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Sonication-induced self-assembly of flexible tris(ureidobenzyl)amine: from dimeric aggregates to supramolecular gels†

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Tris(ureidobenzyl)amine derivatives 1a,b form dimeric aggregates in apolar solution and in the solid state. Specifically, the *meta*-substituted tris(urea) 1a is able to transform into supramolecular gels in certain solvents *via* sonication.

There has been a surge of interest in low molecular weight gelators (LMWGs),[1–3] a class of small organic molecules that can form gels *via* supramolecular interactions, such as hydrogen bonding, π···π stacking *etc*. Bis(urea) derivatives have been proved to be highly effective in forming LMWGs,[4–14] and their gelation ability depends on hydrogen bonding interactions of the urea groups that can form α-tape motif aggregates *via* NH···O=C hydrogen bonding interactions.[15] Besides the bis(urea) motif, the tris(urea) motif has also been applied in a number of effective supramolecular assemblies such as anion recognition,[16–22] dimeric aggregates,[23–25] and gelators.[26–29] In particular, Steed and co-workers reported tris(urea) gelators affording supramolecular gels that are susceptible to fine tuning by anion binding.[28] On the other hand, tripodal tris-urea ligands were also reported as dimeric aggregates both in apolar solution and in the solid state by Alajarin and co-workers.[25,30–32] However, to our best knowledge, there has been no report on tripodal tris(urea) receptors showing tunable transformation between dimeric capsules and supramolecular gels. Motivated by reported interesting results that the gelation ability of bis- and tris(urea) compounds can be dramatically affected by inducing only one CH_2 segment into their structures,[10,14,26] we envisioned that subtle modification of substituent groups of tris(urea) compounds that could form dimeric aggregates might provide the possibility of forming supramolecular gels in certain solvents. We herein designed and synthesized novel *meta*-substituted "foot" tris-(3-ureidobenzyl)amine derivatives **1a,b** (Fig. 1). As a comparison with **1a,b**, novel *para*-substituted "foot" tris(3-ureidobenzyl)-amine derivatives (**1c,d**) were also prepared, and **1e** that was well known to dimerize both in solid state and in solution to form dimeric aggregates[25,30,31] was also synthesized according to the reported literature.[30]

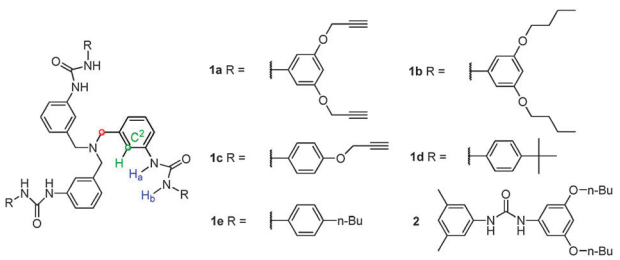

Fig. 1 Chemical structures of tris(3-ureidobenzyl)amines **1a–e** and model compound **2**.

NMR spectra in different solvents proved to be a powerful tool for studying dimeric aggregates in solution.[25] The averaged C_{3v} symmetries of the monomers of tripodal tris(urea)s **1a,b** can be identified in CD_3CN and DMSO-d_6, a hydrogen bonding competitive polar solvent, with the singlet of methylenic protons of the $(ArCH_2)_3N$ fragment in ^1H NMR (Fig. S1–2†).[25,30] ^1H NMR spectra of tris(urea)s **1a,b** in less polar solvent $CDCl_3$ were also investigated (Fig. S1–2†). The results showed that the ^1H NMR spectrum of **1b** in $CDCl_3$ is much clearer than **1a**, due to the better solubility of **1b** in $CDCl_3$. More clearly, the ^1H NMR spectrum of **1b** in $CDCl_3$ indicated that the signals of both NH protons were shifted to lower field at 7.93 ppm, compared to the NH signal (NH δ 7.11 ppm) of the single urea model compound **2** also in $CDCl_3$, indicating the difference between the urea hydrogen-bonding of tris(urea) **1b** and the single urea model compound in $CDCl_3$. In particular, the signals of the methylenic protons of $(ArCH_2)_3N$ fragments were split into two broad peaks, indicating that these protons experience a diastereotopic environment. Moreover, the pendant aromatic groups (C^2–H in Fig. 1) of **1b** in $CDCl_3$ also experience chemical shifts 0.9 and 1.1 ppm to higher field than in DMSO-d_6 and CD_3CN, respectively, for the reason that the protons are pointing to the inside of the dimeric species[25] (Fig. S2, in green, ESI†). In addition, ^1H NMR of **1a**, and the tris(urea)s **1c, d** for comparison and well known **1e**[25] in $CDCl_3$ showed similar solution behavior as **1b** (Fig. S1, 3–4†), in which the methylenic protons of their $(ArCH_2)_3N$ fragments were split into two doublets (**1d**, **1e**) or broad peaks (**1a**, **1c**), indicating the feature of dimeric species formation of **1a–d** in $CDCl_3$.[25,30] The dimeric aggregates of **1a,b** in $CDCl_3$ were also indentified,

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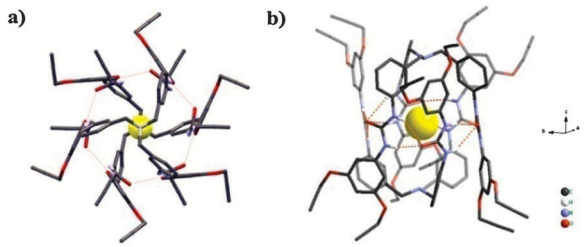

Fig. 2 Crystal structure of the tris(urea) dimer **1a**·**1a** with one enclosed molecule of H_2O (yellow sphere): top view (a) and axial view (b).

respectively, on the basis of DOSY measurement[33] (Fig. S7†). The ROESY experiments of **1b**·**1b** and **1d**·**1d** in $CDCl_3$[34] further confirmed that intermolecular NOE contacts only fit within a dimeric structure instead of monomer (Fig. S5–6†).

Colorless block crystals of tris(ureidobenzyl)amine **1a** for X-ray diffraction measurement were successfully obtained from slow evaporation of its CH_3CN solution. It is notable that a six-membered ring of ureas in a head-to-tail fashion based on hydrogen bonding interactions was observed in the structure of dimeric aggregate (Fig. 2). This capsule-like dimeric aggregate consists of two enantiomeric tripods and exhibits an overall S_6 symmetry.[25] The distance of N–H···O hydrogen bonds between two ureas are 2.932(2) and 3.118(2) Å, implying a rather unsymmetric six-membered hydrogen bonded ring.[30] There are reports that intermolecular CH···π interactions between the aromatic CHs and the aryl rings play an important role for the thermodynamic and kinetic stability of the capsule,[35] and for instance, well known *para*-substituted "foot" tris(ureidobenzyl)amines **1e**·**1e** shows CH···π interactions between the pendant aromatic CHs and the tribenzylamine skeleton aryl rings in the crystalline states.[30,31] Therefore, the CH···π interactions of *meta*-substituted "foot" tris(urea) **1a**·**1a** in our case might be decreased for the reason that the pendant aromatic CHs were substituted by oxygen atoms, resulting in the decreasing of the stability of dimeric aggregate. Further, to our surprise, the X-ray structure shows that the cavity of capsule-like **1a**·**1a** is filled with one molecule of H_2O.

Cooling of a thermally dissolved super-saturated CH_3CN solution of **1a** (1.5% by weight) resulted in precipitation. Surprisingly, an opaque organogel was obtained through ultrasonication during its cooling process,[36] (Fig. 3a) and the resultant gel was stable at ambient temperatures without crystallizing or melting. Although tris(urea) **1a** cannot form a perfect gel in apolar solvents by sonication, such as CH_2Cl_2, $CHCl_3$ (Fig. S8†), it will form opaque weak gels at 2.0% weight by sonication in mixed solvents such as CH_2Cl_2–MeOH (10 : 1 v/v) and $CHCl_3$–MeOH (10 : 1 v/v) (Fig. 3a). Compared to **1a**, tris-urea **1b** formed a white, opaque gel-like precipitate in CH_3CN by sonication and did not form gels in other solvents (Fig. 3a). In contrast, tris(urea)s **1c–e** only formed white precipitates in CH_3CN by long-time sonication, presumably owing to their very poor solubility in CH_3CN even at elevated temperatures.[26]

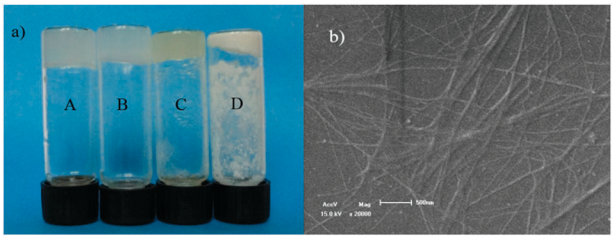

Fig. 3 (a) Gels of 2 wt% **1a** in (from left to right) (A) CH_3CN, (B) 10 : 1 (v/v) CH_2Cl_2–MeOH, (C) 10 : 1 (v/v) $CHCl_3$–MeOH, and as a comparison, (D) gel-like precipitate of 2 wt% **1b** in (right) CH_3CN. (b) SEM micrograph of the xerogel of **1a** gel formed in CH_3CN (solvent) showing the thread-like nature of the gel fibres.

Scanning electronic microscopy (SEM) was usually employed to study the morphologies of aggregation states. SEM images of tris(urea) **1a** xerogel prepared from the CH_3CN gel exhibited a partially intertwined 3D network structures consisting of very thin and irregularly twisted 1D nanofibers (Fig. 3b). The thicker fibers clearly consist of bundles of these very thin fibers. The fibers in turn fuse and intertwine to form an entangled network.

Supramolecular interactions often play important roles in the self-assembly of supramolecular gel in bis- and tris(urea) architectures.[15] To investigate the driving forces for the self-assembly process, ^{1}H NMR experiments of tris(urea) **1a** at various concentrations were carried out in CD_3CN in the concentration range of 1.3–20.1 mg mL^{-1} (Fig. S9†). We found that the NH_a resonance displayed a downfield shift from 7.62 to 7.65 ppm and the NH_b resonance also showed an obvious downfield shift from 7.35 to 7.43 ppm upon increasing the concentration from 3.6 to 20.1 mg mL^{-1}, which indicated the existence of hydrogen-bonding interactions among the urea groups during the formation of supramolecular aggregates.[37] The C^2–H resonance displayed an obvious upfield shift from 7.67 to 7.56 ppm with the concentration increasing from 1.3 to 20.1 mg mL^{-1}. These results indicated that the formation of supramolecular aggregates of **1a** could be driven by hydrogen-bonding and slight π···π stacking interactions in CD_3CN.[38]

The gel formed by hydrogen-bonding interactions could be tuned or destroyed by competitive anion or strong polar solvents. Steed and co-workers reported that the bis- and tris(urea) supramolecular gels were susceptible to fine tuning by anion binding.[10,13,14,28,39] More recently, Yang and co-workers have reported platinum–acetylide gels that can be collapsed by DMF-tuning.[37] In our case, a solvent-tuning experiment was carried out by the addition of DMSO into the gel of **1a** in CH_3CN (Fig. S10†), since DMSO is a well known good acceptor that can form hydrogen bonds with urea groups to disaggregate the urea α-tape motif aggregates. Interestingly, 28 equivalents of DMSO to **1a** were needed to completely destroy the gel network. ^{1}H NMR titration of **1a** with DMSO-d_6 in CD_3CN provides insight of the structures of gelator-solvent binding (Fig. S11†). Upon the addition of DMSO-d_6, tris(urea) **1a** showed a large downfield shifts of both NH_a and NH_b protons. It seems that the addition of DMSO may result in the dissociation of the intermolecular hydrogen bonding of gels, thereby leading to disaggregation of the supramolecular assembly, which again confirms the important role of hydrogen bonding interactions among the urea groups during the generation of the gels.

The pattern of ^{1}H NMR signals of tris(urea) **1a** in CD_3CN is consistent with averaged C_{3v} symmetries characteristic of the monomers. However, the X-ray analysis of **1a** showed the hydrogen-bonded dimeric aggregate which was entangled by a six-membered ring of ureas in a head-to-tail fashion. We supposed that

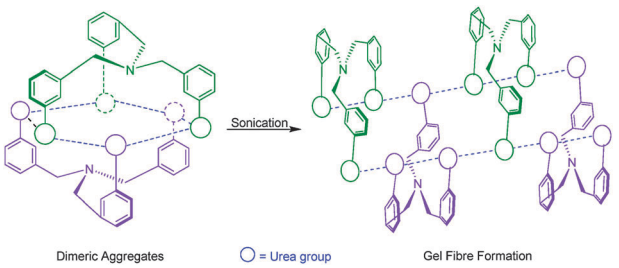

Fig. 4 Possibility of the tris(urea) **1a** related to the transformation between dimeric capsules and supramolecular gels by sonication.

in terms of **1a**, its formed dimeric aggregates in the crystal might be the most highly ordered aggregation in the solid state, and its amorphous precipitate resulted from cooling of its thermally dissolved CH_3CN solution is a random aggregation. The sonication-induced formation of gels may be an intermediate aggregation between these two above states.[40] We presumed that the belt of six hydrogen-bonded ureas of **1a**·**1a** might be biased by ultrasound, which can drive self-assembly to less ordered aggregates[41] resembling the tris(urea) LMWGs[26,28] (Fig. 4), resulting in the hydrogen bonding of the ureas to form one-dimensional polymer-like fibrous aggregates (Fig. 3b)

In summary, we have prepared tris(ureidobenzyl)amine derivatives **1a** and **1b** which can form dimeric aggregates in apolar solution. X-Ray analysis of **1a** showed the existence of a hydrogen-bonded dimeric aggregate entangled by a six-membered ring of ureas in a head-to-tail fashion and the cavity is filled with a molecule of H_2O. Specifically, the tris(urea) **1a** would transform into supramolecular gels in certain solvents *via* sonication. SEM was employed to study the morphology of xerogels of **1a**, which shows the thread-like nature of gel nanofibres. Concentration-dependent ^1H NMR spectroscopy and solvent-tuning experiments confirmed that intermolecular hydrogen bonding plays an essential role in the formation of supramolecular aggregates. This research offers an insight of the transformation between dimeric capsules and supramolecular gels for tripodal tris(urea) receptors.

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