

# Evolution of nano- to microsized spherical assemblies of fluorogenic biscalix[4]arenes into supramolecular organogels†

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**A biscalix[4]arene (1) capable of spontaneous self-assembly into nanoparticles and microspheres in CH<sub>3</sub>CN was serendipitously observed, and it eventually formed stable blue-light emitting supramolecular organogels.**

In recent years there has been great research interest in the area of supramolecular gelators,<sup>1</sup> not only for academic study but also for their potential applications in chemistry, biology, and materials, such as those used in light harvesting,<sup>2</sup> capsules,<sup>3</sup> chiral recognition,<sup>4</sup> and drug delivery.<sup>5</sup> Supramolecular gels derived from low molecular mass compounds are formed through self-assembly by multiple non-covalent interactions such as hydrogen bonding,  $\pi$ - $\pi$  stacking, dipole-dipole interactions, metal-ligand coordination, van der Waals force, and solute-solvent interactions. The common features of the reported gelator molecules are composed of three major parts: (1) functional groups that enable hydrogen bonding interactions, (2) long alkyl chains that facilitate the van der Waals force interactions, and (3) large planar molecular surfaces (usually  $\pi$ -conjugated) that promote the  $\pi$ - $\pi$  stacking interactions.<sup>6</sup> However, there are relatively few examples of so-called 3-D macrocycle-based gelators in the research field of supramolecular gels.<sup>1c,d</sup> In recent years, biscalix[4]arenes have been extensively studied because their structures usually contain interesting properties including the allosteric effect, intramolecular oscillation, and conformational interconversion.<sup>7</sup> To the best of our knowledge, only Rudkevich and coworkers have reported the formation of gels based on bis-calixarene skeletons, in which two calixarene tetraurea moieties were linked by a di-*l*-lysine chain.<sup>3</sup> To date, even the mono-calixarene gelators have been rarely reported.<sup>1d,4,8</sup> Herein we report our serendipitous discovery of biscalixarene gelators, which do not contain any long alkyl chains, exhibiting either nano- or microsphere<sup>9</sup> morphology with fluorescent properties.

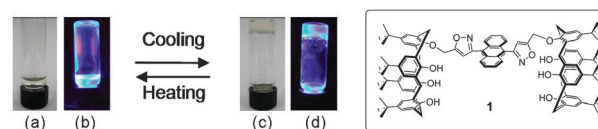
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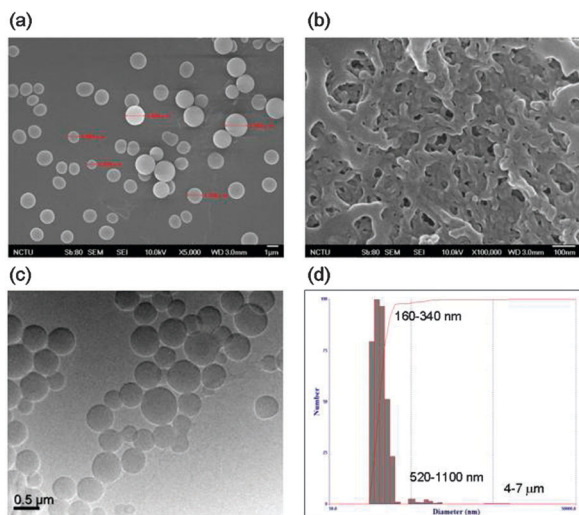
We have previously established a strategy for the synthesis of calixarenes with various bifunctional groups using 1,3-dipolar cycloaddition reaction followed by ring-opening reactions.<sup>10</sup> Biscalix[4]arene **1** was prepared in good yield (62%) based on reported procedures<sup>10d</sup> using double 1,3-dipolar cycloaddition reactions of a lower-rim 25-propargyloxycalix[4]arene with anthracene-9,10-dinitrile oxide. While trying to grow crystals of the biscalix[4]arene compounds, we were surprised to find that compound **1** formed a transparent supramolecular organogel in CH<sub>3</sub>CN (Fig. 1). Further studies showed that the minimum gelation concentration of **1** in CH<sub>3</sub>CN was 3 mM; however, it did not show any gel property in many other organic solvents tested.<sup>11</sup>

The minimum gelation concentration of **1** in CH<sub>3</sub>CN (<2 wt%) was comparable to some of the best reported low-molecular-weight gelators reported in the literature (which is *ca.* 0.63 wt%).<sup>12</sup> The organogel was prepared by heating compound **1** in CH<sub>3</sub>CN until it was completely dissolved followed by cooling the solution to below the gelation transition temperature. The formation of aggregates was spontaneous which did not require ultrasonication or mixed solvents. The formation of gel from compound **1** in CH<sub>3</sub>CN was stable and reversible upon repeated heating and cooling (Fig. 1).

Field Emission Scanning Electron Microscopy (FE-SEM) images of the gel material **1** indicated a vesicular structure with spherical aggregates (Fig. 2a). FE-SEM images of the dried gel samples of biscalix[4]arene **1**, prepared from 0.5–10 × 10<sup>-4</sup> M of **1** in CH<sub>3</sub>CN, are shown in Fig. 2a and b and Fig. S1a–c (ESI†). These FE-SEM images of **1** showed many microspheres with diameters ranging from 0.3 to 2.0  $\mu$ m. The microspheres were



**Fig. 1** Temperature dependent gel properties of **1** in CH<sub>3</sub>CN, where (a) and (c) are photos taken under room light while (b) and (d) are photos of samples of **1** when irradiated with 365 nm light from a TLC lamp. Furthermore, photos (c) and (d) were taken at room temperature.

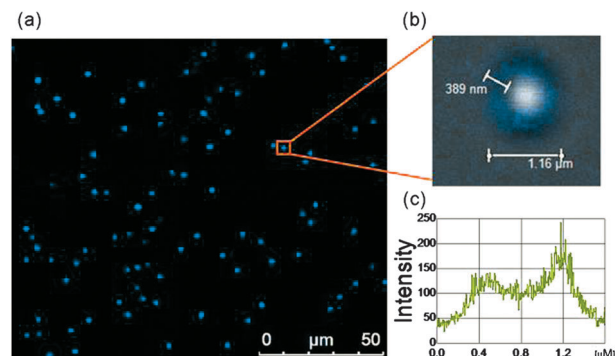


**Fig. 2** Morphology of self-assembled object of **1**, where (a) and (b) are FE-SEM images of the xerogels of **1** (0.5 mM) in  $\text{CH}_3\text{CN}$ , (c) is the TEM image of xerogels of **1** in  $\text{CH}_3\text{CN}$ , and (d) is a Dynamic Light Scattering (DLS) diagram of solution of **1** (0.5 mM) in  $\text{CH}_3\text{CN}$  at 25 °C.

agglomerated and fused in some places with a coralloid morphology, which is in contrast to the individual microspheres. The coralloid-like motif was composed of smaller spheres connected through a two-dimensional pattern (Fig. 2b). The spherical morphology of bisalix[4]arene **1** was confirmed using Transmission Electron Microscopy (TEM, Fig. 2c), which showed that the diameters of the spheres for bisalix[4]arene **1** were about 0.3–1.0  $\mu\text{m}$ , similar to those observed using FE-SEM. The aggregate behavior of **1** in  $\text{CH}_3\text{CN}$  was investigated by dynamic light scattering (DLS) analysis (Fig. 2d). A DLS diagram of a solution of **1** (0.5 mM) at 25 °C showed small particles with diameters in the range of 0.16–0.34  $\mu\text{m}$  (97.9%) and 0.52–1.1  $\mu\text{m}$  (2.0%), which were in accord with the results obtained from FE-SEM and TEM.

The nature of the spherical aggregates of **1** in  $\text{CH}_3\text{CN}$  (0.5 mM) was further studied using confocal laser scanning microscopy (CLSM), which showed that they are hollow spherical aggregates as observed in fluorescence microscopy images (Fig. 3 and Fig. S2, ESI<sup>†</sup>). Moreover, CLSM images provided information about the wall thickness of the microspheres, which is about 0.4  $\mu\text{m}$  (Fig. 3b and c).

In order to understand why molecule **1** forms aggregates, we took a series of  $^1\text{H}$ -NMR spectra of bisalix[4]arene **1** in  $\text{CD}_3\text{CN}$  at different temperatures (VT-NMR), which are illustrated in Fig. S3 (ESI<sup>†</sup>). When the solution temperature was decreased from 333 to 253 K (sol to gel), protons of the methylene bridge and the *t*-butyl groups of calix[4]arene and the  $\text{OCH}_2$  bridge were slightly upfield shifted, whereas signals of the protons of calixarene phenyl, part of the anthracene, and the isoxazole groups were downfield shifted. Furthermore, the signals of phenolic-OH protons became very broad, and the residual acetonitrile- $d_3$  also showed a significant downfield shift (+0.05 ppm). Results from VT-NMR of **1** demonstrated that (1) intermolecular hydrogen bonding between the phenolic-OH protons, (2) van der Waals interactions between the *t*-butyl



**Fig. 3** (a) CLSM images of aggregates of bisalix[4]arene **1** in  $\text{CH}_3\text{CN}$  (0.5 mM), (b) a magnified picture of one nanosphere, and (c) the corresponding intensities of the microsphere, in which  $\lambda_{\text{ex}} = 405 \text{ nm}$  and  $\lambda_{\text{em}} = 415\text{--}500 \text{ nm}$ .

groups, and (3) the interactions between gelator molecules and  $\text{CH}_3\text{CN}$  (solute–solvent interactions) are important factors in the formation of the organogels. Furthermore, dipole–dipole and  $\pi$ – $\pi$  stacking interactions between the bis-isoxazolyanthryl groups should have also played some roles in its organogel formation.

Self-assembly of bisalix[4]arene **1** was also studied using changes in the fluorescence spectra as a function of temperature and concentration (Fig. S4, ESI<sup>†</sup>). As the temperature of the solution decreased from 60 to 0 °C (sol to gel), the intensity of the fluorescence band at 431 nm increased and its  $\lambda_{\text{max}}$  slightly red shifted to 433 nm. As the concentration of **1** in  $\text{CH}_3\text{CN}$  increased from 0.5 to 5 mM (sol to gel), the fluorescence emission maximum,  $\lambda_{\text{max}}$ , also red shifted from 429 to 439 nm. The red shifts of the fluorescence spectra of bisalix[4]arene **1** at low temperature (or high concentration) originated from its self-assembly into larger aggregates which contain some  $\pi$ – $\pi$  stacking interactions.

In order to prove that  $\pi$ – $\pi$  interactions of the anthracenes play an important role in the self-assembly of bisalix[4]arene **1**, we also synthesized a series of analogues **2–6** (Scheme S1, ESI<sup>†</sup>), in which the anthryl bridge of bisalix[4]arene **1** was replaced by 1,4-phenyl (**2**),<sup>10d</sup> 2,5-thieno (**3**), 5-bromo-1,3-phenyl (**4**), and 5-(2-phenylethynyl)-1,3-phenyl groups (**5**). Furthermore, the 9,10-bis(isoxazolyanthryl) bridge in the bisalix[4]arene **1** was replaced by a 9,10-bis(isoxazolyanthryl)methyl-anthryl group (**6**) using the click reaction of 9,10-diazidomethyl-anthracene **13** with 25-propargyloxycalix[4]arene. Control compound **7**<sup>10d</sup> which replaced the bisalix[4]arene scaffold by two *t*-butylphenols was also prepared for comparison (Scheme S2, ESI<sup>†</sup>). Bisalix[4]arenes **2–6** and control compound **7** were prepared in good yields (43–71%) using similar synthetic procedures as those used for **1**. The structures of compounds **1–7** were fully characterized using spectroscopic data (ESI<sup>†</sup>) including  $^1\text{H}$  and  $^{13}\text{C}$  NMR, mass, and high resolution mass spectrometry. After testing in various different solvents at room temperature, we found that none of these bisalix[4]arenes **2–6** or compound **7** formed supramolecular organogels (Table S1, ESI<sup>†</sup>).

The latter results imply that the  $\pi$ – $\pi$  interactions of the 9,10-bis(isoxazolyanthracene) of **1** were quite critical to the self-assembly behavior of bisalix[4]arene **1** in  $\text{CH}_3\text{CN}$ . Moreover, the bisalix[4]arene **6**, which retains the anthracene moiety but

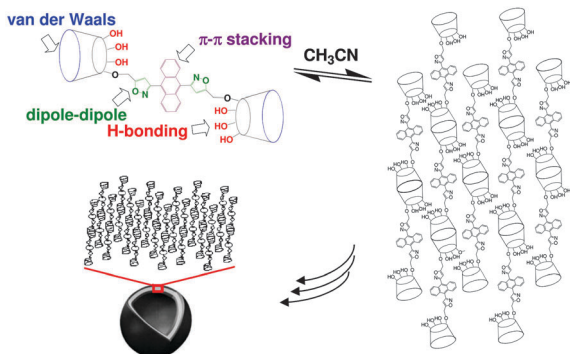


Fig. 4 Schematic representation of the self-assembly of supramolecular gelator 1.

lacks the 9,10-bisoxazole groups, did not show any gelation property under the conditions studied for **1**. Thus, not only the  $\pi$ - $\pi$  interactions of the anthracene but also the dipole-dipole interactions between the isoxazole groups of **1** play important roles contributing to the unique gel formation properties of **1**. The results are reminiscent of those reported by Haino *et al.* for the formation of helical fibers by a series of tris(phenylisoxazolyl)benzene derivatives.<sup>6c,12e</sup> Interestingly, compound **7**, which keeps the 9,10-bisoxazolylanthracene moiety of **1** but lacks the biscalix[4]arene scaffold, did not show any gel properties. The latter results highlight the importance of intermolecular hydrogen bonding interactions between the lower-rim hydroxyl groups of the biscalix[4]arene in dictating the self-assembly of the biscalix[4]arene **1**.

FE-SEM, TEM, and CLSM images of the organogels of **1** indicate that its morphology is a vesicular structure which forms spherical aggregates. VT-NMR spectra of **1** showed that the molecular aggregation at low temperature was due to intermolecular hydrogen bonding interaction and van der Waals interactions. As the concentration of **1** increased, a significant red shift of the  $\lambda_{\text{max}}$  of the corresponding fluorescence spectra implied that strong  $\pi$ - $\pi$  interactions between the anthracene groups were involved. In addition, the series of aryl derivatives **2-6** also clearly demonstrated that not only the  $\pi$ - $\pi$  interactions but also dipole-dipole interactions have played important roles in exerting the special organogel properties of **1**. Based on all the findings described above, we propose a possible molecular packing model for the self-assembly of supramolecular organogel **1** (Fig. 4). The first dimensional assembly of **1** can be formed by intermolecular van der Waals interactions between the *t*-butyl groups of the biscalix[4]arenes.<sup>10d,13</sup> The intermolecular hydrogen bonding interactions between the lower-rim OH groups of each calixarenes contributed to the second dimensional assembly. The  $\pi$ - $\pi$  and dipole-dipole interactions between the 9,10-bisoxazolylanthryl groups of **1** led to the construction of the third dimensional network and eventually formed the spherical aggregates.

We report here an unprecedented fluorogenic biscalix[4]arene **1** capable of spontaneous self-assembly into nanoparticles, micro-spheres, and eventually forming stable blue-light emitting organogels. This represents one of the few examples using functionalized biscalix[4]arenes without long alkyl chains (for van der Waals force interactions), and yet it forms supramolecular organogels. The thermo-responsive and

blue-emitting nature of the supra-molecular organogel **1** makes it potentially useful in controlled release and sensing systems, and we are currently exploring some of these possibilities. Furthermore, we hope that such a discovery will stimulate new directions in future design of 3D organogelators.

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- The gelation property of **1** was tested in seventeen different organic solvents, including CH<sub>3</sub>CN, CHCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, DMSO, DMF, THF, methanol, ethanol, *n*-propanol, isopropanol, *n*-butanol, *tert*-butanol, cyclohexane, hexane, ethyl acetate, toluene, and acetone (Table S1, ESI<sup>†</sup>).
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