LANGMUIR

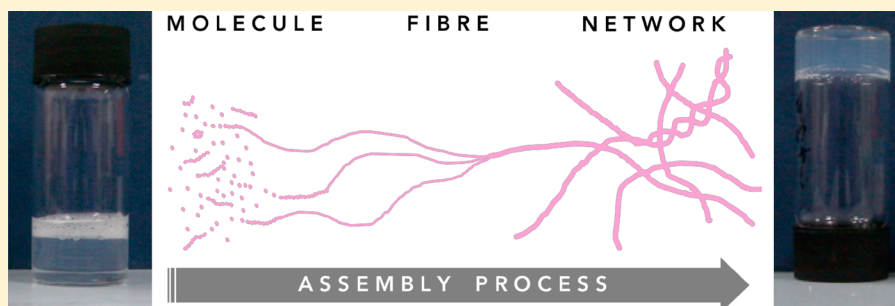# Controlling the Assembly and Properties of Low-Molecular-Weight Hydrogelators

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MOLECULE   FIBRE   NETWORK

ASSEMBLY PROCESS

ABSTRACT: Low-molecular-weight gels are formed by the self-assembly of small molecules into fibrous networks that can immobilize a significant amount of solvent. Here, we focus on our work with a specific class of gelator, the functionalized dipeptide. We discuss the current state of the art in the area, focusing on how these materials can be controlled. We also highlight interesting and unusual observations and unanswered questions in the field.

INTRODUCTION

Gels are hugely important soft materials, both academically and industrially. There are many different types of gel, and indeed even the exact definition of a gel can be hotly debated. Here, we will discuss gels formed by low-molecular-weight gelators (LMWGs).[1−3] These gels are formed by the self-assembly of small molecules into (generally) long anisotropic structures that entangle or otherwise cross-link to form the matrix of the gel (Figure 1). The matrix immobilizes the solvent, resulting in a solidlike material even when around 99% by weight of the material is liquid. Specifically, here we discuss a class of gelator with which we have carried out a large amount of work, the functionalized dipeptide.[4−6] We aim here to provide a personal viewpoint of our current understanding as to how these materials self-assemble to form gels. We purposefully do not consider specific applications here but rather aim to explain the mechanism of assembly and important parameters to consider when making gels. If these are understood, then our contention is that it should be possible to design gels for desired applications. If these are not understood, then irreproducible materials are instead often formed. A recent call to arms for the field as a whole, building on and reinforcing the earlier call from van Esch,[7] highlights the need for increased rigor and understanding,[8] with which we wholeheartedly agree.

We of course are not the only people to be looking at this class. The first report was in 1995.[9] Xu's group then started looking in detail at these materials in the early 2000s,[10] closely followed by Gazit's group.[11] Since then, there has been significant interest in this class of material,[5] which have been used in areas as diverse as tissue engineering,[12] 3D printing,[13] optoelectronics,[14−16] controlled release,[17] and catalysis.[6] In this class of material, typically the N-terminus of the dipeptide is functionalized with a large aromatic group, which was initially fluorenylmethoxycarbonyl (Fmoc), while the C-terminus is usually free. Although we focus mainly on functionalized dipeptides, the concepts translate into similarly functionalized amino acids and tripeptides. Some examples are shown in Scheme 1.

As for all LMWGs,[1,18] gels are formed when the molecules self-assemble into long anisotropic structures. These are typically nanofibers, nanotapes, nanotubes, or helical structures.[1] They tend to have radii of between 3 and 50 nm and lengths on the order of micrometers. For this class of material, the cross-linking seems to be most often simple entanglement as opposed to fiber branching as has been observed for other classes. These structures are formed when the molecules assemble, and this assembly is driven by noncovalent interactions including hydrogen bonding and π-stacking. Although individually relatively weak, the sum of the noncovalent interactions drives the assembly. Because we are focusing on hydrogels, where the solvent that is immobilized is water, there is a significant contribution from the hydrophobic effect. Perhaps therefore unsurprisingly most successful LMWGs in this class contain very hydrophobic amino acids.

It is worth pointing out here that forming gels with this class of LMWGs is not as simple as synthesizing a functionalized dipeptide. Although there are many permutations that can form hydrogels, there are also many examples which do not, instead forming precipitates or crystals. Indeed, small changes in chemical structure can result in an effective LMWG no longer
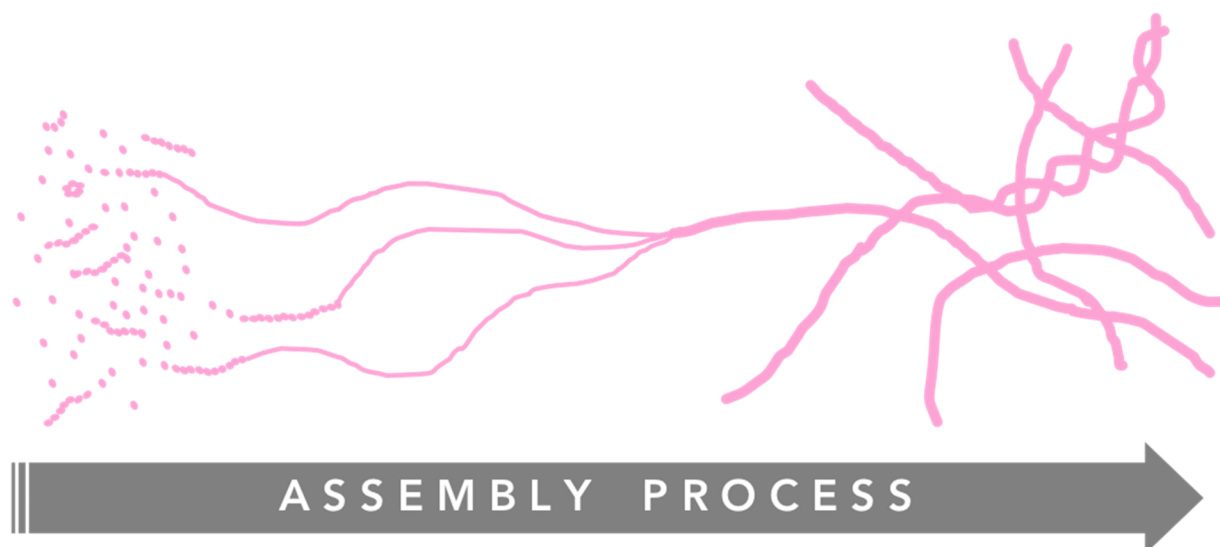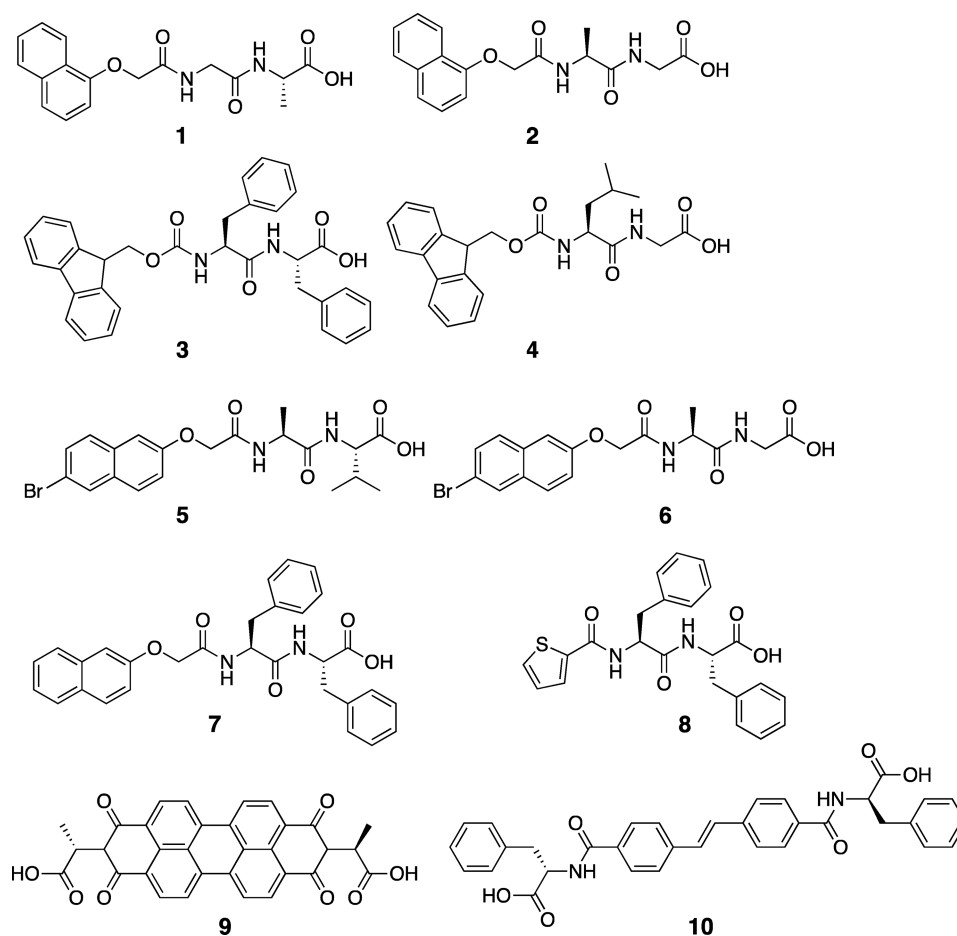
MOLECULE   FIBRE   NETWORK

Figure 1. Schematic showing the assembly across length scales to give a gel matrix.

Scheme 1. Example Functionalized Dipeptide and Related Gelators[a]

[a]We have used numbers to discuss the compounds in the text because the full names are complicated and shorthand notation is available for only some examples.

being able to form gels.[19−21] This can be frustrating, especially if specific functional groups are required to be present. One approach to get around this is to prepare a large library of potential candidates and simply test which can form gels. Using this approach can be useful (and can be used to show trends as to what sequence of dipeptide is most likely to form gels) but
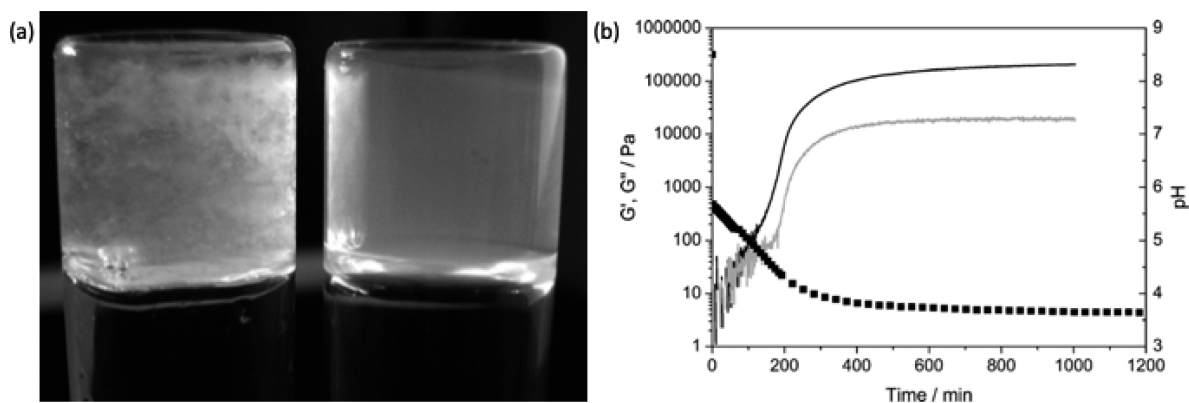
Figure 2. (a) Photographs of hydrogels prepared from **4**. The gel on the left was prepared where the pH was changed with HCl. Turbid inhomogeneities can be seen in this gel. The gel on the right was prepared using GdL, giving a transparent, uniform gel. The final pH in both cases is 3.9, and the same stock solution was used to prepare both gels. (b) Using the slow hydrolysis of GdL, the pH change and rheology can be followed with time. (The black line shows G', the gray line shows G'', and the black squares show the pH.) Reproduced from ref 34 with permission from The Royal Society of Chemistry.

does not become predictive. To get around this, a descriptor-based approach has been used.[22] From a library of known materials (both those that do and those that do not form gels), a predictive tool was developed, which we are finding extremely useful for the design of new LMWGs. However, one issue here is that while this approach is very effective at predicting whether a functionalized dipeptide will be an LMWG (albeit using a single type of trigger at the moment), this tool does not predict the properties of the gels that are formed. Moving toward being able to predict both the gelation ability and a number of properties would be a major step forward in the future.

Another approach that has been taken is to use crystal structure prediction methods. Here, computational approaches were used to predict the crystal energy landscapes for a molecule that could form gels (**1**, Scheme 1, with crystals forming from the gels under some conditions) and for a structurally similar molecule (**2**, Scheme 1) that always formed crystals.[23] This work showed that there was a very close match to the observed crystal structure in the list of predictions for the crystal-forming molecule as the second-lowest-energy structure. For the gel-former, however, the predictions implied that there is a preference for structures with open tapes of hydrogen-bonded molecules and structures with compact columns of molecules within the crystals. It was not possible to reproduce the scattering from the gel phase (collected using fiber X-ray diffraction). A few years wiser, we have shown a number of times that the scattering from a gel phase does not correlate with that collected from crystals (even if they are grown directly from the gel phase),[20,24] raising questions as to how useful it is to predict crystal structures for gels. Although there is a school of thought that suggests that there is a correlation between crystal structures and gel phases,[25,26] it is not clear to us that this is the case, especially because many crystal structures are collected from crystals grown in solvents other than those that can be gelled.[27] A recent paper has suggested that it may be possible to interpret what interactions are important, even if there is little correlation between gel and crystal structural data.[28] However, we highlight again that the crystals were grown by the diffusion of diethyl ether into solutions of the peptides in water/acetonitrile or from mixed solvents, while the gel phases were in water alone. Again, it seems counterintuitive to us that any information can be directly correlated considering the differences in the solvents used.

For this class of gelators, gels are typically formed in a small number of ways. There are rare examples where a suspension of the LMWG is heated and cooled to form a material that can be inverted.[9] This process would typically be used for organogels, but it is rarely successful for this class of LMWGs in water, typically because of the very low solubility of the LMWG in water. Hence, there are more common approaches. First, Gazit's group showed that an effective approach is to dissolving an LMWG such as **3** (Scheme 1) in a water-miscible organic solvent such as DMSO, acetone, or hexafluoroisopropylalcohol (HFIP) and then adding water to drive gelation.[17] The LMWG can also be dissolved in a polymer, and water can be added to form a gel.[29] This results in phase separation and rapid gelation. The properties of such gels can be controlled by the choice of solvent, the absolute ratio of solvent to water, and the gelator concentration.[17,30,31] Usually for this approach, the addition of water to the gelator in an organic solvent results in an immediate turbid solution, which forms a translucent gel over minutes to hours. This seems to be due to an initial phase separation.[32,33] It also needs to be considered that there can be a significant exotherm depending on the choice of solvent (adding water to DMSO alone results in a significant increase in temperature in the absence of a gelator).[31]

A different approach is where a solution at high pH is prepared, deprotonating the C-terminus of the dipeptide and dispersing the LMWG.[19,34,35] The addition of acid results in reprotonation of the dipeptide and gelation. The acid can be a mineral acid, although there are often mixing issues here and irreproducible gels result.[34,36] As such, a range of methods have been developed to slowly and uniformly adjust the pH, including the hydrolysis of a lactone[34] or anhydride[37] as well as using potassium persulfate.[38] We have found that the method of pH change is an extremely important aspect. In many cases, the properties of the gels are very hard to control unless a slow pH change is used. We first showed the power of this approach in 2009, exploiting the slow hydrolysis of glucono-δ-lactone (GdL) to gluconic acid to prepare reproducible gels from Fmoc-dipeptides such as **4** (Scheme 1).[34] The gels were visibly more uniform (Figure 2a) and also significantly stiffer and more reproducible. Using HCl to change the pH of a solution of **4** resulted in gels with a storage modulus (G') of 5.9 kPa; these gels were very mixing-dependent such that in some cases a suspension of gel particles in water was formed as opposed to a

fully gelled material. In comparison, using GdL, translucent uniform gels with a G' of 184 ± 3.5 kPa were obtained. This approach has the added advantage that the slow pH change means that it is possible to follow the gelation process using a range of techniques as well as having the time to be able to transfer the GdL and gelator mixture into, for example, molds or cuvettes without damaging the gel. This can allow significantly more information and understanding to be obtained as compared to the simple mineral acid gelation. For example, the evolution of the gel structure could be followed by rheology (Figure 2b). This shows that there is a two-stage increase in both G' and G'', which we will discuss in more detail below. This GdL approach has now also been used by a number of groups in the field[39] to trap coacervates[40] and for other classes of gelators.[41,42]

When using this pH-triggered approach, the absolute pH is important. For this class of materials, the apparent pK_a of the terminal carboxylic acid is higher than perhaps expected.[43,44] We have shown that this apparent pK_a increases as the overall hydrophobicity of the molecule increases.[44] The apparent pK_a seems to be that of the aggregate as opposed to that of the molecule itself, and there are cases where more than one apparent pK_a can be determined even though there is only one ionizable carboxylic acid, suggesting different aggregated states associated with the different apparent pK_a values.[43,45] The apparent pK_a depends on the concentration of the gelator as well as the temperature.[44] Gelation begins to occur when the pH is slightly below that of the pK_a of the gelator.[44] Hence the pH at which gels form depends on the pK_a of the gelator, which explains why FmocFF (one of the few such gelators in this class with a pK_a higher than 7.4) is a rare example capable of forming gels at physiological pH.

In line with the absolute pH and kinetics being important, a number of approaches to changing the pH can be used. These include the use of photoacids[46] as well as using electrochemical approaches.[47,48] The advantage of electrochemical methods, whereby typically the electrochemical conversion of hydroquinone to quinone results in a decrease in pH at the electrode surface, is that there is a localized decrease in pH. This means that patterned surfaces can be prepared with tailored thickness and composition.

Some of the solutions at high pH can be gelled by the addition of a divalent cation such as calcium.[49−51] In some cases, it is possible to form samples that can be inverted at high pH (especially if a heat/cool cycle is used).[45] It is not always clear that these are true gels, but rather these appear to be extremely viscous liquids which show significant extensional viscosity.[45] A key point here is that it is necessary to have the right structures present at high pH. For the methods that involve dispersing the gelator at high pH, this does not result in molecular dissolution (unlike the situation often depicted in schematics). Instead, these molecules form a range of different surfactant-like aggregates.[44,49,52] There are therefore critical micelle concentrations above which different types of structures are formed, and these depend on the hydrophobicity of the gelator.[53,54] The aggregates at high pH include spherical structures, wormlike micelles, and nanotubes. At higher concentrations, liquid crystal phases can also form.[54] The systems that can be gelled at high pH by the addition of a divalent salt require that wormlike micelles or nanotubes be formed.[49] These wormlike micelles can be linked to the overall hydrophobicity of the functionalized dipeptides, with the more hydrophobic molecules giving viscous solutions at high pH.[49,50]

As well as using viscosity to determine the structures, it is possible to use small-angle scattering to probe the assembly at high pH.[54] We and others have also found that molecules that form wormlike micelles at high pH can be distinguished from those that form spherical structures using NMR.[55] The more hydrophobic molecules forming these anisotropic structures show a lower-than-expected integration in solution-state NMR, while those forming spherical structures typically integrate to the expected value.[55] This can be related to how much time a molecule spends in the aggregated structure as opposed to being free in solution (i.e., it depends on the exchange rate).

It is possible to form gels using enzymatic catalysis, whereby a nongelling molecule is converted to a gelator either by enzymatic removal of a solubilizing group or by enzymatic conversion to a less-soluble molecule (for example, by esterification).[5,56−58] This is often referred to as biocatalytic self-assembly. Related gels can also be formed by dephosphorylation using the photogeneration of nitroxide radicals[59] or by using cerium oxide nanoparticles.[60]

The properties of the gels formed by any of these processes depend on the self-assembly across length scales. This can be quite difficult to understand fully, and it is necessary to use a range of techniques to understand and characterize the systems. A key aspect that we have discussed previously is the idea that the process by which the self-assembly takes place is the dominant factor in controlling the properties of the final material. It is not as simple as stating that a specific LMWG gives gels with certain properties, but rather *how* the LMWG is assembled appears to be the most important aspect.[61,62] This is unsurprising. Gelation by any of the above routes is essentially a formulation science problem, and it is clear that the sample history, assembly method, and processing all have a significant effect. (Figure 3). This is a well-understood concept in other
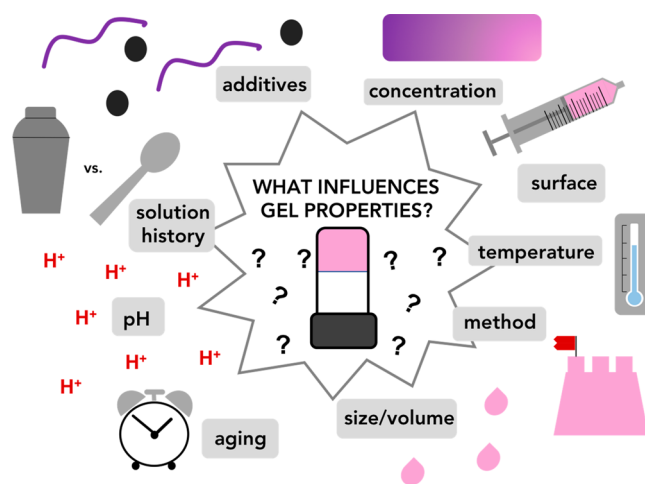

Figure 3. Gelation is essentially a formulation problem, and many parameters affect the final outcome of the process.

fields,[63] but it does not seem to have translated to the gel field. Importantly, the properties of the resulting gels are determined by the method of assembly. Although this can make the understanding complex, one useful aspect of this is that rather than synthesizing a large number of LMWGs until gels with the desired properties are formed, it is instead often possible to work with a small library of effective and reliable LMWGs and tune the process of assembly to give the required gels. We also
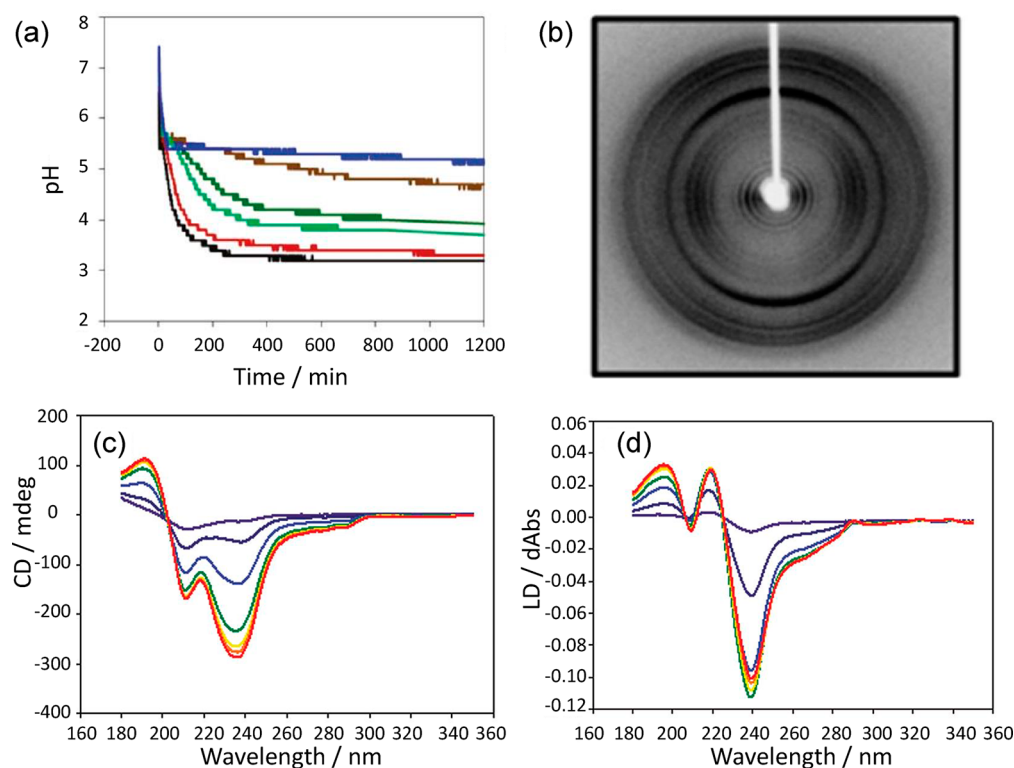
Figure 4. (a) Change in pH with time for aqueous solutions of **5** (0.5 wt %) added to different amounts of GdL. The initial pH was 10.7. Added GdL: (blue) 1.82 mg/mL; (brown) 2.94 mg/mL; (dark green) 4.46 mg/mL; (light green) 5.96 mg/mL; (red) 9.72 mg/mL; and (black) 14.42 mg/mL. (b) X-ray fiber diffraction patterns collected from gels at a final pH of 4.6. The fiber axes are vertical to the diffraction patterns. The major meridional reflection was at 4.5 Å, and the first major equatorial reflection was at 16 Å followed by a second grouping of reflections starting at 7.3 Å. (c) Evolution of CD with time on addition of a solution of **5** (0.5 wt %) to GdL (14.42 mg/mL). Data are shown for 0 min and then subsequently every 10 min. (d) Evolution of LD with time on addition of a solution of **5** (0.5 wt %) to GdL (14.42 mg/mL). Adapted with permission from ref 53. Copyright (2010) American Chemical Society.

highlight that the presence of additives can significantly affect the outcome of the assembly process.[28,29,64]

We should state that of course there have been many libraries of molecule described, with attempts at linking a specific structural aspect to gelation efficiency. Although there may be mileage in this approach, our current preferred option as stated above is to use a small number of robust gelators and adjust the assembly conditions to prepare gels with suitable properties. From our experience, this is pragmatically more time- and labor-efficient.

We are therefore going to focus next on three levels of assembly: the molecular level, the fiber level, and the network level. We will discuss how and why each of these levels can and should be probed and understood in order to fully understand the self-assembly process.

■ MOLECULAR-LEVEL ASSEMBLY

The first level of assembly we will discuss is the molecular level (i.e., how the noncovalent interactions bring the molecules together). This can be difficult to understand. Although we in no way intend to imply that data in the literature are incorrect, it is important to consider and appreciate how the data used to interpret this level of assembly are collected.

For example, to access information as to the hydrogen bonding, typically infrared (IR) spectroscopy would be used. In water, the solvent has stretches in the region where information as to the dipeptide hydrogen bonds can be accessed. As such, it is common to carry out IR in D_2O rather than in H_2O. From

our experience here, in general this is apparently not an issue in most cases because the resulting gels in both solvents are very similar. However, we know that this is not always the case, so care must be taken. Differences between gels formed in H_2O and D_2O have also been reported by Feringa's group, for example,[65] so it is clear that the assumption that direct comparison is possible is not always valid. On top of this, it is difficult to interpret the resulting IR spectra. Typically, data from larger peptides and proteins are used to interpret the spectra for dipeptides, although it is unclear whether this can be used effectively. As a result, there are a wide range of interpretations and (as a single example), and the presence of β-sheets has been suggested for **3** (Scheme 1) on the basis of spectra with stretches at 1653 and 1630 cm^{-1}.[66,67] There are examples where the same LMWG apparently assembled in the same manner gives different results, but the interpretation remains similar. It has been suggested that **3** may form an α-helix in some cases on the basis of the IR spectrum;[68] it is hard to see how this is possible for this dipeptide considering that a single turn in an α-helix requires 3.4 residues and caveats were noted around similar stretches being interpreted as an α-helix in other work on **3**.[29]

It is also possible to interrogate hydrogen bonding using circular dichroism (CD). However, there are again issues with interpretation. As a single example, multiple different CD spectra have been reported for **3**.[19,67−69] As for the IR above, these interpretations are based on signals being in the same (or similar) positions as those obtained from classic polypeptides. It is very unclear if it is correct to extrapolate in this manner. On

top of this, CD is very prone to scattering artifacts. Because these LMWGs most often contain aromatic residues, these tend to absorb strongly, meaning that it is difficult to interpret the packing of the dipeptide. One way around this is to use thinner cells; this can lead to alignment of the self-assembled structures and the introduction of linear dichroism (LD) artifacts, although these can be used to understand the assembly. Another potential way around this is to dilute the system. Here, it is extremely important to show that the same structures are present across this concentration range. At high pH, the LMWGs are not uniformly dissolved but rather dispersed as surfactant-like aggregates. Hence, the structures formed are concentration-dependent, and for gels it is often not clear how dilution affects the structures. CD has often been shown at concentrations lower than the minimum gelation concentration, so it is unclear whether it is representative of the gelling system at the higher concentrations.

It is possible to access information as to the stacking of the aromatic groups at the N-terminus using fluorescence spectroscopy.[35] Shifts in the emission can be used to infer H-type aggregation, for example. There are suggestions that the efficiency of stacking can be ascertained from the fluorescence spectra.[70] Overall, this technique can be useful, but we do note that our experience here is that the tendency for people to provide normalized spectra can lead to artifacts. Gelation tends to lead to a decrease in absolute emission, and normalization can therefore lead to issues. Similarly, turbidity can also lead to problems.

Saying all of this, it is of course possible to interpret and understand the assembly to some degree, although we do not believe that it is yet possible to fully understand this. As a single example, we have described in detail the assembly process for one of our LMWGs (**5**, Scheme 1) gelled via a pH switch.[53] As our understanding has evolved, we have built up a detailed understanding across all length scales. As such, we focus our discussion on this molecule here and in the sections below. Although detailed analysis of the assembly does exist for other examples, we believe that this compound can best exemplify the full process. Again, the advantage of using the slow hydrolysis of GdL is that this allows the assembly process to be followed with time. At high pH, **5** forms a nonviscous solution. Using GdL to decrease the pH results in a slow pH change, with the pH being buffered at around 5.8 (Figure 4a). Although higher than expected for the C-terminus of a dipeptide, this can be interpreted as being the apparent pK_a of the aggregates of **5**. This apparent pK_a is temperature- and concentration-dependent. Below this apparent pK_a, the IR spectra show peaks at 1628 and 1679 cm^{-1}, which could be interpreted as being due to the formation of β-sheets. There is also a strong peak at 1645 cm^{-1} that would be conventionally interpreted as being due to the presence of random coils but could also be due to the presence of the naphthalene group. Fiber X-ray diffraction data were used to show the presence of a meridional 4.5 Å reflection, which is likely to arise from a β-sheet (Figure 4b). CD and LD data showed that initially there was no signal (Figure 4c,d). As assembly occurred over the first hour, intense CD signals became apparent and correlated with the UV absorption of the naphthalene ring. Hence, the naphthalene ring was being placed in a chiral environment. At the same time, LD signals appeared, which we interpret as being due to the formation of aligned fibers resulting from the assembly taking place in a thin cuvette (high tension (HT) scattering issues occurred in thicker cuvettes). From the LD data, it was possible to determine that

the naphthalenes are forming a left-handed helix and the naphthalene long axes are tilted by more than 35° from perpendicular.

Elsewhere, Ulijn's group has a model for the assembly of **3** (Scheme 1), suggesting a so-called $\pi-\pi$ interlocked β-sheet, where nanotubes result from the formation of π-stacks between the Fmoc groups and the dipeptide forms the β-sheet.[67] To come to this conclusion, the authors combined CD, fluorescence, powder X-ray diffraction, and IR data, although the assignment of an antiparallel β-sheet on the basis of the IR data was later shown to be complicated by the carbamate group.[71] Although this model has been used to describe packing in other examples, it is worth noting that other examples show that β-sheets are not formed[72,73] (or at least the IR data are not consistent with the expected spectra for β-sheets). Similarly, hydrogels can be formed using dipeptides linked to alkyl chains, showing that the $\pi-\pi$ interlocked β-sheet is not ubiquitous in this class.[74] A complication in terms of understanding here is that there are many different data reported for a single gelator. Taking the single example of **3** (which is perhaps the most studied in this class), CD data differ dramatically both for gels formed by different methods[38] and in different reports.[19,38,67−69] To us, this further shows how sensitive the assembly is to the exact processing conditions used to form the gels.

■ FIBER-LEVEL ASSEMBLY

Having assembled on the molecular level, a gel is generally achieved as a result of the formation of long anisotropic structures. These are most commonly nanofibers or nanotubes. Characterizing this level of assembly is usually carried out by an imaging technique such as scanning electron microscopy (SEM), atomic force microscopy (AFM), or transmission electron microscopy (TEM). Imaging directly in the gel state is difficult, so most data are collected on dried gels (known as xerogels). There are real issues here, with drying leading to changes in structure and driving further aggregation. We recently showed, for example, how drying (irrespective of the drying method used) leads to lateral association and aggregation of the fibers, meaning that the apparent diameters were significantly larger than in the hydrated gel.[75] To access information on the wet gels, we used cryo-TEM (where a vitrified film of the gel was imaged) and small-angle neutron scattering (SANS), which can be carried out directly on the solution. The method of gelation here can also impact the drying. For example, solvent switches where the solvent is more volatile than water and would evaporate first change the solubility and therefore likely the structure of the gel left behind. Similarly, if salts are present, then they would concentrate upon the evaporation of water, again potentially changing the structure of the network or leaving large salt crystals which are often seen in these imaging techniques.

Because of the issues with drying, we believe that small-angle X-ray scattering (SAXS) and SANS are extremely useful here.[76] These techniques can be used to probe the gels in their hydrated state and provide data on a bulk sample. (Electron microscopy can only ever provide a snapshot of the sample because only a tiny amount of sample is imaged and it is common to often show only one image, so it is unclear whether this represents the whole sample.) An issue can be that the data are generally understood by fitting to a model such as a hollow tube, cylinder, or flexible cylinder. Although generally this is possible, in some cases a suitable model is not available or a
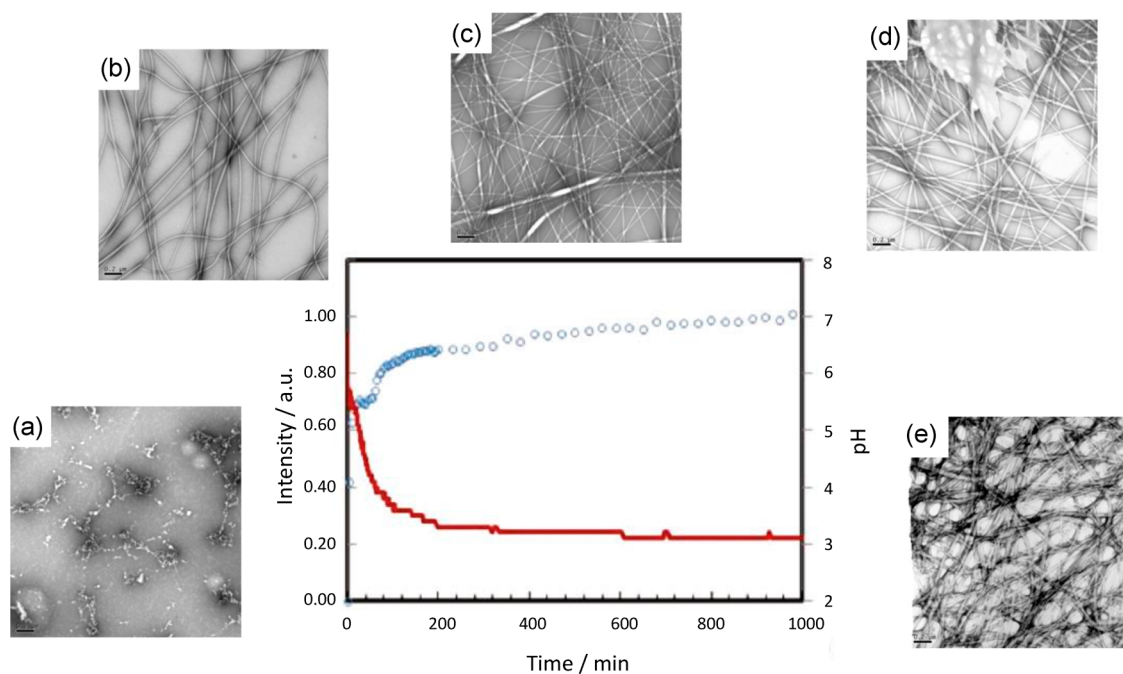
Figure 5. Normalized change in ThT fluorescence at 485 nm on addition of solutions of **5** to GdL (blue data). Overlaid is the change in pH with time (red data). Also shown are TEM images (a) immediately after GdL addition and at (b) 80, (c) 120, (d) 240, and (e) 400 min. Adapted with permission from ref 53. Copyright (2010) American Chemical Society.

purely empirical model has to be used. Combining SAXS and SANS can be useful,[77] and varying contrast within a system by partial deuteration can also enhance understanding.[75]

An interesting observation is that the fibers that are present in some gels are helical, with the helicity apparently being determined by the underlying chirality of the dipeptides.[35] This can be linked to CD data (see above), although we have also found that the handedness measured by CD can invert depending on the dipeptide sequence even when the chirality of the constituent amino acids remains the same.[78]

Returning to the case of **5** which we started to discuss above, adding thioflavin T (ThT) allowed us to follow the assembly process.[53] ThT is an effective molecular rotor, with a fluorescence output that increases with viscosity.[79] As assembly occurs, the ThT binds to the self-assembled structures (Figure 5). Initially, there is no fluorescence. As the pH reaches the apparent pK_a of **5**, the fluorescence increases dramatically. There is a rise to a plateau. After a period of time, there is a second increase in fluorescence, followed by a second plateau. The rate of assembly can be controlled by how much GdL is added. By adding different amounts of GdL, we were therefore able to show that the initial increase and rise to a plateau was controlled by the absolute pH; when the pK_a is reached (irrespective of how quickly this occurs), the fluorescence switches on. However, the second increase was determined by the kinetics of the process and did not occur at a specific pH. Hence, we showed that the assembly and gelation were both controlled by the apparent pK_a but also by the kinetics of the assembly process. This can be understood as being a hierarchical process. Initially, **5** assembles into fibers at the apparent pK_a, but these still have a significant negative charge. Then, as the pH decreases further, the charge on the fibers decreases. This allows entanglement, lateral association, and the formation of the gel. The degree of charge on the fibers could be followed using solution-state NMR experiments, residual

quadrupolar coupling (RQC) of the probe molecules, and T_1 and T_2 relaxation times.[80] The second increase in fluorescence will therefore be controlled by the kinetics of the process because this will determine the extent to which this entanglement can occur. We were able to show using TEM an overall increase in fiber density and also a degree of association of these fibers with time (Figure 5). This could be correlated with an increase in the rheological properties of the gel, which also occurred by a two-stage process.

One aspect to stress here is the power of using a slow gelation trigger. This allows one to directly compare across techniques and determine what is occurring at a specific point in time. For example, for **5**, the CD data evolves at early times before reaching a plateau at about 1 h. Under comparable conditions, the fluorescence of ThT starts to increase only at around 20 min, before reaching the first plateau at around 40 min. This shows that the CD is able to pick up the assembly before the ThT fluorescence, which opens interesting questions as to the number of molecules in an aggregate that must give rise to signals. The rheology lags behind these spectroscopic techniques, which makes sense as the structures need to form to a sufficient degree to span the sample. We are often asked if the GdL or hydrolysis products interact with the final self-assembled structures. We have shown that this is not the case using saturation transfer difference NMR measurements.[81] We collect most of our data by running concurrent measurements on different equipment; as long as the temperature, concentrations, and initial conditions are identical, the rate of hydrolysis should be extremely similar, allowing direct comparisons among different data sets. We have recently developed in situ NMR pH measurements, which have shown that our data collected concurrently is correct.[80]
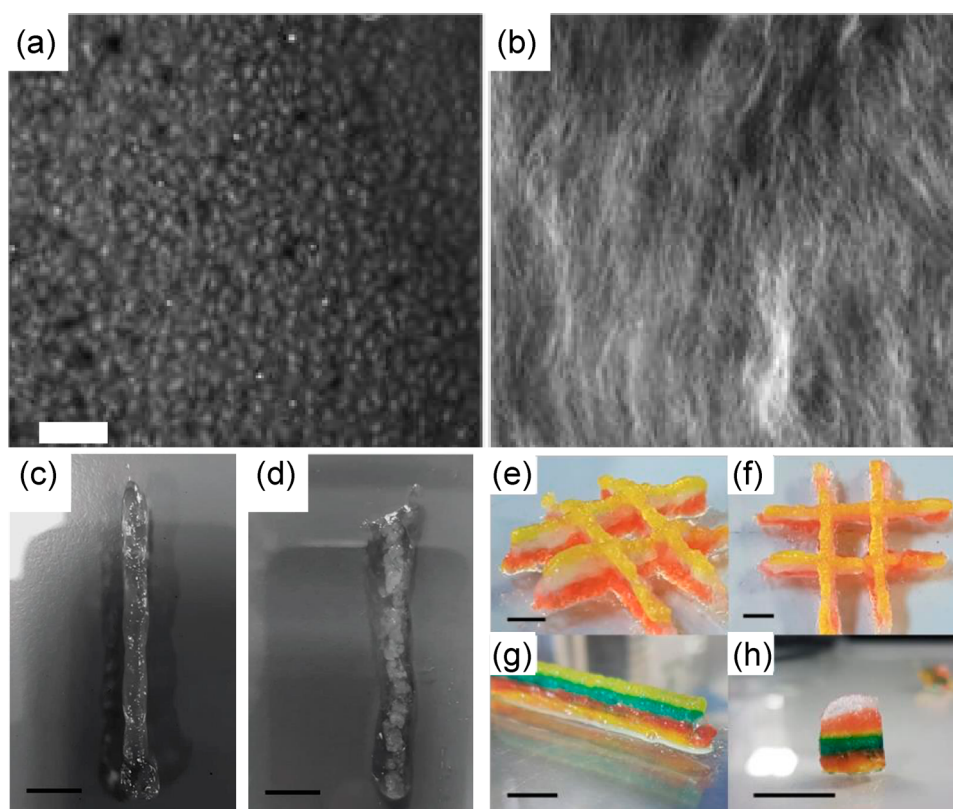
Figure 6. (a) Confocal microscope image showing spherulitic domains of fibers in the gel when a solvent switch is used to trigger gelation. (b) Confocal microscope image showing a uniform distribution of fibers in the gel when GdL is used to trigger gelation. (c) Printing of the gels shown in (a) with poor results. (d) Printing of the gels shown in (b) is much better. (e−h) Examples of printing possible when the gel design is optimized. Adapted from ref 13 with permission from The Royal Society of Chemistry.

■ NETWORK-LEVEL ASSEMBLY

The final level of assembly is at the network level. The fibers entangle or otherwise cross-link to form the network that spans the sample. Clearly, the number and types of cross-links would be expected to have a significant effect on the properties of the gels, but it is often extremely difficult to access information on these cross-links. Although for some gels fiber branching has been observed, we do not routinely observe this. Instead, general lateral association and entanglement seem to occur, but again we have to highlight that this is usually observed in dried samples and so may be an artifact. Although it is simple to state that the network controls the properties, exactly determining the network and number of cross-links is not always easy.

Although the cartoon that is often used for gel fibers would imply a homogeneous network, this is perhaps not always expected. For example, when an enzyme is used to catalyze a reaction that leads to fibers, it would perhaps be expected that this would essentially act as a nucleation site for the formation of fibers. Hence, instead of a uniform network with equal fiber density throughout, one might expect to see clusters of fibers around the catalyst, which are perhaps then linked in some way. By contrast, a slow, uniform increase in pH throughout the system might be expected to provide a more homogeneous network. However, there are few reports that detail the network at longer length scales.

To get around potential drying issues, we have attempted to access information at this longer length scale by using confocal microscopy. Here, the gels can be imaged while hydrated, although a fluorescent dye has to be added. We would always check that the rheological properties are not affected by the

addition of what is typically a small amount of dye, but there is always the potential for changes to occur. Typical suitable dyes include ThT (which can also be used to follow the fiber formation using fluorescence spectroscopy (see above)) and Nile blue.[82] Irrespective of the dyes used, our data shows that there are significant differences in the distribution of fibers within the networks formed by the different gelation methods. When the gels are formed by adding GdL to a solution at high pH, the fibers are uniformly distributed throughout the sample (Figure 6a). By comparison, when the gelator is dissolved in a water-miscible solvent and water is added, there tends to be a very different microstructure, with spherulitic domains of fibers being formed (Figure 6b). Interestingly, this can be the case for gels which overall have similar G' and G'' values. Where there tend to be significant differences is in the ability of the gels to recover after the application of high strain. This can be measured using a rheometer where a strain high enough to break the network (determined by a strain sweep) is applied to a gel and G' and G'' decrease dramatically. A period of no strain is then applied, and the recovery of G' and G'' is recorded. In these cases, the gels formed using GdL tend to recover poorly. This makes sense as the fibers are very hydrophobic at this point, so the application of strain will damage the homogeneous network; recovery would require that the network somehow re-entangles, and it is difficult to see how this can happen. By comparison, the spherulitic domains allow recovery after strain. Linking to ideas suggested by Pochan's group,[83] we interpret this as being that any fiber links between the spherulites break when strain is applied but the spherulites are not strongly affected.[13] Hence, after the strain has been released, the

spherulites can rejam, leading to recovery of the gel properties. We have shown that heating and cooling these gels results in a change in microstructure and the formation of a more uniform network.[32] These do not recover well after the application of strain. This demonstrates that the recovery is not due to the specific gelator or specific solvent conditions but to how the fibers are distributed in space. We have also shown using both SANS and ultra-small-angle neutron scattering (USANS) that there are only small changes at the fiber level before and after the application of a high strain.[13] However, there are differences at longer length scales for the samples that do not recover well, although those that recover are essentially unaffected. These results are extremely useful. We have 3D printed a number of these gels, preforming a gel in a syringe and then printing from this.[13] If the gels are formed using GdL and therefore have a uniform fiber network, then the application of the high strain as the gels are printed results in the gels breaking and the printing is very poor (Figure 6c). By comparison, using the same gelator with a spherultic network formed using a solvent trigger, printing is possible and good-quality structures can be formed despite the high strain resulting from the printing process (Figure 6d). This again shows that process history is critically important.

A key aspect here is the use of rheology to probe and understand gels. There are many examples where gelation is "proved" by simple vial inversion. Although this can be indicative, it is not proof.[84] Even when rheological data are provided, full data are often not, meaning that interpretation is difficult. There is a lot of information in these data,[85] especially when combined with other experiments. Returning to the case of **5**, as mentioned above the rheological data show that these gels form in a two-stage process. This can be interpreted as being due to the initial formation of fibers giving a network, with the second increase in rheological moduli being due to increased lateral association and entanglements. Lateral association will be driven by the increased hydrophobicity of the fibers as the charge is gradually removed. We showed that this was categorically the case using NMR studies correlated with rheology.[80] Similarly, it is possible to demonstrate this two stage process using a number of molecular rotors, as discussed previously.[82] Because these are associated with the fibers that form the network, this shows that the bulk properties correlate with the mechanical properties of the constituent fibers. This is different from the addition of Nile blue as a hydrophobic stain, which instead shows a structural reorganization at the pK_a of the gelator.[82] Over longer times, the gels formed from **5** exhibit syneresis, whereby they shrink, exuding water from the network. This can also be linked to the hydrophobicity of the fibers, with fiber–fiber interactions leading to a significant macroscopic contraction of the entire gel network.[80]

If the networks form by a two-stage process, then there are two questions. First, can the network be arrested in the first stage? Second, can the networks be modified such that the first stage is similar but then some intervention results in a different second stage? To arrest at the first stage, it is necessary to balance the pH very carefully such that it is very close to the apparent pK_a of the gelator. This can be difficult to do in many cases, but we showed for **5** that triggered gelation using carbon dioxide (and hence relying on the in situ formation of carbonic acid) was effective.[86] A gel membrane was formed which was significantly less rigid than if the entire two stage process was allowed to proceed. Subsequent addition of GdL to lower the pH further resulted in the gels becoming much more rigid.[86]

Modification of the fiber network is also rarely discussed. There are two approaches that our groups have used. It is possible to add a polymer additive such as dextran to the system prior to gelation.[64] This was shown for gelator **6** (Scheme 1). Self-assembled fibers are formed as the pH decreases, but it seems that entanglement is difficult due to the presence of the dextran acting as a crowding agent. This results in an increase in the time until gelation as the concentration of dextran increases, with a corresponding decrease in the gel strength. The molecular weight of the dextran is apparently not that important for this process, but rather the absolute concentration is important. The gels are stable up to at least 33 wt % dextran. The second approach to varying the networks is to vary the kinetics of gelation by varying the rate of pH change. This can easily be achieved by using different amounts of GdL, for example. However, the drawback here is that this also affects the final pH.

However, the rate of GdL hydrolysis is also temperature-dependent, which affects the kinetics but not the final pH. Using this approach, we showed that the rate of assembly does not affect the nature of the fibers that are formed and does not strongly affect the final mechanical properties of the gels formed.[86] We showed that the absolute values of G' and G'' and the critical strains at which the gels formed were very similar for gels formed at 10, 20, and 30 °C, despite significant differences in the rate of gelation. The gel that formed at 40 °C showed similar values of G' and G'', although the critical strain was slightly less sharp. We interpreted this as follows. At high pH, there are colloidal aggregates. As the pH drops to around the apparent pK_a, there is a structural transition to wormlike micelles, which start to entangle. These structures still have significant charge at this point, so they will have a long persistence length. As the charge on these structures is further decreased, gelation occurs. Hence, if the dominant and important stage is the formation of wormlike micelles and these structures are long and stiff, then the diffusion rate will be expected to be slow and hence the number of interactions and entanglements will be diffusionally restricted. Hence, the gel networks will be relatively insensitive to the kinetics at which they are formed.

■ OTHER CONSIDERATIONS AND OPEN QUESTIONS

Although we have been working with these systems for a number of years, there are still a number of open questions. For example, depending on the hydrophobicity of the gelator, viscous solutions of wormlike micelles or nonviscous solutions of spherical aggregates are formed. When the pH is decreased, gels can be formed in both cases. We know that there are structural transitions from the spherical structures to wormlike aggregates to gel fibers in the case of the nonviscous solutions.[53,86] For the viscous solutions, however, it is not clear if these wormlike micelles simply "lock in" as the pH is decreased or if there is a structural transition. Adding GdL to a Na$^+$-triggered gel of gelator **7** results in a gel-to-sol transition,[49] which implies that there is a structural reorganization, but this is not completely clear.

There are also a number of aspects that are likely to be important in at least some cases, although they are rarely discussed. For example, the nature of the container in which the gel is formed can be important. For most of our gelators, gels form in all types of container we have tried, including quartz cuvettes, glass sample tubes, and plastic sample tubes. However, there are a small number of examples where the nature of the
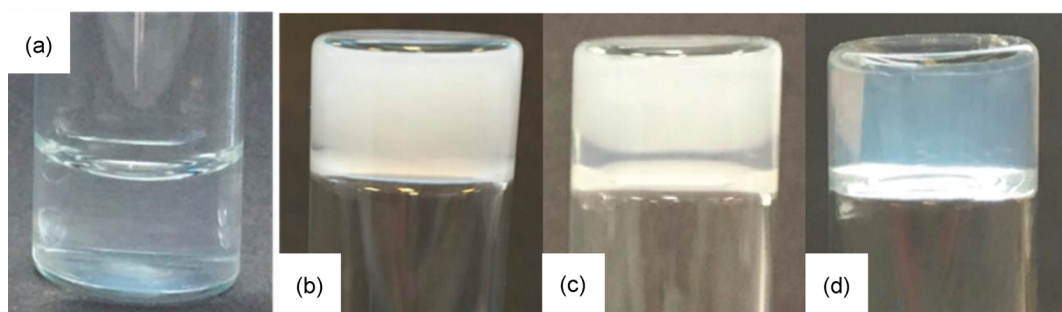
Figure 7. (a) Dipeptide **8** in water at high pH. (b) Turbid gel formed 8 h after adding GdL. (c) The gel becomes transparent after 16 h, starting at the interface. (d) A completely transparent gel is formed after 3 days. Adapted from ref 96 with permission from The Royal Society of Chemistry.
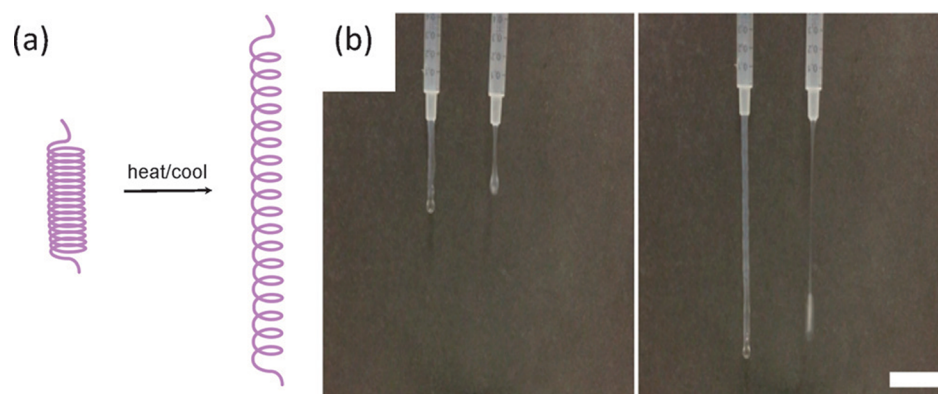

Figure 8. Dipeptide **7** forms hollow tubes at high pH, which entangle to give a viscous solution. Heating and cooling leads to a significant increase in viscosity. (a) Cartoon showing how dehydration of the core of the hollow tube leads to an extension of the length. (b) Still photographs from a video showing solutions of **7** being pushed out of a syringe after ca. 0.3 mL has been pressed out (left) and after ca. 0.7 mL has been pushed out (right). In both cases, the solution on the left has been heated and cooled and the solution on the right has not. Reproduced from ref 45 with permission from John Wiley & Sons.

container matters. This can be where the surface chemistry affects the outcome. As one example, we have observed cases where syneresis occurs in certain containers, but stable gels are formed in others. It has recently been shown that the surface can control and determine the assembly at the surface.[87] The degree of fiber bundling can be different as the hydrophobicity of the surface is changed.[88] These differences can then translate into the bulk, providing gels with different properties. We also have examples where crystallization can occur from the gel phase.[20] This is exacerbated when the sample container is thin, such as in a 2-mm-thick cuvette used for small-angle scattering; crystallization is much slower in a large sample tube. This may correlate with the observed LD effects in thin cuvettes;[53] perhaps the tendency toward fiber alignment in thin cuvettes impacts the rate of fiber-to-crystal transitions.

Linking to this is the idea of carrying out the gelation in confined spaces, for example, gelling in emulsion droplets,[89,90] at curved or interfaces flat,[91−94] or under confined conditions such as from a coacervate.[95] Here, it is possible to induce the environment such that gels ought to be formed on the basis of their bulk behavior. Gelation requires the entanglement of fibers, and hence it becomes an interesting question to ask what happens when at least one dimension in which the gel is formed is close to that of the microstructure or fiber structures. The elucidation of what is actually formed will probably require scattering experiments and is an area that is likely to develop.

On a related note, it is worth considering nucleation sites that may be within the sample. For example, scratches on the surface of the container and impurities such as dust within the sample

are likely to affect the outcome. Additives can affect the gelation process, and these can of course include heterogeneous additives such as dust. Of course, filtering to remove such potential impurities can also remove the gelator if this has assembled into large structures or could induce structural transformations.

It is likely that many examples will be affected by the rate of assembly. For many examples where heat/cool methods are used as a means of inducing gelation, it is extremely common to state neither to what temperature the sample was heated nor what rate of cooling was used. Both of these parameters are likely to be critical. From a personal perspective, when attempting to repeat the work of others, it is often these small experimental details which are missing and mean that it is difficult to be certain if exactly the same gels are formed. We expect that we likewise have included insufficient details in some cases, and this again highlights the need for more robust experimental details to be provided on publication.[7,8]

The atmosphere can be an issue. Carbon dioxide in the atmosphere will be entrained easily into many samples, resulting in the formation of carbonic acid or different carbonate species. Mostly, this is either unimportant or ignored. We have found one system for which this was important.[96] The initially formed gel from gelator **8** (Scheme 1) was turbid after a decrease in pH. Over time, the gel became transparent, starting from the gel−air interface (Figure 7). This is surprising; normally Ostwald ripening would suggest that the structures should get larger with time if there is any change. The increase in transparency implies that the structures are actually
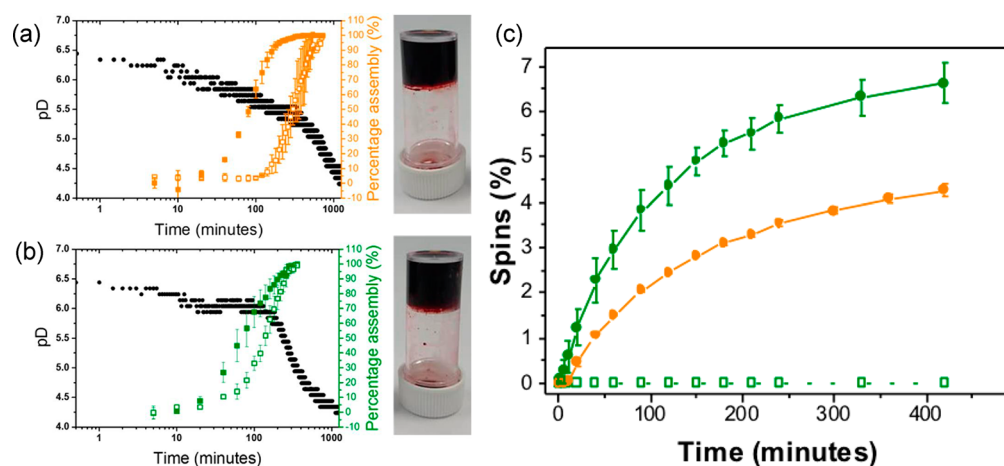
Figure 9. In a mixture of **9** and **10**, the assembly can be monitored by NMR by examining the changes in peak intensity at (a) 25 and (b) 30 °C (solid squares are the data for **9**; hollow squares are for **10**) as the pH changes (black). Also shown are photographs of the final gels. (c) The EPR signal attributed to the radical anion of **9** grows during irradiation with a 420 nm LED light source for (**9** + **10**), as shown by solid circles, and for **9**, as shown by hollow squares at 25 (orange) and 30 °C (green). Adapted with permission from ref 103. Copyright (2017) American Chemical Society.

becoming smaller or thinner. We determined that this was because the uptake of carbon dioxide and the formation of carbonates was changing the gel properties. Gels formed using solutions where carbonates were used to dissolve the gelator instead of hydroxides resulted in transparent gels.

A further environmental factor is temperature. Room temperature is most commonly used, but this can of course vary across laboratories and (in laboratories that are not temperature-controlled) across time. An interesting example of where this matters is with a number of the more hydrophobic gelators such as gelator 7 (Scheme 1).[45] At high pH, viscous solutions are formed. However, if the temperature of these solutions is increased to around 40 °C and then decreased again to room temperature, then the viscosity increases dramatically. The samples show significant extensional viscosity, and they can also be inverted for a number of hours (Figure 8). We showed that these are not gels based on their rheological data but rather very viscous solutions. This reiterates that the simple act of tube inversion is not sufficient to prove gelation (although this is of course ubiquitous). Hence, we have a system which is extremely history-dependent. We explained these observations using SAXS and SANS and could show that initially hollow tubes are formed at high pH. Heating causes a decrease in both the internal and external diameters of the tubes, resulting in elongation of the structures and an increase in the persistence length (Figure 8). Interestingly, gels formed at high pH by the addition of a calcium salt had much higher G' and G'' values when the calcium salt was added to preheated and then cooled solutions as opposed to when it was added to the as-prepared solutions, even though the gels were formed at the same temperature.

Aging is also a key point, although this is rarely discussed. For low-molecular-weight gels, aging has been reported and has been shown to have a significant effect on the gel properties.[97] However, beyond cases where there is clear crystallization from the gel phase or there is a visually apparent transition in the gels, aging is generally not discussed. These gels are nonequilibrium structures, so aging is likely in all cases; it is the time scale over which changes occur that is not clear. We expect, however, that there are aging effects in most examples. For example, we routinely use a temporal trigger to form our gels with a slow evolution of pH. Typically, we would report the gelation after

around 24 h, and we have collected data over 3 days but generally have not looked at the effect over longer times other than by visual inspection.

TRANSLATING INTO MULTICOMPONENT SYSTEMS

In general, for the work described above, single-component systems are used. In these cases, a single molecule acts as the gelator. This can of course be effective and provide useful and interesting soft materials. However, an interesting idea is to move to multicomponent systems where more than one molecule is capable of forming gels.[98] In these cases, there is the potential for either or both components to be structural (i.e., giving rise to a network) and/or have a function. In the context of this review, we would like to highlight how the design elements described above can be translated to multicomponent systems.

Because we have methods to control gelation using pH, we considered that we should be able to form self-sorted multicomponent gels with this approach. The pH at which gelation occurs in a single-component system is determined by the apparent pK_a of the gelator. As discussed above, this is determined by the molecular structure, the concentration of the gelator in solution, and conditions such as the temperature. Hence, it should be possible to choose two (or potentially more) gelators with different apparent pK_a values; as the pH is slowly lowered using (for example) GdL, the pH should sequentially reach the two different pK_a values and hence we should drive sequential assembly. In turns out that this works extremely effectively as an approach for a number of systems.[99−103] From our experience, the two apparent pK_a values would be ideally around 1 unit apart.

Perhaps the most difficult part of carrying out the above process is proving that a self-sorted network has been formed.[104] We have used a range of techniques to do this. Solution-state NMR can be used to monitor the concentration of gelator that has not assembled; when assembly occurs, the gelator becomes solidlike and essentially NMR-invisible.[99] We showed that this could be used to prove sequential self-assembly. It is often difficult to show that the fibers formed from the two gelators are different microscopically. TEM and SEM images generally show similar structures in both cases. Recently,

super-resolution techniques have been used to differentiate between fibers.[105,106] We have been able to distinguish between the networks using SANS, most recently using contrast-matching approaches.[103] Here, the contrast from the networks depends on the molecular structure, and we were able to find conditions by varying the ratio of H_2O to D_2O where either both or only one of the networks scattered. Another effective approach is to use fiber X-ray diffraction, whereby the scattering from a multicomponent gel was shown to be essentially an overlay of the expected scattering from the two components.[99]

Using this approach, it is possible to design systems. The gelator with the highest apparent pK_a will assemble first, followed by the one with the lower apparent pK_a. Hence, the order of assembly is predetermined, and this can be coupled with kinetic aspects by varying the amount of GdL added or the temperature of the self-assembly. In other approaches toward such systems using a controlled cooling rate, it is difficult to predict in advance which gelator will assemble first.

We have had a great deal of success with this approach both for dipeptide-based gelators and related amino acid-functionalized gelators. For example, we have used this method to form a self-sorted network where each fiber contains only one of the gelators. We showed that it is possible to erode one of the constituent networks using light.[101] Similar ideas have been developed by Smith, where a second network was written into a preformed gel using light.[107] We have shown that it is possible to combine a range of gelators and access interesting materials. We showed that we could combine a gelator that assembles into a very weak network with a good network former.[100] The poor network former assembled first, essentially buffering the system for a period of time that was related to the concentration of this molecule in the system. Once this had assembled, the second gel network formed, giving a strong network. Hence, this approach could be used to determine the time in which a network is formed, with a lag period before gelation of many hours.

Recently we have combined this approach to self-sorting with the idea of changing the kinetics of the assembly. Mixing gelators **9** and **10** (Scheme 1) and triggering the decrease in pH using GdL, we were able to form self-sorted systems. The kinetics of the assembly could be controlled by temperature, and we showed by SANS that self-sorted networks were formed at both 25 and 30 °C. We found that the efficiency of electron transfer between **9** and **10** was significantly different, showing that while a self-sorted network had been formed, the interactions between the fibers must be affected by the kinetics of assembly. This shows the complexity of this approach, where again it appears that every aspect needs to be controlled and understood.

■ CONCLUSIONS

The functionalized dipeptide is a really useful class of gelator that can be used to form a wide range of interesting materials. A major challenge is to be able to control and understand the large number of parameters that seem to affect the final outcome and gel properties. Part of the issue here is that the field often does not fully report the exact conditions used to form the gels. As we have gradually learned by working with this system, it seems that essentially every environmental parameter affects the system. Even the simple aspect of preparing a pregelation solution at high pH, for example, is affected by the exact pH, exact concentration, exact temperature, how quickly and for how long the system was stirred, under what atmosphere the solution was prepared, how long the sample was at rest before being used to make a gel, and likely many other variables. As a field, we all need to improve at detailing these aspects and (as referees) demanding that these aspects are fully described. We believe by extending our understanding of these processes we are better equipped to translate these to other gel systems and into gel prediction tools. All of this will potentially aid in predicting gel properties.

Having said this, it is clear that these gels are receiving significant interest probably because of their relative chemical simplicity, ease of synthesis, and cost as well as the apparent ease of preparing a gel. When a robust gelator has been found, it is very easy to prepare gels with a range of properties from this molecule. Design rules for final gel properties are still few and far between. These may come from large experimental studies, although we hope that descriptor-based approaches will be expanded to include gel properties.

There are increasing numbers of studies showing how multicomponent systems can be used to enhance the properties and use of these gels, and LMWGs seem to be very amenable to use in multicomponent systems. Design rules and generic understanding can be readily transferred from the single-component systems to multicomponent gels, and we expect that there will be a significant number of useful multicomponent gels in the future.

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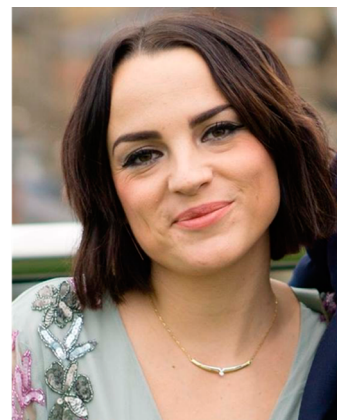*E-mail: dave.adams@glasgow.ac.uk.

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Dave Adams carried out his Ph.D. research at the University of York synthesizing organofluorine compounds. He then carried out postdoctoral work at the Universities of York, Leeds and Leicester. In 2004, he joined Unilever R&D, working in the corporate research division. He returned to academia in 2008 at the University of Liverpool, working his way up from research fellow to professor. In 2016, he moved to the University of Glasgow. He is currently an EPSRC Fellow, is a Fellow of the Learned Society of Wales, and is a Fellow of the Royal Society of Edinburgh. His current research interests focus on self-assembly, supramolecular gels, and soft materials.

■ ACKNOWLEDGMENTS

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