]. The CTVs employed possess shallower bowl-shaped cavities relative to resorcin[4]arenes and these can also act as molecular hosts. CTVs may be modified with upper-rim functionalities so as to coordinate with metal ions such as Ag^+. These metal complexes assemble into discrete tetrahedral metallo-supramolecular species (Fig. 6B).

1.5. Metal-organic pyrogallol[4]arene nanocapsules synthesized with one metal ion

With regard to hydrogen-bonded pyrogallol[4]arene nanocapsules, research on metal-containing pyrogallol[4]arene nanocapsules is much more limited. As we have reviewed recent progress in the formation of metal-organic capsules with one type of metal ion, these advances are described below in brief.

The first metal-organic pyrogallol[4]arene nanocapsule (MONC) was obtained by the reaction of excess copper(II) ions with a solution of *C*-propan-3-olpyrogallol[4]arene [52]. Single crystals of the resulting Cu-MONC showed that 24 copper atoms replace 48 protons from the original hydrogen-bonded nanocapsule motif (Fig. 4B). This Cu-MONC is virtually identical to the hydrogen-bonded analog in both shape and size (Fig. 7A). This very close structural similarity is due to the fact that the O···O hydrogen-bonded distance is 2.7 Å, and the O···O distance for two oxygen atoms bridged by Cu^{2+} is also 2.7 Å. Cu-MONCs based on this motif have now been prepared with a wide variety of pyrogallol[4]arenes [53].

The second MONC motif was obtained by the addition of gallium(III) ions to solution sof *C*-alkylpyrogallol[4]arenes, resulting in the insertion of only 12 metal centers with the concomitant elimination of 36 protons (Fig. 7B) [54,55]. This affords a non-spherical Ga-MONC, which conforms to the shape of a disotorted "rugby-ball", and which incorporates four water molecules embedded in the seam of the framework by means of hydrogen bonding interactions. These water molecules have been viewed as gates to the interior of the Ga-MONC assembly, which is stabilized by a combination of metal-coordination bonds and hydrogen bonds.

Caesium ions were used to form ionic dimeric MONCs [56]. In these experiments, we showed that two cesium ions assemble with two *C*-alkylpyrogallol[4]arene molecules to afford a dimeric capsule arrangement in which two guest acetonitrile molecules are sequestered as shown in Fig. 7C.

The fourth and final MONC motif to be formed with one type of metal ion is an octa-metallated dimeric capsule (Fig. 7D). We found that zinc ions combine with only two *C*-alkylpyrogallol[4]arene molecules in the presence of pyridine solvent affords these dimeric capsules with ease. One pyridine guest molecule is bound in the dimeric nanocapsule, and ^1H NMR analysis indicates its chemical shifts change with the variation of the ligands bound to the zinc ions exterior to the nanocapsule [58]. Recent studies with this system have afforded Ni and Co analogs, the former of which displays unexpected and interesting magnetic properties due to the coordination environments imposed by the capsule seam [59].

Experiments to extend our current library of single metal MONCs are currently underway and we anticipate that, by tuning reaction conditions, it will be possible to isolate these species with any desired transition metal for example. The ability to do this will allow us to access and potentially control supramolecular assemblies with very interesting and possibly targeted magnetic properties.

1.6. Transport to the Ga-MONC interior

Given our observation that Ga-MONCs present aqueous "gates" to the capsule interior, we investigated the possibility of passing ion pairs to the encapsulated space. In order to prove this concept for the purposes of controlling encapsulation chemistry, we carried out experiments involving the addition of salts to solutions containing pre-formed Ga-MONCs [60]. Crystallization of the resulting species allowed us to obtain structural proof of the passage of ion pairs to the capsule interior (Fig. 8). These carefully chosen guests occupy favorable binding sites on the interior, displaying typical poly-hapto aromatic interactions with the calixarenes comprising the MONC framework.

2. Mixed metal-organic nanocapsules

The presence of hydrogen bonding sites in the framework of the Ga-MONCs led to the idea of replacing the remaining protons of the Ga-MONC with metal ions as a type of 'stitching-up' of the capsule seam. An important point to note is that we have not been able to increase the number of gallium ions entering the framework seam above 12 during the process of forming Ga-MONCs. The fulfillment of this idea has led to the mixed metal MONCs which are the thrust of the new work covered as part of this review. Much of the coordination chemistry that follows is exploratory and we are attempting to determine the reasons for the metal ratios that result from the experiments that are described below. These assembly mechanisms are likely complicated and are difficult to elucidate.

2.1. Mixed Ga/Cu metal-organic nanocapsules

Given the propensity of Cu^{2+} to form MONCs with pyrogallol[4]arenes, the first experiments we performed were focused on the reaction of copper(II) nitrate with pre-formed Ga-MONCs (Fig. 9) [53]. Addition of cupric nitrate solutions to suspensions of Ga-MONCs results in rapid dissolution of the precipitate, and slow evaporation affords single crystals that can be studied by X-ray diffraction. Structural analysis confirms the formation of a mixed metal MONC, but due to disorder (and presumably random MONC orientation) within the single crystals, we were unable to arrive at conclusive positions for individual metal centers. ICP analysis affords a Ga:Cu ratio of 1:2, corresponding to 8 Ga and 16 Cu metal centers, indicating that despite the expectation that the Cu centers would 'fill-up' the remaining holes in the capsule seam, this coordination event has resulted in the expulsion of some Ga centers and inclusion of additional Cu. These ratios are consistent, indicating that this is indeed a preferential ratio for this system.

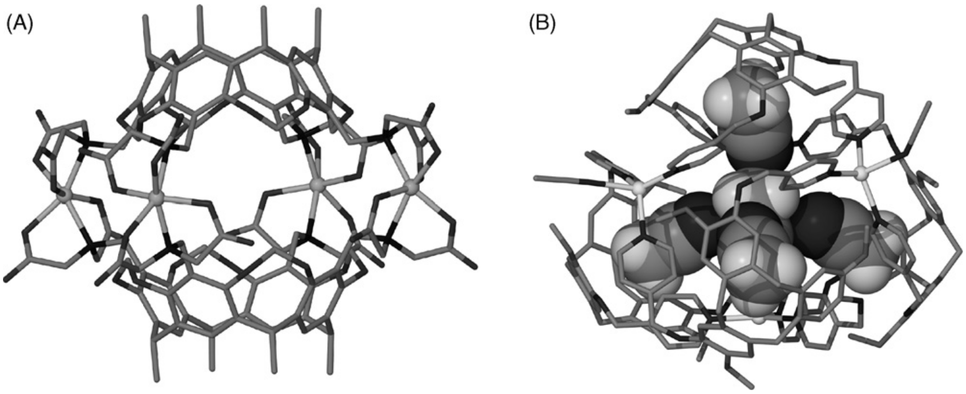

Fig. 6. (A) Metal-organic capsule formed by the reaction of 'upper-rim' functionalized resorcin[4]arenes and iron or cobalt centers [48,49]. (B) Tetrahedral metallo-supramolecular based on the silver directed assembly of CTV building blocks [50,51]. Figures not to scale.

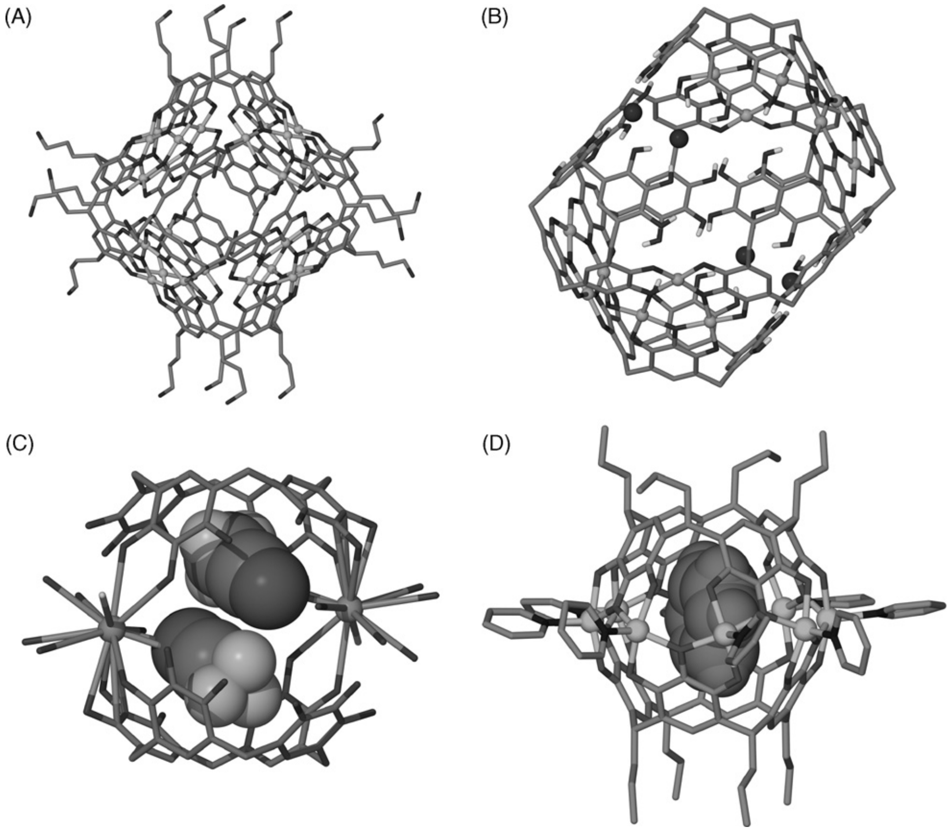

Fig. 7. (A) The Cu-MONC formed by the addition of copper(II) nitrate to a solution of *C*-propan-3-olpyrogallol[4]arene [52]. (B) The Ga-MONC motif formed by the addition of gallium(III) nitrate to solutions of *C*-alkylpyrogallol[4]arenes [54,55]. (C) Ionic dimeric pyrogallol[4]arene capsules [56]. (D) Octa-metallated dimeric Zn-MONC formed by reaction of zinc(II) nitrate with *C*-propylpyrogallol[4]arene in pyridine. Figures not to scale. Hydrogen atoms and 'lower-rim' alkyl chains omitted for clarity.

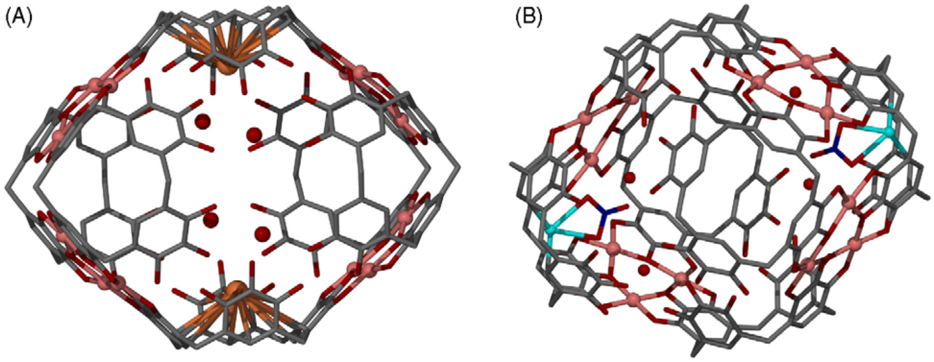

Fig. 8. Structural characterization of ion pair passage to the interior of the Ga-MONC framework showing Cs^+ ions (A) and $AgNO_3$ ion pairs (B) [60].

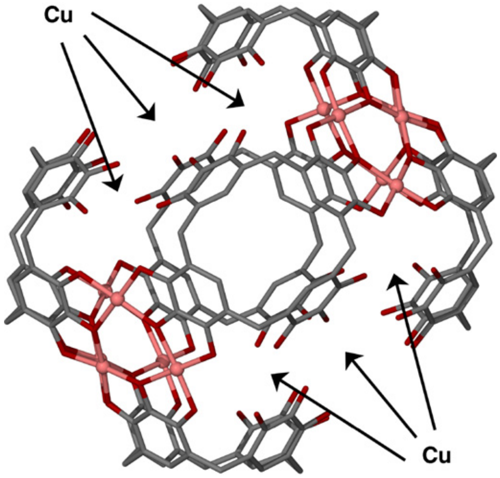

Fig. 9. Schematic showing the addition of Cu^{2+} ions to the remaining binding sites present in pre-formed Ga-MONCs [53].

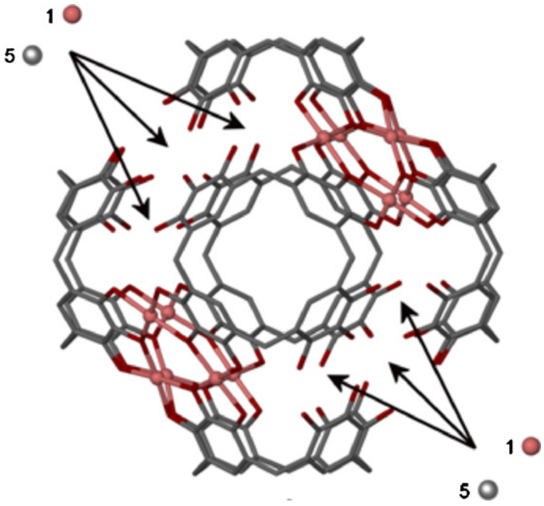

Fig. 10. Schematic showing the addition of two additional Ga^{3+} ions, and 10 Zn^{2+} ions to the remaining binding sites present in pre-formed Ga-MONCs [61].

2.2. *Mixed Ga/Zn metal-organic nanocapsules*

As stated in Section 1.5, we have recently shown that Zn^{2+} ions react with pyrogallol[4]arenes to form dimeric octa-metallated metal-organic capsules [57,58]. Notably, we have yet to obtain a zinc hexameric MONC, but we suspect that this will require further tuning and exploration of the reaction conditions. Although this is the case, we have now shown that Zn^{2+} reacts with pre-formed Ga-MONCs in much the same way as Cu^{2+} (Fig. 10) [61]. Single crystal X-ray diffraction studies show that the reaction produces a pseudo-spherical assembly incorporating 24 metal centers. The overall geometry of this nanocapsule has also changed from the ‘rugby-ball’ shape of the Ga-MONC to the more symmetric spherical shape akin to the Cu-MONCs. Unfortunately it was also not possible in this case to differentiate the 24 metal centers by means of the X-ray structural analysis (through an examination of metal–O bond lengths for example). Given this, we again employed ICP analysis to measure the metal compositions of the crystalline material. The result was an average Ga:Zn ratio of 1.5:1, which corresponds to *ca.* 14 Ga and 10 Zn metal ions per nanocapsule.

The resulting 14:10 Ga:Zn ratio requires that two additional gallium ions be brought into the binding sites during the course of the reaction of the Ga-MONC with zinc ions. Given that pre-formed Ga-MONCs were used in the experimental procedure, we can only conclude that these originate via the decomposition of some Ga-MONCs prior to or during metal recombination. This would clearly be a complex coordination event and we are, as yet, unable to follow the progress of the recombination process.

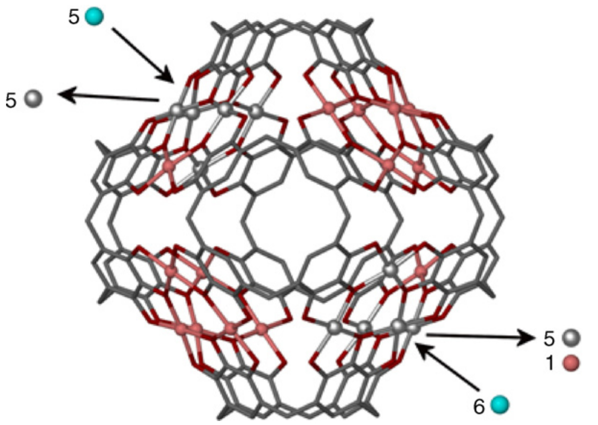

Fig. 11. Schematic showing the ejection of Zn^{2+} ions by the addition of Cu^{2+} ions to pre-formed Ga/Zn-MONCs [61].

In our aforementioned studies into the formation of Cu- and Ga/Cu-MONCs, some of our experiments showed that Cu^{2+} ions have great propensity to induce MONC formation [53]. This is evidenced by the fact that these can be synthesized from methanolic solutions of the molecular components very rapidly. Based on this observation, we investigated the effect of Cu-addition to pre-formed Ga/Zn-MONCs. Addition of a methanolic solution containing excess cupric nitrate to an acetone solution of the mixed Ga/Zn-MONCs results in a color change from colorless to dark red. Slow evaporation affords red single crystals, the structure of which confirms the formation of a 24 metal centered MONC (Fig. 11). As in other cases, it was not possible to elucidate specific metal positions, and as such, ICP analysis showed these crystals to be devoid of Zn centers. Therefore, the Cu^{2+} ions completely eject the Zn^{2+} ions from the Ga/Zn-MONC to afford a new Ga/Cu-MONC in which the Ga:Cu ratio is 1.2:1, corresponding to a MONC containing *ca.* 13 Ga and 11 Cu ions. Notably, this is significantly different to the ratio obtained upon Cu-addition to pre-formed Ga-MONCs [53].

The reason for the higher Ga:Cu ratio obtained by the Zn/Ga-MONC intermediate compared to that from the Ga-MONC is unclear. It may be that with the incorporation of 14 Ga centers into the Ga/Zn-MONC, there is less change in the gallium coordination environment and this leaves the MONC less susceptible to ejection of more Ga^{3+} ions by Cu^{2+} ions. Regardless of the mechanism, it has now been shown that Cu^{2+} has the ability to eject Zn^{2+} from Ga/Zn-MONCs, affording a new Ga:Cu ratio with a controlled metal component composition.

These studies have significantly extended our library of MONCs, and we believe that it will be possible to induce the formation of numerous Ga/TM MONCs that can be used to control the subsequent Ga:Cu ratio through subsequent Cu-addition.

2.3. *Tri-metallic Nanocapsules*

As discussed in Section 1.6, we have recently demonstrated the concept of passing ion pairs through to the capsule interior via the aqueous gates that exist on the surface of the Ga-MONC [60]. Given this we sought to pass such material to the capsule interior, and ‘stitch-up’ the remaining binding sites in the seam by the subsequent addition of a tertiary metal in order to permanently encapsulate a chosen guest species. In the first of these experiments, we examined the passage of cesium hydroxide to

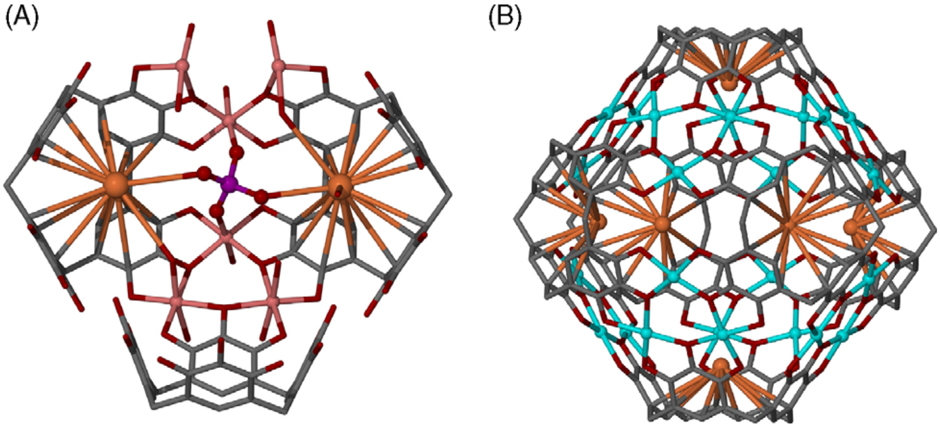

Fig. 12. (A) Part of the MONC assembly showing the structurally characterized cesium sulfate ions on the capsule interior. (B) The 'stitched-up' tri-metallic Ga/Zn/Cs-MONC resulting from Zn-addition to the assembly shown in A [62]. Figures not to scale.

the interior through Cs NMR experiments [62]. Once this was confirmed, Zn-addition was carried out to afford a 'stitched-up' MONC in line with our aforementioned experiments. Both single crystal and elemental analysis show that upon the addition of Zn^{2+} ions, the guest species are ejected from the capsule. Given this negative result, we examined the effect of varying the anion for the Cs^{+} ions, and that had a marked effect on the encapsulation process.

Addition of a cesium sulfate solution to pre-formed Ga-MONCs by our previously employed method affords single crystals that, when studied using X-ray diffraction, showed the remarkable transport of the ion pair to the capsule interior, with the anion interacting with Ga centers from the capsule walls (Fig. 12A). This process can also be followed by Cs NMR experiments and the ions are tightly bound to the interior of the framework.

Subsequent addition of Zn^{2+} ions to this assembly results in the expected 'stitching-up' of the capsule seam, but in this process, the anion interaction with the capsule wall metal centers is interrupted, and expulsion of some ions is evident upon single crystal and elemental analysis. The ions that remain within the capsule are badly disordered over all of the calixarene cavities (Fig. 12B), but by altering the anion in the primary step, we have discovered a route for anchoring guest species on the capsule interior. We are now examining this as a method of increasing the guest occupancy in other MONCs from the library we have characterized to date.

2.4. Mixed Ga/Cd metal-organic nanocapsules

As described in the previous sections, we have been unable to locate or differentiate specific metal center positions in the mixed metal MONCs we have characterized so far. This is likely due to the fact that the metals in question reside in similar regions of the periodic table. Given this, we employed Cd ions for the 'stitching-up' process with a view to incorporating a secondary metal center that would clearly reveal positions from X-ray diffraction studies [62]. This would also allow us to determine (a) if such metal ion insertion is indeed possible within this framework, and (b) what effects larger metal ions will have on the nanocapsule assembly motif. With insertion of either 24 Cu, 24 mixed Ga/Cu, or 24 mixed Ga/Zn centers, the resulting near spherical MONCs have diameters that are very close to those of the hydrogen-bonded analogues. Addition of solutions containing cadmium(II) nitrate to pre-formed Ga-MONCs resulted, following slow evaporation, in the formation of single crystals that were structurally analyzed. These studies show that the resulting mixed Ga/Cd-MONC is based on a new type of near-spherical MONC, and that both the capsule motif and pyrogallol[4]arene skeleton are tolerant toward a degree of distortion (Fig. 13).

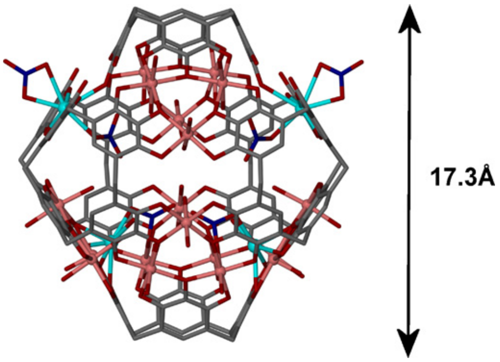

Fig. 13. The mixed Ga/Cd-MONC that results from the addition of cadmium nitrate to a pre-formed Ga-MONC [62]. The assembly is slightly smaller in diameter relative to the 24 Cu-MONC due to distortion of the nanocapsule motif.

From X-ray structural analysis, there are two different environments for the cadium ion, and analysis reveals that the Ga/Cd ratio is approximately 17:3. Notably, the addition of Cd^{2+} ions to the Ga-MONC has also led to the incorporation of an additional five Ga^{3+} ions. In much the same way as for the Cu- and Zn-addition described above, this implies that complex coordination events are taking place in which some capsules may be destroyed, with a process of recombination taking place with incorporation of the secondary metal species. A structural comparison between the shape of the Ga/Cd-MONC and a hydrogen-bonded PgC*n* hexamer or Cu-MONC, reveals that the distance between centroids generated at the bases of PgC*n* molecules opposite to one another is shorter by *ca.* 0.6 Å in the Ga/Cd-MONC.

An additional feature of this assembly lies in the nature of the resulting seam of the Ga/Cd-MONC. In the formation of all of the previously reported mixed metal MONCs, closed-shell assemblies have been formed. This feature has been monitored by MALDI-TOF MS and $^{1}H/^{13}C$ NMR where possible, revealing the presence of solvent peaks below 0 ppm in the ^{1}H NMR spectrum (which is indicative of solvent encapsulation without exchange with external solvent). The structure of the mixed Ga/Cd-MONC shows that the distortion of the pyrogallol[4]arene molecule and the 'pulling-in' of two pyrogallol units results in four small portals in the MONC. The result of this is that the ^{1}H NMR spectrum shows no peaks below 0 ppm, indicating that solvent may be exchanged, presumably through these portals in the MONC framework. Experiments with other larger metals (relative to the Ga in the pre-formed

MONCs) are underway to investigate the influence of these species on the conformation, size and coordination chemistry within the seams of the resulting MONCs.

3. Concluding remarks

We have made strides into exploring the supramolecular chemistry related to the formation of mixed metal *C*-alkylpyrogallol[4]arene MONCs. Although this is the case, this research remains at an embryonic stage, and much is still to be learned about the coordination chemistry of mixed metal MONCs, and the associated mechanisms taking place during the assembly formation process. Magnetic studies may help to clarify the distribution of metals in the framework of the MONCs and provide a handle for elucidating this behavior in the novel species formed. We anticipate that it will be possible to fine tune the association properties of these MONCs both in solution and in the solid state by the choice of pyrogallol[4]arenes that are suitably functionalized at the lower-rim of the calixarene skeleton. This will allow us to control the interactions between MONCs and alter the distance of the metallic ‘cores’ of these species. The redox behavior of the mixed metal MONCs, and the nature of the relationship between dimeric to hexameric MONCs formed from different metal ions is under investigation.

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