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A 68-membered macrocycle undergoes ultrasound-induced supramolecular gelation in acetonitrile. The sonogel shows a remarkable thermostability, indicating that self-assembly is mediated by exceptionally robust non-covalent interactions. Model compounds indicate that the macrocyclic topology is essential for gelation to occur.

Stimuli responsive materials have potential applications in biosensing, controlled release drug delivery, tissue engineering and catalysis.¹ Supramolecular gels are particularly suitable to implement stimuli responsiveness because of the non-covalent nature of the fibrous gel networks that arise from the self-assembly of low-molecular weight gelators in a given solvent. Examples of supramolecular gels based on hydrogen bonding, metal–ligand coordination, aromatic interactions, van der Waals forces and hydrophobic effects have been described.² External stimuli, such as temperature, pH, light, mechanical stress, solvent or additives, can induce gel–sol transitions by modulating the gel-forming interactions.³ The first example of a sol–gel transition triggered by sonication was reported by Naota and Koori.⁴ These sonogels have potential applications as wettability switches, hybrid materials, pollutant decontaminants or cell encapsulators.⁵

Ultrasound is commonly employed to break and disperse particles and supramolecular assemblies in the liquid state. Ultrasound produces high frequency mechanical waves that can create extreme physical and chemical conditions by the formation and collapse of bubbles under the pressure of the surrounding liquid.⁶ This cavitation effect can release enough kinetic energy to induce gelation by helping to overcome the activation barrier of kinetically disfavoured self-assembly pathways. Two different mechanisms of

Ultrasound-induced gelation of a giant macrocycle†

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sonogelation have been proposed. At the molecular level, the activation of gelators can occur by inducing a conformational change, the transformation of intramolecular interactions into intermolecular interactions, or a rearrangement of labile bonds. At the supramolecular level, sonication can disrupt nucleation by fragmenting and dispersing aggregates, so that gelation occurs by the formation of entangled fibrillar structures from the independent propagation of separate assemblies.^{3e,6d,7} The chemical structures of reported sonogelators include organometallics, amino acids, peptides, ureas, cholesterol and heterocycles.^{4,8–12} Although organic macrocycles, such as calixarenes, porphyrins and cucurbiturils, can form supramolecular gels,¹³ macrocyclic sonogelators are rare. Some metallo-macrocycles have been reported, but only one example of an organic macrocyclic sonogelator is known.^{4,8c,14} Here, we describe the ultrasound-induced gelation of a new class of giant macrocycle (**1**, Fig. 1).

Gelator **1** was synthesized in 9 steps from dipropargylamine and mono-methyl terephthalate (see ESI† for details). The compound

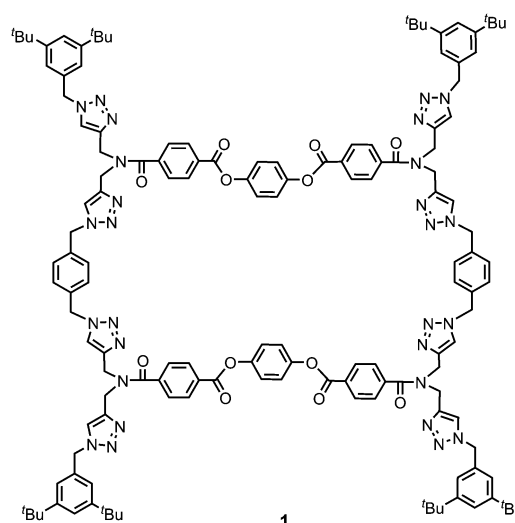


Fig. 1 Chemical structure of gelator **1**.

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† Electronic supplementary information (ESI) available: Detailed synthetic procedures, ¹H and ¹³C NMR spectra of all compounds, experimental details for the gelation including a video, molecular modelling methods, single crystal and powder diffraction X-ray data, SEM/TEM experimental details. CCDC 1838654. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc04742a



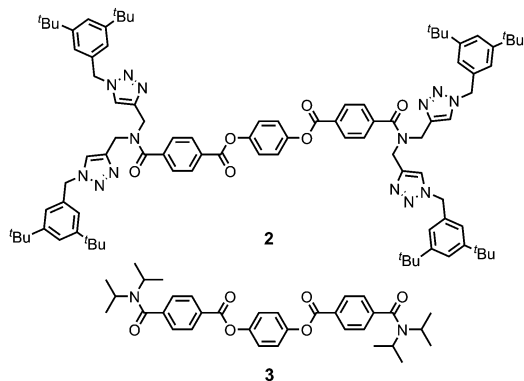


Fig. 2 Chemical structure of control compounds **2** and **3**.

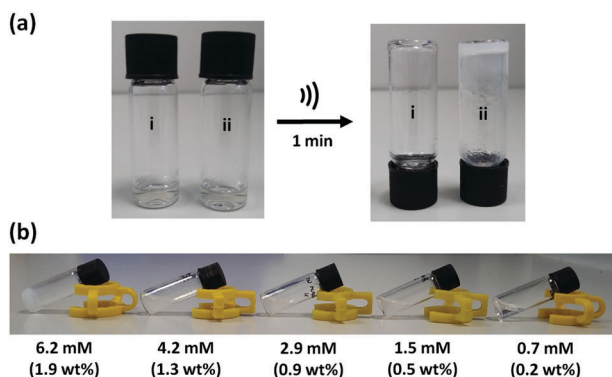


Fig. 3 (a) Ultrasound-induced gelation of compound **1** in CH_3CN at 14 mM. The left image shows two identical solutions of **1**. The right image corresponds to the sonication of solution (ii) for 1 min and solution (i) is the negative control. (b) Gel formed upon sonication of solutions of **1** in CH_3CN at different concentrations.

was assembled using a series of sequential copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) and ester coupling reactions. The key macrocyclization step was achieved by double CuAAC reaction of a bis-propargyl derivative with 1,4-bis(azidomethyl)benzene under high dilution conditions. Control compounds **2** and **3** containing fragments of macrocycle **1** were also synthesised in order to obtain insights into the relationship between the chemical structure and the self-assembly properties (Fig. 2).

When a 14 mM solution of macrocycle **1** in CH_3CN (4.3 wt%) was sonicated for 1 minute (45 kHz , 0.19 W cm^{-2}), a white, opaque, and stable gel is formed. Fig. 3(a) shows the inverted test-tube test for gel formation. When this solution was not subjected to sonication, some turbidity could be observed after a period of hours, but a gel was not formed (Fig. S1a, ESI[†]). A 10-fold more dilute solution of **1** in CH_3CN (1.4 mM, 0.4 wt%) formed a partial gel on sonication (Fig. S1b, ESI[†]). When this solution was not subjected to sonication, it remained clear for days with no signs of gelation. The critical gelation concentration (CGC) of **1** in CH_3CN , the lowest concentration of the gelator which forms a stable gel, is 1.3–1.9 wt% (Fig. 3b). This value is typical for supramolecular gels formed by low-molecular weight gelators (0.1 to 10 wt%).¹⁵ Analysis of the material after ultrasound-induced gelation showed no evidence of any chemical

change in composition, confirming the supramolecular nature of the gelation process (Fig. S2, ESI[†]).

The temperature-dependent behaviour of the gel was analysed in order to assess the strength of the non-covalent interactions that mediate the self-assembly of **1**. The dropping ball method can be used to estimate the gel-sol phase-transition temperature (T_{gel}). For the sonogel of **1**, the temperature at which the ball started dipping into the gel was $105 \text{ }^\circ\text{C}$ (Fig. S5, ESI[†]).¹⁶ However, visual inspection of the sample at this temperature revealed that the gel was stable and had not undergone a gel-sol phase transition. Rather, shrinkage of the gel had occurred due to evaporation of solvent, because the temperature is much higher than the boiling point of CH_3CN . Commonly, supramolecular gels exhibit a thermally reversible gel-sol phase transition, and only a few systems have been reported to show thermally triggered deswelling.¹⁷ The thermostability and unusual thermal shrinking properties of the gel indicate that remarkably robust non-covalent interactions govern the self-assembly of **1**. Only the addition of a competing solvent such as CHCl_3 was found to disrupt the non-covalent network and promote dissociation of the gel (Fig. S1, ESI[†]).

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) were used to study the morphology of the sonogel formed by **1** at the macroscopic level (Fig. 4). SEM micrograph images of the xerogel prepared from the sonogel exhibit an intertwined 3D network consisting of twisted thin 1D nanofibers. The fibres form bundles and intertwine to produce an entangled network. Similarly, the TEM images shows a web of fibres entangled together, with an average diameter of $100 \pm 30 \text{ nm}$. X-ray powder diffraction was used to determine whether the ultrasound-induced aggregation of **1** proceeds with an increase in crystallinity.^{9b} However, both the xerogel and the

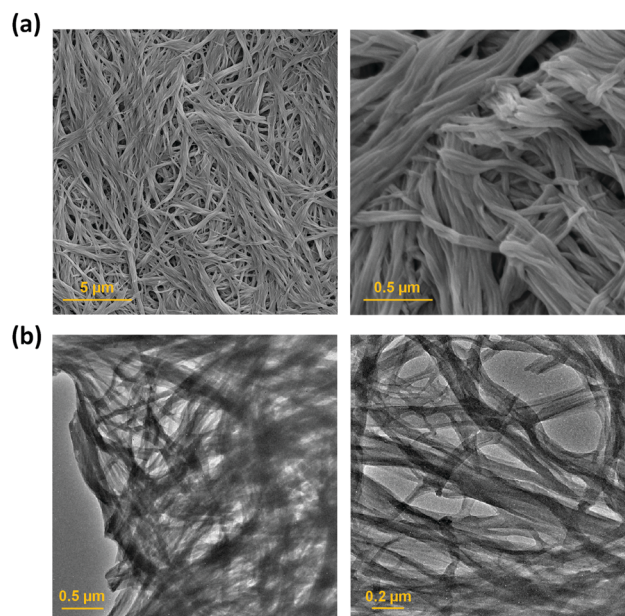


Fig. 4 (a) SEM and (b) TEM micrographs of a xerogel formed by compound **1** at two magnifications.



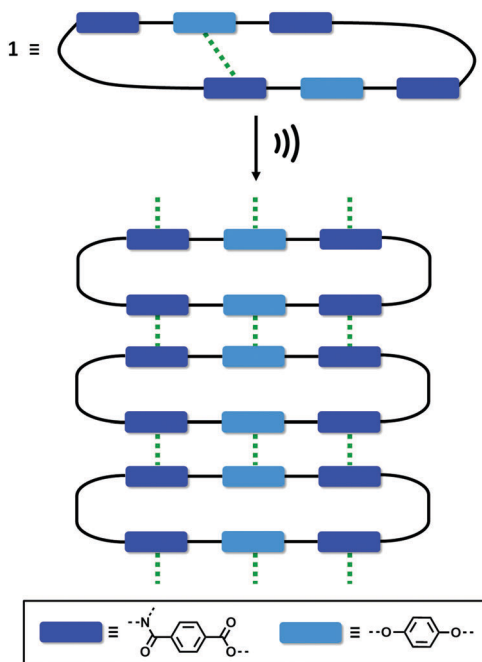


Fig. 6 Proposed mechanism for the self-assembly of **1** upon ultrasound irradiation. The green dotted lines represent aromatic interactions.

The molecular structure of **1** suggests that aromatic interactions mediate the self-assembly process. The macrocyclic structure was found to be essential for sonogel formation: three acyclic analogues all failed to gelate under the same conditions. Molecular modelling, NMR spectroscopy and X-ray crystallography suggest that **1** is kinetically trapped in a folded conformation by weak intramolecular aromatic interactions. We suggest that when ultrasound is applied, the intramolecular interactions are disrupted allowing self-assembly to take place through intermolecular aromatic interactions.

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Conflicts of interest

There are no conflicts to declare.

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