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Review

Low-Molecular-Weight Gels: The State of the Art

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Low-molecular-weight gels are currently a hugely important class of materials that are attracting significant interest. These gels are formed when small molecules self-assemble into one-dimensional structures that entangle and cross-link to form a network that is capable of immobilizing the solvent. Here, we critically discuss the current state of the art and highlight two key areas where we believe there is significant untapped potential. The first is the observation that the properties of the gels are highly process dependent, which means that it is possible to access materials with very different properties from a single gelator. Second, using multiple gelators offers the opportunity to prepare materials with a high degree of information content and with a wider range of properties. We aim to spark thought and discussion on these aspects.

INTRODUCTION

Low-molecular-weight gels (LMWGs), or supramolecular gels, are a fascinating and useful class of material. The gels arise from the self-assembly of small molecules into long, anisotropic structures, most commonly fibers.[1–5] At a sufficiently high concentration, these fibers entangle or otherwise form cross-links, leading to the network that is able to immobilize the solvent through surface tension and capillary forces.[1,2] These gels differ from permanently covalently cross-linked polymer gels because the cross-linking can be reversed by the input of energy, for example, by heating.[6] LMWGs have been around for many years but are receiving considerable current interest.[4] They are also used in industrial products,[7] although this seems rarely discussed in the academic literature.

In addition to the industrial applications, many recent advances and uses are being described.[8–12] The specific self-assembly leading to gel formation can be exploited. For example, the fiber formation is a result of molecular stacking, meaning that the self-assembly leads to aggregates that can be suitable for optoelectronic applications.[13,14] The ready reversibility of gelation can be exploited, for example, to release cells from gels on demand in a manner that does not lead to cell death.[15] Ready gel formation by a simple trigger can also be used to allow easy and efficient gel loading.[16–18] Unsurprisingly, therefore, there is significant interest in these materials (Figure 1).

This is a fascinating area and in many ways holds attention because of the difficulties in probing and understanding the gels. The gels arise from assembly across many length scales, and understanding all of these is difficult. At the molecular level, the molecules must interact in a manner that leads to the formation of suitable aggregates that can eventually entangle. Thus, one-dimensional growth must be favored. From this perspective, it is very frustrating that it is often extremely difficult to predict whether a molecule will form a gel or not; indeed, gelation has been described as an empirical science.[4] Structurally similar small molecules can exhibit

The Bigger Picture

Gels are ubiquitous soft solids that are widely used in everyday life. Most gels are based on polymeric materials, as either entangled biopolymers or covalently cross-linked networks. Low-molecular-weight gels, or supramolecular gels, are another fascinating and useful class of gel. Here, the assembly of small molecules into a network immobilizes the solvent. These materials are becoming increasingly common and offer an opportunity to prepare interesting, designed, and responsive systems. Specific areas where we believe that there will be advances include exploiting the process-dependent nature of gelation and systems that utilize multiple gelators to access new properties.

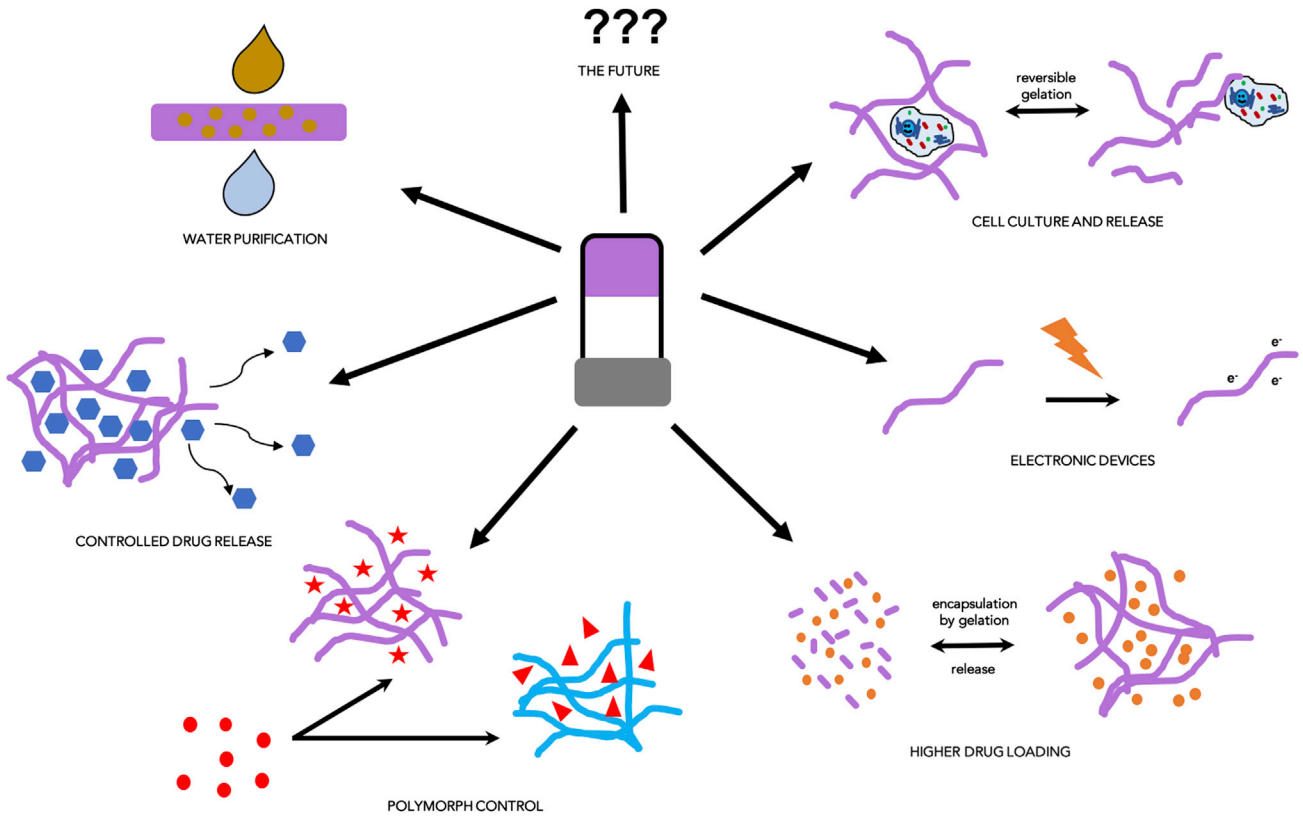

Figure 1. Uses of Low-Molecular-Weight Gels

Cartoon showing some the potential uses of low-molecular-weight gelators, including cell culture and differentiation with non-harmful release from the gelled material, photoresponsive semiconducting gel fibers, high loading of a drug particle with a targeted release, slow and controlled drug release upon addition of a stimulus, water purification by the removal of heavy metals, and the control of polymorph by changing the gel network.

extremely different propensity to form gels. A number of methods have been attempted to overcome this.[19,20] A number of people have attempted to link gelation to crystal structures.[21–23] In many ways, this seems surprising. It is not at all clear that there is (or even that there has to be) a link between the interactions that lead to crystallization in some situations and gelation in others. Indeed, although it has been widely assumed that there is a link, there are a number of examples that now specifically show that packing is different in the gel phase and crystals grown even from the same solvent.[24–26] As a specific example, we showed that fiber X-ray diffraction data from the gel phase did not match the crystal structure of a crystal grown directly from the gel phase.[24] In many cases, the crystals formed in one solvent are compared with a gel formed in another. Here, it is especially difficult to see why there has to necessarily be a link, considering how many properties change on replacing one with another. Even where some crystallinity has been implied in the gel phase,[27] it is not clear how these data can be shown to not arise from simply some (possibly a very small amount of) crystallization within an amorphous gel phase. There is debate here, but to our minds there is no reason to necessarily assume that there is a link between crystallization and gelation.

Other methods that have been used to tackle this inability to predict gelation include using libraries and computational approaches. The library approach simply involves generating a large number of similar molecules and then determining which form gels.[28–30] This brute force approach is often successful in finding gelators, but it is

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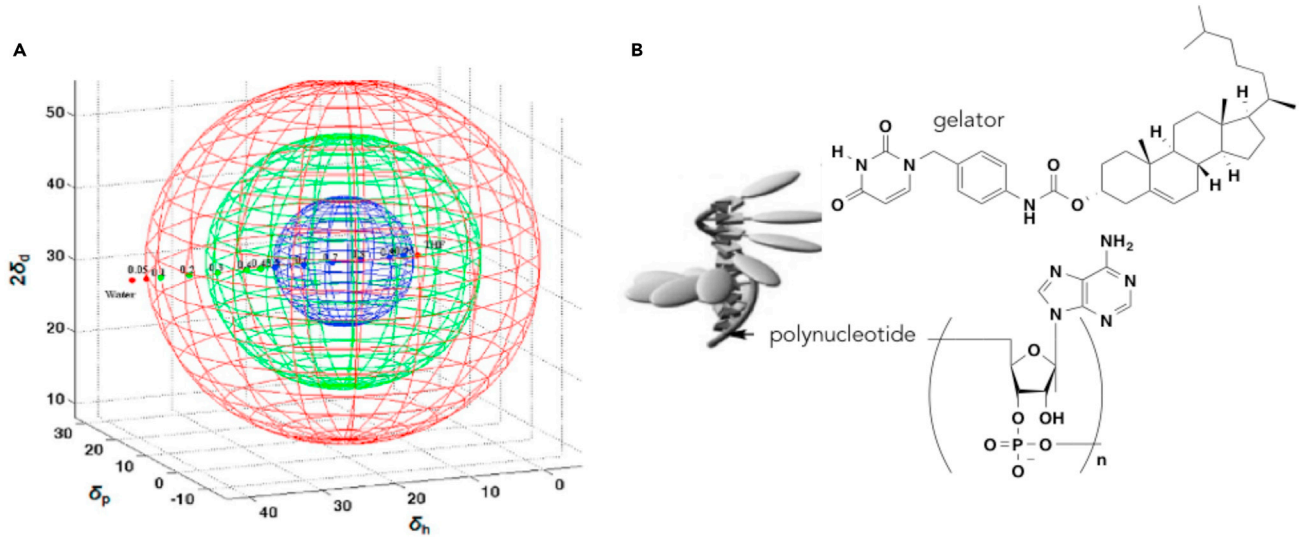

Figure 2. Understanding Gelation

(A) Plot of solubility data for a specific molecule in Hansen space; blue shows where the molecule is soluble, green shows where a gel is formed, and red shows where the molecule is insoluble. Adapted with permission from Yan et al.[39] Copyright 2013 American Chemical Society.

(B) Schematic illustration of a polynucleotide interacting with a gel fiber. Adapted from Numata et al.[40] with permission of the Royal Society of Chemistry.

less effective in explaining why some molecules can form gels and others cannot. Presumably, this is because it is difficult to vary only one parameter at a time. For example, changing one functional group to another will result in a change in the steric bulk of the molecule, the ability to pack, possibly the number of hydrogen bond donors or acceptors, the absolute solubility in a particular solvent, etc. Hence, simple lists of gelators and their efficiency often do not capture the complexity of the system. Recent advances in computational approaches have been successful in predicting gelators. Tuttle's group has effectively predicted tripeptide-based gelators,[31] and we have recently been successful in generating a descriptor-based approach that can be used to predict new gelators.[32] However, in both cases the methods again do not explain why some molecules form gels and others do not.

At this point, the simple statement that a specific molecule can form gels is simplistic at best. This statement holds for the molecule in certain solvents, at certain concentrations and temperatures, potentially in the presence of certain additives; most critically, if the same process has been used as the authors describe in the work. Taking these in order, each molecule will form gels in a specific range of solvents (which might be only one!). Clearly this is simply a result of the interactions between molecule and solvent balancing in certain solvents to favor self-assembly into the required one-dimensional aggregates. Recent key work here has shown that this can often be predicted from the properties of the solvent, for example the Hansen solubility parameters (Figure 2A).[20,33,34] Second, each gelator forms gels only above the so-called minimum gelation concentration (mgc). For LMWGs, this tends to be low (typically <1 wt %), but it is therefore possible that when a molecule is stated to not form a gel in a specific solvent, it could simply be that the mgc has not been reached. Also, although it is often assumed that the molecular packing and supramolecular aggregates are the same above and below the mgc, this is rarely proven. Temperature is a key parameter; most LMWGs melt and the range of temperatures over which the gel is stable is variable and again hard to predict and understand. Additives are known to both hinder and promote gelation,[35,36] often again without a

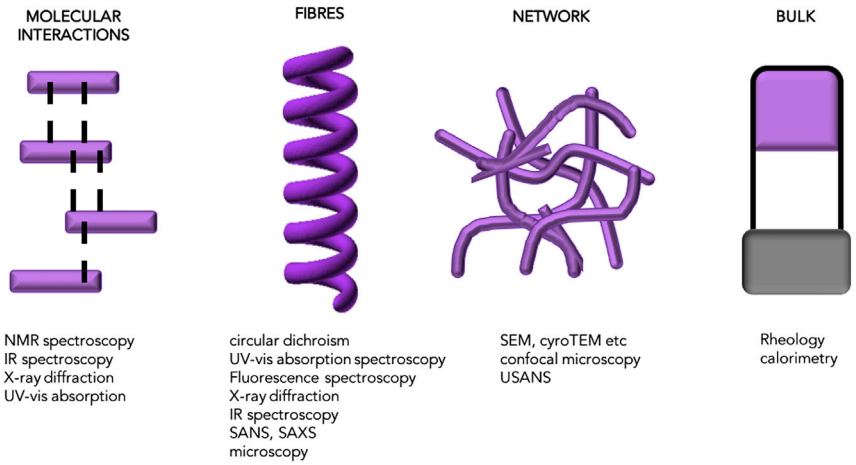

Figure 3. Hierarchical Assembly across Length Scales

Low-molecular-weight gels form as a result of assembly across a range of length scales; different techniques are appropriate for analyzing the structures formed at each length scale.

detailed understanding. In some cases, it has been shown that salts can affect aggregation on the basis of the Hofmeister series,[37] and certain polymer additives have been shown to affect gelation by specific interactions (Figure 2B).[38]

An interesting issue is the process of gelation (or the formulation used to prepare the gel). In our opinion, a simple statement that X gels in solvent Y only holds for the caveat "using the methods described" unless shown otherwise. How one carries out the gelation can lead to very different materials, as well as examples where a molecule can go from being an effective gelator to being ineffective. We return to this below.

Returning to the issue of understanding gels across length scales, assuming the molecules assemble into fibers, the mechanical properties of individual fibers have been shown to be controlled by intermolecular interactions, and so are related to the chemical structure of the gelator.[41] Once fibers have been formed, these can then conceptually interact in a number of different ways. Lateral association is possible, leading to bundling and fiber thickening. Entanglement is also possible. There are also examples where fiber branching has been shown to occur. At the next length scale, the network that is formed from the fibers can be homogeneous or heterogeneous. Finally, the final (often overlooked) parameter is aging. A number of reports of how gels can change in different ways have been reported,[42–44] but it is extremely common for the time at which the gels were analyzed not to be mentioned. Some interesting observations include gel-to-gel transitions,[44,45] syneresis,[46,47] and transient network formation.[48]

Hence, to attempt to understand gelation, a wide range of skills and techniques need to be used (Figure 3). To understand the molecular packing, techniques such as nuclear magnetic resonance (NMR) spectroscopy, infrared spectroscopy, circular dichroism, fluorescence, and X-ray diffraction are used.[49,50] Although all of these can be informative, there are always caveats. Circular dichroism, for example, is very sensitive to concentration, and so good-quality data can often only be collected at concentrations lower than the mgc. There are therefore questions as to whether the packing in aggregates below the mgc is the same as at and above the mgc. Similarly, fluorescence cannot be easily collected on turbid samples, and again higher

concentrations makes this difficult to collect because of quenching, and X-ray diffraction makes the assumption that the diffraction (if any is observed) is from the gel phase as opposed to crystalline impurities. Nonetheless, such techniques can be hugely informative. For example, NMR spectroscopy can be used to both probe the rate of assembly and to infer information about the molecular interactions leading to assembly. Likewise, infrared spectroscopy can be used to show that specific hydrogen bonding is occurring on assembly.

At the next level of hierarchy, the nature of the fibers is usually probed by microscopy or by small-angle scattering. Any electron microscopy image can only represent a tiny fraction of the sample. Also, unless cryo-transmission electron microscopy (TEM) is used, there could be drying artifacts in the sample preparation. However, in general, microscopy most often shows the presence of long fibers, commonly entangled or branched. In the gel phase, this network is of course be in three dimensions, but collapses to two dimensions when examined by microscopy. Three-dimensional imaging can be captured by confocal microscopy. Although there are significant advances in this area, most examples have relatively low resolution. Nonetheless, confocal imaging can provide useful information on the microstructure and distribution of the fibers in space. Small-angle X-ray or neutron scattering are hugely powerful techniques for imaging gels; the imaging can be done *in situ*.[51] Although access to a beamline at a facility is usually required, the quality of more accessible lab-based X-ray equipment is improving constantly to allow access to good-quality data. The scattering data of course have to be fitted to a model, but the advantages are that these are bulk measurements, representing the sample as a whole.

Finally, the mechanical properties of the gels can be measured by techniques such as rheology.[52] A range of different measurements are possible and are able to inform on the gel networks. A typical LMWG will have a storage and a loss modulus (G' and G'', respectively), which are frequency independent, and will break at relatively low strain. It is surprising how often simple vial inversion is used as a means of proving gelation, despite the concern that this does not necessarily demonstrate that a gel has been formed; viscous liquids can also be stable to inversion, albeit for a relatively short time.[53] It is also apparent to the careful reader that some of the inverted samples seem to be in the process of flowing. From the rheological data, different behavior is often shown, which implies that there are different underlying networks, although significantly more work needs to be done here to understand this.

Hence, at the moment, we believe that these soft materials are hugely interesting, but there are still a significant number of areas where there is a lack of understanding. One reason for this is that there are few reports that truly examine a system across all length scales. A highly readable account of a single gelator system has been prepared by Menger and Caran;[54] the length of this single report shows why perhaps such in-depth studies are not common in today's publishing regime.

Here, we now wish to focus on what we believe are two real opportunities for the future: controlling the process and mixing LMWGs. To some degree, these have been covered in previous reviews,[55–60] but as the field is developing rapidly we believe that a further critical analysis is warranted. Both of these areas also allow us to further discuss the assembly process. A typical cartoon of gelation is shown in Figure 4; it is often assumed that the molecules are initially freely dissolved. On applying a trigger, the molecules begin to assemble and then form fibers, which

Figure 4. How Gelation Is Thought to Occur
"Standard" cartoon of gelation.

entangle to form the network. To our current thinking, the veracity of such a cartoon is unclear, and it is worth considering when probing these soft materials.

PROCESS OF ASSEMBLY

Taking these in turn, we touched on the process of gelation above. Essentially here, we are stating that how the gel is formed matters. To some degree, this perhaps seems obvious. A gel is formed by solubilizing or dispersing a molecule, and then triggering the gel formation. It is worth also considering that each solid form of the gelator might not be the same, with different polymorphs potentially having different solubility, etc.[61] It is necessary to initially have the molecule in a more solvated state than at the end. This can be achieved by heating to improve solubility, initially dissolving in a good solvent before adding an anti-solvent, choosing a pH at which the molecule is soluble and then adjusting the pH in one of a number of different ways to render the molecule less soluble,[62] adding a salt to charge screen,[63] using a pro-gelator with a cleavable, solubilizing group,[64] or using a chemical or enzymatic reaction to generate the gelator *in situ* from suitable precursors.[65,66] To the best of our knowledge, there are no examples where a molecule is simply added to a solvent and gelation results (although there are many examples where "instant" gelation can be induced by mixing two components that react or interact to form a gelator on contact).[67] Because of this, how the gelation is carried out matters. Essentially, in many cases, the rate of gelation becomes competitive with the rate of mixing, and so the gel's properties are affected by how the gelation occurs. To some degree, this is caught up in the kinetically driven assembly; because at the point of gelation one is passing across a regime of super-saturation, the system is not at equilibrium, and hence error correction is not possible. We stress, however, that we do not necessarily mean that the local assembly of the molecule is affected (although it could be), but rather that the network is affected, resulting in different gel properties.

Taking what might initially seem to be the simplest method—heating and cooling—heating may or may not fully solubilize the molecule; it might be possible for dispersed aggregates to be formed instead. The absolute temperature and absolute duration of heating will both be critical. Finally, the rate of cooling, the final temperature, and the time after cooling could all be critical to whether a gel is formed and the properties of the gel itself. Surprisingly, these parameters are often not varied or not reported. However, to our minds, it is the properties of the gels that are often most important. Pragmatically, for many applications, it perhaps does not actually matter how or why the molecules assemble into fibers; instead, it is most important what properties the entangled networks provide to the system. It is perhaps reductionist to suggest, but if the gels reproducibly have the "right" properties, how they are formed is perhaps less important.

With this in mind, rather than approach these gels from the perspective of trying to understand how the molecules interact, or designing a library where some molecules gel and some do not, a more effective approach might be to find extremely robust gelators. Such robust gelators would ideally form gels in anyone's hands and preferably in a wide range of conditions. These could then be used to provide gels with a range of different properties by varying how the gels are formed.

Hence, here, it is not appropriate to simply list gelators and their properties. There are many reviews that already provide this information.[1–3,5,68] Rather here we mainly focus on one example where the process of gelation has been used to lead to significantly different outcomes. This example is hydrogelators; this could be one reason why sufficient data exist on the formation of gels under different conditions because, compared with organic solvents, water as a solvent opens up many additional parameters, including variations in ionic strength, pH, and the addition of background salts.

We focus mainly on a N-protected dipeptide. Such protected dipeptides are widely used hydrogelators, such that a significant number of groups have focused on this class of LMWG.[69,70] Naphthalene-protected dipeptides were first reported by Yang et al.[71] We have used this class of material and found that they can be very robust gelators. For example, 2NapFF can form hydrogels by using a range of triggers and is an excellent example of a complicated system that exemplifies how the process of assembly matters (Figure 5).[72]

First, this LMWG can be dissolved in an organic solvent such as DMSO. Addition of water results in a gel. This seems very simple, but there are many parameters that can be varied. First, the concentration of 2NapFF can be changed. Gels form down to a concentration as low as 1 mg/mL, with more turbid gels forming at 10 mg/mL (the highest concentration tested). As for other related gelators,[73] this method of self-assembly proceeds by the addition of water immediately resulting in a highly turbid solution. This clarifies over a period of minutes as the gel forms. Elsewhere, for a related gelator, we have linked this process to the initial formation of micrometer-sized spherical droplets,[74] which then decrease in concentration as the self-assembled fibers are formed. We have no evidence that the spherical objects are directly transformed to the fibers, although it has been suggested that fibers nucleate at the surface of the spheres for Fmoc-diphenylalanine.[75] We also note that Orbach et al.[76] have another interpretation for this change in turbidity for a related gelator. This phase-separation event implies that how the process is carried out will likely determine the outcome of the self-assembly and the gel properties. Again, for related gelators, we have shown that the choice of organic solvent in which the gelator is initially dissolved affects the outcome,[77] which is unsurprising as the solubility of the gelator will be different in each solvent, and different mixing rates of the solvents with water among other variables. Elsewhere, it has been stated that fresh solutions of the gelator in an organic solvent are always prepared to ensure complete dissolution of the LMWG,[73] but this is never actually proven as far as we can see. Mixing of DMSO and water is an exothermic process, which leads to the mixture heating slightly. Changing the ratio of DMSO to water used results in differences in the temperature increase.

Gels can also be formed from 2NapFF in other ways. Solutions of 2NapFF can be prepared at high pH (typically pH > 9) by addition of a base to deprotonate the carboxylic acid. Gels can then be prepared by the addition of an acid to re-protonate the carboxylic acid. Alternatively, a divalent cation can be added to form a gel at high pH; this is conceptually due to the cross-linking of biopolymers.

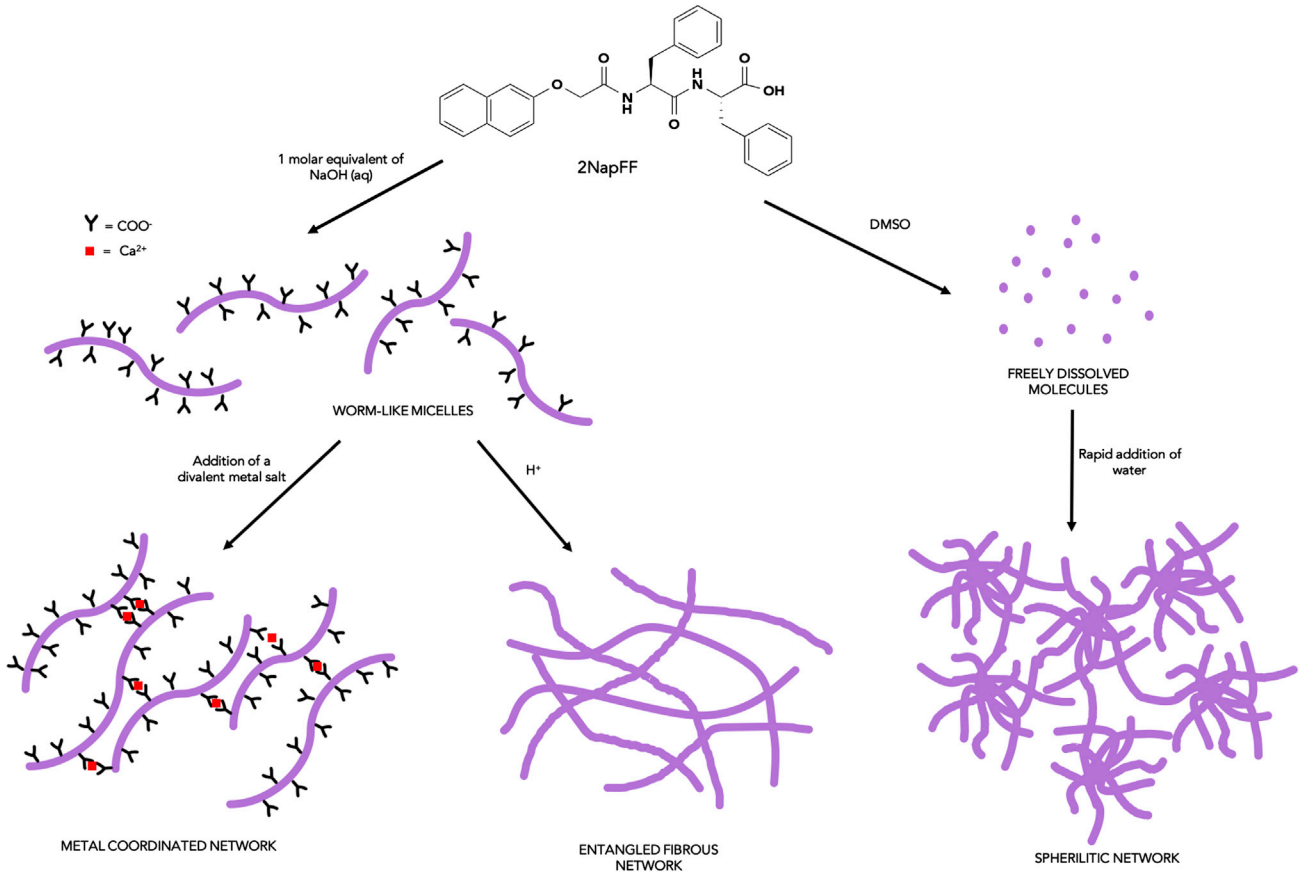

Figure 5. The Process of Assembly Affects the Outcome

The low-molecular-weight gel 2NapFF (at high pH, above the pK_a, the carboxylate will be formed instead) can form a gel in different ways, leading to different types of networks.

In both of these cases, a really important aspect is that the 2NapFF in water at high pH is effectively a surfactant.[78] The preparation of such solutions at high pH as the means of effectively solubilizing the gelator is common, but it is less common to address this surfactancy. It is more common for the schematic to imply that the LMWG is molecularly dissolved. This is not the case. Instead, a range of colloidal aggregates can be formed by this class of LMWG at high pH. These include spherical structures and worm-like micelles. The aggregate formed will depend on the absolute concentration of the gelator, as well as the pH, addition of salts, etc. Thus, there is a phase diagram at high pH of structures. For 2NapFF, we have shown that there is a critical micelle concentration (cmc) at very low concentration, where spherical structures are formed, and then a second cmc at a higher concentration where there is a transition from spherical micelles to worm-like micelles.[78] As the concentration is increased further, the worm-like micelles aggregate to form liquid crystalline phases.

Because of this phase diagram, there is clearly an effect of concentration of the gels of 2NapFF. When a solution of calcium chloride is added to cross-link the 2NapFF at high pH, gels are only formed essentially at concentrations where worm-like micelles are present.[78] Because this cross-linking requires the presence of deprotonated carboxylates on the gelator, the pH is critical. Similarly, the nature of the salt added is important. Weak materials are formed when monovalent cations are added (for example, sodium chloride);[79] in analogy with polymer systems, this is probably

simply a charge screening effect, meaning the worm-like micelles do not repel each other as strongly. Changing the divalent cation affects the gel's mechanical properties, as does changing the counterion for a fixed cation. These data can be linked to the Hofmeister series.

Finally, gels can be formed by lowering the pH of solutions of 2NapFF initially formed at high pH. This again sounds an easy process, but the mechanical properties of the gels and the homogeneity of the gels depend on how this pH drop is achieved. There are many ways that the pH can be decreased described in the literature for a range of low-molecular-weight gelators.[62,80–83] For example, mineral acids such as HCl can be added most simply as an aqueous solution, although for hydrophobic gelators, this often means that gelation and mixing compete strongly so that it is difficult to prepare reproducible gels.[80,84] It is also possible to rely on diffusion of gaseous acid into a sample, although in our hands we have found this difficult to control such that a specific absolute pH can be targeted. We instead tend to use glucono-δ-lactone (GdL), which dissolves quickly in water and hydrolyzes to gluconic acid to allow a slow, reproducible pH decrease.[80] Likewise, addition of glucose, hydrogen peroxide, and an enzyme can be used to produce gluconic acid *in situ*.[85] It is also possible to add other precursors that hydrolyze to give acids.[81] In all of this, reproducibility is really important; to our minds, there is little point in being able to form a gel if that gel does not have the same properties each time it is made.

For 2NapFF, with the use of GdL to lower the pH, the gels are again concentration dependent, and their properties will also depend on the final pH.[72] The apparent pK_a of the terminal carboxylic acid of 2NapFF is around 6.0.[86] This is perhaps surprisingly high for the terminal carboxylic acid of a dipeptide, but this is a common observation for this kind of gelator.[86–88] In fact, the apparent pK_a depends on the hydrophobicity of the gelator, the concentration in solution, and the solution temperature, and should probably be interpreted as the apparent pK_a of the self-assembled aggregate. In analogy with other systems, close packing of carboxylates and carboxylic acids results in an increase in the pK_a. For clarity, we always try to refer to this as the "apparent pK_a," because the data are accessed by a slow titration with acid; this always leads to gel formation to some degree so is not a true titration because there is no equilibrium between the species in solution.

At pH values below the apparent pK_a, gels are formed from 2NapFF solutions. The gel strength increases as the pH is decreased further. This can be interpreted as entanglement and fiber formation as sufficient charge is removed from the self-assembled structures. The gel strength increases as the charge is removed further until the rheological properties stabilize. For related systems, we have shown that it is possible for the gel network to start to contract when sufficient charge is removed, leading to syneresis of the gel; this is not observed for 2NapFF.[89]

It is unclear whether the worm-like micelles at high pH simply protonate as the pH is decreased to form the gel or whether there is a structural re-organization. Certainly, the small-angle neutron scattering (SANS) data show that the worm-like micelles at high pH have a hollow core. On decreasing the pH, the core is lost, and the scattering data can best be fit to an elliptical cylinder.[72] This could be interpreted as the structures re-organizing, or it is also possible that the initial structures fall apart and then new structures form. One interesting observation is that the gels formed at high pH by addition of a calcium salt decrease in gel strength dramatically when the pH is decreased, and then become stronger again as the pH drops below the pK_a.[79]

This implies at the very least that there is a rare gel-to-gel transition as opposed to a gradual change from one type of gel to another.

In all of this, we have simply been referring mostly to a gel being formed. We initially stated that the process was important in controlling the gel properties. So, what do we mean by the properties? There are a number of key aspects. First, we argue strongly that any described property must be reproducible, and we are constantly surprised by how infrequently error bars are included for many reported gel properties. Second, the properties that will be needed will of course be application specific. As such, a range of tests might be needed. Most simply, all of the mechanical properties of a gel will be the result of the self-assembled network. Hence, it is expected that the type of aggregate formed by the self-assembly (fiber, hollow tube, or helical stack), the propensity to laterally associate, the number and type of cross-links, and the homogeneity of the system will all play a role, and it is often difficult to deconvolute the relative importance of any one of these parameters.

In the example of 2NapFF here, the absolute storage and loss moduli (G' and G'', respectively) can be determined by rheological measurements. There are always potential issues here in terms of how the samples are loaded on to the rheometer; we tend to prepare our gels in plastic cups in which the measurements can be carried out directly to avoid loading issues. Looking at the gels formed by the three methods, at a concentration of 2NapFF of 10 mg/mL, the absolute moduli are similar. Hence, one might be tempted to say that the process does not matter. However, the strain sweeps clearly show that the gels break down at different absolute strain, with a different shape to the changes in G' and G'' (Figures 6A–6C) and the recovery after a high strain cycle is very different. Thus, it is likely that were one to want to pass the gel through a syringe for example, the gels formed by one process would be much more effective than the others. Similarly, as mentioned above, the increase in the moduli on increasing the concentration of 2NapFF is not always as expected, and so it would be easier to tune the absolute moduli for gels formed by one method than for another.

The effect of pH and concentration can be seen directly in the rheological data. For this kind of gelator, it is generally expected that increasing the concentration will lead to the formation of more self-assembled structures and hence most likely more cross-linking. Hence, increasing the concentration of LMWG should lead to an increase in the rheological properties. At pH 10.5, this is what we have observed on gelation by adding a calcium salt. In fact, the storage modulus (G') scales with concentration (c) as $G' \propto c^{2.4}$, which is perhaps indicative of a semi-flexible polymer network (if we assume that specific theories hold for this type of gelator).[90] However, at higher pH, G' likewise scales with concentration in the same manner, but critically only until a certain concentration is reached (4 mg/mL at pH 12). At this point, the gels actually become weaker as the concentration of the 2NapFF is increased.[72] This counter-intuitive observation can be explained in line with the observation of liquid crystalline phases, which presumably result from lateral aggregation of the worm-like micelles at these higher concentrations. As more 2NapFF is added, the lateral association increases, rather than there simply being more and more worm-like micelles present that can entangle. This means that the expected model of gelation is not followed. These data correlate with our work elsewhere on determining the pore sizes of gel networks.[91] The pore size at pH 12 was found to be higher at a concentration of 2NapFF of 10 mg/mL as opposed to at 5 mg/mL.

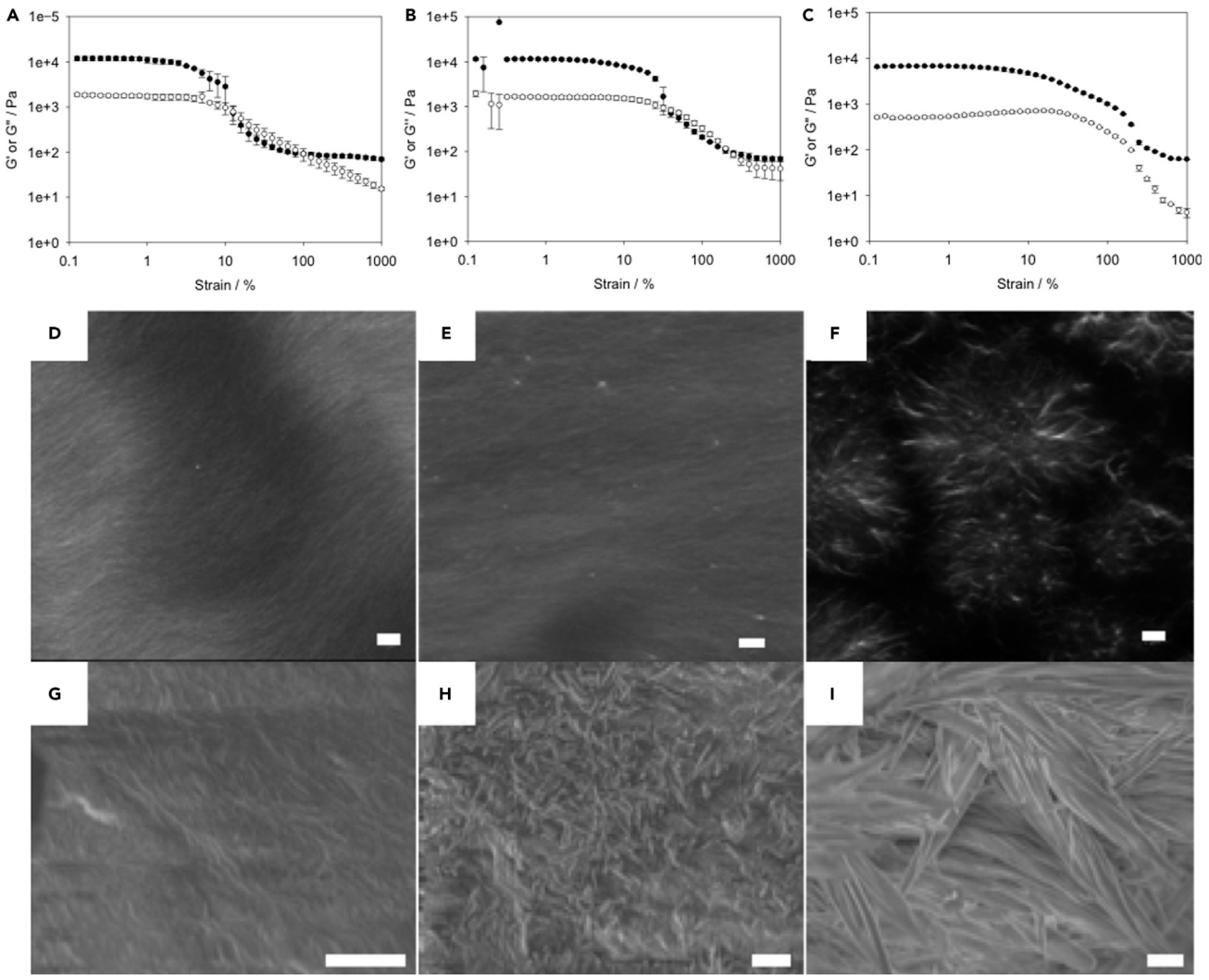

Figure 6. Effect of the Assembly Process on the Final Gel Properties

(A–C) Rheological strain sweeps of gels formed by (A) metal salt, (B) acid-triggered, and (C) solvent switch methods. *G′* is the filled shapes and *G″*is open shapes.

(D–F) Confocal microscopy images of gels formed by (D) metal salts, (E) acid-triggered, and (F) solvent switch methods. Scale bar represents 5 μm.

(G–I) SEM images of (G) metal salts, (H) acid-triggered, and (I) solvent switch methods.

Scale bar represents 1 μm. Adapted from Colquhoun et al.[72] with permission of the Royal Society of Chemistry.

Because these properties are different, it is interesting to consider why this is the case. The SANS data were different for the gels formed by the three processes, indicating different networks. The fibers imaged by TEM and scanning electron microscopy (SEM) were not significantly different, and so on this length scale, the one-dimensional structures are similar. However, the microstructure, imaged by confocal microscopy, was different in each case. Spherulitic fiber domains were found in the sample formed by dilution of DMSO solution with water. This agrees with our work on other systems gelled by this approach and seems to arise from a nucleation and growth process.[74] The gels formed by addition of calcium salts to a solution of 2NapFF at high pH show significant aligned domains, whereas a more typical cross-linked network is found for the acid-triggered sample. Hence, we can link the rheological properties to the network.

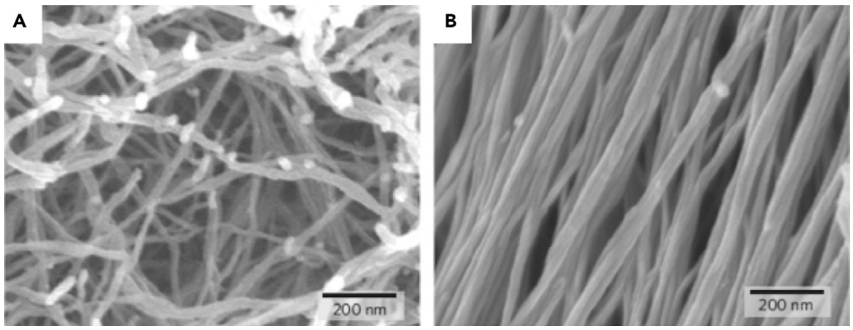

Figure 7. A Heat-Cool Cycle Affects the Solution Properties

(A) Gels formed by adding a calcium salt to a solution of a peptide amphiphile are formed from an isotropic network of fibers.

(B) Gels formed by adding the salt to a solution after a heat-cool cycle contain thicker structures that can be aligned by shear.

Adapted with permission from Zhang et al.[93] Copyright 2010 Nature Publishing Group.

We have focused here on one particular LMWG. However, it is clear that similar observations can be found with other examples. Greenfield et al.[92] have shown that gels with different properties can be formed from the same peptide amphiphile. As with the 2NapFF above, these can be gelled by the addition of a calcium salt to a solution of the LMWG in water or by the addition of acid. For a specific peptide amphiphile, the rheological data for gels formed by the two methods are different, most obviously in the breakage under strain, as well as the relationship between the G' and concentration. Here, the exponent x in the relationship $G' \propto c^x$ is very different, with x being 1.51 for the acid-triggered gels and 2.14 for the calcium-triggered gels, implying a very different underlying network for the gel.

Further interesting results that show how important the process is come from data on heating and cooling. Heating and cooling a solution of a peptide amphiphile results in very different properties, even though the final solution is at the same temperature as the initial solution. For example, the solution viscosity increased significantly.[93] The gel that was formed on addition of a calcium salt was also significantly stiffer than when the salt was added to a solution that had not been heated and cooled before the addition of the salt. The increased viscosity also allowed "noodles" to be drawn out. This was explained by the heating and cooling leading to the formation of aligned bundles of fibers, and so the fibers after heating have a higher diameter than before (Figure 7). These observations show how critical the process is; in many self-assembled, supramolecular systems (especially micellar aggregates as these peptide amphiphiles are), it is often assumed that the state is governed by the energy of the system. Hence, if the temperature is the same (which it is after the cooling cycle), then the structures formed should be the same. However, here, the authors speculate that water molecules associated with the supramolecular structures become bulk water during the heating cycle, leading to dehydration and fusion of the fibers. This is irreversible. Interestingly, we have very recently shown that heating can have a significant effect on the viscosity and extensional viscosity of solutions of 2NapFF.[94] Comparing these systems with the peptide amphiphiles, reduced diameter fibers were formed rather than those with increased diameters, showing that similar macroscopic observations can arise for different reasons.

This is all important as some applications require specific mechanical properties in addition to (or perhaps rather than) a specific chemistry of the fibers. For example,

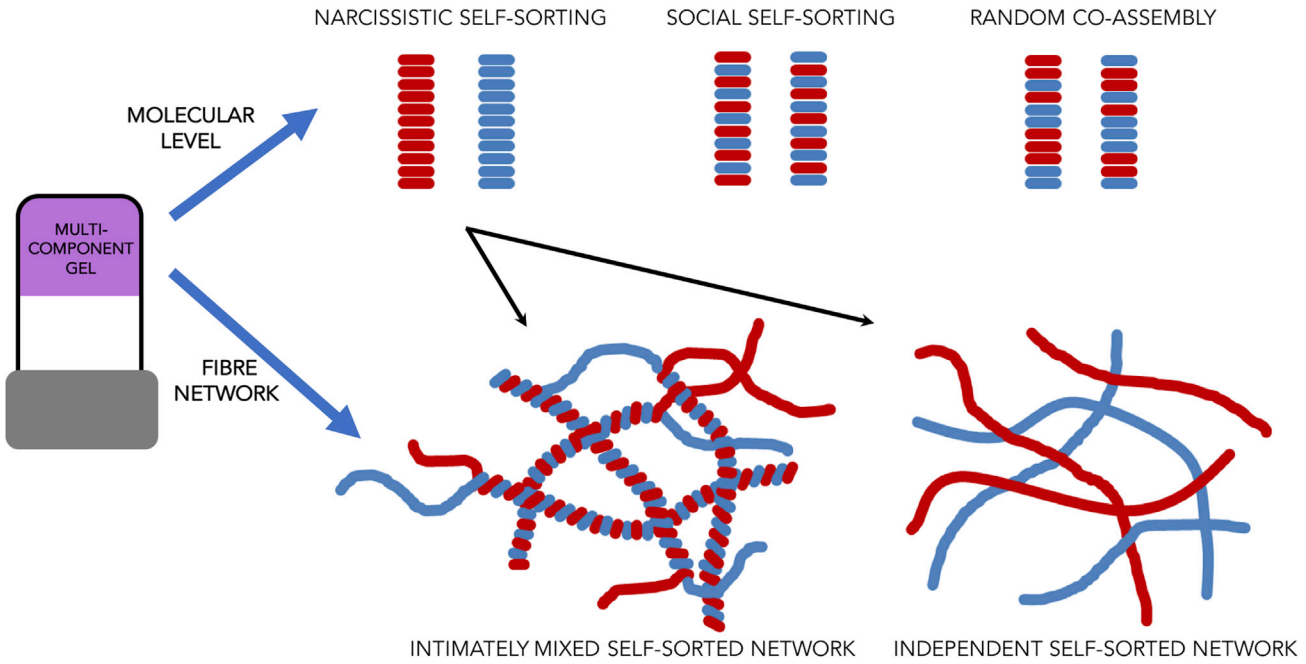

Figure 8. Multicomponent Systems

When both molecules can independently form fibers, mixed systems can lead to different possibilities on a molecular level (top). The properties of the gel will be controlled by this level of assembly and the next hierarchical level of assembly, where (for example) self-sorted fibers could heavily entangle or form an interpenetrating network (bottom).

the ability to pass a gel through a needle and have quick recoverability has been linked to the gel's microstructure.[95] Further changes in the properties of a peptide amphiphile system have been reported recently,[57] where different lengths of self-assembled fibers were prepared by varying the assembly process via dilution and annealing steps. Pre-myoblasts were grown in media containing either short or long fibers, with significantly higher cell death observed in the presence of the shorter fibers. This work clearly shows how an energy landscape can be navigated for a self-assembled system and how sensitive these peptide amphiphiles can be to the process of assembly.

MULTICOMPONENT SYSTEMS

The other area where we believe that there are significant opportunities for LMWGs is in multicomponent systems. Buerkle and Rowan[59] have defined three classes of multicomponent systems: (1) a two-component gel phase, where both components are needed to form a gel; (2) a two-gelator system, where both components can independently gel; (3) a system comprising a gelator and a non-gelling additive. Here, we specifically focus on system (2), which contain two LMWGs, each of which can individually form a gel. Hence, on mixing there are multiple permutations (Figure 8). First, the system could be designed such that there are strong interactions between the two gelators, leading to self-assembled structures where there are alternating gelators. Alternatively, mixing of LMWGs could still occur, but non-specifically, leading to randomly mixed self-assembled structures. Finally, self-sorting could occur, where the two LWMGs prefer to self-assemble with themselves, leading to self-assembled structures that contain only one of the LMWGs.

There are now many examples of mixed LMWGs.[56,59] To our minds, there are two reasons why one might be interested in multicomponent systems. First, intellectually

it is an interesting challenge to be able to finely control the assembly of a system to this degree. Second, multicomponent systems ought to be able to provide gels with a higher degree of information content than single-component systems; there are examples where multicomponent systems have been used to adjust the photoresponse of a gel for example, or to provide a gel that can be positively or negatively patterned by adjusting the assembly of only one of the components post-gelation.

We and others have previously reviewed the area of multicomponent gelators.[56,58,59] We do not simply wish to re-iterate what has been previously said. Rather, we wish to highlight specific aspects. The first key aspect is the idea of design. Because LMWGs are inherently difficult to design, how does one design a multicomponent system? Generating a system with alternating molecules within the self-assembled fiber has been achieved by building in very specific interactions between the molecules. Assuming that there is still a tendency to grow fibrous structures overall, this dimerization leads to fibers with specifically associated gelators.

Generating randomly mixed fibers requires the formation of a system where the two gelators do not mind interacting and then controlling the gelation process in such a manner that assembly occurs in a manner where this mixing is possible. On the other hand, preparing a self-sorted system requires that the interactions between specific gelators are such that they would prefer to assemble only with themselves. Hence, in a mixed system, each fiber only contains a single gelator. This is of course easier to state than to achieve, especially in advance. As stated above, designing gelators from scratch is difficult; it is even more difficult to predict in advance what will occur in a mixed system.

As above, the outcome will be very process dependent. There are a number of examples of self-sorted systems where the gelation is driven by temperature. The self-sorting is brought about by the different gelation temperatures, where generally the two different gelators assemble into fibers at sufficiently different temperatures that the self-sorting can occur. Conceptually, if the molecular design is sufficient, it should be possible to drive the formation of two networks at the same temperature. Of course, this still requires that there is a strong tendency for the two molecules to only want to interact with themselves. This is usually built in by ensuring that the molecular packing is different. For example, Sugiyasu et al.[96] mixed a perylene bisimide-based gelator and an oligothiophene-based gelator to ensure that temperature-driven self-sorting occurred. This example shows the general rules: that the molecules need to be structurally different, and they need to have a sufficiently different solubility in the solvent to ensure assembly occurs at different temperatures. There could be significant opportunities here in terms of driving varying degrees of self-sorting by controlling the rate of cooling for example.

Controlling the gelation temperature is not always easy to predict. We have recently shown that another approach using the apparent pK_a is possible for hydrogels. As mentioned above, for gelators such as 2NapFF, where the gelation can be controlled by the protonation of the terminal carboxylic acid, we and others have observed that the apparent pK_a of this carboxylic acid is affected by the hydrophobicity of the gelator; the higher the hydrophobicity, the higher the apparent pK_a.[87] Hence, if two gelators with sufficiently different pK_a are mixed and the pH can be decreased in a controlled manner, self-sorting should be favored. Using the hydrolysis of GdL to slowly lower the pH allowed us to produce self-sorted systems. We have shown that this approach can be applied to a number of mixtures provided that the apparent pK_a values are around a unit apart.[97,98] We have proven that

self-sorting occurs by a number of techniques. Sequential assembly can be shown by solution-phase NMR. In many cases, at high pH the gelator is detectable by solution-phase NMR; although a self-assembled aggregate is formed, the equilibrium between the freely dissolved molecule and the aggregate is such that the gelator can be observed. On gelation, the molecule becomes undetectable by NMR. Hence, self-sorting can be shown by the sequential disappearance of the signals of each gelator from a series of NMR spectra over time as the pH is slowly decreasing. In the final gel, we used fiber X-ray diffraction to show that the data for the self-sorted gel are essentially an overlay of the expected data from the two individual gelators.[97] Here, we note that in many cases, self-sorting is difficult to prove by microscopy. Although there are some systems where the two individual gelators happen to form self-assembled structures with sufficiently different diameters that microscopy can be used to show that there are two distinct populations,[99,100] in other cases, the structures formed are too similar to distinguish.

We and others have reported a number of systems where self-sorting can be driven in this manner.[97,98,100–102] It seems that the self-sorting is essentially pre-programmed into the system on the basis of the differences in the chemical structures. In our first study, we showed that gelation using a mineral acid resulted in a significantly less homogeneous gel, but the diffraction still showed that there was a propensity for self-sorting to occur. Hence, again we highlight how the process of assembly needs to be considered; the molecular assembly is heavily driven by the chemical structure, but the gel properties are controlled by how the gelation is triggered.

We have a small number of examples where self-sorting does not appear to occur. First, two N-protected dipeptides were found to assemble at the same time by NMR despite the differences in the apparent pK_a of the two gelators.[98] Circular dichroism data implied that the assembly was not simple self-sorting. Here, we believe that the two gelators are co-assembling, and our explanation is the relative similarity in molecular structure (only the terminal amino acid was different in this case). This again highlights the design rules above; for effective self-sorting, the molecules should be significantly different in structure.

However, we have also found an unusual case where the two gelators are molecularly distinct.[103] In this example, 2NapFF was mixed with a second N-protected dipeptide. In this (so far) unusual case, it appears that there is a degree of mixing at high pH, and this leads to a degree of mixing as the pH is decreased. Hence, instead of a well-behaved self-sorting system, the first fibrous network seems to incorporate both of the gelators: all of the 2NapFF and some of the second component. After this has completely assembled, the remaining 2NapVG assembles as a single component. The degree of mixing and co-assembly is apparently determined by the relative concentration of the two components.

Our previous data would imply that this mixture should form a self-sorted system. We believe that it does not for two reasons. First, 2NapFF forms worm-like micelles at high pH as mentioned above. The other examples that we have investigated tend not to do this, and we hypothesize that this persistence of structure at high pH results in hydrophobic incorporation of the second component within the micellar structures at high pH that persists as the pH is decreased. Hence, this can be thought of as being to do with the encapsulation of one gelator within the self-assembled aggregate of the second. Once the first has completely assembled, the second then acts as if it is independent and assembles alone. This highlights that simple

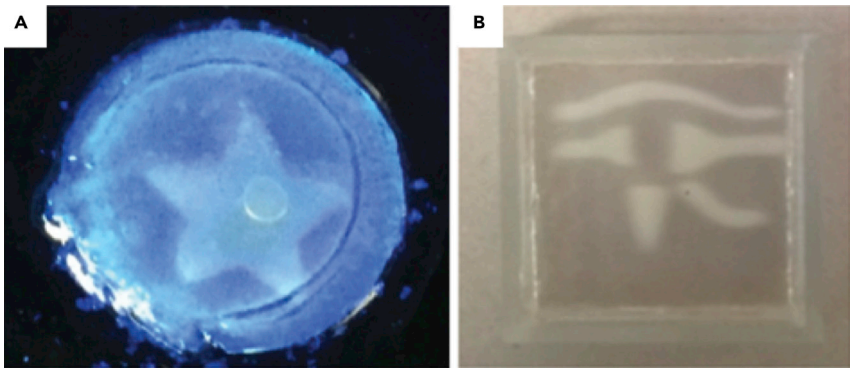

Figure 9. Writing in Multicomponent Systems

(A) Irradiation of a two-component system can be used to negatively "write" into a gel. Adapted with permission from Draper et al.[104] Copyright 2015 Nature Publishing Group.

(B) Positive "writing" is also possible. Adapted with permission from Cornwell et al.[101] Copyright 2015 American Chemical Society.

assignment as either self-sorted or co-assembled might be too simplistic in some cases.

As in the discussion dealing with the process of gelation above, the assignment of the assembly type is only the first level of assembly hierarchy. The mechanical properties of the gels, as well as potentially properties such as optoelectronics in the case of suitably mixed gelators, will be determined not only by the primary fibrous structures but also by how these fibers are located in space. For example, self-sorting might occur such that the primary fibers each consist of only a single gelator. However, in terms of the cross-linked network, the fibers might laterally assemble or otherwise cross-link such that each fiber interacts with only fibers of the same gelator, with only fibers of the other gelator, or randomly. Hence, self-sorting at the molecular level does not necessarily mean that self-sorting will occur at the fiber level. Our data where we proved self-sorting by using fiber diffraction show that this sorting occurs on the molecular level. However, we do not see how this can show any information on the next level up; to our minds, the data are entirely consistent with either random co-assembly or the formation of an interpenetrating two-component network on the fiber level. We were, however, able to show that two independent networks exist by self-sorting two gelators where one gelator was photoresponsive.[104] On irradiation with UV light, this gelator underwent *trans*-to-*cis* isomerization. The *cis* isomer is incapable of forming gel fibers, so this network fell apart. From rheological data, we were able to show that the other network remained intact and had similar properties as if this network had been formed in a single-component system. In addition, the area exposed to irradiation was optically different (Figure 9A). This irradiation represents a negative writing; one component is removed from a two-component system. In related work, Cornwell et al.[101] showed how positive patterning could be carried out in a multicomponent system (Figure 9B).

The importance of the assembly hierarchy for optoelectronic applications is critical. As mentioned above, Sugiyasu et al.[96] have shown that a self-sorted gelling system can be used to prepare the equivalent of p-n heterojunctions where the two types of fiber cross. Hence, to optimize such a system, one would like to know how many p-n heterojunctions there are (i.e., how many points at which the two fibers interact), how these are distributed in space, and how effective different types of interaction are. For example, one could easily imagine that a point where two fibers touch

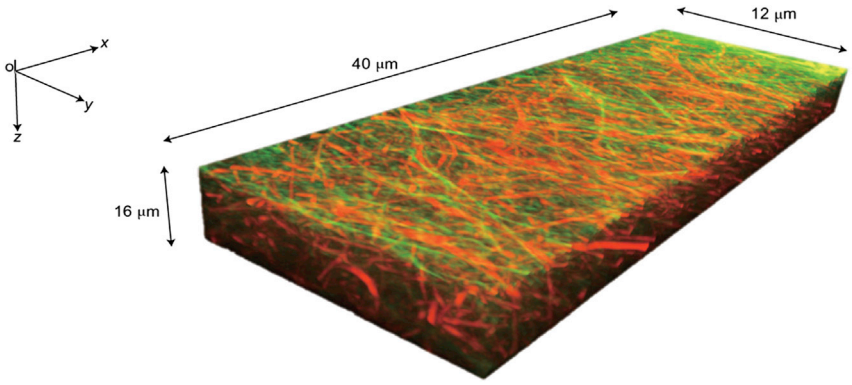

Figure 10. Imaging a Self-Sorted Gel

Three-dimensional confocal laser scanning microscopy image of a self-sorted two-component hydrogel network showing that the fibers are orthogonally assembled. Adapted with permission from Onogi et al.[105] Copyright 2016 Nature Publishing Group.

would be very different in efficiency to where two fibers wrap around each other (Figure 8).

Understanding the assembly on the fiber level is however a major challenge. There are almost no methods that are suitable for distinguishing between self-assembled fibers. As we noted above, in some rare cases, it is possible to differentiate between fibers by electron microscopy. However, this requires drying of the sample, and hence it is extremely difficult, to say the least, to interpret how these fibers were arranged in space before drying. Small-angle scattering experiments can potentially be used, but generally the length scales that can be probed mean that one can again show that (for example) there are two different fiber types present, but the information as to fiber interactions is usually interpreted in terms of power law scattering and hence again different to interpret. Here, it might be possible to use selective deuteration as a means of rendering the scattering from each network only detectable by SANS under different ratios of H_2O and D_2O.

A recent impressive insight into self-sorted gel networks was achieved by Onogi et al.[105] who used super-resolution microscopy to independently visualize two-gelator networks in a self-sorted system. Here, the gelators were mixed with fluorescent analogs that were designed to strongly associate with only one of the gelators. On mixing and gelation, impressively two independent fiber networks could be seen (Figure 10). This methodology could really open up the area, allowing an understanding of how the two sets of fibers interact.

A final comment is that it is very unclear what the outcome will be on the rheological properties when two gelators are mixed in a multicomponent system. We have examples of self-sorted systems where the absolute rheological moduli are higher than one might expect when comparing with the individual gels; we also have examples where the moduli are around an average of the values of the two individual systems.[98] When the relative ratios of two gelators are mixed, we have also found that there can be a non-linear effect on the absolute moduli.[103] Interestingly, Nagy-Smith et al.[106] have recently shown that mixing two gelators that are simply the enantiomeric isomers of each other results in the formation of a co-assembled system. The rheological data show that the co-assembled gel is much stiffer than those formed by either of the enantiomerically pure gelators. This is due to different

packing of the molecules, leading to local stiffening of the fibers. From this short discussion, it can be seen that multicomponent systems can be used to access a range of rheological properties that may not always be that expected from simple addition of the individual components, and further highlights how understanding the assembly across multiple length scales is important.

CONCLUSIONS AND OUTLOOK

We have set out here to critically analyze the current state of the art in low-molecular-weight gelators. There are increasingly more and more reports of such gelators, and the number of applications being described is ever increasing. This is a fascinating area of science, and we believe that there are many more opportunities here than have been currently explored. The idea of adjusting the process of assembly is essentially stating that formulation is key. This is widely applied in industry, where formulation science is a critical aspect. However, the importance of formulation is perhaps less commonly applied in academia labs. Although it is clearly interesting to discover new gelators, a pragmatic approach could very well be to instead wonder whether current gelators might be better able to address a specific need by simple variation of the assembly process. To our minds, the time for papers describing a specific new gelator and an in-depth study into its self-assembly leading to gelation has perhaps past without new insight into why gelation has occurred. Multicomponent systems also offer many potential opportunities. Here, as for the discussion regarding the gelation process, it is important to consider the assembly across multiple length scales, and it might be the case that there are occasions where simple assignment as one type of assembly or another might not be appropriate. Overall, we believe that there are significant opportunities here, but we highlight that some questions that need answers to enable a true understanding of the assembly across multiple length scales are extremely difficult to answer. This in itself provides new opportunities for new techniques to be developed and applied. We expect lots of further exciting developments in the near future and hope that this review stimulates debate and discussion.

AUTHOR CONTRIBUTIONS

E.R.D. and D.J.A. conducted the literature search and wrote the manuscript.

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