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Halogen-bonding-triggered supramolecular gel formation

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Supramolecular gels are topical soft materials involving the reversible formation of fibrous aggregates using non-covalent interactions. There is significant interest in controlling the properties of such materials by the formation of multicomponent systems, which exhibit non-additive properties emerging from interaction of the components. The use of hydrogen bonding to assemble supramolecular gels in organic solvents is well established. In contrast, the use of halogen bonding to trigger supramolecular gel formation in a two-component gel ('co-gel') is essentially unexplored, and forms the basis for this study. Here, we show that halogen bonding between a pyridyl substituent in a bis(pyridyl urea) and 1,4-diiodotetrafluorobenzene brings about gelation, even in polar media such as aqueous methanol and aqueous dimethylsulfoxide. This demonstrates that halogen bonding is sufficiently strong to interfere with competing gel-inhibitory interactions and create a 'tipping point' in gel assembly. Using this concept, we have prepared a halogen bond donor bis(urea) gelator that forms co-gels with halogen bond acceptors.

Tunable gel-phase materials with novel properties such as switchable rheology and controlled flow characteristics are of potential interest in applications as diverse as pharmaceutical crystallization, catalysis, drug delivery and controlled release, wound healing and the stabilization of drilling mud[1–9]. Within this context, supramolecular low-molecular-weight gelators (LMWG), with their reversible and dynamic intermolecular interactions, are achieving increasing prominence[10–15]. Work on switchable gels is focused on systems with photo-, pH- and redox-based switching, ultrasound-induced gelation and switchable catalysis[16–23]. To develop smart materials systematically, with controllable and also well-understood bulk properties, it is necessary to have an understanding of the intermolecular interactions in the system and the way in which these interactions engage in hierarchical self-assembly to produce emergent morphologies with complex behaviour. However, the link between even primary supramolecular interactions and bulk material properties is often unclear. Recent work has highlighted some simple approaches to controllable or smart materials that have met with considerable success.

A key theme is that of setting up a 'tipping point' in a system comprising competing intermolecular interactions that contribute to either gel assembly or gel dissolution. In this regard, a number of research groups have shown that anion binding in competition with urea self-assembly can be used to 'turn-down' and ultimately 'turn-off' gelation behaviour[24,25]. Interestingly, in other systems, anion binding has also been used to induce gelation[26,27]. Metal coordination has been used similarly to tune gel properties[25]. In a series of bis(urea) gels we have shown how a combination of metal and anion binding can allow comprehensive control over the system. Competitive anion binding reduces gel strength by inhibiting urea α-tape hydrogen bond formation[28–31]. Conversely, metal coordination in pyridyl–urea compounds results in metal binding to the pyridyl group, which suppresses the alternative, gel-inhibiting urea–pyridyl hydrogen-bonding interaction, freeing the urea groups to form fibrils, and hence gels, as a result of the urea tape hydrogen-bonding motif[32–34]. These competitive interaction modes are summarized in Fig. 1.

Logically, the concept of suppressing an inhibitory interaction so as to turn on gelation is a general one, and suggests the possibility of manipulating key materials properties and hierarchical self-assembly based on a combination of urea tape formation and a dominant, crosslinking interaction. Hence, in principle, a detailed understanding of supramolecular synthon structure and relative stability gleaned from the wealth of crystal engineering literature[35–37] should provide a means to produce finely balanced, smart materials with controllable properties. To demonstrate this approach, we turned from metal coordination to the area of halogen bonding[38].

Halogen bonding—for example, between electron-deficient heavier halogen substituents and halogen bond acceptor atoms such as basic nitrogen ligands[39]—is now well established as an important solid-state interaction in molecular crystals[40–42]. Recently, halogen bonding has also been demonstrated to be useful in solution, for example in anion binding by pre-organized tripodal anion hosts[43]. In our hypothesis, halogen bonding should be of sufficient strength to 'tip the balance' and engender a switch from pyridyl urea hydrogen bonding to urea tape interactions, even in competitive media[44,45], and result in multicomponent gels[46–48]. We now report the use of halogen bonding to turn on gelation in bis(pyridyl urea) gelators **1** and **2** in the presence of 1,4-diiodotetrafluorobenzene **3**, as well as halogen bonding-induced gelation in the halogen bond donor gelator **4** when treated with either 4,4′-bipyridine **5**, tetrabutylammonium iodide or pyridyl derivative **1** (Fig. 2).

Results and discussion

Gelation by competitive inhibition. The previously reported X-ray crystal structure of **1** shows a combination of urea tape and pyridyl urea hydrogen-bonding interactions as part of a gradual transition in the dominant intermolecular interaction in the solid state as the length of the oligomethylene chain increases across a series of

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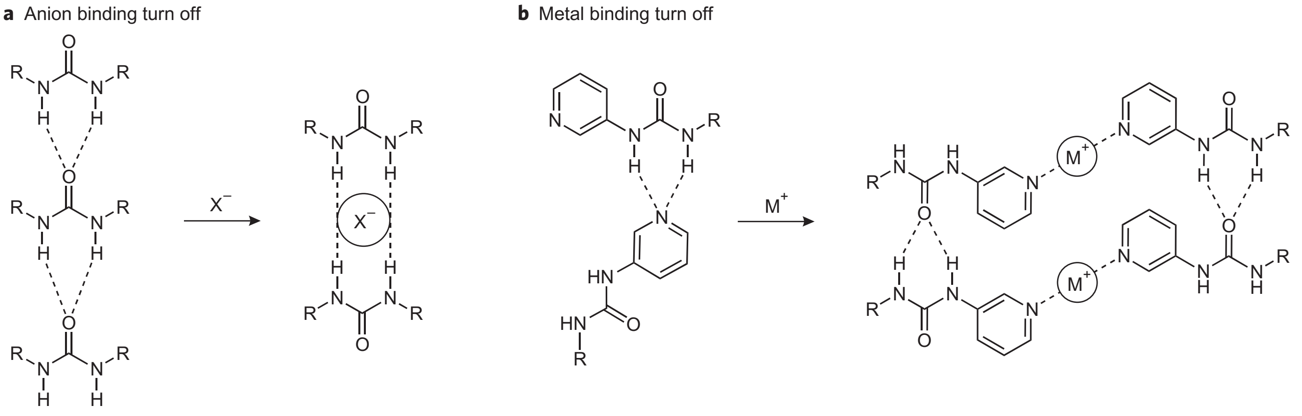

Figure 1 | Manipulation of gel formation and destruction through competitive intermolecular interactions. a, The urea α-tape hydrogen-bonding motif is responsible for gel fibril formation in bis(urea) LMWG. Competitive anion binding results in a reduction of gel strength because of the strongly competitive urea–anion interaction. **b**, Pyridyl ureas are generally poor gelators because of the formation of the pyridyl urea supramolecular synthon, which is not compatible with fibril formation. Metal coordination frees the urea moieties to produce parallel gel-forming α-tape motifs, crosslinked by metal pyridyl groups. Halogen bond donors may be substituted for the metal ion.

compounds[49]. In contrast, the sterically hindered **2** exhibits either a highly asymmetrical, helical urea hydrogen-bonded motif or interactions with included solvent[50]. Compounds **1** and **2** are non-gelators as free ligands, but form a variety of metallogels in the presence of copper(II) and silver(I) salts[32–34].

Fast cooling from $\sim$60 °C in a dry ice bath of an equimolar solution of **1** and **3** in either methanol or mixtures of methanol, acetonitrile or dimethylsulfoxide (DMSO) with water (for example, methanol-water (4:1 vol/vol) mixture at 1% by weight) results in the formation of an opaque hydrogel. The opacity suggests a relatively large fibre size and hence a high degree of crystallinity. The gel-like nature of the material was confirmed by stress sweep rheometry with a plateau elastic modulus (G') of $\sim$3 kPa and yield stress of 5 Pa. The G' value is approximately one order of magnitude above the G'' (viscous modulus) value, confirming the solid-like nature of the material. The gel strength increases in proportion to the amount of **3** added; in the absence of **3**, no gel is formed, but the addition of 0.4 and 0.5 equivalents of **3** relative to **1** results in a weak, partial gel. Although a 4:1 methanol/water mixture results in optimum gelation, gels are formed with other ratios (above 50% methanol) as well as with other solvent mixtures, such as acetonitrile/water (>50% MeCN). If the mixture is allowed to cool to room temperature much more slowly (over a period of 1–2 h), a fibrous crystalline precipitate comprising a 1:1 co-crystal of **1** and **3** is isolated instead of a gel. Scanning electron microscopy (SEM) analysis of the crystals of pure pro-gelator **1** and the corresponding **1**·**3** co-crystal shows that the crystal habit changes from two-dimensional hexagonal plates to one-dimensional needles on going from **1** to the **1**·**3** co-crystal (Fig. 3a). This dependence on cooling rate highlights the close relationship between ordered crystalline material and more disordered gels[51,52]. The structure of the co-crystal material was analysed by single-crystal X-ray crystallography (Fig. 3). The X-ray structure reveals a conventional nearly symmetrical, double, anti-parallel urea α-tape hydrogen-bonding motif. The pyridyl groups are involved in a symmetrical halogen-bonding interaction with the diiodotetrafluorobenzene, with an N$\cdots$I distance of 2.819(3) Å, consistent with related systems[38]. The halogen bonds link one urea tape to another to provide a two-dimensional sheet structure. For details of the preparations and analysis of gels, see Supplementary Section S1.

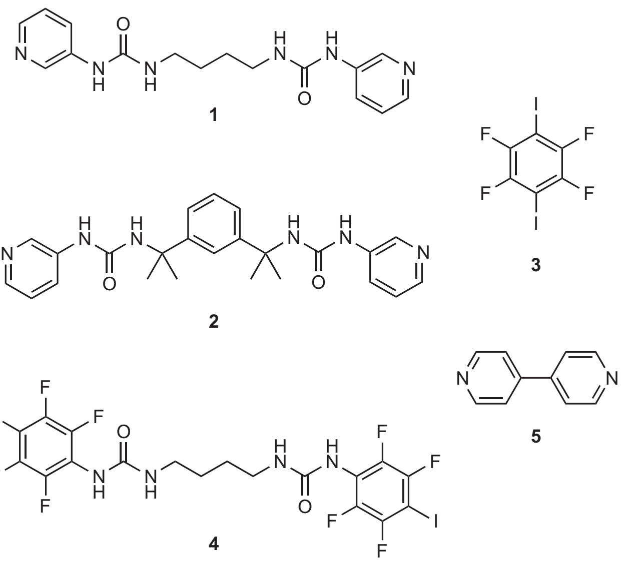

Figure 2 | Chemical formulae of the compounds used to obtain supramolecular LMWGs. The bis(pyridyl urea) gelators **1** and **2** form co-gels in the presence of 1,4-diiodotetrafluorobenzene **3**, and the halogen bond donor bis(urea) derivative **4** forms co-gels when treated with either 4,4′-bipyridine **5**, tetrabutylammonium iodide or pyridyl derivative **1**.

The dried xerogel was analysed by X-ray powder diffraction (XRPD), which showed a close match between the xerogel and the XRPD pattern calculated from the single-crystal structure. This suggests that the gel has the same structure as the crystals, with gelation a result of the more disordered network morphology forming on fast cooling (see Supplementary Information).

Generality of the halogen bond-induced gelation mechanism. Compound **2**, because of its highly sterically hindered nature, has a strong tendency to form solvates and is not strongly predisposed to form a symmetrical urea tape hydrogen-bonding motif. However, rapid cooling of a 5:4 (vol/vol) methanol–water mixture containing equimolar amounts of **2** and **3** also resulted in the formation of a fairly robust gel, albeit only at concentrations above 1% by weight of the gelator components. The gel was characterized by stress sweep rheometry, where a G' of $\sim$1 kPa, one order of magnitude larger than G'', confirmed the solid-like nature of the material. The yield stress proved fairly high at 30 Pa. This gel proved intolerant of variations in the solvent mixture; no other solvent combinations formed gels, consistent with the tendency towards solvate formation, presumably as a result of

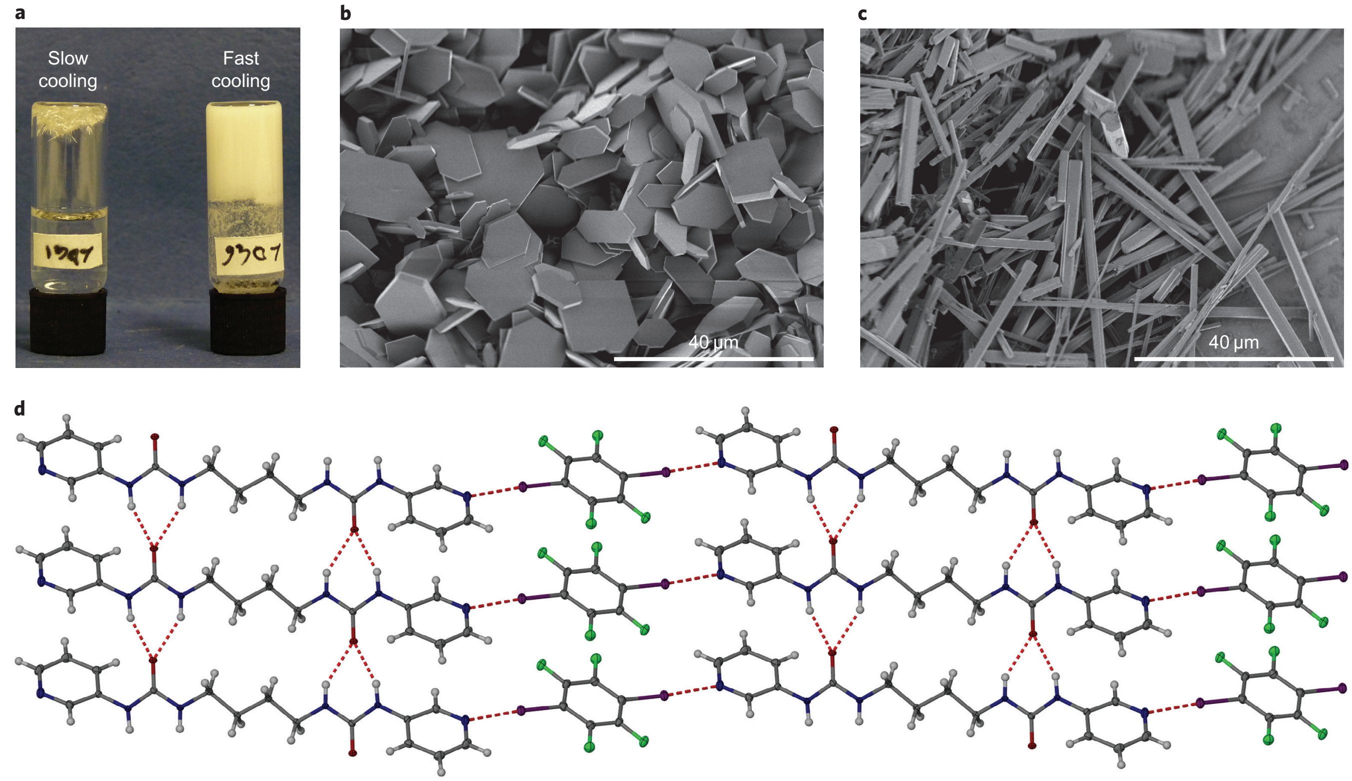

Figure 3 | Gel formation by halogen bonding. a, Rapid cooling of an equimolar mixture of bis(pyridyl urea) **1** and diiodotetrafluorobenzene in methanol/water (4:1 vol/vol) results in a robust hydrogel, while slow cooling gives a fibrous crystalline precipitate. **b**, SEM image of crystalline **1**, which has a plate-like morphology. **c**, SEM image of **1·3**, which has a needle morphology. **d**, X-ray crystal structure of **1·3** showing the anticipated gel-forming urea–tape interaction and the halogen-bonding crosslinks involving the pyridyl groups. The crystalline materials in **b**–**d** were obtained under slow cooling conditions.

steric difficulties in forming a urea tape hydrogen-bonded motif in this system. As with **1**·**3**, slow cooling resulted in the formation of a fibrous, crystalline precipitate, which was characterized by single-crystal X-ray crystallography (Fig. 4). This material also proved to be a 1:1 co-crystal of the bis(pyridyl urea) and diiodotetrafluorobenzene, which also includes water (formula **2**·**3**·$2H_2O$). The structure, however, exhibits two very different types of diiodotetrafluorobenzene environment. One molecule of **3** engages in halogen-bonding bridges between the pyridyl groups of pairs of molecules of **2** in the same way as for **1**·**3**. However, the second crystallographically independent diiodotetrafluorobenzene is not involved in any halogen bonds, but is held in place between pairs of *m*-phenylene groups of the bis(pyridyl urea) backbone by weak H···F contacts and residual I···I interactions. As a result, one of the two crystallographically independent pyridyl nitrogen atoms is not involved in a halogen bond and instead hydrogen-bonds to solvent water. Both independent urea groups form a six-membered hydrogen-bonded ring involving an included water molecule, so there is no urea tape motif present in the system, perhaps explaining the relatively weak nature of the gel formed by **2**·**3** and its intolerance to solvent variation. Repeated attempts to isolate non-hydrated structures were unsuccessful.

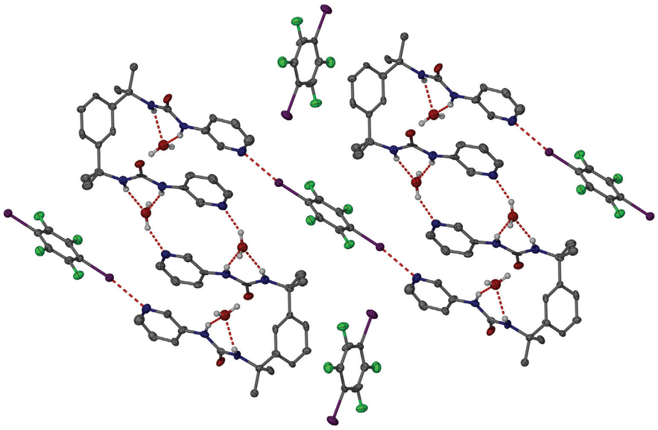

Figure 4 | Halogen bonding and water inclusion in the hydrate gel 2·3·$2H_2O$. The N···I halogen-bonding motif links pairs of dipyridyl molecules through one pyridyl group, while the other pyridyl unit interacts with included water. A second independent molecule of diiodotetrafluorobenzene does not engage in any halogen bonding and stacks between pairs of *m*-phenylene groups of the bis(pyridyl urea) backbone. There is no direct urea α-tape interaction.

Comparison of the XRPD patterns of the dried gel and the pattern simulated from the single-crystal data revealed close similarity, suggesting that the gel adopts the same structure. Water inclusion as an integral structural element within gel fibres has precedent and may well further contribute to the very specific conditions needed to form this gel[53].

The crystal structure of **1** and those of co-crystals **1**·**3** and **2**·**3**·$2H_2O$ were analysed by the Partial Atomic Charges and Hardness (PACHA)[54,55] method based on the observed X-ray coordinates. The structure of pure **1** contains three different types of hydrogen bond involving the urea groups. The first corresponds to the urea α-tapes found in the gels and has an energy (by PACHA) of -8.8 kJ mol^{-1} per bond (four per molecule)—a weak to medium-strength hydrogen bond. Each molecule also forms two instances of a second type of hydrogen bond from a urea N–H to the urea carbonyl group on an adjacent molecule. These have energies of -11.1 kJ mol^{-1}—stronger because the interaction

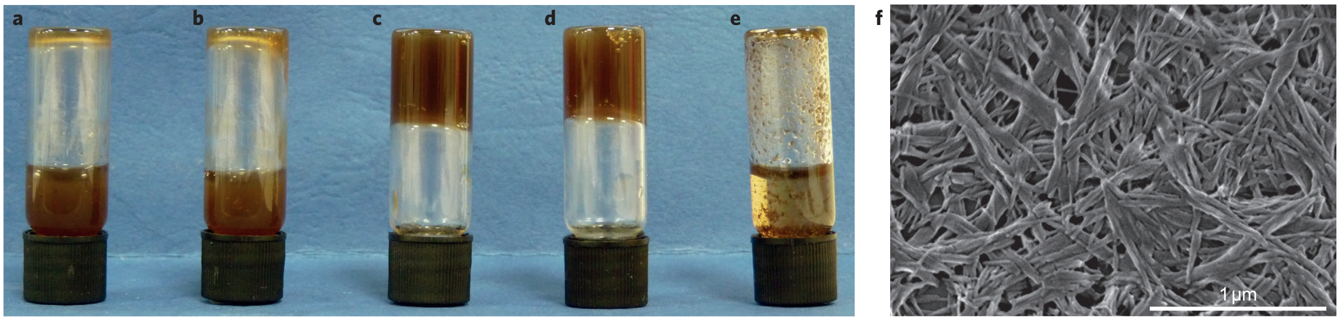

Figure 5 | Halogen bonding gel formation by two-component mixtures based on compound 4. a–e, Mixtures are 1% by weight of **4** in DMSO/water (3:1) either alone (**a**), or in the presence of potential co-gel-forming halogen bond donors pyridine (**b**), 4,4′-bipyridine (**c**), tetra-*n*-butylammonium iodide (**d**) and tetramethyl ethylenediamine (**e**). Gels are formed only in **c** and **d**. However, the iodide gel in **d** breaks down over a period of ~3 h under ambient conditions. **f**, SEM image of the dried gel obtained with bipyridine (**c**).

is more direct and more linear. The third hydrogen bond is donated from the remaining free urea N–H group to the pyridyl group of an adjacent molecule (two interactions per molecule) and is stabilized with an energy of −5.1 kJ mol^{-1}. In total, this structure is stabilized by hydrogen bonds amounting to −67.6 kJ mol^{-1}, among other interactions. In co-crystal **1**·**3**, the hydrogen-bonding scheme changes. The pyridyl group is involved in the halogen bond, which, with an energy of −6.7 kJ mol^{-1}, is slightly more favourable than the urea–pyridyl hydrogen bond in pure **1**. In addition, this halogen bond facilitates the formation of a total of eight hydrogen bonds in the urea α-tape with a total energy of −76.3 kJ mol^{-1}. Thus, the hydrogen bonding and halogen bonding account for a total energy of −89.4 kJ mol^{-1}.

In the structure of **2**·**3**·2H_2O, the halogen bonding contributes an energy of −5.2 kJ mol^{-1} per bond to the overall lattice energy. Interestingly, a very low energy of −2.9 kJ mol^{-1} is exhibited by the I···I interactions between the two molecules of **3**. However, the whole structure is dominated by several strong hydrogen bonds between the urea and pyridyl groups of **2** and the water molecules (Fig. 4), which stabilizes the overall lattice by 22–30 kJ mol^{-1} per bond. The halogen bonding in this case facilitates the host–water interaction in combination with the sterically hindered geometry of the dipyridyl component. Crucially, the halogen bond energies of −6.7 kJ mol^{-1} and −5.2 kJ mol^{-1} in the two co-crystals compare favourably with the strength of the urea–pyridyl hydrogen bond in the structure of free **1** (−5.1 kJ mol^{-1}) obtained by the same method, suggesting that the halogen bond is indeed competitive with the urea–pyridyl interaction.

Attempts were also made to form gels or co-crystals between **1** and weaker halogen bond donors, namely 1,4-dibromotetrafluorobenzene and 1,4-diiodobenzene[56]. However, no gelation or co-crystal formation was observed in any case, confirming the requirement for halogen bonding strong enough to compete with urea···pyridyl hydrogen bonding in polar media.

A halogen bond donor bis(urea). If halogen bonding-induced gelation is a general phenomenon then it should be possible to design a halogen-bonding donor gelator combining bis(urea) and perfluoroaryliodide components in the same molecule. Accordingly, compound **4** was designed and synthesized from 4-iodotetrafluoroaniline and the 1,4-diisocyanatobutane. It is unclear from a theoretical standpoint whether **4** would be expected to be a single-component gelator in its own right. Although the presence of the bis(urea) functionality could in principle bring about gel fibre formation, halogen bonding from the urea carbonyl lone pairs to the electron-deficient iodo groups could interfere with urea α-tape formation, so gelation will depend on factors such as the relative strength of these competing interactions as well as factors such as the π-stacking propensity of the perfluoroaryl groups. In fact, **4** proved to be soluble only in DMSO and DMSO–water mixtures, and was a non-gelator in these media.

However, if halogen bonding to the urea carbonyl is inhibiting gel formation, then gelation should be turned on by the addition of stronger halogen-bonding acceptors. Accordingly samples of gelator **4** at 1% by weight in DMSO/water (3:1) were treated with 1–4 molar equivalents of a range of possible halogen-bonding partners, namely pyridine, 4,4′-bipyridine, iodide (as the tetra-*n*-butylammonium salt) and tetramethyl ethylenediamine (TMEDA). The mixtures were heated with sonication to give complete dissolution, then allowed to cool to room temperature over a period of 1–2 h. No gels were observed in the pyridine- or TMEDA-containing samples. However, both the 4,4′-bipyridine and tetrabutylammonium iodide two-component mixtures gelled effectively (Fig. 5). Gels were characterized by a simple inversion test, SEM and by stress sweep rheometry. The iodide-containing gel proved to be relatively weak and unstable, gradually losing cohesion over a period of ~3 h for all compositions. The bipyridine co-gel proved to be stable indefinitely, however. Interestingly, unlike the two-component gels based on **3**, the **4**·bipyridine system formed without the need for rapid cooling and was far less crystalline in appearance, with much smaller fibres, as shown by the SEM micrograph of the xerogel in Fig. 5f. The much less crystalline nature of the gel was also demonstrated by the XRPD pattern of the xerogel, which displayed very broad peaks consistent with limited long-range order. The **4**·bipyridine co-gel proved to be relatively weak when examined by stress sweep rheometry, but its strength improved with increasing amount of bipyridine. Indeed, the 1:1 mixture was only just self-supporting, but both the G' value and yield stress increased when bipyridine was added, such that a 1:3 mixture was of comparable elastic modulus to the **2**·**3** co-gel (1 kPa) and of slightly higher yield stress (60 Pa). However, the generally poorly reproducible nature of the rheometry data suggests that this difference is not likely to be significant.

The fact that the gel does not form successfully with TMEDA is attributed to the insolubility of the two-component system, which precipitates in solid form under our experimental gelation conditions. On the other hand, lack of gelation with pyridine suggests that a bifunctional donor is required to crosslink adjacent urea α-tape strands into sheets, with their resultant enhanced mechanical robustness.

The successful gelation with bipyridine suggests that gelation might also be expected for combinations of halogen bond donor bis(urea) **4** and halogen bond acceptor bis(pyridyl urea) **1**. Accordingly, gelation was attempted for a mixture of **1** and **4** totalling 1% by weight (that is, 0.5% of each component) in DMSO/water 3:1 vol/vol. The mixture was warmed to provide complete dissolution, and a transparent brown gel formed upon

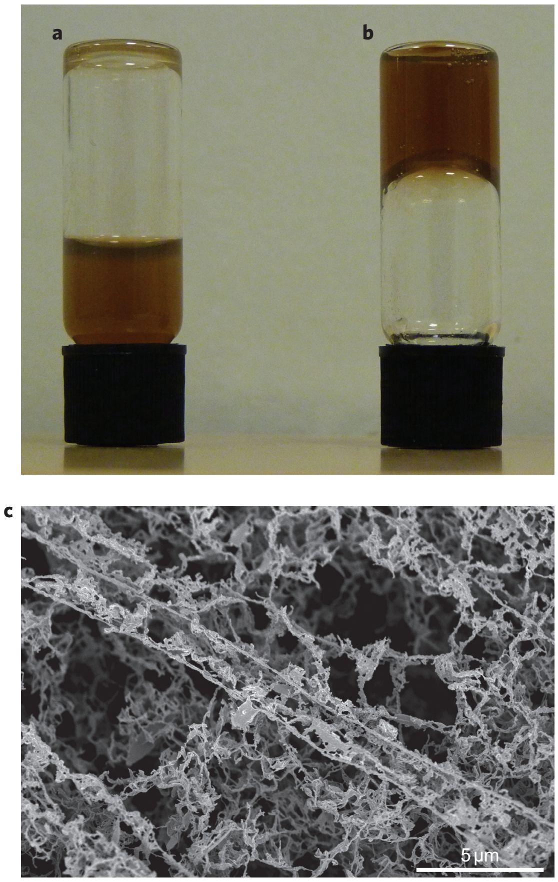

Figure 6 | Co-gel formation between halogen bond acceptor and halogen bond donor bis(urea)s 1 and 4. a,**b**, Compound **4** in DMSO/water (3:1) does not undergo gelation (**a**), but in the presence of **1** it forms co-gel **1**·**4** in DMSO/water (3:1) (**b**). **c**, SEM image showing the morphology of the **1**·**4** co-gel.

cooling. The gel proved relatively weak, but comparable in strength to the bipyridine analogue. Examination of the xerogel by SEM revealed an intricate network of thin, homogeneous fibres showing some co-alignment on the scale of tens of micrometres, linked by a more disordered secondary mesh of material (Fig. 6). The very thin fibres are consistent with the optical transparency of the gel, in contrast to the opaque co-gels formed with **3**.

Conclusions

In summary, we have shown that halogen bonding—even in polar, aqueous media—is sufficiently strong to tip the balance between two competing supramolecular synthons and favour fibre formation and hence gelation, in a manner similar to metal coordination by bis(pyridyl urea) gelators. Halogen bonding is a versatile, general gel-forming interaction that may be incorporated into either the gelator structure or introduced through a gel-forming partner compound. The addition of halogen bonding to the toolbox of controllable supramolecular gel formation substantially expands the possibilities for manipulating these smart soft materials and eliminates complications arising from metal coordination to solvent, anions and other components of the gel.

Methods

Gel formation was carried out by weighing the appropriate amount of gel components (~1 wt%) in a vial and adding a suitable solvent. The suspension was then sonicated and heated until all solid had dissolved. The sample was then flash-cooled in a dry ice/acetone bath (−78 °C) or allowed to cool under ambient conditions (21 °C). Rheology was carried out in a parallel-plate geometry using a 40 mm steel plate with a gap of 500 μm on a 4 ml scale using a TA Instruments AR2000. Samples prepared for SEM were applied directly to silicon wafer chips (Agar Scientific) using a cocktail stick for gels or pipettes for liquids, and the solvent was allowed to evaporate. Samples were stored under vacuum at 1×10^{-5} mbar then sputter-coated with 5 nm platinum in a Cressington 328 coating unit, at 40 mA (density 21.09 and tooling set at 1), with rotation and a 300° angle of tilt. Samples were imaged using a Hitachi S-5200 field-emission scanning electron microscope at 1.5 kV. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre: CCDC 905040 (**1**·**3**); CCDC 905041 (**2**·**3**).

Compound **4**, a solution of 2,3,5,6-tetrafluoro-4-iodoaniline[57] (0.7 g, 2.4 mmol) and triethylamine (0.045 ml) in 2 ml of toluene, was added dropwise, over several hours, to a refluxing solution of 1,4-butane diisocyanate (0.152 ml, 1.2 mmol) in 5 ml toluene. The mixture was then stirred under reflux for 4 days and the resulting precipitate isolated by filtration before being purified by trituration in methanol. Yield 0.34 g, 0.48 mmol, 40%; m.p. 217–219 °C; ^{19}F NMR (DMSO-d_6), $\delta = -124.25$ (d, 2F), -145.33 (d, 2F); ^{1}H NMR (DMSO-d_6), $\delta = 1.43$ (m, $2CH_2$), 3.08 (m, $2CH_2$), 6.55 (s, 2NH), 8.35 (s, 2NH); HR-MS ES$^-$: m/z 720.8865 [M–H]$^-$, calc. for $C_{18}H_{11}N_4O_2F_8I_2$, 720.8844.

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Author contributions

L.M. and J.A.F. undertook the synthesis of gelators, experimental studies and rheology measurements. K.F. carried out crystallographic measurements and PACHA calculations. P.M., G.R. and J.W.S. were responsible for the overall project concept, direction and coordination. All authors contributed to writing the manuscript.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permission information is available online at http://www.nature.com/reprints. Correspondence and requests for materials should be addressed to P.M., G.R. and J.W.S.

Competing financial interests

The authors declare no competing financial interests.