

# Synthesis and structural characterisation of lower rim halogenated pyrogallol[4]arenes: bi-layers and hexameric nano-capsules†‡

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Two lower rim halogenated pyrogallol[4]arenes have been synthesised and structurally characterised as either bi-layer or hexameric nano-capsule motifs depending upon chain length and functionalisation.

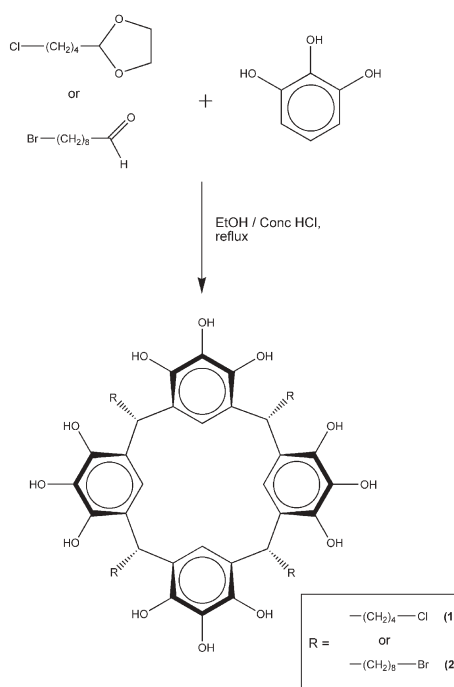
The assembly of nanometre scale assemblies through non-covalent interactions is an important goal in supramolecular chemistry.<sup>1</sup> These assemblies offer the potential for encapsulation of space or molecular material in a unique chemical environment, with a view to further developing applications that encompass nano-reaction vessels or drug delivery systems.

The synthesis, structural characterisation, and solution phase behaviour of large hexameric hydrogen bonded nano-capsules based on *C*-methylresorcin[4]arene (CMRC) have attracted significant interest in recent times.<sup>2,3</sup> The CMRC nano-capsule is composed of six host molecules and eight structural water molecules, all hydrogen bonding in concert to afford a robust structural motif that has an internal volume of  $\sim 1375 \text{ \AA}^3$ .<sup>2</sup> The closely related *C*-alkylpyrogallol[4]arenes (PgC, general calixarene structure shown in Scheme 1) have been shown to assemble into nano-capsules of comparable size to CMRC in both solution and the solid state.<sup>3d-i,4-8</sup> The general PgC assembly is stabilised by a larger number of hydrogen bonds per calixarene due to the four additional upper rim hydroxyl groups of the calixarene (relative to CMRC) and the concomitant omission of structural water molecules (prerequisite for nano-capsule formation with CMRC).

The structural characterisation of large non-covalent nano-capsule and nano-tube arrangements based on PgC's has been the focus of a number of our recent studies.<sup>4a,6-9</sup> Ethyl acetate was found to be a particularly good solvent for quantitative nano-capsule assembly in the solid state,<sup>7</sup> and more recent studies with these systems have demonstrated the encapsulation of fluorescent probe molecules that report on the interior order of the nano-capsule in both solution and the solid state.<sup>8</sup> For the PgC's, crystallisation from methanol, ethanol, and aqueous acetonitrile in the absence of other molecular components typically results in the formation of bi-layer arrangements, although nano-capsule formation has been observed from some of these solvents on occasion.<sup>4a</sup>

Herein we present the synthesis (Scheme 1) and structural characterisation of two new host molecules, *C*-chlorobutylpyrogallol[4]arene (**1**) and *C*-bromooctylpyrogallol[4]arene (**2**). Both **1** and **2** were synthesised by the acid catalysed condensation of the corresponding aldehyde and pyrogallol in ethanol.§ Attempts to crystallise both compounds from methanol, acetonitrile, aqueous acetonitrile (10% H<sub>2</sub>O) and ethyl acetate showed **1** to favour the formation of bi-layer arrays whilst **2** preferentially formed nano-capsules in the solid state under the majority of conditions studied (Table 1). In addition, crystallisation of the crude reaction mixture from the synthesis of **1**, from acetonitrile, resulted in the formation of an additional bi-layer structure containing **1**, acetonitrile, and the ethylene glycol by-product from the deprotection of chlorobutanol (structural characterisation and description in ESI, Fig. S1–S3‡).

Slow evaporation of a methanol solution of **1** afforded single crystals that were suitable for X-ray diffraction studies.¶ The asymmetric unit consists of one molecule of **1** and three methanol molecules. The hydrophobic CH<sub>3</sub> group of one methanol molecule resides in the cavity of the calixarene with one CH $\cdots\pi$  interaction to an aromatic ring of the host (CH $\cdots$ aromatic ring centroid distance of 2.823 Å). The chlorobutyl chains of **1** were found to be



**Scheme 1** The synthetic route to lower rim halogenated pyrogallol[4]arenes **1** and **2**.

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† The HTML version of this article has been enhanced with colour images.

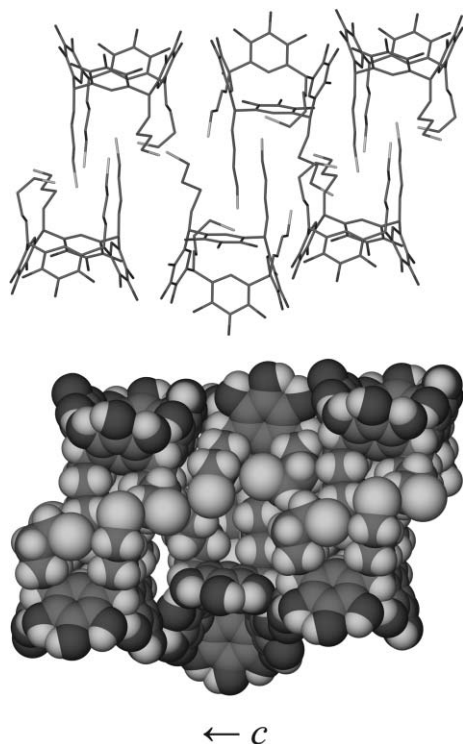
‡ Electronic supplementary information (ESI) available: Crystal data and structural description of (1·MeCN)<sub>2</sub>·ethylene glycol. Structural description of dimer found in 1·1.5EtOAc. <sup>1</sup>H and <sup>13</sup>C NMR data for **1** and **2**. XRPD experiments to determine bi-layer or hexameric nano-capsule structure of microcrystalline materials. See DOI: 10.1039/b605147b

**Table 1** Types of solid state assembly formed by **1** and **2** as crystallised from methanol, acetonitrile, aqueous acetonitrile or ethyl acetate (× denotes the formation of microcrystalline material [examined by XRPD])

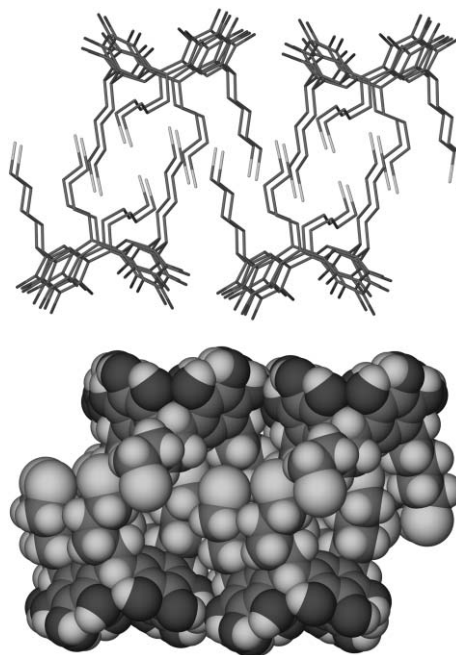
	<b>1</b>	<b>2</b>
MeOH	Bi-layer	×
MeCN	×	Nano-capsule
Aqueous MeCN	×	Nano-capsule
EtOAc	Bi-layer	Nano-capsule

disordered to varying extents over two or three closely related positions. The extended structure reveals a distorted bi-layer arrangement that shows the pyrogallol[4]arenes to pack in an alternating side-to-side fashion along the *c* axis (Fig. 1). Notably the chlorobutyl chains of **1** are randomly oriented within the hydrophobic section of the bi-layer (Fig. 1), and neighbouring pyrogallol[4]arenes from adjacent layers are offset, thereby precluding the formation of dimeric capsule arrangements in the solid state.

When an ethyl acetate solution of **1** was subjected to slow evaporation, large single crystals that were suitable for X-ray diffraction studies formed. Given that pyrogallol[4]arenes generally assemble as hexameric nano-capsules when ethyl acetate is used as a solvent, the formation of a capsule assembly composed of **1** was anticipated.<sup>7</sup> The structural solution of the crystals formed from **1** showed the asymmetric unit to contain one molecule of **1** and 1.5 ethyl acetate molecules. In the extended structure, the molecules pack in an unexpected bi-layer motif, even when crystallised from ethyl acetate. In comparison to **1·MeOH**, the chlorobutyl chains in **1·EtOAc** are ordered and well defined



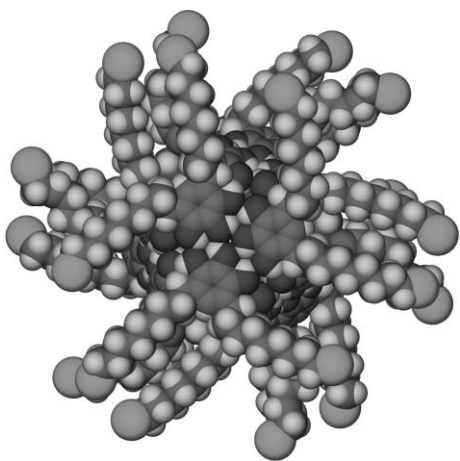
**Fig. 1** Stick and space filling representations of the bi-layer structure found in **1·3MeOH** showing the different orientations of the calixarene chlorobutyl chains (disordered chlorobutyl groups only shown in one position). The alternating calixarene packing along the *c* axis is also shown (solvent molecules omitted from both views for clarity).



**Fig. 2** Stick and space filling representations of the bi-layer structure in **1·1.5EtOAc** showing the inter-digitation of the calixarene chlorobutyl chains (solvent molecules omitted from both views for clarity).

(Fig. 2). Further to this, the pyrogallol[4]arenes form a regular bi-layer motif with the hosts packed in a more planar fashion relative to the axis running along the bi-layer (indicated by the two space filling representations of **1·MeOH** and **1·EtOAc** in Fig. 1 and Fig. 2, respectively). The pyrogallol[4]arenes come together to form a skewed dimeric capsule arrangement around the ‘half’ crystallographically unique ethyl acetate molecule that resides on an inversion centre (ESI, Fig. S4†). The dimeric capsule arrangement was found to be stabilised by a number of hydrogen bonding interactions that are of typical magnitude for such arrangements.<sup>10</sup> When **1** was recrystallised from acetonitrile or aqueous acetonitrile with slow evaporation, suitable single crystals could not be grown, but the resulting microcrystalline material was examined using X-ray powder diffraction (XRPD). These experiments, when compared with the calculated powder patterns of **1·MeOH** and **1·EtOAc**, suggest that the molecule is also in a bi-layer arrangement (ESI, Fig. S5–S6†).

Recrystallisation of **2** from HPLC grade acetonitrile resulted in the formation of large single crystals that were suitable for X-ray diffraction studies.\*\* The crystals were weakly diffracting and although a number of different crystals from different crystallisation batches were screened, this problem could not be resolved. The asymmetric unit consists of one molecule of **2** and 1.35 identifiable acetonitrile molecules. Some of the upper rim pyrogallol[4]arene hydroxyl groups are disordered over two positions. In addition to this, two of the four bromooctyl chains at the lower rim are disordered. In one chain, the bromine atom is disordered over two positions, whilst in the other, the end of the chain is severely disordered but modelled as effectively as possible in the crystal structure. Symmetry expansion of the asymmetric unit shows the structure to be a hexameric nano-capsule based on **2** (Fig. 3). The extended structure differs from those previously reported by the fact that bromooctyl chains occupy the positions



**Fig. 3** Space filling representation of a hexameric hydrogen-bonded nano-capsule constructed from C-bromooctylpyrogallol[4]arene (**2**).

at the base of each symmetry equivalent pyrogallol[4]arene, a position normally occupied by solvent molecules. Recrystallisation of **2** from ethyl acetate or aqueous acetonitrile resulted in the formation of isostructural hexamers, and similar diffraction and structure solution problems were also encountered.<sup>††</sup> Recrystallisation of **2** from methanol did not afford suitable single crystals, and slow evaporation only resulted in the formation of microcrystalline material (Table 1). XRPD showed the material to be amorphous, therefore little can be said about the solid state behaviour of **2** with MeOH (ESI, Fig. S7<sup>†</sup>).

To conclude, we have synthesised two new pyrogallol[4]arenes bearing lower rim halogenated chains. For **1**, the lower rim chains are versatile in packing ability and the molecule has a propensity for bi-layer formation in the solid state, even when crystallised from a particularly good 'sphere forming' solvent (ethyl acetate, Table 1). In contrast, **2** has yet to be crystallised in a bi-layer arrangement, suggesting that the hexameric nano-capsule motif is preferential for this chain length and functionalisation under the majority of conditions studied herein. Clearly the presence of halogens at the calixarene lower rim dramatically affects the packing behaviour of the molecule in the solid state. Halogen bonding has been found to be particularly influential in a number of supramolecular systems.<sup>12</sup> Although it is unclear at this stage whether such interactions determine the self-assembly of these halogenated pyrogallol[4]arenes, a broader study of varied chain lengths may prove useful in determining halogen effects. Work continues on the synthesis of other halogen bearing lower rim pyrogallol[4]arenes, with a view to discerning the dominant factors in nano-capsule or bi-layer formation with these new host molecules. Alternative crystallisation conditions for **1** and **2** are being examined to determine the true nature of the materials formed from MeCN/aq. MeCN and MeOH respectively. Other synthetic avenues that use these molecules as intermediates are also under investigation.

We would like to thank the NSF for financial support.

## Notes and references

§ 2-(4-Chlorobutyl)-1,3-dioxolane and pyrogallol were obtained from Fluka and Aldrich respectively and used as supplied. Bromononanal was synthesised by literature methods.<sup>11</sup>

**Synthesis of C-chlorobutylpyrogallol[4]arene, 1:** Concentrated hydrochloric acid (2 ml) was added to an ethanol solution (15 ml) containing

2-(4-chlorobutyl)-1,3-dioxolane (1.99 g, 12.1 mmol) and pyrogallol (1.53 g, 12.1 mmol). The mixture was heated to reflux overnight and upon cooling, the product precipitated as fine white crystals. The crude product was collected by vacuum filtration, washed with cold ethanol (5 ml), diethyl ether (2 × 10 ml) and dried. Yield 55%.

**Synthesis of C-bromooctylpyrogallol[4]arene, 2:** Concentrated hydrobromic acid (0.3 ml) was added to an ethanol solution (15 ml) containing bromononanal (2.51 g, 11.3 mmol) and pyrogallol (1.43 g, 11.3 mmol). The mixture was heated to reflux overnight and upon cooling, removal of the solvent *in vacuo* afforded a thick brown oil. Heating the oil in acetonitrile followed by slow evaporation over two to three days and filtration afforded the pure product as large cubic colourless crystals. Yield 28%.

¶ **Crystal data for 1·3MeOH:** C<sub>47</sub>H<sub>64</sub>Cl<sub>4</sub>O<sub>15</sub>, *M* = 1010.78, monoclinic, *a* = 20.607(11), *b* = 12.792(7), *c* = 19.014(9) Å,  $\alpha$  = 97.721(9)°, *U* = 4967(4) Å<sup>3</sup>,  $\mu$  = 1.352 mm<sup>-1</sup>, *T* = 173(2) K, space group *P2<sub>1</sub>/c*, *Z* = 4, Mo-K $\alpha$  radiation ( $\lambda$  = 0.71073 Å), final GOF = 1.345, *R*<sub>1</sub> = 0.1387, 33811 reflections measured, 10946 unique (*R*<sub>int</sub> = 0.1695) which were used in all calculations. The final  $\omega R(F^2)$  was 0.3193 (all data). CCDC 604862. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b605147b

|| **Crystal data for 1·5EtOAc:** C<sub>50</sub>H<sub>64</sub>C<sub>14</sub>O<sub>15</sub>, *M* = 1046.81, triclinic, *a* = 12.048(4), *b* = 12.069(4), *c* = 18.233(6) Å,  $\alpha$  = 95.141(5),  $\beta$  = 93.711(6),  $\gamma$  = 106.383(5)°, *U* = 2522.1(14) Å<sup>3</sup>,  $\mu$  = 1.378 mm<sup>-1</sup>, *T* = 173(2) K, space group *P1*, *Z* = 2, Mo-K $\alpha$  radiation ( $\lambda$  = 0.71073 Å), final GOF = 1.018, *R*<sub>1</sub> = 0.0632, 14554 reflections measured, 10780 unique (*R*<sub>int</sub> = 0.0467) which were used in all calculations. The final  $\omega R(F^2)$  was 0.1822 (all data). CCDC 604863. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b605147b

\*\* **Crystal data for 2·nMeCN:** C<sub>62</sub>H<sub>88</sub>0.5N<sub>1.35</sub>O<sub>12</sub>Br<sub>4</sub>, *M* = 1372.33, rhombohedral, *a* = 36.984(3), *c* = 25.824(4) Å, *U* = 30590(6) Å<sup>3</sup>,  $\mu$  = 1.341 mm<sup>-1</sup>, *T* = 173 (2) K, space group *R* $\bar{3}$ , *Z* = 18, Mo-K $\alpha$  radiation ( $\lambda$  = 0.71073 Å), final GOF = 2.614, *R*<sub>1</sub> = 0.1743, 89238 reflections measured, 14967 unique (*R*<sub>int</sub> = 0.0874) which were used in all calculations. The final  $\omega R(F^2)$  was 0.4637 (all data). CCDC 604864. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b605147b

†† Unit cell parameters from structure determination of **2·nEtOAc:** Rhombohedral, *a* = 36.9543(79), *c* = 25.6407(54) Å. The structure showed significantly more disorder than the acetonitrile solvate, and this could not be resolved satisfactorily.

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