Rapid formation of metal–organic nano-capsules gives new insight into the self-assembly process†‡

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Metal–organic pyrogallol[4]arene nano-capsules, mixed pyrogallol[4]arene nano-capsules, and mixed metal analogues have been rapidly synthesised by addition of excess copper nitrate to a methanol solution of the corresponding macrocycle(s) (or gallium nano-capsules for the mixed metal system); improved solubility allows for thorough study and elucidation of the assembly process for these discrete metal–organic assemblies.

Discrete multi-component organic or metal–organic assemblies have attracted significant attention due to the generation of novel materials with defined architectures such as non-covalent capsules[1] and metal–organic polyhedra (MOPs)/cages[2] for example. Large covalent assemblies, some termed 'superbowls',[3] have been the focus of other recent studies, as have the concerted and selective formation of similar assemblies from many component reactions (24 bonds in an 18 component reaction).[4]

While we have been primarily interested in the self-assembly of hydrogen-bonded nano-capsules based on *C*-methylresorcin[4]arene or the *C*-alkylpyrogallol[4]arenes (general notation PgC*n*, where *n* corresponds to alkyl chain length),[5,6] several of our recent studies also focused on the assembly of metal–organic nano-capsules (MONC's) based on the PgC*n* capsule template.[7] We assumed this involved metal insertion into square planar theoretical binding sites in the hydrogen-bonded 'seam', with elimination of the corresponding number of protons.[7a] However, the assembly process could not be conclusively assessed; pre-formed capsule to MONC, or monomer to MONC *via* metal templation. Cupric nitrate reacts with *C*-propanol-pyrogallol[4]arene, with slow formation of single crystals of the Cu-MONC, and with insertion of 24 Cu metal centres into all of the theoretical square planar binding sites.[7a] These capsules further assemble through coordination of the propanol tails to Cu centres of neighbouring MONC's, the result being an insoluble coordination polymer (Fig. S1 and S2, ESI‡). Gallium nitrate was also found to react with particular PgC*n*'s with the formation of Ga-MONC's, with 12 Ga centres eliminating 36 protons.[7b,c] Whilst the Cu-MONC retains spheroidal character, Ga-MONC's assume a distorted 'rugby ball' like shape.

Herein we report the rapid formation of Cu-MONC's from any reported *C*-alkylpyrogallol[4]arene, including two new molecules that cannot be assembled into H-bonded nano-capsules in the solid state.[5b] We have also formed mixed (Cu/Ga) metal MONC's and hetero-PgC*n* MONC's by these methods. These new assemblies are highly soluble in a number of common organic solvents and allow for study using MALDI-TOF mass spectrometry which, for the MONC's, shows that although large void spaces in closed molecular assemblies are rare, these MONC's can, to some extent, be assembled with little solvent inclusion within the resulting spheroid that has a large internal volume of $\sim$1250 Å^3.[8]

Addition of a vast excess of methanolic $Cu(NO_3)_2\cdot{\times}H_2O$ to a methanol solution of any chosen PgC*n* (PgC_2–PgC_{11}, $PgC_{isobutyl}$) resulted in the rapid formation of a fine pale brown precipitate that was filtered, washed and found to be highly soluble in common organic solvents. In the interest of brevity only the PgC_3 Cu-MONC (**1**) will be shown, although reference is made to the other Cu-MONC's where general phenomena are described. Slow evaporation of a 1 : 1 acetone : chloroform solution of **1** afforded small red single crystals that were weakly diffracting, but which provided a partial structure confirming the formation of the MONC (Fig. 1A). As the quality of the single crystal data was poor (final $R_1 \approx 20\%$), it was not possible to identify all the ligands around the copper centres. Given the highly soluble nature of **1**, MALDI-TOF mass spectrometry was performed on the material and was found to provide evidence for the rapid formation of the assembly (Fig. 1B; for other PgC*n* Cu-MONC's see Fig. S3–S12, ESI‡). We believe that the rapid formation is evidenced by the bi-modal distribution in the mass spectrum, which poses questions about the association of PgC_3 with methanol, and suggests that a number of different/unknown events could take place during the assembly process. The most left-hand peak of the shoulder in the bi-modal distribution correlates to the mass of 5802 Da for an 'empty' (or rather 'skeletal') Cu-MONC that has no axial Cu ligands (Fig. 1B). Subtraction of this value from the right hand maximum affords a ΔM value of 633 Da, which roughly corresponds to the encapsulation or ligation of $\sim$20 methanol or $\sim$35 water molecules, or any combination of both which would not be unexpected. This is a common feature in the series (PgC_2–PgC_{11}, $PgC_{isobutyl}$), with a consistent ΔM value of 633–635 observed. It is also likely that the centre of the bi-modal distribution contains

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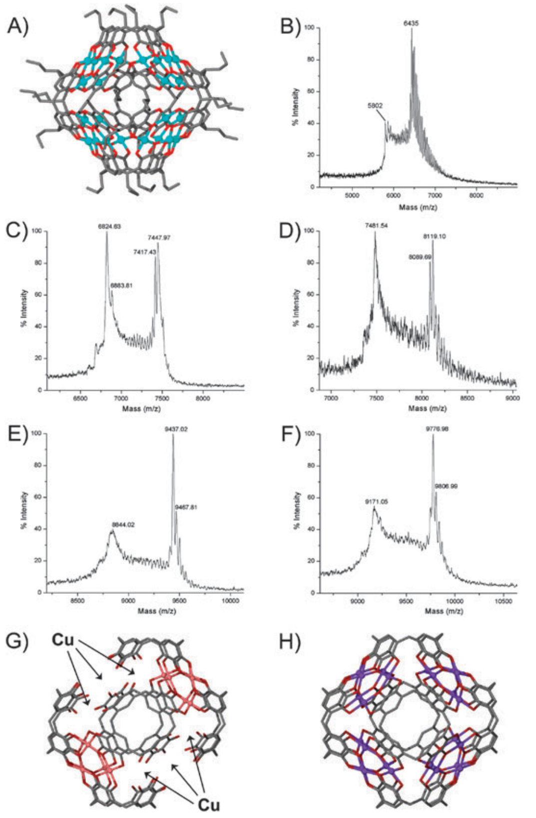

Fig. 1 (A) Partial structure of the PgC$_3$ Cu-MONC. (B)–(F) MALDI-TOF mass spectra of PgC$_3$, PgC$_6$, PgC$_8$, PgC$_{12}$ and PgC$_{13}$ Cu-MONC's, respectively. (G) Potential entry points for Cu into **2**. (H) Structure of the PgC$_3$ Cu/Ga-MONC. In (G) and (H) *C*-propyl chains as well as hydrogen atoms, apical metal ligands and solvents of crystallisation have been omitted for clarity. Colour code for (G): carbon – grey, oxygen – red, gallium (G) – pink, mixed metal sites (H) – purple (single colour as copper was used at all metal positions during structure refinement).

peaks corresponding to partially filled/ligated MONC's (*i.e.* various combinations of encapsulated and or ligated MeOH and H_2O). From these studies, it appears that Cu has such high affinity for the bis-bidentate nature of pyrogallol in the cyclic tetramer that they attack the PgC*n*'s with little to no consideration for the presence of solvent for example, given the speed of MONC formation. We believe that the rapid capsule formation precludes the growth of large and good quality crystals by recrystallisation given the occupancy variation, which would result in extreme internal disorder and weak diffraction. Furthermore it is unlikely that the capsules break apart (with loss of either a PgC*n* or a Cu centre) allowing solvent release from the interior of the capsule, as this would result in a large loss in weight that would be clearly visible in the mass spectrum. Perhaps most importantly, the presence of the 'shoulder' suggests that the PgC*n*'s are possibly not interacting with the solvent molecules prior to MONC formation as much as one might expect.

Copper concentration was examined as a variable, and a 'combinatorial matrix' was performed at PgC$_3$: Cu concentrations ranging from 1 : 2 to 1 : 200, respectively in three separate runs where the total volume of methanol used in each run was varied as either 5, 10, or 15 ml (runs A, B, and C, respectively). Under dilute conditions, the expected precipitate formed over a number of seconds rather than rapidly, but with respect to all variables in runs A–C, MALDI-TOF mass spectrometry showed the intensity of the shoulder to vary with no real trend. This was surprising until it was discovered (in experiments for other PgC$_n$Cu-MONC's^9) that the dilution of the mixture (with dithranol as matrix) can also significantly affect the shoulder signal intensity. Therefore it is difficult to predict the effect of copper concentration on MONC formation. Further examination of the bi-modal distributions in the mass spectra for the brown precipitates formed for PgC$_2$, PgC$_4$–PgC$_{11}$, and PgC$_{\text{isobutyl}}$ shows that although each material is similar (Fig. S3–S12, ESI‡), the peak intensity of the shoulder/empty MONC was variable compared to that observed for **1** (Fig. 1C–F).^{9} In some cases, this peak was in fact found to be (considerably) larger than the higher mass peak corresponding to the 'fuller' MONC. Given that the Cu concentration appears to have little effect on the speed of capsule formation, and that **1**·matrix dilution is also a factor, this suggests that although the copper rapidly binds the molecules, certain PgC*n*'s may interact very differently with methanol depending on alkyl chain length, thereby resulting in different shoulder intensities. When longer chain pyrogallol[4]arenes (PgC$_{12}$ and PgC$_{13}$) were employed, a brown precipitate also formed rapidly and analysis showed similar results with regard to the shoulder presence (Fig. 1E and F). Notably it was not possible to form H-bonded nano-capsules for these molecules by crystallising from ethyl acetate, a solvent consistently found to facilitate quantitative solid state capsule formation for PgC$_4$–PgC$_{11}$.^{5b} Rather the PgC*n*'s crystallise in bi-layer arrangements with inter-digitated alkyl chains in the extended structure as is common for such molecules (Fig. S13–18, ESI‡).^{10} Although PgC$_{12}$ and PgC$_{13}$ may form nano-capsules in solution (a feature we are exploring), metal-assisted assembly facilitates the synthesis of Cu-MONC's from PgC*n*'s that may not typically form nano-capsules in the solid state.

As it was possible to rapidly form purely 'Cu-based' MONC's, we explored the possibility of 'stitching-up' remaining theoretical binding sites present in a PgC$_3$ Ga-MONC (**2**).^{7b} Excess copper addition to an acetone–methanol suspension of **2** resulted in dissolution of the crystals (that are otherwise poorly soluble) with a solution colour change from blue/green to red/brown. In the absence of precipitate, slow evaporation resulted in the growth of large red single crystals, the structural elucidation of which (using synchrotron radiation) afforded a well resolved MONC (final $R_1 \approx 8\%$) containing 24 metal centres. Given that it was not possible to identify particular metal sites in the structure, inductively coupled plasma (ICP) analysis on crystalline material was undertaken to arrive at a Cu : Ga ratio. In addition of copper, one might expect Cu to either (a) completely fill the remaining potential binding sites left in **2** to afford a 12 : 12 Ga : Cu MONC, or (b) completely displace the Ga from **2** to form the highly favourable 24 Cu-MONC (**1**). Unexpectedly, ICP analysis shows a 2 : 1 Cu : Ga ratio that equates to 16 Cu and 8 Ga centres in the resulting MONC's. This suggests that a remarkable coordination event has occurred, necessarily resulting in some mixed metal 'faces'. We postulate that Cu attacks the remaining binding sites presented by **2** (Fig. 1G)

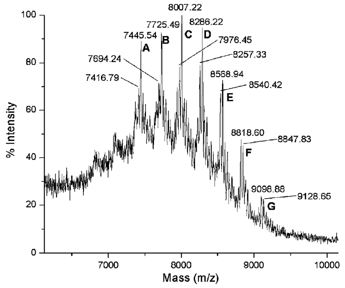

Fig. 2 MALDI-TOF spectrum of the PgC_6 and PgC_{11} 'hetero-Pg' Cu-MONC showing a series of maxima corresponding to each permutation.

imparting a degree of strain on the Ga panels in the assembly. In **2**, structural distortion is due to curvature induced by the Ga centres, and these may not tolerate the Cu-induced 'structural correction'. Such strain may force some gallium centres to dissociate, and these vacant sites may then be filled by additional Cu (Fig. 1H). If this proposed mechanism were true, this would result in four purely Cu 'faces' and four mixed Cu/Ga 'faces' in each MONC.

Given all of the above, in addition to solution phase studies by Cohen *et al.* (which showed that hydrogen-bonded hetero-capsules exist only after 24 h once self-recognition within PgC*n* mixtures is overcome[11]) we also examined whether it was possible to form 'hetero-PgC*n*' Cu-MONC's. Copper addition to a 1 : 1 mixture of PgC_6 : PgC_{11} in methanol resulted in rapid brown precipitate formation.[12] MALDI-TOF analysis showed there to be a clear series of maxima in a broad overlapping spectrum corresponding to each possible permutation of PgC_6/PgC_{11} in a Cu-MONC (Fig. 2). Each maximum occurs with the favourable ΔM of 634–635 Da above the value of each calculated 'empty' hetero-PgC*n* Cu-MONC. This broad overlapping spectrum is also presumed to incorporate the 'empty' MONC's, which is suggested by the presence of some smaller maxima further to the left of the first 'full' maximum at *ca.* 7446 Da, although many of these would be masked. The ΔMW between PgC_6 and a PgC_{11} is 280.53 g mol^{-1}, which is observed between each maximum (Fig. 2). This rapid synthesis of a statistical mixture of hetero-PgC*n* Cu-MONC's shows the truly indiscriminate nature of the assembly process, and suggests that the metal 'sequesters' any PgC*n* during MONC formation process.

Discovery of rapid Cu-MONC formation from methanol has important implications in the challenging area of metallo-supramolecular self-assembling capsule chemistry and can be widely applied as shown above. Clearly the self-assembly process in these cases is driven by a huge propensity for copper to bind the PgC*n*. Whilst this method should facilitate the formation of most likely any PgC*n* Cu-MONC, it should also allow for the formation of any 'hetero-PgC*n*' Cu-MONC. The rapid formation of 96 Cu–O bonds offers great potential in guest encapsulation and retention, a process that may show little discrimination toward the guest (other than steric restriction), thereby offering an unlimited range of new materials. The encapsulation of numerous species within these newly formed assemblies, as well as the formation of other mixed metal MONC's and a series of hetero-PgC*n* Cu-MONC's is currently underway.

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