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## Metal 'Turn-off', Anion 'Turn-On' Gelation Cascade in Pyridinylmethyl Ureas

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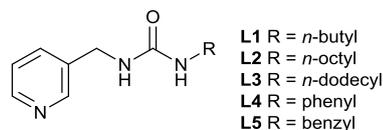
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**Pyridinylmethyl ureas form strong gels in aromatic solvents. The gels are weakened or destroyed by addition of transition metals but gelation is recovered by adding bromide anion giving rise to a gel-sol-gel chemically triggered cascade.**

Supramolecular gels based on small, tuneable molecules are highly topical.<sup>1-6</sup> The ease with which these low molecular weight gelators (LMWG) can be synthesised and the fact the properties of their gels can be modified by light, pH, redox or chemical stimuli suggests potential applications in areas such as drug delivery, biomedicine and pharmaceutical solid form control.<sup>3, 7-10</sup> *N*-pyridyl ureas have attracted considerable attention because their competitive hydrogen bonding properties allow particularly well-controlled gelation behaviour.<sup>11-14</sup> Typically aryl ureas with electron withdrawing substituents such as a pyridyl moiety do not form the common urea  $\alpha$ -tape motif frequently implicated in gelation behaviour because the urea carbonyl is sterically blocked by competing intramolecular CH $\cdots$ O interactions and NH $\cdots$ N<sub>pyridyl</sub> hydrogen bonding.<sup>15-18</sup> Gelation can be 'turned on', however, by the introduction of a metal ion which bonds to the pyridyl group and promotes the alternative urea  $\alpha$ -tape interaction, leading to unidirectional fibril growth and hence gel formation.<sup>13</sup> In contrast, anions, particularly strong hydrogen bond acceptors such as chloride and acetate, tend to 'turn off' gelation by competitive hydrogen bonding to the urea NH groups.<sup>19, 20</sup> Indeed reports of anion-promoted gelation are very rare.<sup>21, 22</sup> We anticipate that changing from pyridyl ureas to simple pyridinylmethyl ureas (Scheme 1) should radically change the aggregation behaviour of the urea since the introduction of a methylene spacer between the urea and heterocycle means

that the oxygen acceptor is no longer sterically hindered, hence markedly favouring urea $\cdots$ urea hydrogen bonding *via* the  $R_2^1(6)$  urea  $\alpha$ -tape motif.<sup>23-26</sup> In the presence of metal ions able to bind the pyridyl group and anions capable of both binding to the metal ion and hydrogen bonding to the urea NH groups, complex, stimuli-responsive behaviour is anticipated. We now report preliminary results into systems capable of gel-sol-gel behaviour by a cascade of cation and anion interactions.



Scheme 1. pyridinylmethyl ureas used in the present work

## Results and Discussion

A series of pyridinylmethyl ureas **L1** – **L5** were readily prepared by reaction of 3-picolyamine with an equimolar amount of isocyanate in toluene. After sonication at room temperature products generally precipitated in good yields (see supplementary information). Ligand **L5** was characterised by single crystal X-ray crystallography. The structure shows the expected urea  $\alpha$ -tape hydrogen bonded motif with N $\cdots$ O distances 2.84 and 2.95 Å (Figure 1). The pyridyl nitrogen atom engages in a CH $\cdots$ N interaction with a pyridyl CH group from an adjacent molecule (C $\cdots$ N 3.52 Å). The packing mode contrasts sharply with *N*-3-pyridyl phenylurea in which there are no NH $\cdots$ O interactions because of competing intramolecular CH $\cdots$ O hydrogen bonding.<sup>16</sup> The presence of this urea  $\alpha$ -tape motif in **L5** suggests that even simple monourea ligands such as **L1** – **L5** might exhibit gelation behaviour and their gelation ability at 2.5 % w/v was tested in various solvents ranging in polarity from water to toluene (see SI Table S1). Gelation was observed only for aromatic solvents toluene, nitrobenzene and 1,3-dichlorobenzene for the aliphatic derivatives **L2** and **L3** with a minimum gelator concentration of 1.5 % w/v.

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Electronic Supplementary Information (ESI) available: synthesis and characterisation of ligands, rheological, SEM and gelation details, and details of single crystal structure determinations in CIF format; CCDC 1517412-1517413. See DOI: 10.1039/c000000x/. The underlying research data for this paper is available in accordance with EPSRC open data policy from DOI: 10.15128/r12f75r800k.

Compound **L1** formed partial gels in toluene and nitrobenzene. The dodecyl derivative **L3** also partially gelled acetone. The aromatic derivatives **L4** and **L5** formed crystalline precipitates in aromatic solvents, possibly because of edge-to-face aromatic interactions<sup>7, 27, 28</sup> seen in the structure of **L5** giving rise to faster growth perpendicular to the urea  $\alpha$ -tape axis. The ligand gels were characterised by oscillatory stress-sweep rheometry in a rough, parallel plate geometry at 2% w/v. Gels of **L3** proved to be robust with yield stresses of 170 Pa, 99 Pa and 38 Pa in 1,3-dichlorobenzene, nitrobenzene and toluene, respectively. Plateau storage moduli ( $G'$ ) values at low stress are 40 kPa, 72 kPa and 20 kPa, and are approximately an order of magnitude higher than the loss moduli,  $G''$  as expected for solid-like gel phase materials.<sup>5, 29, 30</sup> Gels of **L2** proved somewhat less robust with lower  $G'$  and yield stress values.

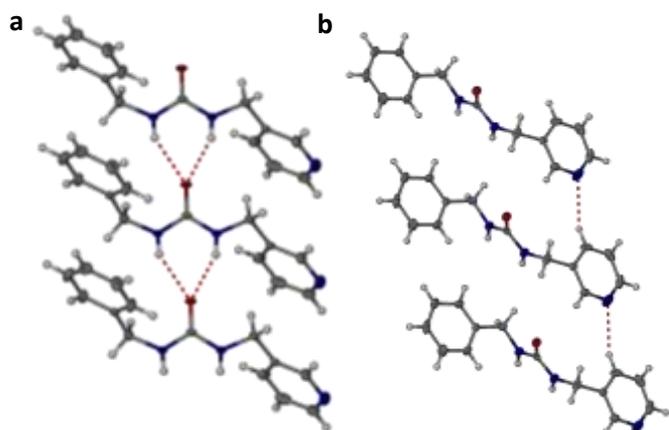


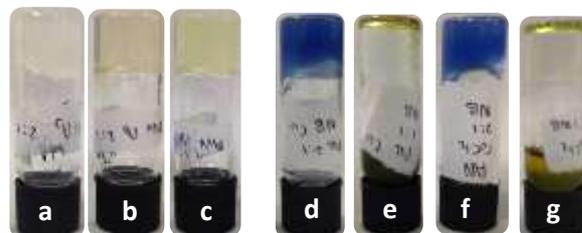
Figure 1. X-ray crystal structure of **L5** showing (a) the urea  $\alpha$ -tape arrangement, and (b) the CH...N interaction.

Gels were also characterised by SEM as the dried xerogels. For both **L2** and **L3** the SEM images revealed large, flat and relatively crystalline ribbons (see supplementary information).

In *N*-pyridyl ureas metal coordination increases gel strength markedly.<sup>13, 31</sup> Gelation experiments in the aromatic solvents gelled by the free ligands were repeated in the presence of a range of metal salts (added in 0.04 mL methanol solution to 1.96 mL ligand solution). Ligands **L2** and **L3** formed metallo gels with 0.5 molar equivalents of copper(II) chloride, cobalt(II) chloride and silver(I) tetrafluoroborate. Ligand **L3** additionally formed metallo gels with zinc(II) chloride. All metal complex combinations gelled nitrobenzene and silver(I) complexes gelled all three aromatic solvents. The copper(II) complexes also gelled toluene. However, with the less coordinating nitrate anion as both zinc and cobalt(II) salts no gel formation was observed. Gels also formed with one molar equivalents of  $\text{AgBF}_4$ , however increasing the amount of  $\text{CuCl}_2$  to one equivalent in nitrobenzene resulted in complete disruption of the gels, Figure 2, possibly because of interference with the urea  $\alpha$ -tape hydrogen bonding by the strong hydrogen bond acceptor chloride ion.<sup>32</sup> Both **L2** and **L3** formed transparent green gels in toluene with one equivalent of  $\text{CuCl}_2$  (Figure 3).

However, these gels proved unstable and within 24 hours they transformed into a blue solution in the case of **L2** or a green precipitate in the case of **L3**. This precipitate was collected by filtration and dried. Elemental analysis indicated a formula of  $[\text{Cu}(\text{L3})_2\text{Cl}_2(\text{H}_2\text{O})_2]$  (supplementary information). The colour changes suggest chloride coordination directly to the copper(II) centre at high concentration, but chloride dissociation at 2:1 ligand to copper ratio.<sup>33</sup>

Figure 2. 2.5 % weight by volume metallo gels formed from **L3** and  $\text{AgBF}_4$  in: a)



toluene, b) 1,3-dichlorobenzene and c) nitrobenzene. 2.5 % weight by volume metallo gels or precipitates formed by ligands **L2** and **L3** with  $\text{CuCl}_2$  in nitrobenzene. d) **L2**: $\text{CuCl}_2$  2:1, e) **L2**: $\text{CuCl}_2$  1:1, f) **L3**: $\text{CuCl}_2$  2:1, g) **L3**: $\text{CuCl}_2$  1:1.

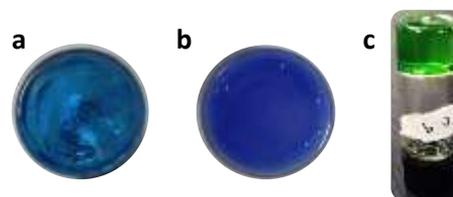


Figure 3. a-b) top view of 2.5 % weight by volume metallo gels formed from **L3** and  $\text{CuCl}_2$  (2:1) in toluene, a) transparent form, b) opaque form. C) unstable metallo gel formed from **L3** and  $\text{CuCl}_2$  at close to 1:1 ratio.

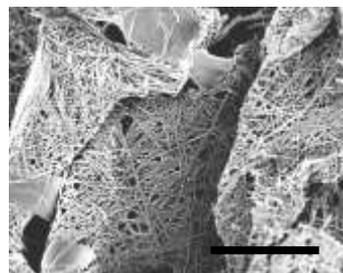


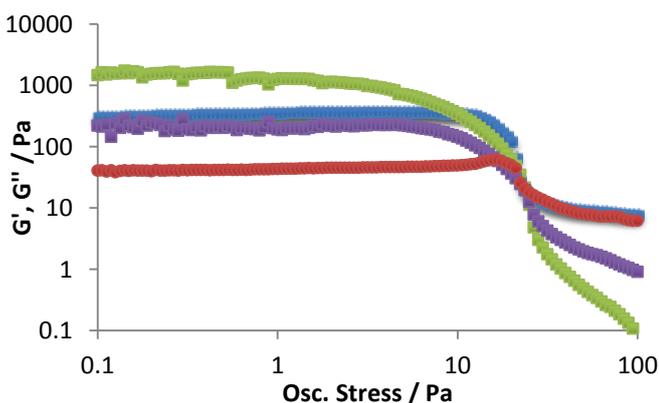
Figure 4. SEM micrograph of a xerogel prepared by drying the opaque form of a 2.5 % weight by volume metallo gel formed from **L3** and  $\text{CuCl}_2$  (2:1) from toluene. Both fibrous and homogeneous crystalline regions are present (scale bar 10  $\mu\text{m}$ ).

Interestingly, the blue gels formed with 0.5 equivalent of  $\text{CuCl}_2$  with both **L2** and **L3** in toluene have two 'gelmorph' forms. Initially the gel is light blue and transparent but becomes darker blue and opaque after a day at ambient temperature, Figure 3. SEM analysis of the xerogels (Figure 4) shows that both forms of gel exhibit narrow, interlinked fibres, however the opaque form also contains regions of more homogeneous crystalline material and hence the evolution from transparent to opaque gel is likely to represent a form of Ostwald ripening in which thin fibres dissolve and transform into larger crystalline particles.

Zinc(II) chloride 'turns off' gelation for both **L2** and **L3** in toluene and 1, 3-dichlorobenzene, although **L3** gels in nitrobenzene can tolerate up to 0.5 equivalents of ZnCl<sub>2</sub> but not higher amounts. Both **L2** and **L3** formed blue gels with cobalt(II) chloride in nitrobenzene at 2:1 and 1:1 ratios. The colour suggests a tetrahedral Co(II) centre. Coordination to Co(II) allows **L2** to gel nitrobenzene whereas only partial gels are formed by the free ligand.

The new metallogels were studied by stress sweep rheology which indicated, surprisingly, that all of the metallogels are substantially weaker than the corresponding gels of the free ligands. The silver(I) metallogels in nitrobenzene exhibit a  $G'$  of 10<sup>4</sup> Pa, approximately one order of magnitude lower than the free ligand gels and a yield stress around half that of the free ligand gels. The copper(II) gels are extremely weak. In toluene the copper(II) gels are somewhat more robust but still not comparable to the free ligand. The opaque and transparent forms of this gel exhibit similar yield stresses (18 and 16 Pa, respectively) but the opaque form has a significantly higher  $G'$  consistent with the presence of larger solid particles, Figure 5. The transparent form of the gel exhibits weak strain overshoot. Weak strain overshoot is a result of network rearrangement under stress creating a competition between creation and breaking of network junctions.<sup>34</sup>

Figure 5. Stress sweep rheology for the transparent (circles) and opaque



(squares) forms of the 2:1 **L3** : CuCl<sub>2</sub> metallogel 2.5% w/v.

Reaction of **L3** with CuCl<sub>2</sub> and ZnCl<sub>2</sub> in methanol resulted in the precipitation of the corresponding complexes. Elemental analysis indicated a 2:1 ligand:metal ratio in both cases. While the phenyl derivative **L4** does not form any gels, single crystals of its zinc(II) complex [Zn(**L4**)<sub>2</sub>Cl<sub>2</sub>] were obtained by heating ligand **L4** in water with a solution of ZnCl<sub>2</sub> in methanol and allowing the solution to stand for a period of 3 weeks. The resulting colourless blocks were analysed by X-ray crystallography revealing a tetrahedral zinc(II) centre linked to two chloride ions and bound to the ligand via the pyridyl nitrogen atoms. The urea groups form a continuous polar  $\alpha$ -tape, Figure 6. The N...O hydrogen bonded distances are highly unsymmetrical with one short at *ca.* 2.8 Å and one much longer at *ca.* 3.2 Å. While this complex itself is a non-gelator it provides insight into the likely structure and stoichiometry of the metallogels based on **L2** and **L3**. The asymmetrical

hydrogen bonding with one long, weak bond may explain the poor gelation properties of the metallogels compared to the free ligands.

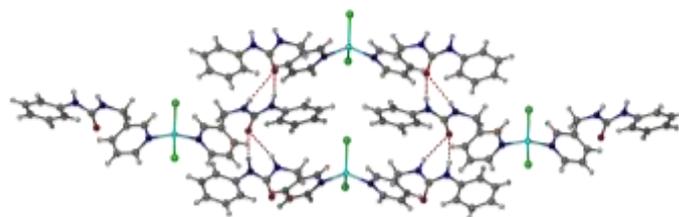


Figure 6. X-ray crystal structure of [Zn(**L4**)<sub>2</sub>Cl<sub>2</sub>] showing the urea  $\alpha$ -tape arrangement. N...O hydrogen bond distances 2.7950(16) and 3.2707(17) Å.

In general all of the metallogels are markedly weaker than the corresponding free ligand gels to the point where addition of zinc(II) and cobalt(II) nitrate in methanol to solutions of **L2** and **L3** in aromatic solvents completely disrupts gelation and the resulting product is soluble. Hence metal ions can be said to 'turn off' gelation to varying degrees. Interestingly, however, addition of 0.3 equivalents or more of tetrabutylammonium bromide (TBABr) (dissolved in 0.01 mL of methanol) followed by sonication for five minutes results in metallogels for both **L2** with zinc(II) nitrate and **L3** with cobalt(II) nitrate. In the latter case addition of bromide is accompanied by a colour change from pink to blue (Figure 7). The gels are stable indefinitely and are thermoreversible in the case of cobalt(II). This anion triggered gelation behaviour is thought to arise from a transformation of a non-gelator octahedral [M(L)<sub>2</sub>(NO<sub>3</sub>)<sub>2</sub>(solvent)<sub>2</sub>] to tetrahedral [M(L)<sub>2</sub>Br<sub>2</sub>] resembling the structure shown in Figure 6 which allows self-assembly via urea  $\alpha$ -tape formation. Gelation was not observed with tetrabutylammonium chloride (TBACl) in the case of zinc(II) but **L3** and Co(NO<sub>3</sub>)<sub>2</sub> did gel in the presence of TBACl. Examination of the UV-vis spectra of a 2:1 mixture of **L3** and Co(NO<sub>3</sub>)<sub>2</sub> in methanol before and after addition of 2 molar equivalents of bromide (relative to cobalt) provides good evidence for the octahedral-tetrahedral transition. Before bromide addition the UV-vis spectrum shows a weak absorbance at 508 nm assigned as the octahedral complex's Laporte-forbidden transition  ${}^4T_{1g}(P) \leftarrow {}^4T_{1g}$ . After addition of bromide a strong band is observed at 640 nm assigned as the transition  ${}^4T_2 \leftarrow {}^4A_2$  in a tetrahedral complex with shoulders at 614 nm and 587 nm corresponding to the transitions from the ground state ( ${}^4A_2$ ) to  ${}^4T_1(F)$  and to  ${}^4T_1(P)$ , respectively (supplementary information, Figure S10).

## Conclusions

Balancing intermolecular interactions in LMWG systems allows fine tuning of the behaviour of the bulk materials. In previous work anion complexation by the urea groups in urea gelators has resulted in anion 'turn off' of the gelation properties, while in pyridyl ureas addition of metal ions resulted in gelation 'turn-on' behaviour. Unlike pyridyl ureas, the present

pyridinylmethyl ureas **L2** and **L3** are effective gelators in their own right, however that gelation propensity is surprisingly weakened by metal ion coordination to the point where metal nitrate salts completely disrupt gelation in aromatic solvents. However, addition of bromide results in a change in metal coordination geometry from octahedral to tetrahedral and gelation behaviour is recovered. This cascade of metal and anion triggered gel-sol-gel behaviour represents a step forward in the use of chemical stimuli to control bulk materials properties.

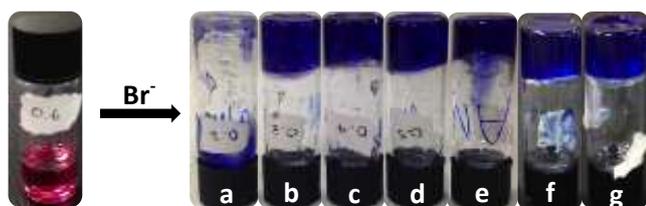


Figure 7. Addition of TBABr and sonication to a 2:1 solution of **L3** and cobalt(II) nitrate in nitrobenzene. Equivalents of TBABr added: a) 0.2, b) 0.3, c) 0.4, d) 0.5, e) 1, f) 2, g) 4. Note that 0.3 equivalents of  $\text{Br}^-$  are needed for gelation and gels are still formed with excess  $\text{Br}^-$ .

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**Graphical Abstract**

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