Halogen-Bonding-Triggered Supramolecular Gel Formation

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Abstract

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 formation of multi-component systems exhibiting non-additive properties that emerge from the 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 unknown, 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 an emerging topic of interest in potential applications as diverse as pharmaceutical crystallization, catalysis, drug delivery and controlled release, wound healing, and 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 includes

systems involving photo-, pH, and redox based switching, ultrasound induced gelation, and switchable catalysis[16-23]. In order to systematically develop smart materials with controllable and well understood changes in bulk properties, an understanding of the intermolecular interactions in the system and the way in which they engage in hierarchical self-assembly in order to produce emergent morphologies with complex behavior is required. The link between even primary supramolecular interactions and bulk material properties is often unclear, however. Recent work has highlighted some simple approaches to controllable or smart materials that have met with considerable success. A key theme in particular is setting up a 'tipping point' in a system comprising competing intermolecular interactions which contribute to either gel assembly or gel dissolution. In this way 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 behavior[24,25]. Interestingly, in alternative systems, anion binding has also been used to induce gelation[26,27]. In a similar way metal coordination has also been used 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 summarised in Figure 1.

(a) **Anion binding turn off**   (b) **Metal binding turn on**
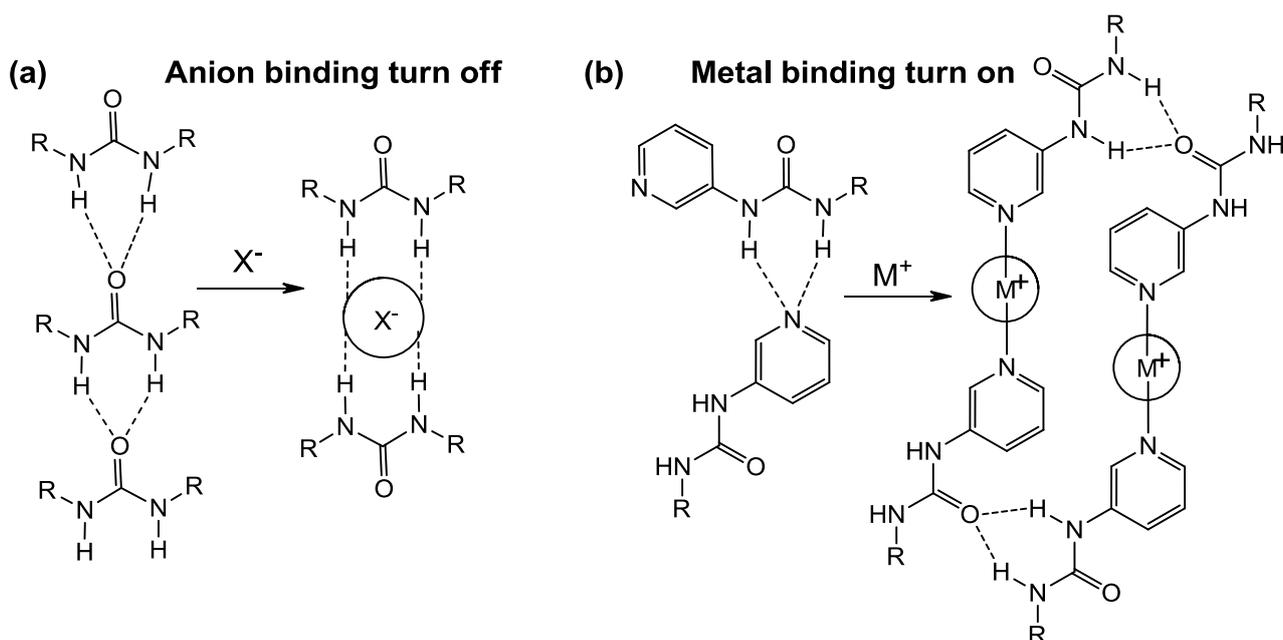
Figure 1 Manipulation of gel formation and destruction through competitive intermolecular interactions. (a) The urea α-tape hydrogen binding motif is responsible for gel fibril formation in bis(urea) LMWG. Competitive anion binding results in a reduction of gel strength because of the strongly competitive 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, cross-linked by metal pyridyl groups. Halogen-bond donors may be substituted for the metal ion.

Logically, the concept of suppressing an inhibitory interaction in order to 'turn-on' gelation is a general one, and allows the possibility of manipulation of key materials properties and hierarchical self-assembly based on a combination of urea tape formation and a dominant, cross-linking 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. In order to demonstrate this approach we turned from metal coordination to the area of halogen-bonding[38].

Halogen-bonding, *e.g.* 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]. More recently, halogen-bonding has been demonstrated to be also useful in solution, for example in anion binding by preorganised 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**, and 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** (Figure 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 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].
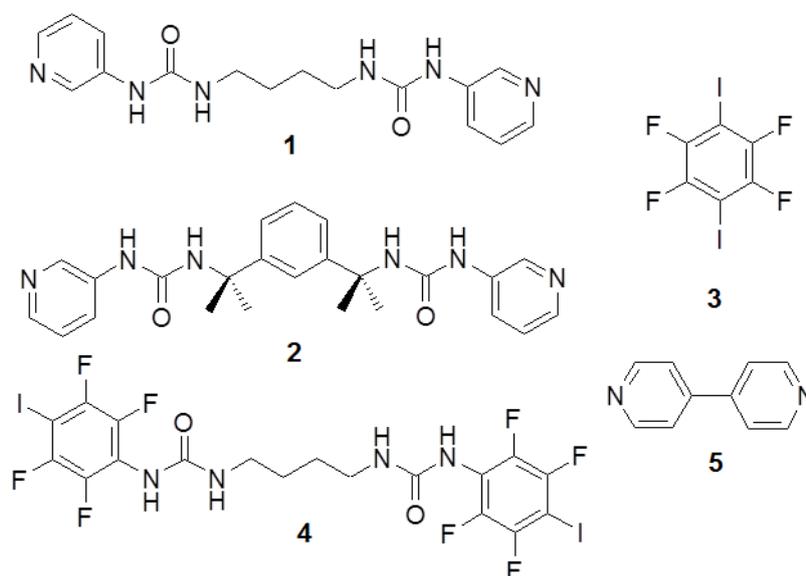
Figure 2 Chemical formulae of the compounds used to obtain supramolecular low molecular weight gelators (LMWG). The bis(pyridyl urea) gelators **1** and **2** form co-gels in the presence of 1,4-diiodotetrafluorobenzene **3**, and the halogen-bond donor bis(urea) derivative **4** forms co-gels when treated with either 4,4'-bipyridine **5**, tetrabutylammonium iodide or the pyridyl derivative **1**.

Fast cooling from approximately 60 °C in a dry ice bath of an equimolar solution of **1** and 1,4-diiodotetrafluorobenzene (**3**) in either methanol or mixtures of methanol, acetonitrile or DMSO with water, *e.g.* methanol-water (4:1 v/v) mixture at 1% by weight, results in the formation of an opaque hydrogel. The opacity suggests 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 approximately 3 kPa and yield stress of 5 Pa. The *G'* value is approximately one order of magnitude above the *G''* value confirming the solid-like nature of the material. The gel strength increases in proportion to the amount of diiodotetrafluorobenzene **3** added, thus in the absence of **3** no gel is formed while addition of 0.4 and 0.5 equivalents of **3** relative to **1** results in a weak, partial gel. While a 4:1 methanol/water mixture results in optimum gelation, gels are formed in other ratios (above 50% methanol) and other solvent mixtures, *e.g.* acetonitrile/water (above 50% MeCN). If the mixture is allowed to cool to room

temperature much more slowly over a period of 1-2 hours then a fibrous crystalline precipitate comprising a 1:1 co-crystal of **1** and **3** is isolated instead of a gel. SEM analysis of the crystals of pure pro-gelator **1** and the corresponding **1·3** co-crystal shows that the crystal habit changes from 2D hexagonal plates to 1D needles on going from **1** to the **1·3** co-crystal, Figure 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, Figure 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 to the diiodotetrafluorobenzene with N···I 2.819(3) Å, consistent with related systems[38]. The halogen-bonds link one urea tape to another to give a 2D sheet structure. For details of the preparations and analysis of gels see the supplementary information.
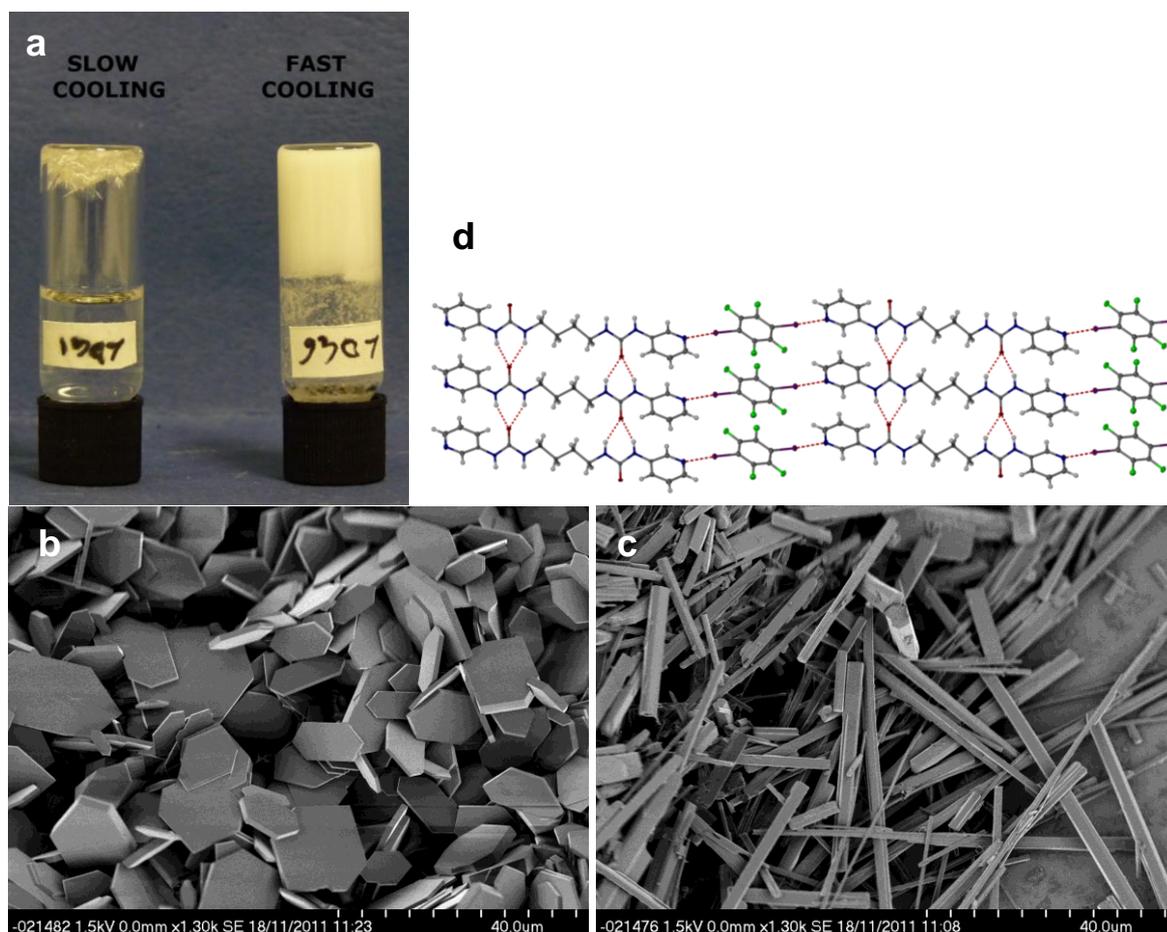
Figure 3 Gel formation by halogen-bonding. (a) Rapid cooling of an equimolar mixture of bis(pyridyl urea) **1** and diiodotetrafluorobenzene in methanol/water (4:1 v/v) results in a robust hydrogel while slow cooling gives a fibrous crystalline precipitate. (b) SEM micrograph of crystalline **1** showing plate-like morphology, (c) SEM micrograph of **1·3**

showing needle morphology, (d) X-ray crystal structure of **1·3** showing the anticipated gel-forming urea-tape interaction and the halogen-bonding cross-links involving the pyridyl groups. The crystalline materials shown in b–d obtained under slow-cooling conditions.

The dried xerogel was analysed by XRPD which showed a close match between the xerogel and the XRPD pattern calculated from the single crystal structure suggesting 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 (v/v) 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 the *G'* of approximately 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 solvent mixture and no other solvent combinations formed gels, consistent with the tendency towards solvate formation, presumably as a result of 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 that was characterized by single crystal X-ray crystallography (Figure 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 to an included water molecule and hence 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.

Comparison of the XRPD patterns of the dried gel to 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 is precedented and may well further contribute to the very specific conditions needed to form this gel.[53]

The crystal structure of **1** and of the co-crystals **1·3** and **2·3·2H$_2$O** 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 which has an energy of -11.1 kJ mol^{-1}; stronger, because the interaction 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 by -67.6 kJ mol^{-1}, amongst other interactions. In the co-crystal **1·3**, the hydrogen-bonding scheme changes. The pyridyl group is involved in the halogen-bond, which is with an energy of -6.7 kJ mol^{-1} slightly more favourable than the urea-pyridyl hydrogen-bond in pure **1**. In addition, this halogen-bonds 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 accounts for a total energy of -89.4 kJ mol^{-1}.

In the structure of **2·3·2H$_2$O**, 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 (Figure 4), which stabilises 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 of halogen-bonding strong enough to compete with urea⋯pyridyl hydrogen-bonding in polar media.
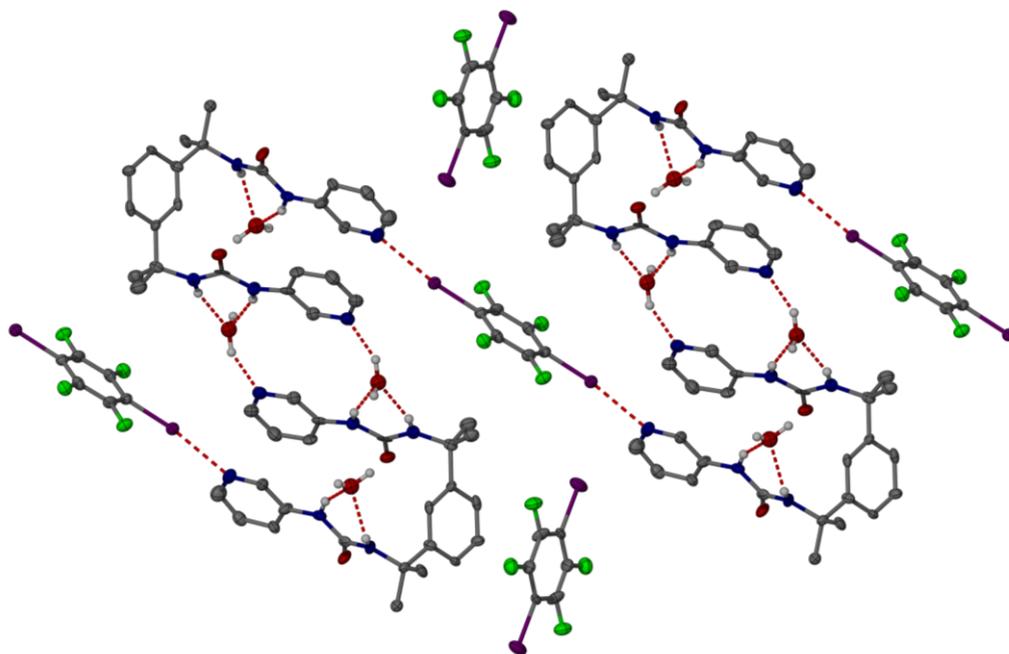
Figure 4 Halogen-bonding and water inclusion in the hydrate gel 2·3·2H$_2$O. The N⋯I halogen-bonding motif links pairs of dipyridyl molecules together by one pyridyl group while the other pyridyl unit interacts with included water. A second independent molecule of diiodotetrafluorobenzene does not engage 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.
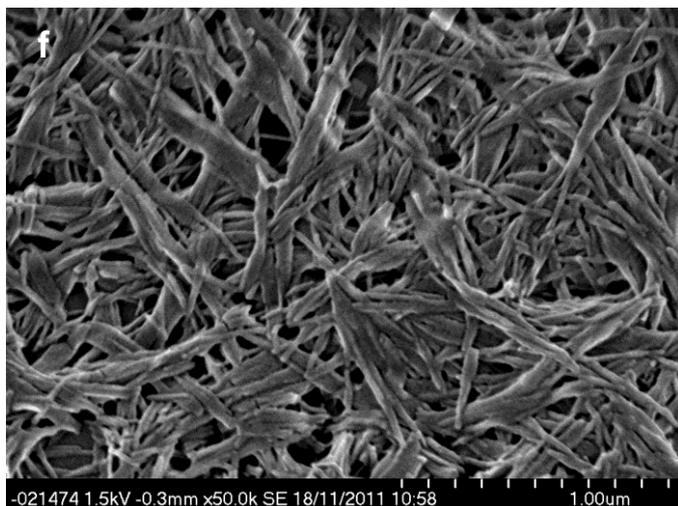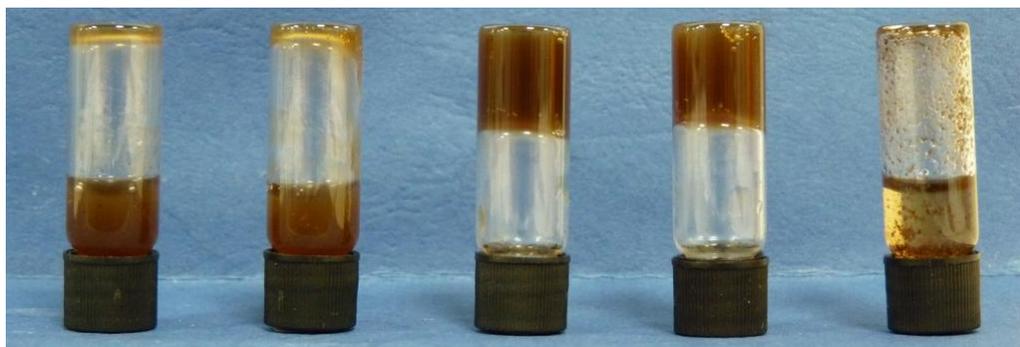
A Halogen bond donor Bis(urea)

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. While 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 and hence 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 only soluble 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 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 then heated with sonication to give complete dissolution and allowed to cool to room temperature over a period of 1–2 h. No gels were observed in the case of the pyridine or TMEDA containing samples. However, both the 4,4′-bipyridine and tetrabutylammonium iodide two component mixtures gelled effectively, Figure 5. Gels were characterized by means of 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 *ca.* 3 hours at all compositions. The bipyridine co-gel proved to be indefinitely stable, however. Interestingly, unlike the two-component gels based on **3**, the **4**·bipyridine system forms without the need for rapid cooling and is far less crystalline in appearance with much smaller fibres as evidenced by the SEM micrograph of the xerogel, Figure 5f. The much less crystalline nature of the gel was also exemplified 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, however its strength increased with increasing amount of bipyridine: while a 1:1 mixture is only just self-supporting, both the *G'* and yield stress increase with added bipyridine such that a 1:3 mixture is of comparable elastic modulus to the **2**·**3** co-gel (1 kPa) and of slightly higher yield stress (60 Pa), although the generally poorly reproducible nature of rheometry data mean that this difference is not likely to be significant.

      a   **b**   **c**   **d**   **e**

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

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 in the experimental gelation conditions. Lack of gelation with pyridine on the other hand suggests that a bifunctional donor is required in order to cross-link adjacent urea α-tape strands into sheets with consequent 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 (i.e. 0.5% of each component) in DMSO/water 3:1 v/v. The mixture was warmed to give complete dissolution and a transparent brown gel formed upon 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 tens of micron scale, linked by a more disordered secondary mesh of material (Figure 6). The very thin fibres are consistent with the optical transparency of the gel in contrast to the opaque co-gels formed with **3**.
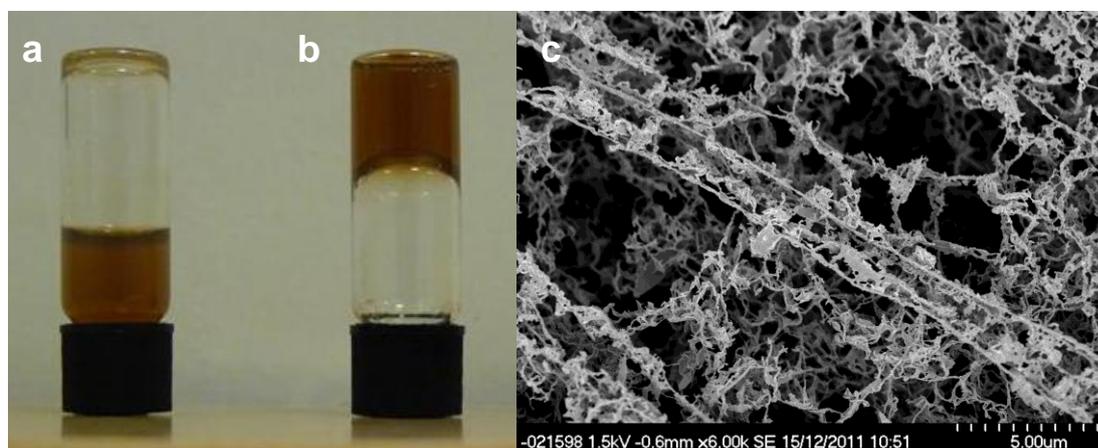
Figure 6 Co-gel formation between halogen-bond acceptor and halogen-bond donor bis(urea)s 1 and 4. (a) Compound **4** in DMSO/water 3:1 does not undergo gelation whereas, (b) in the presence of **1** it forms a co-gel **1·4** in DMSO/water 3:1. (c) SEM micrograph showing the morphology of the **1·4** co-gel.

Conclusion

In conclusion we have shown that halogen-bonding, even in polar, aqueous media, is sufficiently strong to tip the balance between two competing supramolecular synthons in order to favour fibre formation and hence gelation in a similar way 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 the gel components (approx. 1 wt%) in a vial and adding a suitable solvent. The suspension is then sonicated and heated until all solid has dissolved. The sample is then either 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 allowed to evaporate. Samples were stored under vacuum at 1×10^{-5} mbar then sputter coated with 5nm platinum in a Cressington 328 coating unit, at 40mA (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 1.5kV.

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 of 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), δ= −124.25 (d, 2F), −145.33 (d, 2F). ^{1}H NMR (DMSO-d_6), δ= 1.43 (m, 2 CH_2), 3.08 (m, 2 CH_2), 6.55 (s, 2 NH), 8.35 (s, 2 NH). HR-MS ES⁻: m/z 720.8865 [M-H]⁻, calc. for $C_{18}H_{11}N_4O_2F_8I_2$, 720.8844.

Acknowledgements

Author contribution

Lorenzo Meazza and Jonathan A. Foster undertook the synthesis of gelators, experimental studies and rheology measurements. Katharina Fucke undertook crystallographic measurements and PACHA calculations. Pierangelo Metrangolo, Giuseppe Resnati, and Jonathan W. Steed were responsible for overall project concept, direction and coordination. All authors contributed to writing the manuscript.

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Graphical Abstract
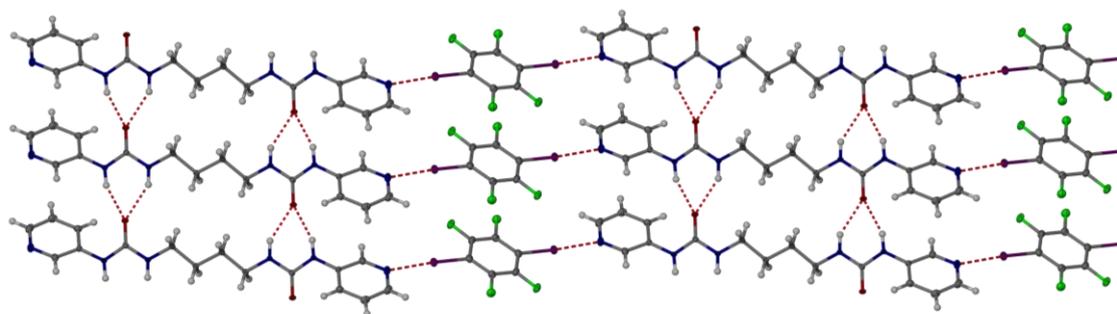
Summary for Table of Contents

Supramolecular gels whose properties can be tuned through non-covalent interactions - typically metal coordination or hydrogen bonding - are attracting attention in various fields. Researchers have now shown that halogen bonding is also strong enough to be relied on; it interferes with competitive, gel-inhibitory hydrogen bonding to induce co-gelation between two urea-based components.