

# Gelation is crucially dependent on functional group orientation and may be tuned by anion binding†

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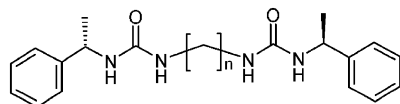
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**The gelation ability of a series of chiral bis(urea) gels alternates between even and odd chain length and for the even numbered spacers the rheological characteristics can be tuned by the addition of anions according to the anion binding constant.**

There is considerable current interest in low molecular weight organogelators (LMWG) both in terms of the fundamental relationship between molecular structure and gelation, and applied aspects.<sup>1–3</sup> The tuning of gel properties by anion binding is beginning to receive particular attention.<sup>4–6</sup> Potential applications include the use of gels in tissue engineering, as vehicles for controlled drug delivery, in the templated synthesis of nanoparticles and inorganic nanostructures, in template polymerisation and in pollutant capture and removal.<sup>7</sup> We are particularly concerned with the understanding and use of supramolecular interactions such as anion binding to tune gel properties such as rheological characteristics and supramolecular structure.<sup>8–12</sup> Bis(urea)s are a well known class of LMWG and their gelation ability depends on hydrogen bonding interactions of the urea tape type.<sup>13–18</sup> We reasoned that in a homologous series of bis(urea) gelators (**1**, Scheme 1) based on oligomethylene spacers the urea orientation should be dependent on the spacer length ( $n$  in compound **1**), assuming that the oligomethylene chain adopts the sterically favourable all-*trans* conformation. For  $n = \text{odd}$  the urea NH groups should point in the same direction, while for  $n = \text{even}$  they should point in opposite directions. By then appending an awkwardly shaped, chiral substituent (here (*S*)-1-phenylethyl) the alternation in urea group orientation should translate into an alternation in the physical properties of the materials since the gel structure depends on urea hydrogen bonding interactions. Moreover it should be possible to interfere with and



**Scheme 1** Gelator compound **1** with  $n = 2–8$ .

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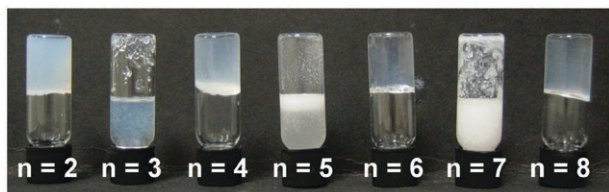
hence tune these hydrogen bonds by competitive binding of hydrogen bond acceptor anions in a dynamic way.<sup>4–6</sup> Alternation in the properties of crystalline *n*-alkyl derivatives such as melting point is well known<sup>19</sup> and is also known to affect some gel properties.<sup>20–25</sup> We now present preliminary results on the structural gelation and anion-binding properties of a homologous series of bis(urea) gelators, **1**.

The seven compounds of type **1** ( $n = 2–8$ ) are readily synthesised by reaction of the appropriate  $\alpha,\omega$ -diaminoalkane with (*S*)-(–)- $\alpha$ -methylbenzyl isocyanate (see supplementary information†). The gelation ability of the new compounds was assessed by dissolving the compounds 1% by weight in a variety of solvents, namely MeCN, CHCl<sub>3</sub>, MeOH, toluene, and solvent mixtures such as DMSO–H<sub>2</sub>O and MeOH–H<sub>2</sub>O (Table 1). The compounds with  $n = 6$  and 8 gelled CHCl<sub>3</sub> to form completely transparent gels at 1% weight and the compounds with  $n = 2$  and 4 readily formed semi-transparent organogels in MeCN and CHCl<sub>3</sub> after slow cooling from the hot solutions. Gels for  $n = 6$  could also be obtained in MeCN, but were opaque, probably indicating a more structured assembly. For  $n = 8$  gels in MeCN could only be formed upon sonication of the compound in solution.<sup>8,26,27</sup> In general sonication was found to significantly increase the rate of gelation and to improve the homogeneity of the organogels. DMSO–H<sub>2</sub>O and MeOH–H<sub>2</sub>O mixtures also gelled all compounds with  $n = \text{even}$  and the gelling conditions for all compounds in all solvents and solvent mixtures investigated are listed in Table 1. No gels were formed by the  $n = 5$  and 7 compounds. The  $n = 3$  compound generally also did not form gels, although in a few, poorly reproducible experiments a weak

**Table 1** Phases achieved for compounds  $n = 2–8$

Compound	Solvents	Phase <sup>a</sup>
$n = 2$	CHCl <sub>3</sub> –MeCN–DMSO : H <sub>2</sub> O <sup>b</sup>	G
$n = 3$	All solvents <sup>c</sup>	SP
$n = 4$	CHCl <sub>3</sub> –MeCN–DMSO : H <sub>2</sub> O <sup>d</sup> MeOH : H <sub>2</sub> O <sup>e</sup>	G
$n = 5$	All solvents	SP
$n = 6$	CHCl <sub>3</sub> –MeCN–DMSO : H <sub>2</sub> O <sup>f</sup> MeOH : H <sub>2</sub> O <sup>e</sup>	G
$n = 7$	All solvents	SP
$n = 8$	CHCl <sub>3</sub> –MeCN <sup>g</sup> –DMSO : H <sub>2</sub> O <sup>d</sup> MeOH : H <sub>2</sub> O <sup>e</sup>	G

<sup>a</sup> G = gel; SP = Sol or Sol and Precipitate. <sup>b</sup> A ratio range of 7 : 1 to 1 : 9 results in gel formation (Fig. S2–S4†). <sup>c</sup> Occasionally forms gels in CHCl<sub>3</sub>. <sup>d</sup> Range of 3 : 2–1 : 1. <sup>e</sup> Gel + crystals mixed phases for all ratios. <sup>f</sup> Range of 4 : 1–2 : 3. <sup>g</sup> Requires sonication for gelation to occur.

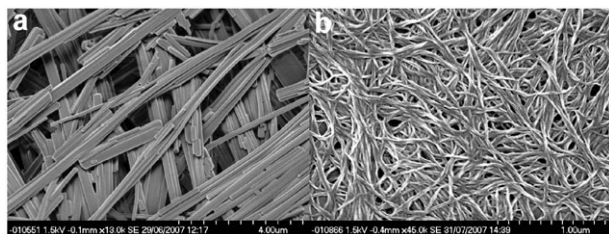


**Fig. 1** Alternation of gel (even  $n$ ) and sol (odd  $n$ ) formation in  $\text{CHCl}_3$  by compound **1**.

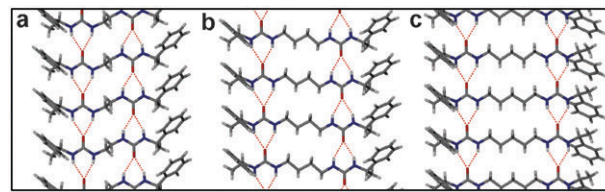
gel in  $\text{CHCl}_3$  was observed. The sols/precipitates and gels formed by each compound from 1% by weight in  $\text{CHCl}_3$  are shown in Fig. 1.

The gels were characterised by temperature sweep and stress sweep rheometry. In each case, the solid-like nature<sup>28</sup> at 20 °C was reflected in the storage modulus,  $G'$ , being typically an order of magnitude greater than the loss modulus,  $G''$ . The gel to sol transition temperatures,  $T_{\text{gs}}$ , of the even numbered compounds, as determined by the dropping ball method, decreased with an increase in oligomethylene linker length when measured at 1% by weight in  $\text{CHCl}_3$ . For the even numbered spacers, the xerogels were imaged by SEM after drying and coating with Pt, which revealed the characteristic threadlike morphology for gels from compounds  $n = 4, 6$  and 8. In the case of  $n = 2$  a rod-shape morphology was observed. The molecular chirality of the LMWG is manifested in the  $n = 4$  gel where a left-handed helical twist in the xerogel fibres is seen (Fig. 2).

The  $n = 2, 4$  and 5 members of the series were characterised by single crystal X-ray crystallography. Crystals of the  $n = 2$  and 4 compounds were obtained from aqueous DMSO, while the  $n = 5$  sample was obtained from aqueous MeOH. In the case of the  $n = 2$  compound PXRD measurements showed that the single crystal structure is retained in the xerogel, while for the  $n = 4$  compound there is some structural change on going from crystal to gel (Fig. S5–S7†). In all cases the most obvious feature of the crystal packing is the  $R_2^2(6)$  urea tape motif<sup>18</sup> formed by both urea substituents on each molecule. The structures of the  $n = 4$  and 5 materials display the expected all-*trans* conformation of the alkylenic chain and hence the two independent urea tapes are antiparallel for  $n = 4$ , whereas they are all co-aligned in the  $n = 5$  case giving an overall polar as well as chiral structure, Fig. 3. The orientation of the bulky phenylethyl groups is strongly correlated to the urea orientation because of the need to minimise steric bulk round the urea carbonyl group which acts as an acceptor for two NH donors.<sup>16,29</sup>



**Fig. 2** (a) SEM image of the xerogel of  $n = 2$  gel from acetonitrile (solvent) showing the rod-shaped nature of the gel fibres. (b) SEM image of the xerogel of  $n = 4$  gel from acetonitrile (solvent) showing the thread-like nature of the gel fibres and the helical twist induced by the chiral gelator.

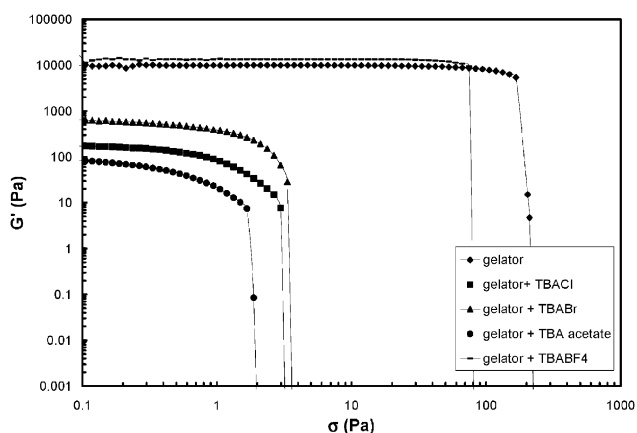


**Fig. 3** Crystal packing diagrams showing the urea tape motif of compounds  $n = 2$  (a), 4 (b) and 5 (c).

The packing of the *gauche* substituents is more awkward, resulting in a lower density for the  $n = 4$  case ( $1.22 \text{ g cm}^{-3}$  vs.  $1.25 \text{ g cm}^{-3}$ ) and crystallisation in a space group with rotational rather than screw symmetry ( $C2$  instead of  $P2_1$ ), a less efficient packing mode.<sup>30</sup> The structure of the  $n = 2$  compound, which is also a good gelator, has antiparallel chains and a *gauche* arrangement of phenylethyl groups. For this very short chain, however, the two terminal C–C–N torsional angles are *ca.*  $80^\circ$  rather than  $180^\circ$  giving a ‘kink’ in the chain and allowing a higher density and more efficient packing than the  $n = 4$  case, in  $P2_1$ . Hence it is not poor crystallinity or bad packing that gives gelation but it is the antiparallel urea hydrogen bonded chains in bis(ureas) that result in gelation behaviour. A parallel, polar arrangement does not. The antiparallel mode is postulated in gels of a number of cyclic bis(urea)s.<sup>18</sup> In tris(urea)s (which mimic bis(urea)s in their crystal packing) the known gelator structure is antiparallel,<sup>14</sup> whereas our work on a tris(urea) analogue of **1** resulted in a structure with a parallel arrangement being isolated in the presence of  $\text{Cl}^-$ .<sup>11</sup> The role of the anion may well be to switch the ureas from a gelling antiparallel arrangement to a crystalline colinear arrangement.

If this postulated anion-induced rearrangement is the case then adding anions to gels based on **1** with even numbers of methylene linkers ( $n = 2, 4, 6, 8$ ) should significantly reduce their gelling ability according to the degree of interaction with the anion, resulting in tunable rheology. To test this theory we therefore carried out stress sweep rheometry measurements and  $T_{\text{gs}}$  determinations on compound **1** with  $n = 6$  in the presence of small amounts of a variety of simple anions as their  $\text{NBU}_4^+$  salts, namely  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{MeCO}_2^-$  and the non-coordinating  $\text{BF}_4^-$  as a control with  $\text{CHCl}_3$  as the solvent. While  $\text{BF}_4^-$  had no effect on the observed storage and loss moduli ( $G'$  and  $G''$ ), chloride, bromide and acetate dramatically compromise the gel strength and greatly decrease the values of the moduli. Fig. 4 shows that addition of small amounts of these anions (0.1 equiv. with respect to the gelator concentration) reduces the storage modulus by up to two orders of magnitude depending on the identity of the anion. For a fixed concentration of gelator, such a decrease suggests a lower interconnectivity of the individual threads,<sup>31</sup> supporting our hypothesis that the anion disrupts the gelation process. In addition to the decrease in  $G'$ , the anions cause a decrease in the yield stress of the gel, also indicating a weakening of the gel.

A similar trend was observed for the gelling behaviour of ligand **1** with  $n = 2$  upon addition of  $\text{Cl}^-$ ,  $\text{NO}_3^-$ ,  $\text{MeCO}_2^-$  and  $\text{BF}_4^-$  with MeCN as the solvent (Fig. S8–S9†). Again acetate showed the strongest effect to the point that even at 0.1 equiv. added gel formation was completely inhibited. Addition of chloride and nitrate showed strong effects on the rheology of



**Fig. 4** Influence of different anions (0.1 equiv. of anion added as their  $\text{NBU}_4^+$  salts) on the storage modulus ( $G'$ ) at a frequency of 1 Hz and a temperature of 20 °C, as a function of oscillation stress ( $\sigma$ ) of the 1% by weight gel of compound **1** with  $n = 6$  in  $\text{CHCl}_3$ . The lines are a guide for the eyes only.

this gelator, but gelation was not completely inhibited. Fig. S8† and S9† also show preliminary results of increasing anion concentrations on the gelator resulting in weaker gels and lowering of the sol-to-gel temperature ( $T_{\text{sg}}$ ) for higher concentrations. Quantification of these effects for all gelators is ongoing.

As the gelator and anion are interacting in the solution state before the nucleation of the gel formation, anion binding by the gelators was probed using  $^1\text{H}$  NMR spectroscopic titration techniques (Fig. S10–S12†). By carrying out the titrations at 50 °C in MeCN gelation was avoided, allowing the assessment of individual gelator–anion binding constants. All titrations revealed the formation of 1 : 1 gelator–anion complexes (confirmed by Job plot analysis) and that the anion binding competes with the dimerisation of the molecule, an obvious precursor step to gel formation. Acetate proved to be the strongest anion bound with a binding constant  $K_{11} = 18\,000 \text{ mol}^{-1} \text{ dm}^3$  in competition with a dimerisation constant of  $6000 \text{ mol}^{-1} \text{ dm}^3$ . Chloride and nitrate are bound with  $K_{11} = 3300 \text{ mol}^{-1} \text{ dm}^3$  and  $850 \text{ mol}^{-1} \text{ dm}^3$ , respectively, again in competition with the dimerisation process. For the  $\text{BF}_4^-$  anion the binding was too weak to determine binding strengths. The trend of the anion binding affinity in this pre-gel solution mirrors the inhibitory effect anions have on the gel formation and the gel rheology. Thus acetate, the strongest bound anion and the only one that competes effectively with solution dimerisation, has by far the most significant influence on  $G'$ ,  $G''$ ,  $T_{\text{sg}}$  and yield stress, to the effect that gel formation is severely impaired for the  $n = 6$  compound and completely inhibited for  $n = 2$ . Similarly, chloride has a significantly greater effect than  $\text{NO}_3^-$  on the gel physical properties. A full study of the effects of anion type and concentrations on all of the gelators  $n = 2, 4, 6$  and  $8$  is currently under way and will be the subject of a subsequent paper.

In conclusion, we have shown that gelation in this series is a consequence of strong, anisotropic, multiple hydrogen bonding interactions coupled with packing difficulties perpendicular to the hydrogen bonded direction. There is a close relationship between molecular structure and hence hydrogen bonding group orientation and crystallisation or gelation tendency. Antiparallel arrange-

ments of urea groups promote gelation while reducing crystallinity in some cases. While alternation effects are known in gels, the alternation between gelation and complete lack of gelator behaviour has not been observed previously.<sup>20–25</sup> The gel self-association and hence rheology can be tuned by the introduction of sub-stoichiometric amounts of anions which compete for the urea hydrogen bonding groups and influence their directionality. The degree to which anions inhibit gelation is to some extent correlated with the anion–gelator binding affinity. These results augur well for the development of designer gels with rheology dependent on control of structural and supramolecular characteristics.

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