Solvent-free, direct synthesis of supramolecular nano-capsules

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The single step direct synthesis of pyrogallol[4]arene *via* a solvent free protocol yields the pure product as a self-assembled nano-capsule, comprised of six macrocyclic building blocks.

Traditional methods employed in the preparation of supramolecular nano-capsules involve the dissolution of previously prepared pure building blocks into an appropriate solvent system.[1,2] This approach uses at least two solvent-based processes and potentially more if a purification step is required after the synthesis. As a result, guest inclusion chemistry in such supramolecular systems is dominated by entrapment of solvent molecules within the nano-architectures.[2] Implementation and application down stream of technologies based on these nano-capsules can therefore be problematic, in particular for those processes that require the use of volatile organic solvents.[3] Environmental awareness globally has led to a rise in the implementation of benign chemical processes whenever possible. The rapidly emerging field of green chemistry seeks to deal with issues of sustainability, pollution and economics.[3] By adopting the principles of green chemistry we are making advances in the benign synthesis of supramolecular compounds.

Solvent-free reactions are becoming established in a wide range of reactions,[4] and have been successfully employed in the synthesis of calixarenes and related macrocycles.[4–6] Pyrogallol[4]arenes in the cone conformation are typically synthesised in an alcohol solution by an acid catalysed condensation reaction between pyrogallol and an appropriate aldehyde.[7] The reported solvent-free preparation of the *C*-resorcinol[4]arenes by Roberts *et al.*[5] results in the formation of the both the *cis–cis–cis* (*rccc*) and the *cis–trans–trans* (*rctt*) isomers. Attempts at synthesising the cone (*rccc*) conformation exclusively were unsuccessful.[5] Although the reported method is a significant improvement over traditional methodologies, the separation of the different structural isomers by chromatography is counter productive when addressing the minimisation of chemical waste. Herein, we report the near quantitative formation of *C*-isobutylcalix[4]pyrogallolarene, **1**, in the cone conformation and its subsequent spontaneous formation into nano-capsules in the absence of solvent.

Isovaleraldehyde (0.89 ml, 7.9 mmol) was added dropwise to a fine dispersion of pyrogallol (1.00 g, 7.9 mmol) and a catalytic amount of solid *p*-toluenesulfonic acid (50 mg, 0.3 mmol) with constant milling using a mortar and pestle (Fig. 1).[8] The condensation reaction yielded a brittle white solid within two minutes of grinding. This solid was easily milled to a fine, yellow powder upon further aggregation. The reaction was followed by TLC and NMR techniques and was found to have reached completion within five minutes of constant grinding. This method is significantly faster than the solvent-based methods traditionally employed in the synthesis of calix[4]pyrogallolarene.[7] The reduced reaction time, elimination of energy needed for heating and/or cooling, minimal quantities of catalyst, elimination of solvent and subsequent waste-related issues are all important factors in complying with the underling principles of green chemistry.[3]

The aggregation behaviour of pyrogallol[4]arenes in alcohols and in chloroform has attracted much recent interest.[9] The macrocycles are observed to exist as monomers in alcohol, and crystallise out of solution as bilayer-type structures.[9] Remarkably, treatment of the pyrogallol[4]arenes with chloroform affords the spontaneous self-assembly of six monomers into a nano-capsule held together by an extensive hydrogen bonded network, as previously reported in the solid state.[9,10] It is therefore clear that

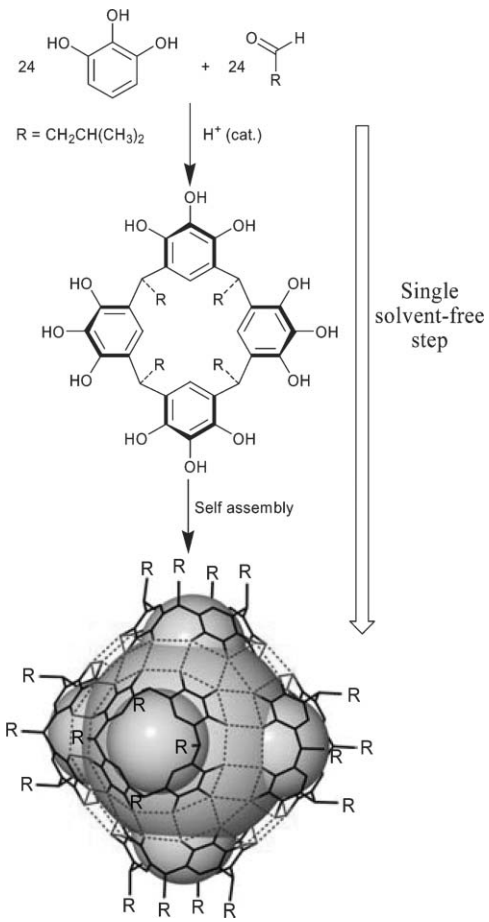

Fig. 1 One pot solvent-free synthetic route to nano-capsule formation.

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any dissolution of the material resulting from the solvent-free synthesis would preclude structural analysis of the product as prepared.

Solid state ^{13}C-NMR analysis† of the solvent-free product was compared to the known bilayer and nano-capsule forms of the pyrogallol[4]arene **1** prepared using conventional protocols,[8–10] and crystallised from methanol and chloroform, respectively. The solid state ^{13}C-NMR spectra of the pyrogallol[4]arene **1** crystallised from methanol (bilayer structure) and chloroform (nano-capsules) are markedly different, as is shown in Fig. 2. The bilayer structure affords more signals than that from the nano-capsule sample. These results are interpreted as resulting from a decrease in molecular symmetry of the macrocycle in the bilayer structure compared to that of the nano-capsules. This is also observed in the solution studies, and is attributed to the additional hydrogen bonds between the methanol and the macrocycle in the bilayer structure.[9] By comparison, the nano-capsule provides a high degree of symmetry between the six pyrogallol[4]arene building blocks. Comparison of the ^{13}C-NMR spectrum of the product from the solvent-free reaction with those of the two standards (Fig. 2) demonstrates that the material from the solvent free synthesis exists as hexameric spheres. In fact, the spectra of the nano-capsule materials from the two different reaction pathways vary only slightly, with the product from the solvent-free reaction having a shoulder on the signal at 114 ppm and a low intensity peak at 50 ppm. These signals occur at the same chemical shifts as the pure *p*-toluenesulfonic acid catalyst, and therefore arise as a result of the obtaining the spectra without removal of the catalyst.

The nano-capsule formed by the self-assembly of six pyrogallol-[4]arene macrocycles is known to enclose an internal molecular volume of over 1300 Å^3.[10] Studies of this molecular capsule show it to contain solvent guest molecules.[9,10] In an attempt to ascertain the guest species within the nano-capsule from the solvent-free reaction we studied the nano-capsule in solution. The resulting ^{1}H and ^{13}C NMR spectra were analogous to those of the nano-capsule made using traditional synthetic techniques, with the additional signals corresponding to water and the catalyst. There are also traces of unreacted starting materials. We were unable to observe a distinct separation of chemical shifts attributed to guest molecules *exo* and *endo* with respect to the nano-capsule. DOSY NMR studies of the product from the solvent-free reaction confirm the existence of nanometre scale aggregates but did not conclusively indicate the existence of water within the cavity. Diffusion studies of the chemical shifts arising from the unreacted starting materials indicate that they are entombed within the nano-capsules. A diffusion coefficient of 3.8775×10^{-10} m^2 s^{-1} (at 298 K in acetone-D_6, 3 mM) was calculated for the solvent-free pyrogallol[4]arene corresponding to an estimated solvated molecular diameter of approximately 3.7 nm. A similar experiment was performed on the pyrogallol[4]arene **1** crystallised from methanol, resulting in a diffusion coefficient of 7.221×10^{-10} m^2 s^{-1} (at 298 K in acetone-D_6, 3 mM) relating to a solvated diameter of 1.8 nm. These results are in excellent agreement with our previously reported molecular structure of the nano-capsule and the solid-state structures of the pyrogallol[4]arene, **1**, in the bilayer conformation.[9,10] Electrospray ionisation mass spectrometry of the product from the solvent-free reaction in ethyl acetate substantiates the existence of the nano-capsule formation, exhibiting a $[M - 3H]^{3-}$ molecular ion of the nano-capsule (calcd.: 1551.75; found: 1552.16).

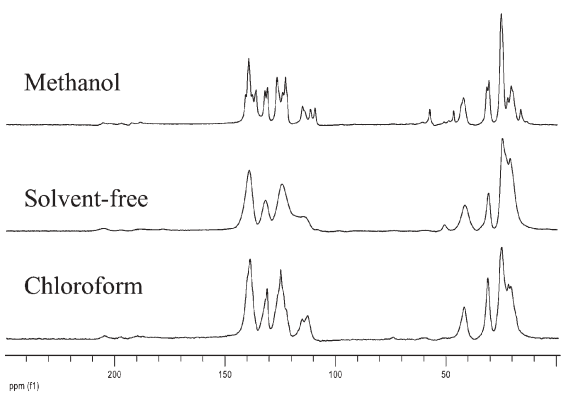

Fig. 2 Solid-state ^{13}C-NMR analysis of *C*-isobutylcalix[4]pyrogallolarene, **1**, crystallised into bilayer (from methanol) and nano-capsule (chloroform and solvent-free methods) morphologies.

We speculate that the nano-capsule entraps the water molecules liberated by the condensation reaction during the formation of the macrocycle, arising from atmospheric moisture and the deliquescent nature of the catalyst. Trace amounts of the starting materials also help to fill the internal volume of the nano-capsule during formation. These polar guest molecules interfere with the hydrogen bonding network that holds the nano-capsule together, allowing them to exchange and diffuse into the surrounding solvent system. A similar solvent–guest exchange mechanism has been reported by Rebek and co-workers for the nano-capsules formed by the self-assembly of six calix[4]resorcinarene and eight water molecules.[11]

We have demonstrated that the facile formation of pyrogallol-[4]arene macrocycles in the cone conformation using green chemistry methodologies is attainable. The spontaneous self-assembly of these supramolecular building blocks even in the absence of solvent into nano-sized molecular capsules provides an insight into polar guest inclusion logistics. We are continuing our studies of these molecular containers, investigating their potential as drug delivery systems and as affordable biological cell models.[10] Acid functionalised potential guests are also being investigated as an alternative catalyst in the formation of the nano-capsule and subsequent inclusion, with resulting increased atom efficiency.

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Notes and references

† Solid state ^{13}C-NMR analysis was carried out on a Bruker ARX 300 with a MAS probe. Samples were packed in 7 mm ZrO_2 rotors spinning at 5000 Hz. DOSY NMR studies were performed on a Bruker DRX 500 spectrometer equipped with a Acustar II gradient system using a 5 mm TXI probe and a simulated echo and LED sequence,[12] with the following parameters: relaxation delay 7.5 s, diffusion time 50 ms, pulse gradient duration 2 ms. The diffusion gradients were increased incrementally from 2 to 96 G mm^{-1} in 64 equal steps.

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