Anion-switchable supramolecular gels for controlling pharmaceutical crystal growth

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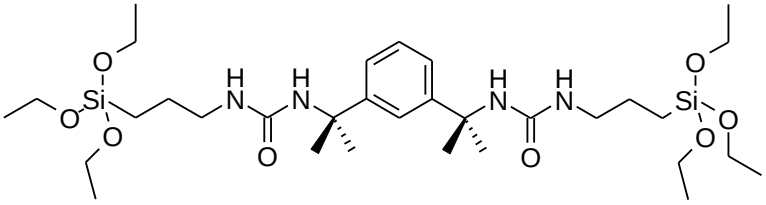
Abstract

The use of low molecular weight supramolecular gels as a medium for the growth of molecular crystals is described for the first time. Growth of a range of crystals of organic compounds including pharmaceuticals was achieved in bis(urea) gels. Low molecular weight supramolecular gelators allow access to an unlimited range of solvent systems in contrast to conventional aqueous gels. A detailed study of carbamazepine crystal growth in four different bis(urea) gelators, including a metallogelator is reported. The crystallization of a range of other drug substances, namely sparfloxacin, piroxicam, theophylline, caffeine, ibuprofen, acetaminophen (paracetamol), sulindac and indomethacin was also achieved in supramolecular gel media without cocrystal formation. In many cases crystals can be conveniently recovered from the gels by using supramolecular anion-triggered gel dissolution, however crystals of substances that themselves bind to anions are dissolved by them. Overall supramolecular gel phase crystallization offers an extremely versatile new tool in pharmaceutical polymorph screening.

Gel media have been utilized for over a century for the growth of inorganic, organic and protein crystals.[1-5] The improved physical characteristics of the resulting crystals (better optical quality, larger size and fewer defects) are usually ascribed to the suppression of convection currents, sedimentation and nucleation afforded by the viscous gel environment.[6-7] In many instances the gel is thought to act as an inert matrix within which crystal growth occurs, however in some cases, the gel structure has been shown to influence the polymorphism, enantiomorphism and habit of crystals.[2] Occasionally gel fibres may become incorporated into the crystal, giving rise to composite materials.[8] Conventional gels are formed using polymeric or clay-like materials such as gelatine, agarose, polyacrylamide or silica.[1,9] More recently, a new class of low molecular weight gelators (LMWGs) has emerged.[10-12] The supramolecular nature of such systems gives

them a potential inherent advantage in that their formation is readily reversible. This sol-gel transition can be triggered by a range of stimuli such as changes in temperature, pH, sonication, irradiation or, as in the present work, addition of a chemical trigger in the form of anions.[13-15] Moreover, the chemically diverse nature of LMWG means that almost any solvent can be gelled. A diverse range of chemical species form gels including surfactants, sugars, fatty acids, amino acids, bis(ureas), and others, in a variety of solvents.[10,13] However, the potential of LMWG's as a medium for crystal growth is largely unexplored.[16-18] with the exception of some elegant work on the use of LMWG's for the growth of calcium carbonate[19] and other inorganic minerals,[20] as part of studies on biomineralization.

The reversible nature of supramolecular gels can be utilized to allow easy recovery of crystals. In contrast, conventional hydrogels are limited to water as a solvent and removal of the gel may involve either acid hydrolysis or heating, both of which may also dissolve the crystals. The diverse array of chemical functionalities that can be introduced in small molecule gelators allows for tuning of interactions between the gel and growing crystal. LMWG are generally readily synthesized and hence, depending on the system, are relatively inexpensive, particularly if required on a large scale. In this communication we aim to show proof of principle for the growth and recovery of organic crystals, from anion-triggered supramolecular gels,[21] and to explore the potential of this medium for influencing crystal growth and form, particularly in active pharmaceutical ingredients (APIs) for which crystal habit and polymorphism is a key economic and formulation problem.[22]



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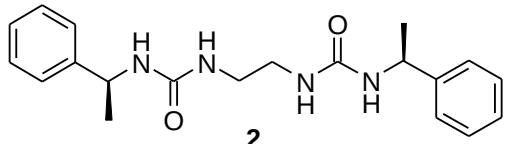

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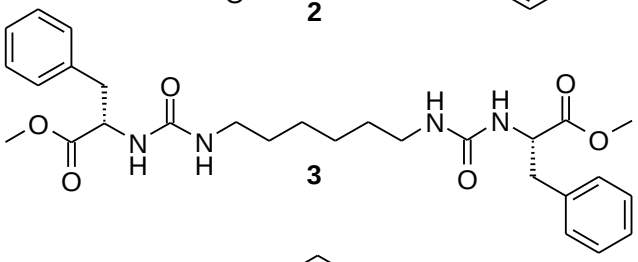

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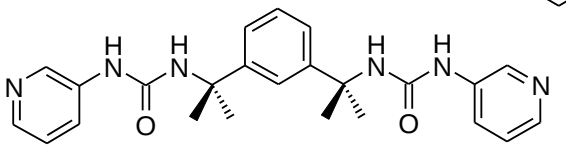

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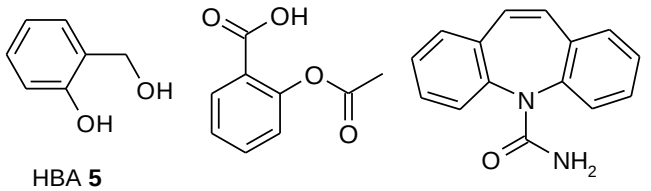
Four bis(urea) gelators (**1**–**4**) with different spacers and end groups and varying solubility were investigated to demonstrate their potential to act as crystallisation media for molecular organic compounds. Compounds **2**, and **4** have been reported previously.[23-24] Novel compounds **1** and **3** were prepared by standard methods as detailed in the supplementary information. Gelators **1** – **3** were chosen because they reliably form gels in a number of solvents ranging from aqueous systems to toluene. The fibrous nature of the gels is evidenced by SEM images of the dried xerogels (Figure 1a,b). Compound **4** is a metallogelator which forms blue coloured gels with substoichiometric amounts of $CuCl_2$ in methanol:water.[23] Between them, these gelators can gel a range of solvents, at different temperatures (T_{gel}), and with a different critical gelator concentration (CGC). This class of compound has the potential to form the basis of a library of gelators which will allow the selection of gel properties and specific functionalities to match the compound and crystallisation conditions of interest. The synthetic versatility of these gelators could also in principle allow the incorporation of tailored heteronucleating functionality. While we focus upon bis(urea) compounds, the concepts outlined herein equally apply to any LMWG.

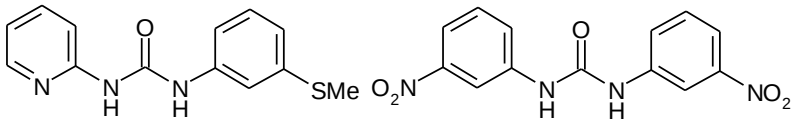
Crystallisation experiments were undertaken using a range of organic compounds of both drug and non-drug species in parallel in both gel and solution media. We undertook an initial screen using candidate compounds 2-hydroxy benzyl alcohol (HBA, **5**), Aspirin (ASP, **6**), carbamazepine (CBZ, **7**), 1-(3-methylsulfanyl-phenyl)-3-pyridin-2-yl-urea (SPU, **8**) and 1,3-bis(*m*-nitrophenyl)urea (NPU, **9**). We then carried out a detailed study on CBZ

with all gelators, and a follow up study on gelator **3** with a much wider range of pharmaceutical compounds.

For the initial screen HBA was chosen because it forms a co-crystal[25] as well as a pure phase and hence might exhibit further polymorphism. ASP is an example of a very common drug substance that shows little polymorphism and its two closely related forms have been the subject of recent controversy.[26-27] In contrast CBZ, an anticonvulsant, serves as a model compound for many groups engaged in the study of crystal polymorphism.[28-32] There are four known polymorphs of CBZ as well as a number of co-crystals. Recently the fourth form was grown using a polymer heteronucleus.[33] Details of the forms relevant to this paper are shown in table 1.[28] The two urea derivatives were included because they bear the same functional groups as the gelators themselves and hence might potentially interfere with gelation or be templated by the gelators. Both 1,3-bis(*m*-nitrophenyl)urea (NPU) and 1-(3-methylsulfanyl-phenyl)-3-pyridin-2-yl-urea (SPU) are also highly polymorphic.[34-35] Results on CBZ crystallisation proved to be the most diverse and hence this substrate was studied in detail with all gelators. Experiments on the remaining compounds, along with a larger and more diverse set of pharmaceuticals focussed on **2** and particularly **3**.



HBA **5** ASP **6** CBZ **7**



SPU **8** NPU **9**

Table 1. Solvent-free polymorphs and selected solvated forms of CBZ.

Form	Space group	Habit	Stability order	Crystallisation method
I	Triclinic $P\bar{1}$	Needle	2	Melt
II	Trigonal $R\bar{3}$	Needle	4	Rapid cooling (5ºC) from EtOH
III	Monoclinic $P2_1/c$	Block	1	Slow cooling (25ºC) from EtOH
IV	Monoclinic $C2/c$	Prism	3	Heteronucleation
Dihydrate	Monoclinic $P2_1/c$	Needle	n/a	Recrystalisation from wet ethanol
Acetone/ DMSO solvate	Triclinic $P\bar{1}$	n/a	n/a	Evaporation from solvent

Gel-Drug Interactions

In crystallising drug molecules from supramolecular gels it is important to establish whether the presence of the drug molecule has any effect on the gelation process. This aspect was studied using compound **1** and carbamazepine. Compound **1** is a versatile gelator, forming transparent gels in a variety of apolar solvents, consistent with the lipophilic triethoxysilane moiety. For CBZ crystal growth, toluene and $CHCl_3$/toluene solvent mixtures dissolve both gelator and crystallisation substrate in the sol state and form a gel upon cooling. The typical solid-like rheological properties of the pure gels were confirmed by stress-sweep rheometry where the storage modulus (*G′*) proved to be *ca.* 1.5 orders of magnitude larger than the loss modulus (*G″*) consistent with solid-like behaviour (Figure 2a). The relatively large value of *G′* obtained confirms that **1** forms strong gels.[10] The rheological properties of **1** were also examined in the presence of CBZ in order to confirm and quantify the gelation in the presence of the crystallisation substrate. CBZ had essentially no effect on the magnitude of the storage and loss moduli of the gel, however, interestingly the presence of CBZ (one percent by weight) resulted in a marked *increase* by *ca.* one order of magnitude in the yield stress. This effect is in direct contrast to anion binding by bis(urea) gels in which the competition between anion binding and gelator self-association results in marked anion-dependent decreases in gel strength and yield stress.[24] The CBZ does, however, lower the gel-sol transition temperature (T_{gel}; see supplementary material Figure S1). NMR titration experiments showed only very weak

apparent binding of CBZ to **1** with log K_{11} = 0.84(8) in $CDCl_3$ and a similar (albeit less precise) value in toluene at 70°C above the T_{gel}. VT NMR spectroscopic experiments show that the gelator has a marked effect on the chemical shift of CBZ which is likely to be linked to the disruption of CBZ dimer formation[28] in solution (see supplementary data). Because of its gelation ability the host itself is also likely to undergo significant self-association and hence the competition between both gelator and CBZ aggregation and gelator-CBZ binding results in a low overall apparent binding constant. We therefore conclude that the increased yield stress may not be a result of specific binding of the CBZ to the gelator, but could arise from the physical support of the gel by solid CBZ crystals. This support can be visualised by examination of Fig. 1c which shows the xerogel of **1** in which CBZ crystals have grown.

The influence of acetate anions on the gelation of **1** was also probed by stress-sweep rheometry. Acetate was chosen since it is strongly bound by ureas and previous work on **2** has shown that acetate induces the most significant reduction in gel strength.[24] Anion addition was carried out on 10 mL samples of **1** in toluene in a concentric cylinder couette with addition of 100 µL of MeCN, in which a varying amount of tetrabutylammonium (TBA) acetate was dissolved. Consistent with previous work, acetate binding brings about a significant weakening of the gel both in terms of *G'* and yield stress (Figure 2b). Addition of one molar equivalent of acetate is sufficient to completely dissolve the gel. The acetonitrile was required for solubility reasons, and addition of the same volume of pure acetonitrile without anion does not significantly influence the gel strength. Thus addition of acetate anions represents a feasible way to conveniently break down the gel matrix and hence retrieve crystalline material formed within the gel.

Crystallisation from solutions containing one weight percent of CBZ was realised in toluene gels of different concentrations of **1** (Figure 3). The drug and the gelator in each case were warmed in the solvent and the sample allowed to cool resulting in the formation of a clear, transparent gel over *ca.* five minutes. Crystals of CBZ form typically 8-12 h after gelation. Control crystallisations of CBZ under identical conditions without gelator were undertaken in parallel. The polymorphic form of the resulting CBZ crystals was analysed by single crystal and/or XRPD (supplementary material). In both gel and reference samples at all concentrations studied, the kinetically stable needle-like form II appeared first. Over a period of 2 days, conversion to the thermodynamically favourable form III was observed in the reference samples. This process is significantly slowed down in the gel matrix. The reasons for this retardation are unclear but may relate to the much more limited convection in the gel samples, slowing down dissolution of the kinetic form (Figure

3c). Although no unusual polymorph progression or crystal habit were detected, crystals grown inside the gelator network exhibited a tendency to more well-defined crystal faces and larger sizes, in some cases up to 20-30 times the size of the reference samples (Figure 3d).

The formation of form II can be completely avoided in a mixed solvent system of $CHCl_3$:toluene 1:9 v/v. CBZ and **1** were dissolved in the chloroform with heating. After cooling of the solution the addition of toluene results in immediate formation of a rigid gel. Crystals of CBZ form III are produced 1-2 days after gelation. Crystallisation is faster in the non-gel reference sample and occurs after *ca.* 1-12 h. For all samples the crystals were smaller than in the comparable pure toluene gels, but again crystals obtained from the gels tend to grow to larger sizes (Figure 3). Crystal growth results on CBZ are summarised in Table 2.

Recovery of the CBZ crystals grown in the gel phase was readily achieved by anion-switching. Adding excess TBA acetate as a solid on top of the crystal-containing gel leads to rapid dissolution of the gel. From the resulting solution the crystals can be easily recovered by filtration. There was no visible degradation of the crystalline sample observed by optical microscopy or by X-ray crystallography. This facile breakdown of the surrounding gel network is a distinct advantage of LMWGs in comparison to polymer gels such as silica.

Table 2. Crystallisation of CBZ in gels of **1** – **3**.

Solvent[a]	Crystal forms in pure solvent[b]	Crystal forms from gel **1**[b]	Crystal forms from gel **2**[b]	Crystal forms from gel **3**[b]
Toluene[c]	II and/or III	II transform to III	II and/or III	II and/or III
MeCN:Toluene	II and/or III	n/a[e]	III	II and/or III
$CHCl_3$:Toluene	II and/or III	II transform to III	n/a[f]	II and/or III
Ethyl Acetate	II	n/a[e]	III	II
Acetone	No crystals[d]	n/a[e]	Acetone solvate	n/a[e]
MeOH:H_2O[c]	Dihydrate	n/a[e]	Dihydrate	n/a[e]
DMSO:H_2O[c]	Dihydrate	n/a[e]	n/a[e]	I

[a] Crystallization performed at the same concentration, heating and cooling rates for samples of gel and pure solvent. [b] Gels of **2** are 0.1% by weight and of **3** are 1% by weight [c] Crystals not retrieved by dissolving the gel with anions [d] Crystallization of the

acetone solvate structure occurs upon further super-saturation by evaporation or addition of more CBZ [e] no gelation in this solvent. [f] CBZ retards gelation.

Crystallization of CBZ from other Gels

Analogous CBZ crystallization experiments were undertaken using gelators **2** and **3**, which are particularly versatile in their ability to gel a wide range of solvents. Results are summarised in Table 2 and selected photographs are given in the supplementary information (Figure S3). Gel characterisation data for **2** has been reported previously[24] SEM data of a xerogel of **3** is shown in Fig. 1b and rheometry and additional SEM data is given in the supplementary information (Figures S4 and S5). In contrast to **1**, gel formation by **2** in solutions containing chloroform was found to be retarded by the presence of CBZ. Other solvents gelled successfully, although at high concentrations of CBZ in 1:9 $CHCl_3$:toluene samples of **3** formed only partial gels. TBA acetate was found to break down gels of both **2** and **3** in all cases except for the pure toluene gels, where the acetate salt is insufficiently soluble, or the aqueous gels where the anion binding is apparently too weak to destroy the gel. Figure 4 shows an example of the use of acetate to recover a single crystal of CBZ form III grown in a 1:9 $CHCl_3$:toluene gel of **3**.

As observed with **1**, the toluene gels of **2** and **3** resulted in a mixture of needles of form II and blocks of form III. By adjusting the concentration of CBZ it proved possible to grow either form; higher concentrations of CBZ results in form II needles, lower concentrations give form III blocks. Varying the ratio of co-solvent to toluene had a similar effect with more $CHCl_3$ or acetonitrile requiring higher concentrations of CBZ to induce crystal growth and growth of form II. In 1:9 v/v acetonitrile:toluene mixtures, only form III blocks were observed with slightly higher concentrations of CBZ required to induce crystal growth in the gel samples of **3** (>20mg/ml) compared with solution (>15mg/ml). Some of the crystals showed different morphology to the normal equant shape and were elongated block shaped.[2,36] These crystals proved to be twinned, explaining their different morphology.[37-38] In ethyl acetate solutions in the absence of gel, form II grew rapidly before gradually converting to form III over several days. In gels of **3**, form II was also produced, with nucleation appearing to occur on the glass and crystals growing into the gel. No evidence of conversion to form III was observed even after several months. In contrast, crystallisation from ethyl acetate gels of **2** resulted in the isolation of CBZ as the thermodynamic form III even at high concentrations of CBZ (50mg/mL).

Other forms of carbamazepine were also encountered. Acetone gels of **2** containing 50 mg of CBZ after two weeks formed a large single crystal characterised as the triclicinic acetone solvate.[39-40] Parallel experiments in pure acetone did not produce any crystals. In this case, the gel induces crystallisation at lower saturation than the level required for a pure solvent crystallisation.

Crystallisation of CBZ in MeOH:H_2O (8:2) gels of **2** at 0.1% by weight containing 50mg of CBZ and parallel reference crystallisation without gelator at the same concentration of CBZ both proved to be the monohydrate form of CBZ and were similar in size and shape to that from the pure solvent crystallisation.[31-32]

In DMSO:water solution in the absence of gel, CBZ formed long, needle like crystals (at concentrations in excess of >30g/ml) shown to be pure carbamazepine dihydrate by XRPD.[28] At low CBZ concentrations no crystal growth was observed in the gels of **2** and **3**. However, at higher concentrations clumps of very fine crystals formed inside the gel of **3** exhibiting a powder diffraction pattern corresponding to the relatively unusual CBZ form I (supplementary data Figure S6). Form I is the high temperature form of CBZ and is normally produced from the melt at 170 ºC. It has also been shown that dehydration of the dihydrate can lead to form I under conditions of low humidity.[41] The formation of form I in the gel under the same conditions that give the dihydrate from solution is a surprising result and suggests that the LMWG can have a significant effect on crystal form. IR spectroscopic experiments carried out on the wet samples confirmed that a pure form I rather than the dihydrate is formed in the gel phase.

Crystallization of Other Substrates

In addition to the detailed work on the highly polymorphic CBZ, we also undertook a range of crystallisation and control experiments on ASP, HBA, SPU and NPU with gelators **1** – **3**. Aspirin was crystallised from a gel of **2** with 50mg mL^{-1} of ASP at 0.3% by weight gelator in MeCN. Crystallisation occurred after one week (Figure S7). An equally concentrated solution of ASP in MeCN does not to crystallise under the same conditions suggesting that the gel can be used to induce crystallisation. The crystal form proved to be the conventional form I. Crystals of HBA were successfully grown from both toluene gels of **3** and toluene solution and proved to be the known polymorph.[42] The crystals obtained from the gel were significantly larger, however, with better developed and more regular faces (Figure S8).

The urea derivative SPU crystallised or precipitated from a wide range of gels of gelators **1** – **3** in a range of solvents: toluene, ethyl acetate, DMSO and methanol. Solution

phase methods give a variety of polymorphs I – IV depending on conditions,[35] while gels generally give the most thermodynamically stable form IV.

The other urea derivative, NPU has three concomitant polymorphs, designated as α, β and δ. Growth on siloxane SAMs also recently revealed a fourth polymorph and a hydrate form is known.[43] There are few reliable means to crystallise these forms free of one another with the exception of growth on Au-thiol SAMs,[44] although slurry methods and fast cooling from a supersaturated acetic acid solution were found to be effective at producing pure β form.[34] Crystallisation of NPU from gels of **2** in MeCN, ethyl acetate, $CHCl_3$ and MeOH:H_2O was successful but resulted in no control over crystal form. In general the yellow prism α form was found at the air/gel interface and the white needle β form within the gel matrix in the $CHCl_3$, ethyl acetate and MeCN gels. Interestingly in the case of ethyl acetate gel phase crystallisation gave a distinctive needle shaped morphology, while from solution plate-shaped crystals are obtained. The MeOH:H_2O gels gave the hydrate form at most concentrations although the needle morphology, β form was also observed in more concentrated samples.

Attempts to recover NPU crystals by adding acetate anion as the TBA salt to the gels resulted in the dissolution of both the gel and also the crystals in the cases of gels in MeCN, ethyl acetate and $CHCl_3$. The gels and crystals of NPU from MeOH:H_2O are unaffected by the addition of acetate. We suspected that this dissolution results from a specific anion-NPU interaction. Solution phase ^{1}H NMR spectroscopic titration confirmed that NPU binds strongly to acetate with binding constant log β_{11} = 3.7(1) in acetonitrile, and the host:anion species is more soluble in the solvents used therefore leading to the rapid dissolving of any crystalline material. Hence the anion-recovery method is likely to be limited to compounds that do not themselves compete with the urea gels for anion binding.

Scope for Crystallistion of Drug Substances

Compound **3** is a particularly versatile gelator and we decided to focus attention on the breadth of the technique using this compound. Gel-phase and parallel solution phase crystallisations were carried out for the following pharmaceutical compounds: sparfloxacin, piroxicam, theophylline, caffeine, ibuprofen, acetaminophen (paracetamol), sulindac and indomethacin. Experiments were carried out under empirically determined conditions designed to bring about crystallisation in the following solvents: 1:9 CH_3CN:toluene, 1:9 $CHCl_3$:toluene, ethyl acetate, 1:1 DMSO:H_2O and 3:2 MeOH:H_2O. All of these solvent mixture form thermoreversible gels with **3**, and the first three break down upon the addition of acetate anion. The substrates were chosen as commonly available drug substances

that represent a wide range of structures and functional group types and are either polymorphic, form hydrates or otherwise exhibit interesting crystal packing. The results of these experiments are tabulated in the supplementary material (Table S1). Of the 40 combinations tested, gel formation was observed in all but 7 cases. In 19 cases gels formed in the presence of drug substances were at least as strong and of similar appearance to the native gels. In 14 cases gels appeared weaker, leaked solvent or appeared disrupted by the presence of the drug substance. The high solubility of many of the compounds meant that often the concentration of drug molecules was equivalent to, or greater than, that of the gelator. In 8 cases no crystallisation occurred from either the gel or solution phases over a period of 3 weeks. Crystallisation was found to occur in solution but not the gel on 6 instances. In many cases the crystals obtained from both gel and solution were the same form and of similar appearance, although some different morphologies were noted. A particularly interesting difference in gel phase and solution crystallisation behaviour occurs in the anti-inflammatory drug piroxicam (supplementary data Figure S9). Piroxicam has three anhydrous forms and a hydrate which are readily distinguished by IR spectroscopy.[45] Crystallisation from 1:9 acetonitrile:toluene gels of **3** produced fast growing, needle-like form II in the gel and large block shaped crystals of the slow growing form I. In 1:9 chloroform:toluene gels a clump of form II was obtained from solution and at the gel surface, whilst blocks of form I were obtained from the bulk of the gel. In ethyl acetate the gel was partially disrupted by the growth of several clumps of form II. In DMSO:water, the yellow blocks of the hydrate was identified from solution whilst the kinetic form II was recovered from the gel. In methanol:water, small yellow blocks of the piroxicam hydrate were seen dispersed throughout the gel systems and on the bottom of the corresponding solution. Addition of TBA-acetate led to the dissolution of the crystals as well as the gel and samples were extracted for analysis manually.

Crystallisation in a Metallogelator

In order to demonstrate the versatility of the LMWG approach to crystallisation we also studied one substrate (CBZ) with metallogelator **4** which gels in methanol the presence of copper(II) halides.[23] Crystal growth of CBZ from copper(II) chloride / **4** in 1:1 v/v MeOH:water was studied in parallel with gelator-free reference samples. Under these conditions **4** forms clear blue gels after the addition of 0.4 – 0.7 equivalents of $CuCl_2 \cdot 2H_2O$ with brief sonication.[46] In all cases gelation was rapid and occurred long before any visible crystallisation. Figure 5 shows CBZ crystallisation in the metallogel of **4** after 1 week. Remarkably, there is a clear change of crystal habit as compared to the needle-like CBZ

hydrate crystals grown in the reference samples. Unit cell determination by single crystal X-ray diffraction, however, confirmed this material to be the dihydrate form of CBZ. The presence of the labile copper(II) does not result in the isolation of any copper-CBZ coordination complexes, although complexation could be an issue for other drugs that are more able to ligate the metal centre. In the absence of complex formation, however, metallogelators offer an added dimension to the possible options for gel tuning. Interestingly, the difference in habit between gel and solution-grown CBZ dihydrate is dependent on the amount of copper salt added in the formation of the metallogel. At 0.3 equivalents of $CuCl_2$, gelation is incomplete, but crystals are clearly shorter than the reference samples. With the addition of 0.4 equivalents of the copper chloride complete gelation is achieved, and only small crystals are observed. At higher concentrations of the metal ion, the formation of long blade-like structures was observed (0.5 equivalents), as well as small daughter platelets growing from a central strut (0.6 equivalents) and tree-like growths (0.7 equivalents). Recently, oriented attachment growth has led to similar appearing metal nanostructures in a surrounding polymer matrix.[47-49] One possible explanation for the formation of these morphologies is that the amount of copper salt influences the gel strength[23] and hence rate of convection within the gel. This factor in turn influences the degree of nucleation with the result that daughter crystals nucleating on a parent CBZ needle become predominant over spontaneous nucleation. SEM micrographs (Figure 6) reveal what we believe is early stages of CBZ growth inside the gel and show crystals encased by the fibrous matrix. Frequently daughter crystals growing on a large central mother crystals are observed, similar in appearance to the larger structures observed under the optical microscope. It appears that the gel fibre network “chokes off” regions on the central crystal, perhaps restricting crystal surface area and leaving only certain regions available for further growth to occur.

Conclusion

We have demonstrated the use of LMWGs as a medium for organic crystal growth. The supramolecular nature of these gels allows for the facile recovery of crystals upon the addition of acetate anion without damage to the crystals. Although the effectiveness of anion-triggered reversal of gel formation is limited by solvent and the ability of the crystalline substrate itself to interact with the anion, gelators can be designed which respond to a variety of external stimuli. The ability of LMWGs to gel a wide range of solvents allows for detailed screening of compounds. LMWGs may act as an inert matrix, slowing down crystallisation and leading to larger, more uniform crystals and inhibiting the

conversion of metastable polymorphs. In some cases crystallisation was found to occur in the gel but not in solution, whilst in others nucleation required higher levels of supersaturation in the gel phase. No gelator-substrate co-crystals were observed suggesting effective phase separation between the rapidly forming gel and the slower growing substrate crystals. This important observation indicates the general applicability of these systems. Clear differences in crystal habit have been seen in the gel phase compared with solution and in some cases the gel-phase crystallisation results in the formation of different polymorphs compared to the parallel solution phase experiments. The vast body of literature on supramolecular gels provides a library of gelators which can be chosen to match the crystallisation conditions of interest. The diversity of this class of gelator also allows for tuning of interactions between gel and solute. Supramolecular gels could find application as an important tool within the context of polymorph screening methodologies that are routinely applied at several stages of the drug development pipeline and work is in progress on new API materials in collaboration with industry. The high quality single crystals that result from gel phase crystallisations are of great potential use in macromolecular crystallography where crystal quality, particularly in synchrotron work on small samples, is of paramount importance.

Methods

Gel phase crystallisations were carried out by weighing the appropriate amount of substrate (1-5 wt%) and gelator (0.1-1 wt%) in a vial and adding a suitable solvent from a stock solution. The sealed vial was then heated until both solids were fully dissolved and the mixture was then allowed to cool to room temperature. In each case the gel is formed over a period of a few minutes whilst crystallisation takes place over tens of minutes to weeks. Where possible, recovery of the crystals was achieved by adding a measured amount of acetate as the TBA salt to break down the gels, followed by filtration of the resulting solution and washing with water or diethyl ether. Polymorph were identified from their characteristic solid state IR spectra (PE Spectrum 100) or where crystal size permitted, from the unit cell dimensions of a number of representative single crystals (Bruker 6000) or by comparing experimental X-ray powder diffraction patterns (D5000) with those calculated from the known single crystal coordinates. Rheology was carried out in a concentric cylinder couette on a 10 mL scale using a TA Instruments AR2000 Rheometer with a standard-size double concentric cylinders geometry and a gap of 1000 μm for all samples.

Acknowledgements

We thank the ESPRC, GSK and the Association of the Commonwealth Universities for funding.

Author contribution

Jonathan A. Foster, Marc-Oliver M. Piepenbrock and Gareth O. Lloyd undertook the synthesis of gelators, experimental studies and rheology measurements. Nigel Clarke supervised the rheology work, Judith A. K. Howard supervised the crystallographic work and Jonathan W. Steed was responsible for overall project concept, direction and coordination. All authors contributed to writing the manuscript.

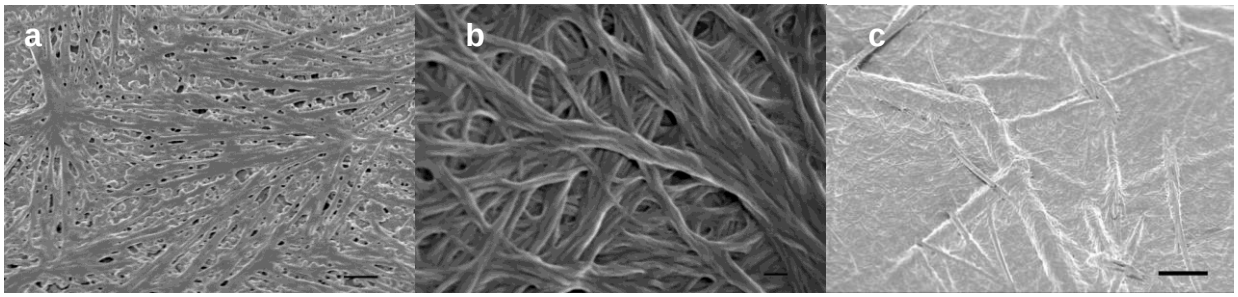


Figure 1 SEM images of xerogels of 1 and 3 obtained from drying a 1 weight % gel in toluene. (a) compound **1** (scale bar = 1μm), (b) compound **3** showing a helical twist in the fibres arising from the molecular chirality (scale bar 100 nm), (c) xerogel of **1** containing crystals of CBZ (scale bar = 10 μm) showing the much smaller size of the gel fibres compared to the CBZ crystals that the gel is surrounding. The fibrous structure of the gels in each case is clearly evident.

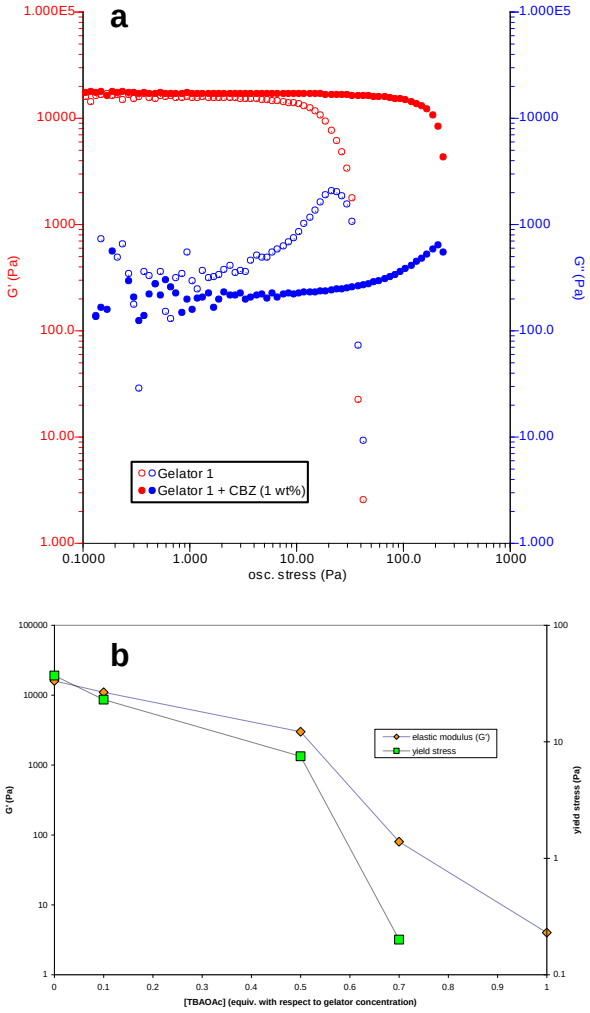
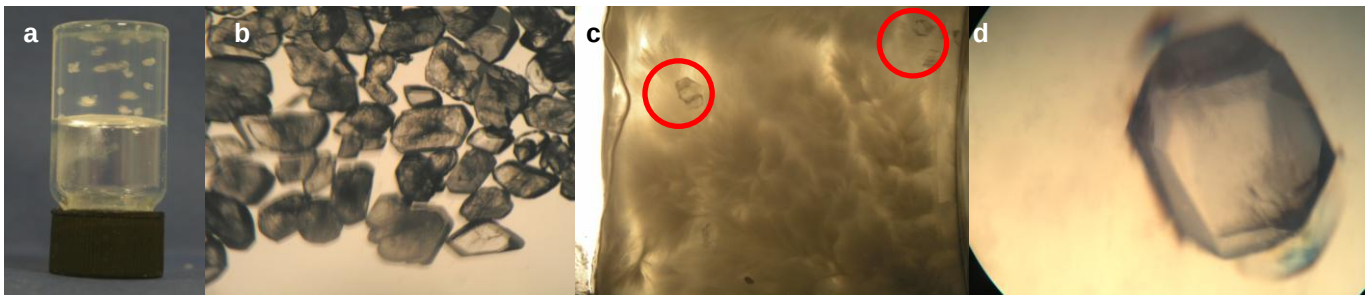


Figure 2 Stress sweep rheology of gelator 1. (a) In toluene with and without CBZ (1 wt%) showing that the gel is not disrupted by the introduction of CBZ and indeed exhibits a higher yield stress. (b) In toluene with 100 μL of MeCN with varying amounts of tetrabutylammonium acetate showing the anion-induced weakening and eventual dissolution of the gel.



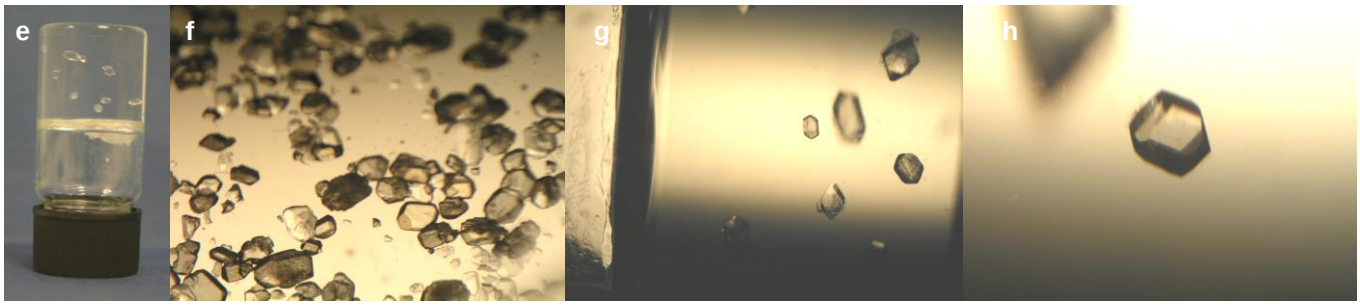


Figure 3 CBZ crystals of grown in solutions or gels of 1. a) Form III in 1 weight% of **1** in toluene, b) Form III from toluene without gelator (40x magnification), c) forms II (mass of needles) and III (red circles) in 1 weight% of **1** in toluene (7x magnification), d) form III in 6 weight% of **1** in toluene (40x magnification), e) Form III in 1 weight% of **1** in 1:9 v/v $CHCl_3$:toluene, f) Form III in 1:9 v/v $CHCl_3$:toluene without gelator (25x magnification), c) form III in 1 weight% of **1** in 1:9 v/v $CHCl_3$:toluene (7x magnification), d) form III in 6 weight% of **1** in 1:9 v/v $CHCl_3$:toluene (25x magnification).

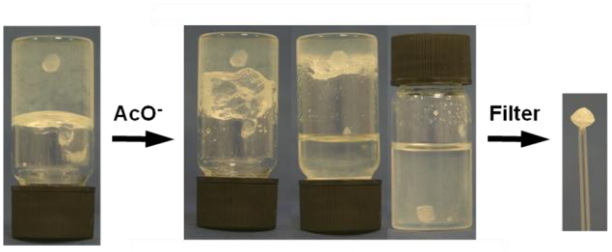


Figure 4 Recovery of a single crystal of CBZ form III by acetate anion triggered gel dissolution of a 1:9 $CHCl_3$:toluene gel of gelator 3. A single large CBZ crystal is grown in the gel. The gel is then dissolved by addition of acetate anion. The crystal can be redily recovered by filtration or manual extraction and mounted for an experiment such as single crystal X-ray crystallography.

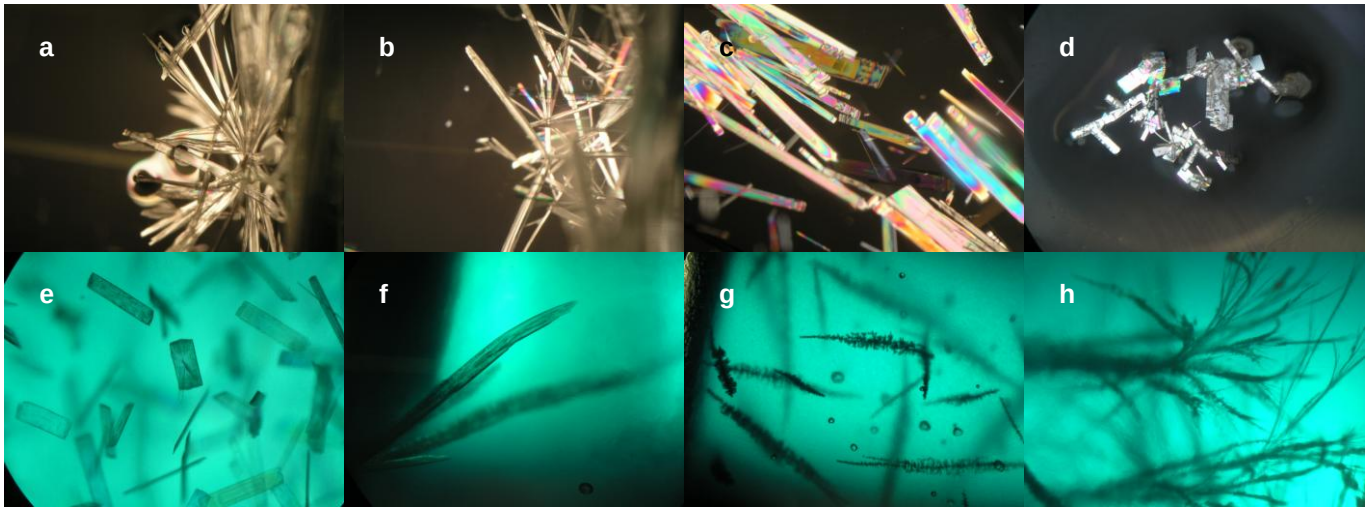


Figure 5 Optical microscopy of CBZ (1 weight%) grown in a metallogel medium along with control experiments showing the effect of the gel. (a) CBZ from 1:1 MeOH:water reference crystallization from solution, (b) with 0.3 equivalents of $CuCl_2$ present showing that the copper salt alone does not significantly affect the crystal morphology, (c) with 1 weight% of **4** showing the gelator alone does not significantly affect the crystal morphology, (d-h) in metallogels of **4** / $CuCl_2$ with (d) 0.3, (e) 0.4, (f) 0.5, (g) 0.6 and (h) 0.7 equivalents of $CuCl_2$ showing the change in morphology according to the strength and composition of the gel.

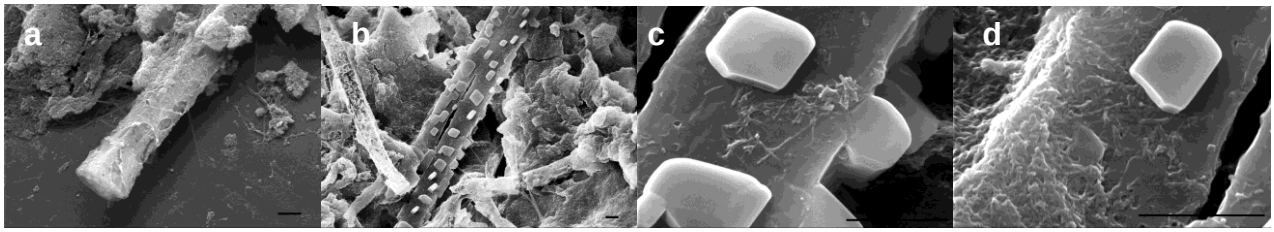


Figure 6 SEM images of CBZ in metallogels of 4 with $CuCl_2$, showing crystals of carbamazepine grown within the metallogel. (a) The large needle-shaped crystals are parent crystals of CBZ and their surface is predominantly covered by gel fibres. (b) In some cases carbamazepine daughter crystals are clearly visible nucleating on the parent needles being encased by the gel fiber matrix. (c) and (d) show a close up image of the daughter crystals. The gel fibres covering the surface of the parent crystal are also visible. (scale bar = 1 μm).

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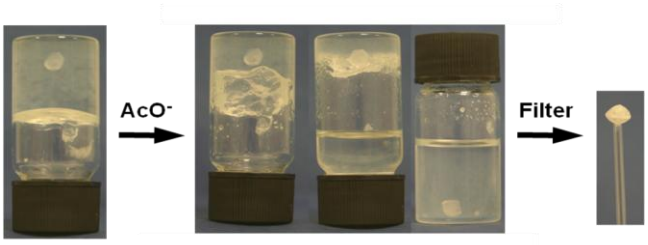
Graphical Abstract



Summary for Table of Contents

Supramolecular gels based on small molecule gelators are effective media for the growth of novel forms of organic crystals including pharmaceutical compounds. The gels/sol transition may be triggered by molecular recognition with anions allowing facile recovery of the crystals.