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Supramolecular Gel Phase Crystallization: Orthogonal Self-Assembly Under Non-equilibrium Conditions.

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This tutorial review charts the history of gel phase crystallization from its origins in Liesgang ring formation to current research in the generation of new pharmaceutical solid forms in low molecular weight organogels. The growth of molecular crystals under a supersaturation gradient within the same space and timescale as the formation of a gel phase material is placed into context as an example of orthogonal self-assembly. Such multi-component, weakly coupled orthogonal self-assembly processes occurring far from equilibrium represent a powerful conceptual paradigm for generating fascinating emergent behaviour in chemical systems.

Key Learning Points

- Orthogonal self-assembly results in phase separation on the micro to nanoscale depending on the degree of coupling between the components.
- Non-equilibrium self-assembly of multicomponent mixtures under a supersaturation gradient gives rise to emergent structures with novel morphologies and properties.
- Non-equilibrium self-assembly can be subdivided into dissipative and metastable outcomes.
- Gelation and crystallization are closely related orthogonal processes, often kinetically resolved because of their different timescale but mutually influencing one another's outcome in terms of polymorphic form, morphology and mechanical properties.
- Low molecular weight supramolecular gels are versatile crystallization media that can be tailored to the crystallization substrate, used in any solvent and exhibit reversible gelation.

Supramolecular Gels

Gels are ubiquitous solid-like materials found in everyday applications such as contact lenses, lithium grease, jelly and hair gels. They are generally based on polymers of low crystallinity and can be recognised by a simple 'inversion test' – the material doesn't flow when turned upside down. Commonly gels comprise a two-or-more component mixture of a gelator (*ca.* 1–2 % by weight or lower) and a fluid component that is immobilised by surface tension. Gels have a fibrous structure that spans the entire sample in one continuous, three dimensionally cross-linked network and are solid-like in their rheological properties.[1] While most gels are based on polymeric components, this is growing recent interest in a class of gelators termed low molecular weight gelators (LMWG) that are based on small molecular species that form gel fibres by supramolecular interactions such as hydrogen bonding and hydrophobic effects. The formation of a gel from a LMWG can occur in a variety of solvents and is a non-equilibrium self-assembly process closely related to crystallization in as much as it occurs under supersaturation conditions and has identifiable nucleation and growth phases. Indeed gelation is sometimes colloquially referred to as 'crystallization gone wrong'. The topic of LMWG has been the subject of a number of excellent reviews of which the most recent by Huang and co-workers is a good entry into the literature.[2]

Non-Equilibrium Self-Assembly

For several decades thermodynamic (strict) self-assembly has proved to be an enormously useful paradigm in the construction of stable, equilibrium structures of increasing complexity. Beautiful examples include metallocages and hydrogen bonded capsules with internal dimensions sometimes markedly in excess of a cubic nanometre, capable of including guest molecules and controlling their reactivity.[3] Thermodynamic self-assembly has also been used to construct complex self-assembled architectures such as helicates, racks, ladders, grids and catenanes.[4] It has truly opened up a whole world of complex topological synthesis, given access to nanoscale molecular containers and, in some cases, functional molecular devices such as shuttles, rotors and switches.[5] Crucially, however, systems produced by equilibrium self-assembly are 'dead ends' as far as exhibiting complex, emergent or adaptive behaviour. Because they represent a thermodynamic minimum they cannot do any work on their surroundings and require energy input in order to change state. The distinction has been elegantly articulated by Leigh in his conceptual description of molecular machines.[5] Nature does use equilibrium self-assembly, for example in the construction of information storage media as in DNA or in structural applications like the assembly of viral capsids (*e.g.* the tobacco mosaic virus).[4]

However, Nature's systems are much better characterised as being self-organised, exhibiting dynamic and adaptive properties that are far from equilibrium.[6] Non-equilibrium systems can give rise to complex, emergent morphologies and properties, while their adaptability offers the possibility of much richer stimulus- and environment-dependent functionality.

It is possible to distinguish two types of out-of-equilibrium self-assembled aggregates, namely metastable structures and dissipative structures. Metastable structures are essentially static and kinetically trapped. They exist because the available thermal energy is not sufficient to overcome the activation barrier required to transform them into the most thermodynamically stable state. Dissipative structures are dynamic and require the active and continuous input of energy in order to push the system out of equilibrium. Dissipative structures are common in biology, for example microtubules formed from tubulin dimers activated by reaction with guanosine 5'-triphosphate. These activated building blocks are hydrolysed over time to guanosine diphosphate tubulin resulting in microtubule collapse. The assembly thus requires constant renewal and hence exhibits interesting properties such as self-healing.[7] Recently, an artificial dissipative self-assembled supramolecular gel phase material has been reported by the van Esch group based on the methyl iodide consuming esterification of the non-gelating anionic form of dibenzoyl-(L)-cystine.[8] Ester formation converts the compound to an effective hydrogelator, however under basic conditions the gelator is continually hydrolysed requiring constant, energy dissipating input of MeI.

An interesting example of non-equilibrium self-assembly is the crystallization (and gelation) process. Crystallization occurs under far-from-equilibrium conditions driven by a supersaturation gradient. According to classical nucleation theory it includes an energetically unfavourable nucleation step, followed by an energetically favourable growth phase that minimises the interface between crystal and solution. The degree of supersaturation determines the degree of interfacial instability that can be tolerated, with more metastable assemblies requiring higher supersaturation to nucleate.[9] Once a nucleus of critical size is attained, the non-equilibrium nature of crystallization means that it is a one-way process in which crystal growth occurs in a run-away fashion until the local supersaturation is depleted. Classical nucleation theory is an oversimplification of the mechanism of crystallization and homogeneous, primary nucleation is rarely dominant in the crystallization of molecular species. There is growing evidence for two-step nucleation involving local concentration variation[10] and crystallization outcome is often determined by nucleating high energy surfaces. The recent book by Beckmann is recommended as an introduction into the field.[9]

Under conditions of high supersaturation it is well known that relatively unstable crystal forms can be produced since the supersaturation is sufficient to overcome the nucleation barrier even for less stable nuclei. This phenomenon gives rise to Ostwald's rule of stages in which increasingly stable polymorphs form over time.[9] In the extreme case, if very high supersaturation levels are reached very quickly, then amorphous material can be produced since there is insufficient time for an orderly nucleation and growth process. While crystallization is often referred to as a self-assembly process, it is crucial to remember that there are both kinetic and thermodynamic aspects involved and hence metastable structures are common. Even the observed molecular structure of a labile compound in the crystalline state may be very different from its solution structure. The non-equilibrium nature of crystallization is highlighted by the occurrence of polymorphism and hence both stable and metastable solid forms.[9]

Multicomponent Self-Assembly

For simplicity chemical self-assembly often focusses on a single component, however molecular biology almost invariably employs richly diverse, multi-component systems. The self-assembly and self-organisation of a biological cell, for example, involves the self-sorting and parallel assembly of components such as phospholipid cell walls, cytoskeletal elements that impart structural rigidity such as actin and tubulin, genetic material such as DNA and RNA, proteins, enzymes and glycopolymers. The individual assembly of each unit may also be a result of hierarchical processes with additional components such as chaperone proteins assisting in the correctly folded product.[11] Each component assembles in a distinct, emergent way according to the molecular information encoded in its chemical structure and its environment and history. This diversity allows the ensemble to exhibit multifunctional behaviour and brings about compartmentalisation allowing the simultaneous operation of mutually incompatible processes. The origins of this coupled, orthogonal self-assembling, self-organising and self-perpetuating system are emergent, and in principle the end product of a series of incremental, evolutionary steps. Theories concerning the precise prebiotic origins and nature of these steps represent a fascinating and enduring research endeavour and include 'RNA-world' in which RNA catalysis by ribozymes (as in the peptidyl transferase centre of the ribosome) represents the core of the first self-replicating systems. Alternative theories include self-replicating proteins, self-assembly of abiotic amphiphiles ('lipid-world') and even the transmission of crude genetic information by clay minerals such as montmorillonite.[12]

Abiotic self-assembly is also increasingly turning to multicomponent self-assembly in order to understand and engender systems exhibiting more sophisticated functionality and morphology. In the polymer community phase separation of incompatible polymers has been used extensively to bring about compartmentalisation on the micro- to bulk scale. In contrast, intimately covalently linked block co-polymers exhibit phase separation on the nanoscale.[13] Phase separation is not unique to polymers and equally can be found in non-covalent self-assembly, *e.g.* of amphiphiles, liquid crystals or gelators.

Where different components do not exhibit any interaction between them during a multi-component self-assembly process we can regard the system as being self-sorting, in which case the different assemblies based on the different components are orthogonal to one another. At the other end of the scale two components that are strongly coupled either *via* a strong interaction or a covalent bond as in block co-polymers, may form an intimately blended or nanoscale phase separated assembly.[14] Introduction of weak coupling between the two or more orthogonal assembling components offers the possibility of compartmentalised or self-sorted systems on varying length

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scales in which the presence of each component influences or modifies the outcome of the assembly of the other without losing the distinct identity of each one.

In this review we focus upon the combination of small molecule crystallization and gelation; two closely related self-assembly processes that occur under non-equilibrium conditions, driven by a supersaturation gradient. A range of possible outcomes of a two-component, orthogonal self-assembly process (such as the one between a gelator and crystallization substrate) as a function of the degree of coupling between small molecule components are summarised in Figure 1. Where there is essentially no interaction between the two components then the outcome of the process is the same as if the self-assembly of each component occurred separately. The supersaturation gradient drives an unfavourable nucleation step followed by a growth phase resulting in two separate crystals or two non-interacting gel networks. The two orthogonal materials may be physically entangled in longer length scales. The nucleation of each component may be primary, secondary or follow a non-classical two-step mechanism,[10] and crucially the presence of more than one component offers the opportunity for each of the two orthogonal assembly processes to influence the outcome of the other one. However, solubility constraints and kinetic factors mean that each process may not occur at the same rate and hence there is the possibility of temporal as well as spatial separation of the individual assemblies. Examples of such uncoupled processes have been demonstrated in gelation by Smith who showed that independent assembly of a mixture of two different gelators can give rise to two independent, non-interacting networks described as 'multi-gelator' gels.[15] One of the most elegant demonstrations of orthogonal self-assembly in this context has been reported by van Esch and co-workers who looked at the co-assembly of surfactants and 1,3,5-cyclohexyltricarboxamide hydrogelator systems to give a variety of compartmentalised nanostructures. Their striking cryo-TEM images of co-assembled compartmentalised vesicle and gel fibre assembly are shown in Figure 2.[16]

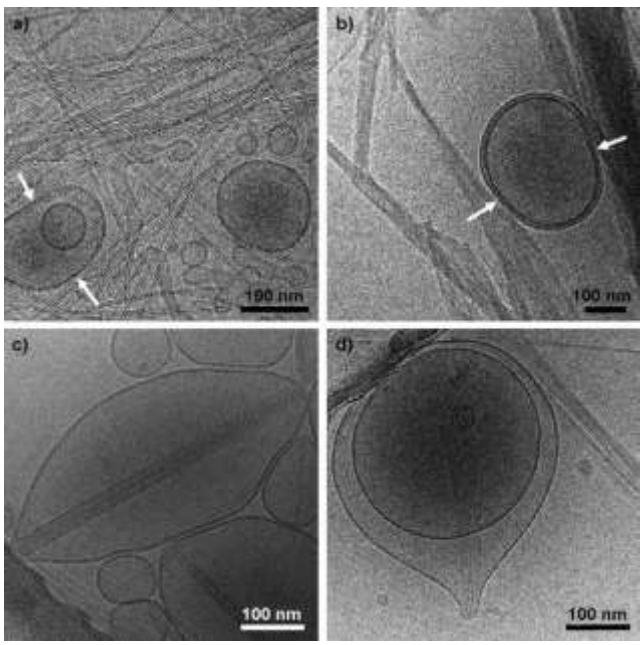

Fig. 2 Cryo-TEM images of unilamellar a) dioleoylphosphocholine vesicles coexisting with a network of well-defined 1,3,5-cyclohexyltricarboxamide gel fibres with a high aspect ratio; b) dioctadecyldimethylammonium bromide vesicles with thicker 1,3,5-cyclohexyltricarboxamide gel fibres; c) and d) dioleoylphosphocholine vesicles deformed by the growth of gel fibres directly contained in their aqueous compartment (reproduced with permission from ref. 16)

In crystallization processes spontaneous separation is commonplace and forms the basis of the method of purification by recrystallization. An interesting, if more unusual case is spontaneous conglomerate formation in which two enantiomers of the same material spontaneously form separate left and right handed crystals in a 'chiral' (formally, Sohnke) space group.[17]

At the other end of the scale strongly coupled orthogonal self-assembly (Figure 1c) as in covalently bonded block copolymers[13] and small-molecule 'multi-segment assemblers' leads to nanoscopic phase separation. The length scale of the compartmentalisation may be less than the length of the molecule itself, significantly constraining the architecture of the assembly. If the self-affinity of one component is significantly greater than the other then the structure of the final assembly will reflect the intrinsic assembly tendency of that dominant component. For example assembly of a two-segment molecule comprising a cyclohexyl trisamide hydrogelator (with a tendency to form fibres by anisotropic hydrogen bonding interactions) covalently bound to a non-ionic surfactant (with a tendency to form spherical micelles due as a result of hydrophobic effects) results in the assembly shown Figure 3.[18]

In intermediate systems where there is some degree of non-covalent interaction between the two components (Figure 1b) a range of very interesting possible behaviour types arise, some commonplace and some offering extremely intriguing possibilities. Crystallization processes involving two components present in similar amounts are rarely completely orthogonal. Crystallization in the presence of an impurity component can result in occlusion of the second compound within the crystal lattice of the first giving rise to local instabilities or defects and hence melting point depression or even eutectic formation.[9] Where the non-covalent interaction is particularly strong a stoichiometric co-crystal or non-stoichiometric solid solution can arise.[19] Particular types of complementary interaction can give rise to the stabilisation of unique phases such as lattice inclusion compounds or clathrates, as in the stabilisation of open hydrogen bonded arrays of water by space-filling hydrocarbon guests in clathrate hydrates. An interesting example is the case of the copper(II) chloride complexes of *N*,*N*′,*N*″-trimethyltriazacyclononane (L) which convert from monomeric $[Cu(L)Cl_2]$ to binuclear $[\{Cu(L)\}_2(\mu\text{-}Cl)_3]^+$ during the crystallization process, with the yellow binuclear crystals growing on the surface of the green mononuclear parent phase, Figure 4.[20]

Crystallization of inorganic salts in the presence of surfactants can lead to fascinating emergent morphologies that shed light on mechanisms of biomineralisation and biotemplated hybrid materials chemistry. One elegant example is the crystallization of $BaCrO_4$ nanoparticles in ordered chains in the presence of an AOT microemulsion, Figure 5.[21]

In terms of gel formation, the co-assembly of weakly interacting orthogonal gelators is less well explored. Coupled

orthogonal self-assembly can give rise to single continuous gel networks comprising two or more intimately mixed gelators either in a stoichiometric ratio to give a co-gel arising from a well-defined gelating supermolecule, or in continuous, non-stoichiometric blends (analogous to polymer blends). Stoichiometric supramolecular co-gels have recently become topical, as in the work of Dastidar on dipyridylurea-carboxylic acid derivatives[22] and the work of Smith on diamine-linked dendrons.[23] There is also a significant field based on metallogelators where the components are metals and gelating ligands.[24] These examples build on earlier work on aminopyrimidine/dialkylbarbituric acid mixtures.[25] Non-stoichiometric multicomponent gel blends based on different amino acid derivatives of bis(urea) gelators are currently under exploration by our own group in which the gelation and sol formation can be probed by fluorescent reporter groups blended with the principal gelator.

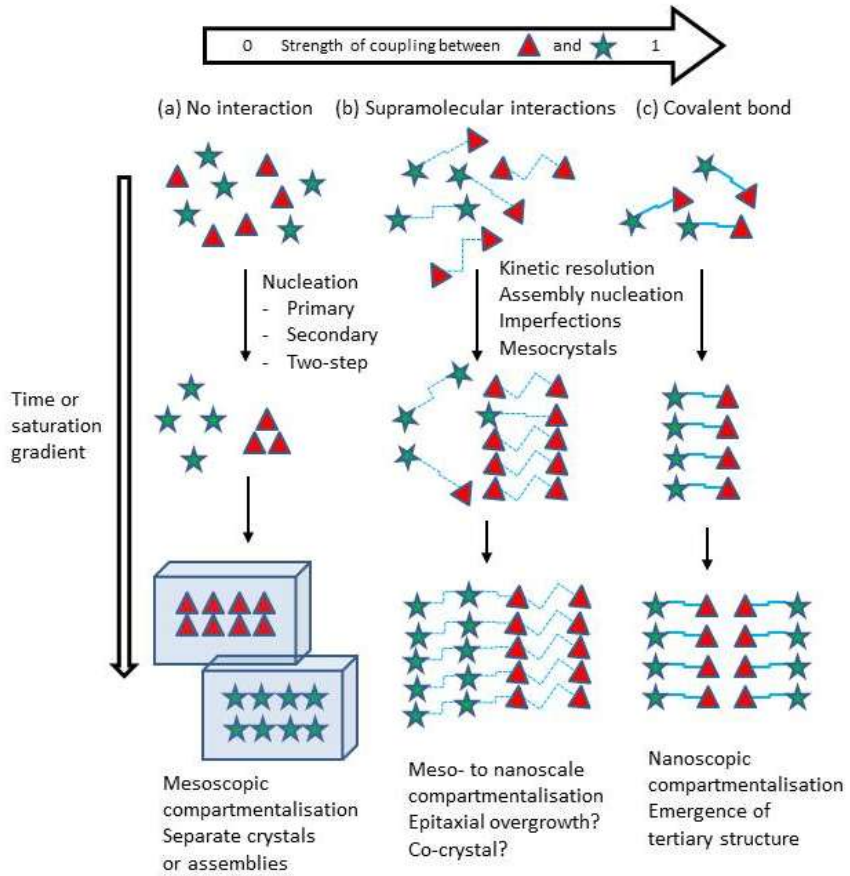

Fig. 1 Two-component, orthogonal self-assembly under a supersaturation gradient as a function of the degree of coupling between the individual components

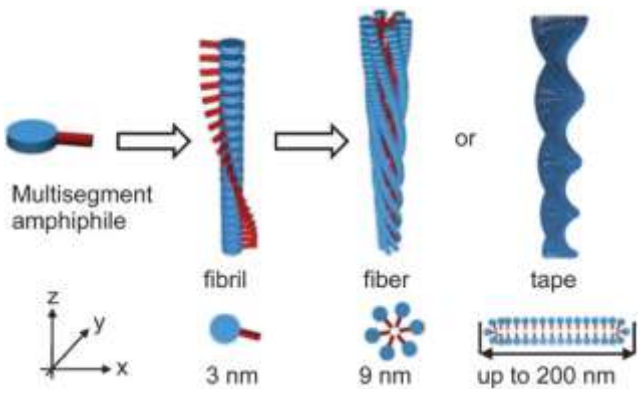

Fig. 3 Self-assembly of a covalently linked gelator/amphiphile into a fibril, hydrogen bonded in the z-direction. Additionally, due to hydrophobic interactions between the surfactant segments, five to seven fibrils assemble into 9 nm fibres or up to 200 nm tapes depending on the concentration (reproduced with permission from ref. 18)

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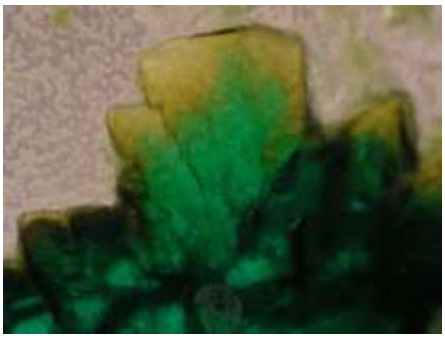


Fig. 4 Growth of yellow $[\{Cu(L)\}_2(\mu\text{-}Cl)_3]^+$ daughter phase on the green parent crystals of $[Cu(L)Cl_2]$ (reproduced with permission from ref. 20).

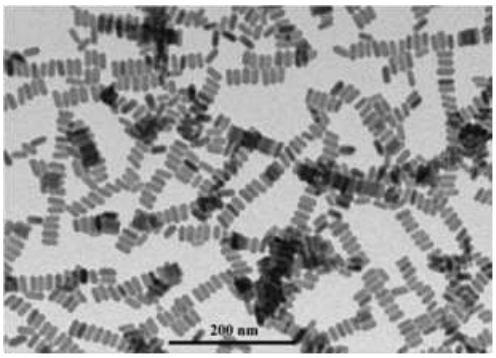


Fig. 5 TEM image showing ordered chains of prismatic $BaCrO_4$ nanoparticles prepared in AOT microemulsion (reproduced with permission from ref. 21)

Crystallization in Hydrogels

A well-known example of multi-component self-assembly is the formation of crystals within a gel medium. The technique of growing crystals in gels has its origins in the work of German chemist Raphael Eduard Liesegang who observed the famous periodic precipitation in gels known as 'Liesgang rings'.[26] These gorgeous patterns arise from the periodic precipitation of a weakly soluble salt such as silver chromate as a soluble precursor such as silver nitrate diffuses through a hydrogel containing potassium chromate, Figure 6. In this case the gel is pre-formed before the crystallization process begins but in other cases both the gel and crystal formation start from a homogeneous solution into which both gelator and crystallization substrate are both dissolved. A review on the early work on gel crystallization was published as long ago as 1917,[27] but it was not until the 1970's that the search for semiconducting and laser active materials prompted a surge in interest in the technique, summarised in a 1976 book on the topic by Henisch.[28] Gel phase crystallization represents a prime *de facto* example of orthogonal self-assembly of the crystals and gel network, which are generally microphase separated and retain a distinct identity, although in some cases the gel influences the outcome of the (generally slower) crystallization process. Formation of crystalline minerals, or protein crystals from aqueous silica gel or organic biogels such as agar or gelatin is a commonly used contemporary technique often resulting in higher quality, larger crystals suitable for protein crystallography, as shown in Figure 7.[29] There is even speculation that the formation of metallic gold deposits in quartz has its origins in the reduction of aqueous gold salts in gelatinous silicic acid, and this geological phenomenon parallels recent work reporting the use of gels to bring about the controlled formation of gold and silver metallic nanoparticles in supramolecular gels.[30, 31] The role of the gel in a crystallisation process is generally taken to involve slowing down the diffusion of reactants, preventing convection currents and sedimentation and reducing the number of nucleation sites, for example by passivating high energy defects on the glass container. Potentially, the gel may also itself act as a high energy surface capable of actively nucleating new crystal forms, although this aspect is underexplored. For example, chitosan gels, can template the formation of the metastable vaterite form of calcium carbonate by hydrogen bonding to carbonate anions to create a nucleating surface onto which successive layers of calcium ions and thence more carbonate can deposit.[32] A classical gel phase crystallisation therefore involves very slow diffusion of two reactants together in an aqueous silica gel to produce an insoluble product that deposits in the gel medium. The product is then isolated by mechanical removal or chemical dissolution of the gel, *e.g.* by strong acid. In a particularly novel recent report laser-induced nucleation has been used to grow crystals in an agarose gel in a highly patterned manner.[33] Another interesting aspect is the use of the chirality of biopolymer gels to influence the handedness of a crystalline product such as sodium chlorate, $NaClO_3$. Sodium chlorate is an achiral salt but it crystallises as a conglomerate (mixture of individual left and right handed crystals) in the Sohnke space group $P2_13$. Crystallization of this material from solution gives a statistical 50:50 mixture of left and right handed forms. However, a study by Petrova and co-workers showed that crystallization in agarose appears to bias this distribution because of the chirality of the gel.[34] The same group have also examined the effect of biopolymer gels such as agarose, carrageenan and gelatin on the morphology of the amino acid L-asparagine monohydrate as a model of a small molecule molecular crystal.[35] They conclude that gel methods can be an effective means to modify the crystal morphology of small molecules in ways that are not attainable using conventional solution phase crystal growth. The spectacular image of asparagine monohydrate crystals grown from agarose hydrogels or aqueous DMSO is shown in Fig. 8.

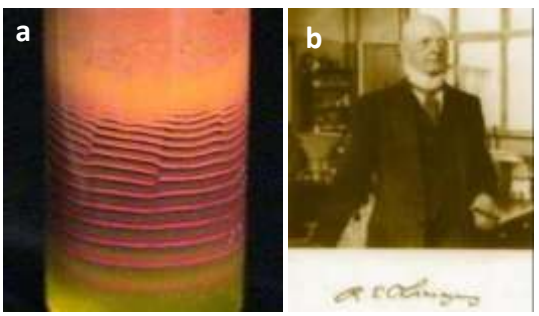


Fig. 6 (a) Liesgang rings arising from the diffusion of silver nitrate through potassium chromate in silica gel (reproduced with permission from http://polymer.bu.edu/ogaf/html/chp62exp1.htm), (b) Raphael Eduard Liesegang

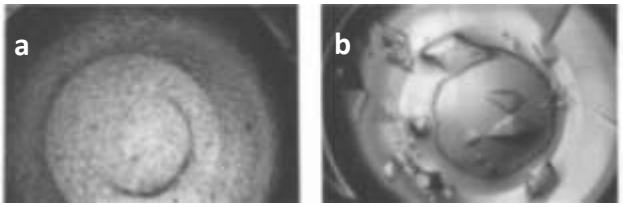


Fig. 7 Crystals of thaumatin grown (a) in the absence of gel, (b) in the presence of silica gel (reproduced with permission from ref. 29)

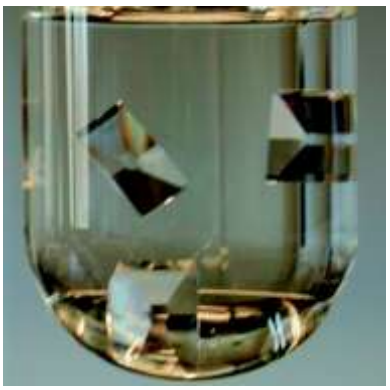
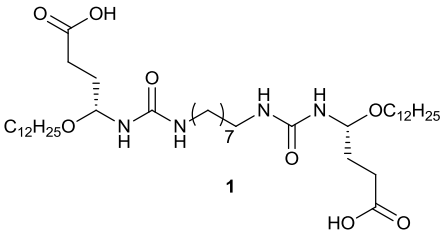


Fig. 8 asparagine monohydrate crystals with an unusual habit growing in an agarose hydrogel (reproduced with permission from ref. 35)

Crystallization in Low Molecular Weight Supramolecular Gels

Low molecular weight (supramolecular) gels can potentially offer a number of advantages as crystal growth media because of their synthetic and structural versatility and the fact that their supramolecular nature means that the sol-gel transition is readily reversible (*e.g.* by stimuli such as changes in temperature, pH, sonication, irradiation or addition of a chemical trigger such as a metal, cation, an anion or a molecular additive). The fact that a very wide range of simple LMWG can be readily synthesised means that their structure can be readily adapted to tune their solubility allowing access to a huge range of organogels as crystallization media. In general, while there are a few reports of crystallization from non-aqueous media such as the crystallization of 1:1 complexes of quinones with hydroquinones out of Sephadex LH.20 (an alkylated cross-linked dextran) or the crystallization of silver bromide from polyvinyl chloride in dimethyl sulfoxide,[36] organogels are highly under-utilised as crystal growth media. LMWG also offer the potential to synthesise gelators that match the chemical structure of the crystallization substrate and hence provide an active nucleation surface. This aspect is currently the object of intense focus in our laboratories.

LMWG have only very recently been employed as media for crystal growth. The first report came from work by the Hamilton group in 2004 who used a hydrogel formed by gelator **1** which bears a carboxylate calcium binding domain, to grow calcite crystals.[37]



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There is good evidence for the occlusion of gel fibres within the growing crystal and indeed a fascinating report uses TEM tomography to demonstrate the occlusion of agarose fibres within a calcite crystal (Figure 9). The channels created by the gel fibres can be induced to close up upon removal of the organic matrix by heating at 400 ^{o}C to give 'bubbles' within the crystal.[38] This is an interesting result because the force exerted by the crystal as it grows is thought to be sufficient to break most polymer gels.[37] This means that there must be an attractive interaction between gel and crystal, reinforcing the idea that gels such as **1** are capable of binding calcium ions.

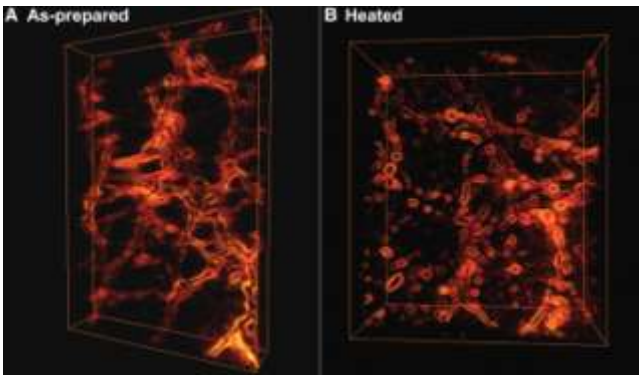

Fig. 9 Tomographic reconstructions of (a) an agarose network inside of a section of as-prepared calcite crystal and (b) cavities inside of a section of heated crystal (reproduced with permission from ref. 38)

Obtaining single crystal structures of the gelators themselves in order to understand their structure and hence gain at least some insight into the way they may pack in gel fibres, is notoriously difficult and examples tracing the relationship between supramolecular crystal-forming motifs and their ability to transform into the fibril-like structures are rare.[39] Gels can transform slowly to crystalline substances over time, highlighting their sometimes metastable nature. For example, the LMWG *N*,*N*′-bis(4-pyridyl)urea can be crystallised by from its gelling solvent system of ethylene glycol / water when the gel is kept at room temperature under ambient conditions in an open test tube for about a month. The resulting three-component structure can be regarded as a snapshot of the gelator interacting with its gelling solvents.[40] Extensive efforts have been made to investigate the structural relationship between the gel fibres and crystal phases but it can be very difficult to correlate gelator crystal structure with gel structure.[41] There are a few reports of crystallization of gelator components or the gelators themselves crystallizing from their gels. For example, Tang and co-workers have reported the spontaneous transition of a *meta*-hydroxy pyridinium salt of a 1,2,4,5-benzene tetracarboxylic acid gelator into macroscopic crystals.[42] *In situ* gel-to-crystal transitions of silver(I) complex of bisbipyridines and a fluorinated cyclic β-

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aminoalcohol gelator have been reported by Gao and co-workers.[31] A lovely example was reported by the Braga group of four different polymorphic forms of a silver(I) complex of 1-phenyl-3-(quinolin-5-yl)urea being obtained by drying gels in a sealed tube, presumably representing a form of a gel-to-crystal transition.[43] Serendipitous conversion of labile pyridyl urea coordination complex gelators to crystals within their gels has also been observed by our own group.[44] In our work we have focussed on the use of supramolecular organogels to influence the habit, crystal quality and polymorphic outcome of the crystallization of small molecular organic compounds, particularly pharmaceuticals. The crystallization of pharmaceuticals from gels is highly underexplored although Coquerel and coworkers have obtained two polymorphs of the drug (±)-modafinil from a gel medium obtained from the hydrolysis and condensation of tetramethoxysilane. In addition to the known monoclinic form I these workers also obtained single crystals of the predicted orthorhombic form III. A third morphology isolated from the gel proved to be a twinned sample.[45]

Pharmaceutical solid form selection and polymorph screening is an issue of tremendous and growing industrial and commercial importance. Different crystal forms (polymorphs, solvates, salts or co-crystals) have different bioavailability and solubility characteristics, and the crystal morphology (needle, plate, block *etc.*) significantly affects processing and tabletting behaviour. There have been a number of high profile cases where failure to identify the most stable crystal form of a drug has led to severe formulation problems in manufacture. In one famous case, Abbott Laboratories introduced the anti-AIDS drug ritonavir in 1996. After 18 months on the market a previously unknown polymorph was suddenly detected during manufacture. The reasons for the change were unknown but were thought to be due to some subtle alteration in manufacturing conditions, particularly impurity profile, and seeding by microscopic particles of the second polymorph.[46] The new form proved to be thermodynamically more stable than the original polymorph. In this regard it obeys the classic Ostwald's step rule which states that in general it is not the most stable, but the least stable polymorph that crystallizes first with increasingly more stable forms crystallising out in stages. From a legal standpoint different solid forms are sometimes independently patentable. In a famous case GlaxoSmithKline defended its patent for the polymorph type II of ranitidine hydrochloride, the active ingredient in Zantac, a stomach acid production inhibitor, against competitors when the patent on polymorph type I had already expired.

We have crystallized a range of drug substances such as carbamazepine, sparfloxacin, piroxicam, theophylline, caffeine, ibuprofen, acetaminophen (paracetamol), sulindac and indomethacin in supramolecular organogels such as **2**.[47] A typical procedure comprises warming a solution of gelator and drug substance in a compatible solvent to give a homogeneous solution and allowing the mixture to cool. The gelation and crystallization processes are orthogonal and generally time-resolved with gelation occurring over a period of minutes followed by crystallization over a period of hours to days. As a result no co-crystal formation is evident. The supramolecular gel results in alteration of the polymorphic outcome in the case of carbamazepine including the observation of the unusual form I, and the growth of larger, better quality crystals in many cases. Bis(urea) organogels can be readily dissolved by addition of good hydrogen bond acceptor anions such as acetate and hence crystals can be conveniently recovered from the gels (Figure 10). However, one drawback is that crystals of substances that themselves bind to anions are dissolved by them.

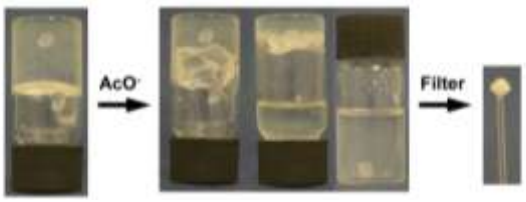
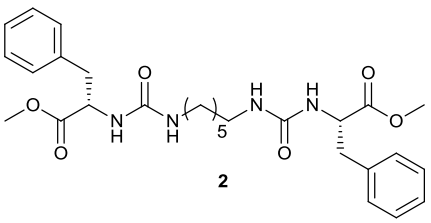
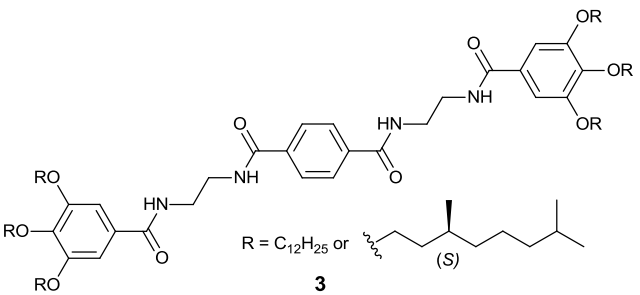


Fig. 10 Recovery of a single crystal of carbamazepine form III by acetate anion triggered gel dissolution of a 1:9 $CHCl_3$:toluene gel of gelator **2**. A single large drug crystal is grown in the gel which is then dissolved by addition of acetate anion (reproduced with permission from ref. 47)



2

The crystallization of carbamazepine, aspirin, caffeine and indomethacin within supramolecular gels have been reported by Sànchez and co-workers[48] who used organogelators of type **3**. In pure toluene and in gels of achiral **3** the thermodynamic form III carbamazepine was observed, however the chiral gelator gave a mixture of forms II and III.[48]



3

A recent report demonstrates the potential of polymer microgel particles to markedly influence the polymorphic outcome of the crystallization of carbamazepine and ROY (so-called because of its many red, orange and yellow polymorphic forms). The crystallization process is governed by the effects of nanoconfinement, interfacial interactions and gel-induced nucleation kinetics, which in turn depend on the polymer microstructure and the chemical composition.[49] Finally, Gunnlaugsson and co-workers have very recently reported the fascinating growth of single crystal halide (e.g., NaCl, KCl, and KI) nanowires from supramolecular gels upon dehydration to give "chemical nanogardens".[50] This unusual result suggests that supramolecular gels have interesting applications in controlled morphology modification.

Conclusions

Overall supramolecular gel phase crystallization offers an extremely versatile new tool in the search for novel, metastable or hard-to-nucleate polymorphs with potential applicability in pharmaceutical polymorph screening and solid form discovery. Gel phase crystallization is an effective way to grow high quality crystals for X-ray diffraction and can shed light on the crystal nucleation and growth process particularly in the context of crystal habit modification. Crystallization and gelation have many features in common in that both occur under non-equilibrium conditions driven by a supersaturation gradient. Bringing about such supersaturation conditions in multi-component systems containing weakly interacting molecules offers intriguing possibilities in terms of the formation of segregated, orthogonal gel networks, gels and crystals, or intimate co-gel blends. The influence of a co-located gel network on the outcome of a crystallization process represents one example of a range of emergent phenomena that such weakly coupled, multi-component, non-equilibrium self-assembly process can offer.

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Notes and references

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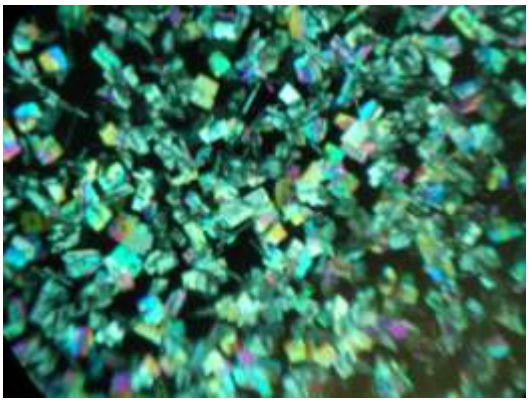
Graphical Abstract



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