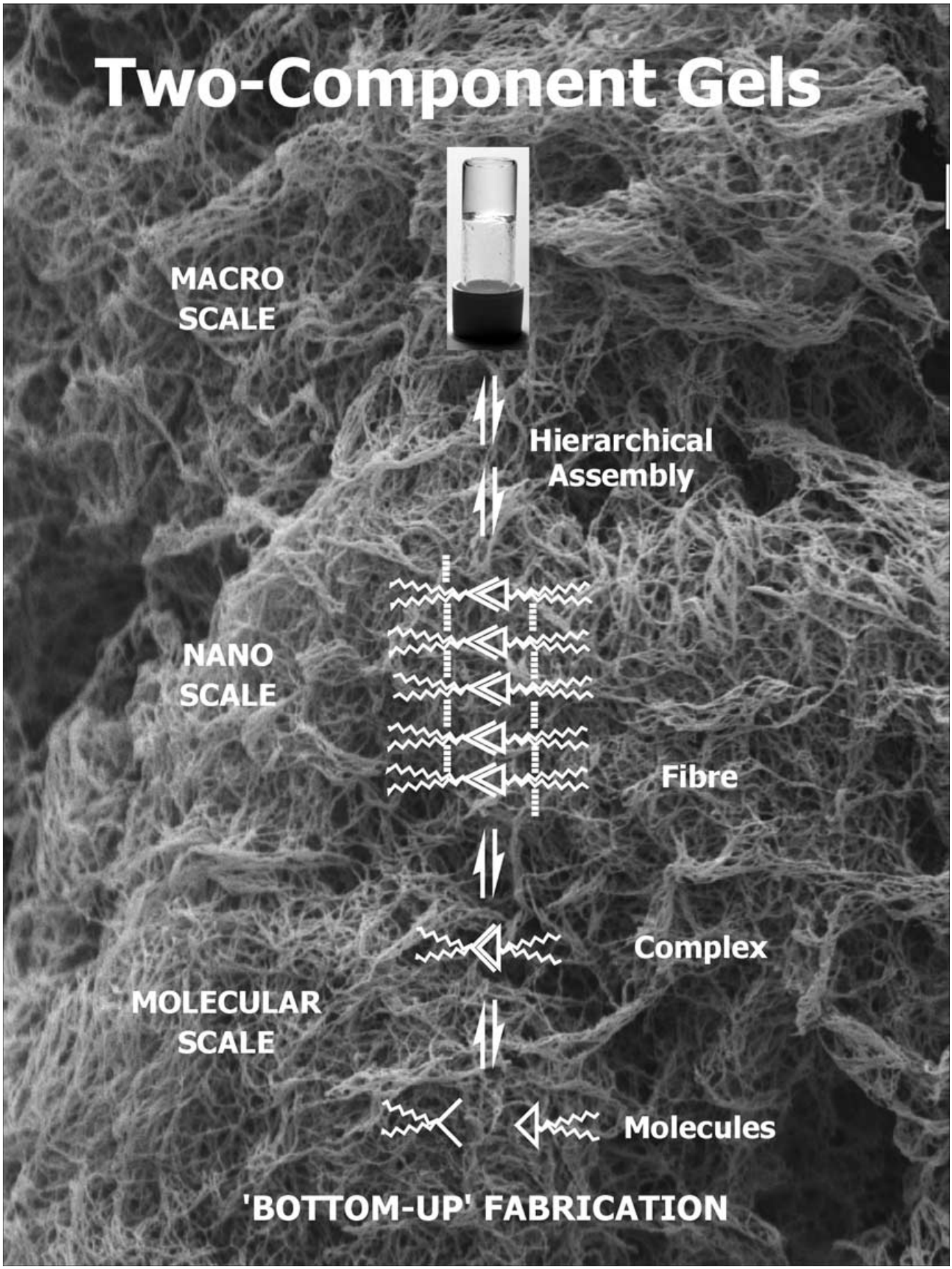

DOI: 10.1002/chem.200500241

Two-Component Gel-Phase Materials—Highly Tunable Self-Assembling Systems

Andrew R. Hirst and David K. Smith*[a]

Abstract: In the past 10 years, the molecular self-assembly and network formation of small molecule gelators has become one of the most active frontiers of the emergent area of nanochemistry. Increasingly, research efforts have begun to focus on multicomponent gelators, which rely on the initial interaction of distinct individual components to form a complex that subsequently self-assembles into a fibrous supramolecular polymer. In true two-component systems, an individual component can be present in isotropic solution, and only on addition of the second component will a gel actually form. In some cases, however, two-component gels are reported in which the second component significantly modifies the behaviour of a known gelator. Both systems are discussed in this article. The additional level of supramolecular control in the hierarchical self-assembly of two-component gels confers exquisite tunability and controllability. Functionality can be readily built into the material by simple variation of one of the individual components. This article discusses the key approaches used to control self-assembly by manipulating single molecular-recognition events and illustrates how controlling the transcription of information from the molecular to the macroscopic level by the simple addition of a second component allows complex functional materials to be selectively assembled from simple building blocks.

Keywords: gels · materials science · nanotechnology · self-assembly · supramolecular chemistry

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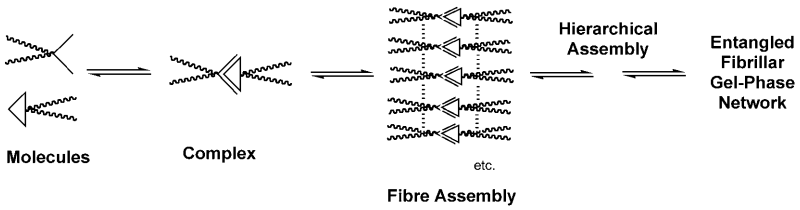
Introduction

The properties of a material depend both on the nature of its molecular constituents and the precise spatial positioning of functional groups. Supramolecular chemistry has provided a means of exploiting this exciting frontier of chemistry by the rational design of molecular components or building blocks capable of programmed self-assembly.[1] Modifying the covalent structural framework of a molecule can lead to the explicit manipulation of the molecular recognition event, a process that ultimately controls the function or macroscopic behaviour of the material. The structural framework of the building block can be considered to be programmed with molecular information (e.g., chirality, hydrogen-bonding capacity, steric demands, electrostatic properties, hydrophilic or hydrophobic character and metal-ion-binding capability). Self-assembly provides a route to ordered nanomaterials that would be impossible to generate by more traditional synthetic approaches. For example, "bottom-up" fabrication, using simple molecular building blocks to fashion nanoscale assemblies, has enabled the creation of remarkable architectures ranging from helices and grids to rotaxanes and catenanes.

In addition to the assembly of intriguing architectures, self-assembly has also been applied to the construction of nanostructured materials that extend over macroscopic length scales. Supramolecular gel-phase materials[2] based on low-molecular-weight gelators are a prime example of the way in which bottom-up fabrication can be used for the assembly of nanoscale architectures. Supramolecular gels are constructed from individual molecules organised through a self-complementary network of interactions, enabling them to assemble into extended fibres and hence form a self-supporting gel. In most cases, these gels are based on a single molecular component. Indeed, using this approach a vast array of organogels and hydrogels based on different molecular building blocks have been reported, and a good understanding is gradually beginning to emerge.[2] Typically, these building blocks assemble by means of self-complementary

hydrogen bonds, π–π interactions, solvophobic interactions, van der Waals forces and so forth.

This article, however, focuses on two-component gelation systems, which have a significant conceptual difference to their one-component analogues. In two-component gels, self-assembly relies on the initial interaction between two distinct, complementary components to form a complex. This complex subsequently self-assembles into a fibrous supramolecular polymer (Scheme 1). The formation of the complex prior to fibrillar assembly offers an additional level of control in the hierarchical self-assembly process, and, as will be illustrated in this article, provides exquisite tunability and control—indeed this level of control is difficult to replicate in one-component gelation systems. In two-component systems, structural modifications of either one of the two components readily enable the introduction of functional behaviour into the materials. Finally, the ratio of the two-components offers another parameter that can be varied to generate new morphologies and tune the materials behaviour.



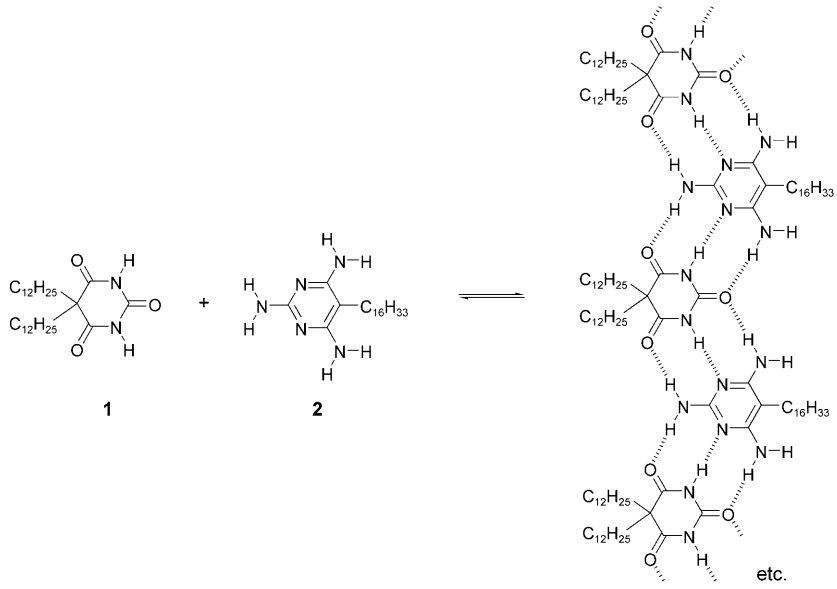
Scheme 1. Schematic illustration of the self-assembly of a two-component gel-phase material.

This concept article describes the different types of two-component self-assembling gelation systems. It is shown that the use of hydrogen bonding, chirality, reversible metal–ligand interactions and charge-transfer interactions to build self-assembling two-component systems confers tunability and responsiveness to different stimuli. Strictly speaking, in two-component gels, one of the individual components should form a solution, and only on addition of the second component will a gel form. It should, however, be noted that in some of the two-component gels discussed here, one of the components forms a gel in its own right and the addition of the second component modifies the gelation process as a consequence of complex formation with the first component; such systems although not strictly two-component gels, will also be discussed in this article.

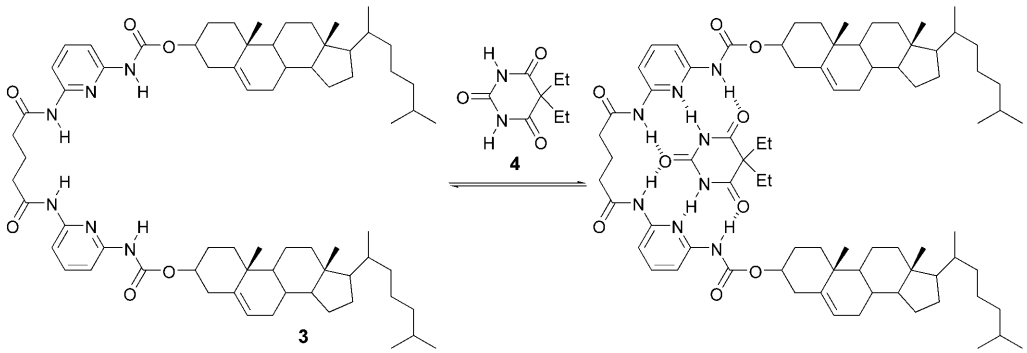
Two-Component Organogelators

Hydrogen-bonding/electrostatics: The first two-component gelators were reported in 1993,[3] and it was Hanabusa and co-workers who were perhaps the first to realise the potential of this general approach to gelation. This group reported a two-component gel based on the well-known interaction between barbituric acid and pyrimidine units. These building blocks (**1** and **2**, respectively) were functionalised in such a manner as to encourage the one-dimensional assembly of an extended complex. This was achieved by sterically blocking one face of each of these "three-faced" noncovalent building blocks, and the authors proposed that this should give rise to self-assembly as illustrated in Scheme 2.

Indeed, gel-phase materials were generated by applying precisely controlled 1:1 mixtures, although the concentrations required for gelation were relatively high (40–160 mM, depending on the solvent). IR spectroscopic measurements supported the formation of the proposed hydrogen-bond interactions. Transmission electron microscopy (TEM) indicated a fibrillar architecture, with large fibre diameters (80 nm), consistent with the hierarchical self-assembly of smaller strands. Mülhaupt and co-workers made use of this type of self-assembling system to assemble nanoscale fibres within a polypropylene matrix and illustrated that these



Scheme 2. Assembly of compounds **1** and **2** through hydrogen-bond interactions gives rise to an extended fibrous nanostructure, and hence a gel-phase material.



Scheme 3. Complex formed between compounds **3** and **4** which leads to enhanced gelation in 1,2-dichloroethane.

types of two-component assemblies can lead to modified materials behaviour of the polymer.[4]

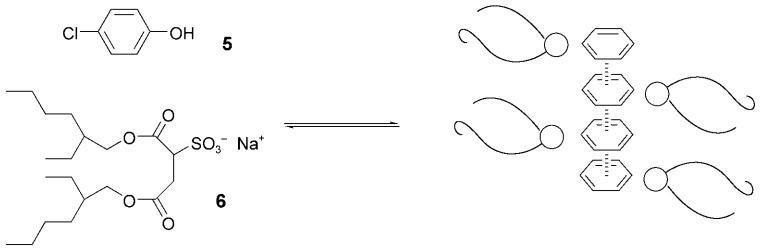
Shinkai and co-workers have also made use of barbiturate derivatives to generate two-component gels.[5] In their case, they developed barbiturate receptors functionalised with cholesterol units (compound **3**, Scheme 3). Cholesterol is a building block that is known to encourage gelation, primarily as a consequence of solvophobicity. Indeed, compounds such as **3** do form gels in certain solvents (e.g., toluene) in their own right. However, in selected solvents (e.g., 1,2-dichloroethane), addition of a barbiturate guest (**4**) enhanced the gelation properties. Recently, Yagai, Kitamura and co-workers reported a related gelation system based on melamine/barbiturate interactions that exhibited good gelation, even at relatively low concentrations (e.g., 0.2 wt %).[6]

In interesting recent studies, hydrogen-bond interactions between nucleobases have also been employed to generate two-component gelation systems.[7] Shinkai and co-workers have made use of an organogelator based on thymidine, which yielded opaque gels in benzene, and demonstrated that when complementary (poly(A)) RNA was added (with an appropriate lipid to aid solubility), a new transparent gel phase was formed. It was reported that in addition to a change in optical properties, the thermal behaviour of the two-component gel was also modified. Noncomplementary RNA (poly(C)) did not modify the gel properties in this way.

Beginning in 1993, McPherson and co-workers have made a detailed and informative study of organogels that form when substituted phenolic compounds, such as *p*-chlorophenol (**5**) are added to anhydrous solutions of the twin-tailed anionic surfactant sodium bis(2-ethylhexyl)sulfosuccinate (**6**, AOT; Scheme 4).[8] Using this two-component system, they found that gel phase materials could be generated in nonpolar solvents including isooctane, toluene and hexadecane. The propensity for gel formation was most evident when using a 1:1 molar ratio of phenol/AOT. In nonpolar solvents AOT typically forms spherical inverse micelles. Upon addition of the phenolic component, however, the low-viscosity micellar solution spontaneously transformed into a rigid organogel.

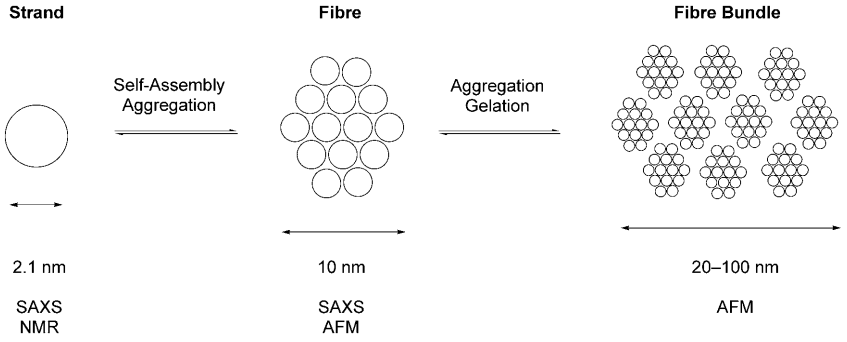
It was proposed that gelation begins through the formation of a hydrogen-bonding interaction (possibly with associated proton transfer) between the phenol and the sulfonate head group of the AOT. This proposal was supported by the observation that gels form efficiently when *para*-substituted phenols were used; however, *ortho*-substituted phenols do not form gels—presumably as a consequence of steric hindrance of the phenolic OH group. Furthermore, the thermal stability of the gel increased with the pK_a value of the phenolic component. For example, the gel–sol transition temperature (T_{gel}) of the gel based on *p*-nitrophenol gels was significantly higher than the corresponding *p*-chlorophenol-based gels. Once again, these observations are consistent with the involvement of the phenolic OH group in a hydrogen-bond (or proton-transfer) interaction. This class of material has also been shown to form gels if the phenol building block is replaced by a dihydroxynaphthalene.[9]

Evidence suggested that after the initial complexation between phenol and AOT, the gel-phase materials were constructed from strands of stacked and motionally restricted phenol molecules, with the surfactant molecules hydrogen bonded to the outer surface, coating the fibres, ensuring compatibility with the surrounding solvent environment (Scheme 4). The microstructure was later determined in more detail using small-angle X-ray scattering (SAXS) and



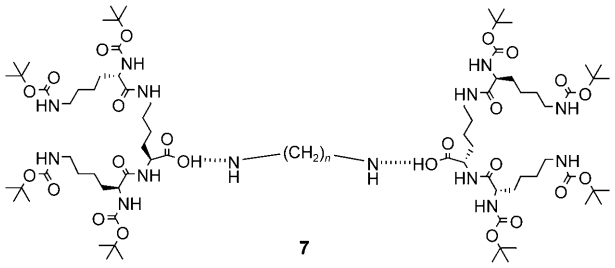
Scheme 4. Association of *p*-chlorophenol (**5**) and bis(2-ethylhexyl) sulfosuccinate (**6**, AOT) and proposed mode of self-assembly.

atomic force microscopy (AFM). In summary, it was found that AOT–phenolic strands, each composed of individual phenol stacks (ca. 2 nm in diameter, as shown in Scheme 4), self-assemble into fibres (ca. 10 nm diameter). These fibres then aggregate further into fibre bundles (ca. 20–100 nm in diameter) (Scheme 5). Above a critical threshold concentration the gel-phase material behaves like a cross-linked, or entangled three-dimensional network.



Scheme 5. Diagram illustrating three hierarchical levels of organisation present in the phenolic organogels (strand, fibre, fibre bundle). Each individual strand also has an internal level of hierarchical supramolecular organisation; that is, the interaction between the phenol and AOT.

In early 2001, Smith and co-workers communicated the basic design principles of the first dendritic two-component gelator.[10] This system utilised the interaction between dendritic building blocks based on L-lysine repeat units and an aliphatic diamine (complex **7**). Complex **7** forms as a consequence of acid–base hydrogen-bond interactions (with possible associated proton transfer). It was proposed that this gelator complex is the species that hierarchically self-assembles to form fibrous gel-phase aggregates. Notably, when the acid was protected as an ester, no gelation occurred. It was argued that complex **7** assembled into fibres as a consequence of intermolecular dendron–dendron hydrogen-bond interactions.



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Detailed further studies performed by Smith, Hirst and co-workers included solvent investigations, which supported the hydrogen-bonding hypothesis.[11] Apolar, non-hydrogen-bonding solvents were the preferred solvent environment for gel formation; indeed the thermal properties of the gel could be correlated with the polar solubility parameter δ_a and the Kamlet–Taft hydrogen-bonding parameter α.

The aliphatic diamine spacer chain length was shown to have a marked effect on the supramolecular chiral assembly.[12] Remarkably, as the length of the spacer unit was incrementally increased from six to twelve carbon atoms, the T_{gel} value increased profoundly from 4 to 105 °C. This illustrates the remarkable tunability that is inherently possible for two-component gelation systems. ^{1}H NMR spectroscopy of the self-assembled state indicated that using longer spacer units enhanced the formation of the intermolecular dendron–dendron hydrogen bonds responsible for the self-assembly of complex **7** into fibres. Scanning electron microscopy (SEM) demonstrated that the length of the spacer unit dictated the aggregate morphology, and that formation of long, intertwined fibres with widths of approximately 20 nm underpins gelation, a situation that was only achieved with the longer aliphatic diamines. Intriguingly, circular dichroism (CD) spectroscopy indicated that the spacer unit also controlled the nanoscale chirality of the self-assembled state.

The effect of dendritic generation on self-assembly has also been reported.[13] Notably, in contrast to some other reports of dendrimer assembly,[14] an optimum size of gelator unit was identified; second-generation branching gave a more thermally stable gel-phase material than first- and third-generation analogues. It was argued that the optimal gelation conditions are reflected in a balance between the formation of more enthalpically favourable hydrogen bonds and the steric and entropic cost of immobilising larger dendritic branches. This observation was in contrast to the results obtained with analogous one-component dendritic systems based on covalently linked L-lysine building blocks.[15] This may reflect the fundamental differences in the mode of hierarchical self-assembly between one- and two-component gelators.

The effect of the stereochemistry of the lysine groups during self-assembly was also investigated and shown to play a key role.[16] Notably, the T_{gel} value, which reflects the macroscopic properties of the gel, was dependent on the stereochemistry, with the gel formed from a racemic mixture of L,L,L- and D,D,D-lysine possessing lower T_{gel} values than its single enantiomer analogues. Interestingly, SEM investigations indicated that the racemic gel possesses a dramatically different nanostructured morphology (Figure 1). CD spectroscopy confirmed that the presence of even small

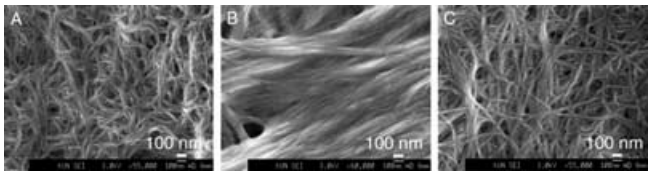


Figure 1. Effect of chirality on the nanoscale morphology of the two-component gelation system. A) L,L,L. B) 50% D,D,D, 50% L,L,L. C) D,D,D.

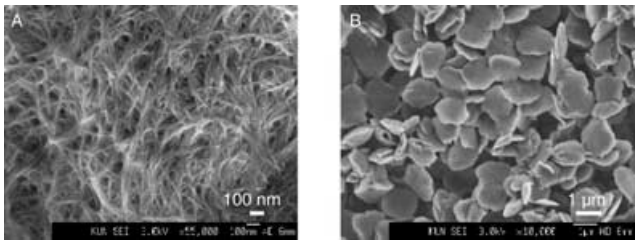


Figure 2. The nanoscale morphologies observed by using SEM for the two-component gelation system. A) 2:1 dendron/diamine ratio. B) 1:4.5 dendron/diamine ratio.

amounts of the "wrong" stereoisomer was able to disrupt the nanoscale chiral organisation.

Stereoisomeric gels, in which one chiral centre of the dendritic peptide was changed, were also investigated. This important study proved that a subtle stereochemical change to a single chiral centre had a pronounced effect on the self-assembly process. The T_{gel} values of these gels decreased and SAXS data indicated that the mode of molecular packing was also modulated as was the helicity of the fibres (CD spectroscopy). This is a clear example of the surprising impact that subtle changes in chirality can have, indicating that hydrogen-bond interactions can enable exquisite levels of control over materials behaviour.

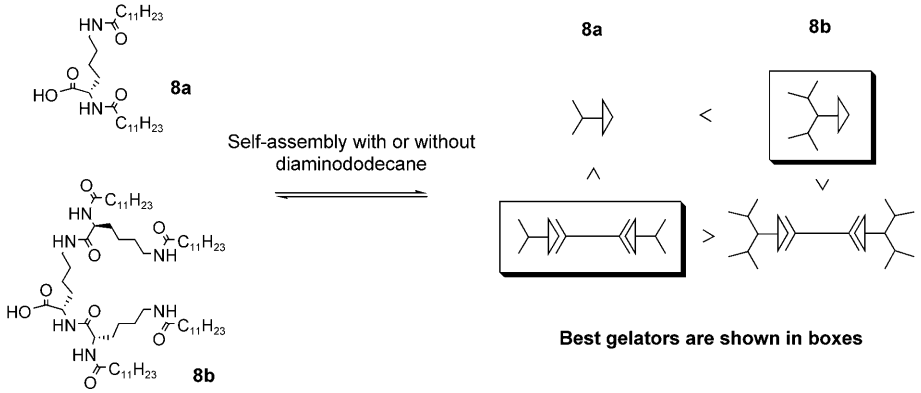
In a key study, Smith, Hirst and co-workers reported the effect of varying the ratio of the two-components, and illustrated that this offers a unique method of achieving morphological tunability.[17] Increasing the amount of diamine relative to the dendritic branch changed the propensity of this system to induce macroscopic gelation, and ultimately gave rise to a completely new morphology in which micrometer sized platelets were observed (Figure 2).

It is argued that as the amount of dendron was decreased relative to the diamine, it became less able to stabilise the extended fibrous morphology, and instead, microcrystalline chunks of diamine formed, the surface of which could be stabilised by the small amounts of dendron present. Recently, we have shown that changing the spacer chain can also modify the size of the platelets being formed, with nanoscale squares (ca. 300 nm diameter) being accessible when using diaminononane.[17b] These observations illustrate a way in which two-component gels can be tuned that is simply not accessible for single-component gelators.

Recently, Smith and co-workers replaced the Boc protecting groups with long alkyl tails to generate dendrons **8a/b**, which are, in their own right, one-component gelators.[18] These dendrons, however, can still form a complex on the addition of aliphatic diamines. Interestingly, addition of the diamine component modified the materials properties of the gel. Furthermore, these differences were dendritically controlled (Scheme 6). For the first-generation dendron, addition of the diamine enhanced gelation, whereas when using the second-generation dendron, gelation was inhibited by the diamine. This indicates that when self-assembly is possible by two different mechanisms (either using one- *or* two-components) interesting synergistic effects can be observed. This result begins to hint at ways in which switchable two-component gelation systems may be developed.

Hanabusa and co-workers have also reported gelators based on acid–amine interactions between the two components.[19] They employed a combinatorial approach by using small libraries of seven different bile acids and twelve different alkylamines. They found that certain combinations gave rise to effective gelation of organic solvents. This combinatorial mixing approach is an ideal method for enabling the discovery of new two-component gelation systems.

Shinkai and co-workers have also recently reported a gelation system that requires an acid–amine type interaction for the formation of the initial complex.[20] Interestingly, this system, in addition to being thermally responsive, was also responsive to light. The two-components were anthracene-9-carboxylate (photo-responsive unit) and an alkylammonium group (the structuring unit). This example therefore, clearly illustrates how a two-component approach can generate gels from building blocks that have different functions. On irradiation ($\lambda > 300$ nm), the anthracene undergoes dimerisation



Scheme 6. System capable of both one- *and* two-component gelation with the effect of the second component being controlled by dendritic generation.

and the gel was observed to break down. A complex heat–cool cycle was eventually able to regenerate the gel, although with some loss of absorbance, ascribed to partial photoinduced decomposition.

Similar systems, reliant on acid–amine interactions have been reported by Dastidar and co-workers.[21] Interestingly, they reported that a simple system was able to gelate food oils, as well as commercial fuels such as kerosene and diesel. Furthermore, it was capable of the selective gelation of oil from oil/water mixtures.

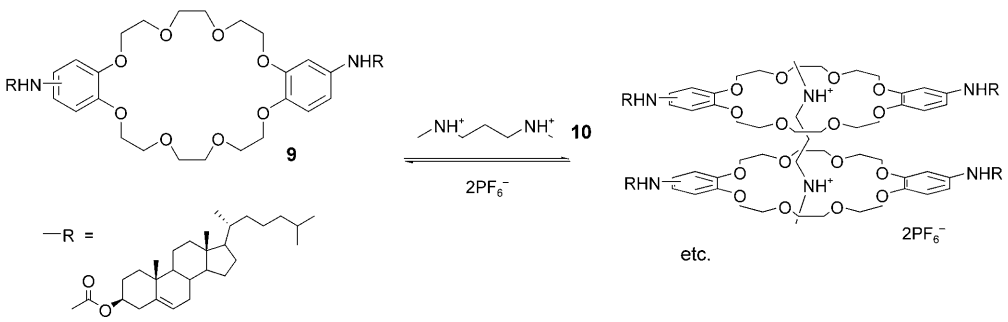
Crown ethers are one of the most widely used motifs in supramolecular chemistry, and have been used by a number of groups in the development of gel-phase materials. In 1999, Shinkai and co-workers developed a two-component crown ether based system.[22] The first component was an azacrown ether appended with cholesterol, whilst the second component was one of a range of different amines. The authors demonstrated that, whilst the cholesterol-functionalised crowns acted as gelators in their own right, the thermal stability of the gels were enhanced by the addition of amines. It was also noted that a degree of chiral discrimination between enantiomeric amines could be observed.

More recently, these workers have used larger dibenzo[24]crown-8 derivatives functionalised with two cholesterol derivatives (compounds **9**) in order to form two-component gels based on pseudo-rotaxane type complexation (Scheme 7).[23] In this case, the second component was a bis-secondary ammonium cation (**10**), which can thread through the crown ether macrocycle. It was argued that the complexation of the guest additive induced a conformational change in the crown ether building block, hence promoting gelation (increasing T_{gel} by ca. 10 °C). Specifically, in the absence of the guest, the crown ether was folded over so that the cholesterol units can undergo an intramolecular interaction, whilst it was proposed that addition of the guest caused the crown to unfold, with intermolecular interactions between cholesterol units becoming favoured. Monitoring the thermal properties of the gel, as well as the NMR shifts of key protons, at different ratios of crown/bis-ammonium cation, led to the conclusion that the bis-ammonium cation threaded through two crown ether derivatives. This exciting paper succinctly shows how the spatial distribution of the components can control the "degree of interaction" between individual complexes in the formation of extended nanostructures.

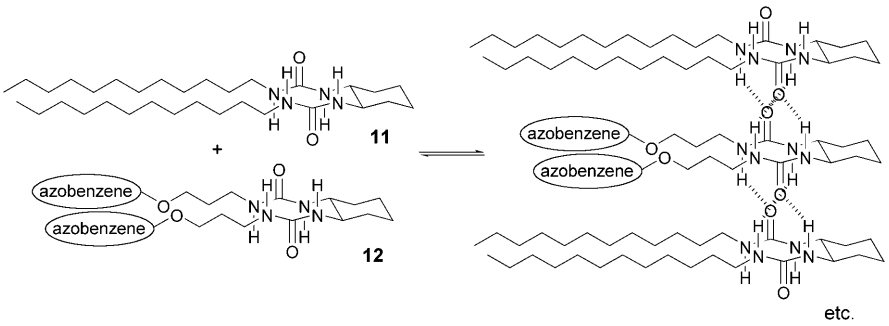
Smith and co-workers have also incorporated a crown ether into their two-component gelation system and importantly illustrated the generality of their two-component approach to gelation. The acid–amine interaction between the two-components in complex **7** was replaced with the interaction between dendritic crown ethers and a protonated aliphatic diamine.[24] This gave rise to a complex that still supported the formation of a gel.

In a different approach dependent on hydrogen bonding, Marcelis and co-workers reported that cholic acid derivatives coupled through an ester linkage to an alkyl chain formed gels in the presence of specific carbohydrates (isomannide and isosorbide) in hexane or octane.[25] Using transmission electron microscopy (TEM), the authors proposed a mode of self-assembly analogous to wormlike inverted micelles. They suggested that the carbohydrate units were located in the centre of the fibres, with the steroid groups surrounding the carbohydrate core. It was argued that the steroids had their polar face pointing towards the carbohydrate (forming hydrogen-bond interactions), and their apolar face and alkyl tail projected into the surrounding apolar solvent. It was noted that if the amount of isomannide was too low in comparison with the alkyl cholate, the T_{gel} value decreased. This again indicates that the molar ratio of two components can control materials properties, in agreement with Smith's studies described above.[17] Mattay and co-workers also reported a two-component system in which the ratio of components appeared to control the rheological properties of the gel.[26]

Van Esch and co-workers have made use of their versatile bis-urea-based gelation system to generate two-component systems based on cooperative hydrogen-bond interactions.[27] This is not strictly a two-component gelator, as the second component did not significantly enhance the gelation ability, and it is probably better considered as a mixed gelation system. By using a mixture of gelators, as shown in Scheme 8, van Esch and co-workers were able to probe chiral recognition phenomena. Compound **11** was a gelator in its own right, and the addition of compound **12** was of interest, because the chromophoric groups could be used to monitor its incorporation into the self-assembled gel-phase fibres by means of CD methods. This gave rise to useful insights into the chiral preference for recognition within a gelator stack. This experiment illustrates how using mixtures



Scheme 7. Two-component gel based on 2:1 rotaxane-type complexation between compounds **9** and **10**.

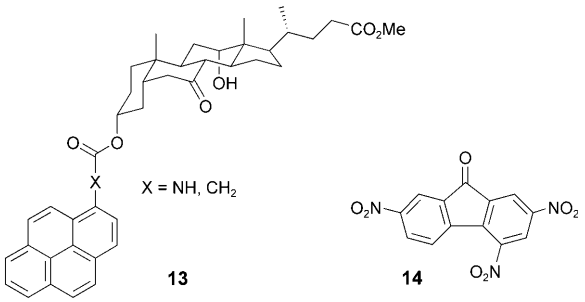


Scheme 8. Mixed gelation system developed by van Esch and co-workers.

of different gelators can give fundamentally important information about molecular recognition pathways and gelation.

We believe that in the future, the use of mixed gelation systems will continue to be a theme of increasing importance, both for understanding fundamental gelation processes, but also for the creation of truly functional gels in which different components can have intriguing synergistic effects.

Donor–acceptor interactions: In 1999, Maitra and co-workers were the first group to report a two-component gelation system based on a specific donor–acceptor π–π interaction.[28] Bile acid derivatives functionalised at the 3-position with an aromatic group (**13**) formed gels in organic solvents (particularly alcohols) in the presence of trinitrofluorenone (**14**, TNF). Interestingly, the most effective gelation was achieved using a 1:1 stoichiometry of the two components. By using variable-temperature UV-visible spectroscopy, it became clear that the gelation process was associated with a general increase in the donor–acceptor interaction because of the substantial increase in the charge-transfer band observed around the T_{gel} point. Indeed, whilst the two individual components are colourless or pale yellow, the two-component gel is coloured due to the charge-transfer band.



A subsequent paper[29] investigated these (and related) gelators in more detail. In particular, the nature of the linkage between the bile acid and the pyrene unit was explored. The linkers chosen included ester (normal and reversed), urethane, ether, urea and aliphatic CH_2 moieties. Interestingly, building blocks that had no hydrogen-bonding functionality only formed colourful gels in the presence of TNF (1 equiv) as a consequence of charge-transfer interactions, suggesting the formation of a supramolecular self-assembled state composed of an alternative stack of donor and acceptor surfaces. It was also found that the bile acid could be replaced by aliphatic chains, and in certain cases, two-component gelation was still observed. In one case, a chiral gelator gave rise to a gel-phase material with nanoscale chiral ordering, as observed by CD methods. Building blocks possessing an amide linker, however, did not form charge-transfer gels in the presence of TNF, but instead formed one-component gels in the absence of TNF. Replacing the pyrene with naphthalene, however, prevented the formation of a one-component gel. These observations indicated that both hydrogen-bonding and π–π interactions were necessary to induce gelation in the one-component system. This research offers an interesting example of the way in which nanoscale objects can be underpinned by different molecular recognition pathways.

The concept of donor–acceptor gelators has been further extended by Reinhoudt, Shinkai and co-workers.[30] They synthesised two saccharide-based gelators—one containing a donor moiety (*p*-aminobenzylidene), the second containing an acceptor group (*p*-nitrobenzylidene). Gelation studies were performed by using different molar ratios of the two components in water, octanol and diphenyl ether. In the last two (less polar) solvents a colour change was observed, from colourless to yellow, when the system was cooled below the T_{gel} value. This phenomenon was further investigated by UV-visible spectroscopy, which once again revealed the presence of charge-transfer interactions in the gel-phase material. Furthermore, T_{gel} measurements showed that in diphenyl ether, the two-component gel exhibited increased thermal stability at a 1:1 ratio, independent of the solvent. Indeed, the two-component system was 30–40 °C more stable than the single-component analogues.

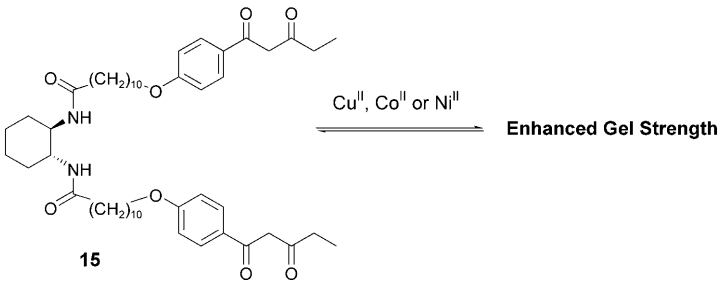
Furthermore, Shinkai and co-workers used donor–acceptor interactions between a porphyrin unit (appended with an assembling cholesterol group) and a [60]fullerene.[31] It was noted that the presence of the fullerene could stabilise the gel-phase materials formed, and this was ascribed to the formation of a stacked superstructure with interactions between alternating porphyrins and fullerenes enhancing the assembly process.

Very recently, Shinkai and co-workers have assessed the gelation ability of complexes formed between dibenzo[24]-crown-8 derivatives and bipyridinium cations.[32] These complexes are formed primarily as a consequence of charge-transfer interactions. On the basis of ^{1}H NMR and IR spectroscopy, and XRD results, the host–guest interaction stabilised gelation, with the complexes assembling into fibres as

a consequence of hydrogen-bonding, hydrophobic and charge-transfer interactions.

Metal coordination: Metal coordination can provide strong interactions between individual components. Although metal coordination formally relies on the formation of dative covalent bonds (rather than intermolecular interactions) it is often considered to be "supramolecular" as a consequence of its reversibility. Metal coordination gives rise to well-defined geometries as a consequence of ligand-field stabilisation, and this, in turn, can lead to interesting novel architectures. Metal ions also introduce functionality to the materials, as they often have redox, optical, catalytic or magnetic properties.

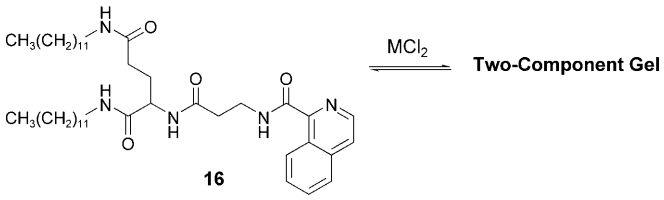
In 2000, Hanabusa and co-workers made use of metal complexation to enhance the stability of gel-phase materials.[33] Their gelator, **15** (Scheme 9), was based on *trans*-



Scheme 9. Two-component gelator based on coordination interactions between β-diketonate ligands and divalent metal ions.

(1*R*,2*R*)-diaminocyclohexane functionalised with two β-diketonate ligands. It was reported that in the presence of metal ions (Cu^{II}, Co^{II} or Ni^{II}) and a base (triethylamine), the mechanical strength of the gels formed by this compound increased. Furthermore, the T_{gel} values increased on metal ion addition—indeed solvent loss was observed rather than a gel-sol transition. Transmission electron microscopy (TEM) showed a high-contrast fibrillar architecture. The high contrast of this image was consistent with the incorporation of "heavy" metal ions into the fibrillar aggregate.

Ihara and co-workers developed a two-component gelation system that utilised a metal ion as one of the components.[34] They synthesised compound **16**, incorporating an L-glutamide moiety (unit of chirality), two long-chain alkyl groups (lipophilic components) and an isoquinoline head group (metal-binding unit) (Scheme 10). The ligand did, in its own right, form gel-phase materials in apolar solvents (e.g., toluene, cyclohexane) after a heat–cool cycle. Most interestingly, it was reported that the mode of self-assembly could be controlled by the judicious use of metal chlorides. Furthermore, the transcription of chirality and the morphology of the self-assembled state were controlled by the choice of metal ion. The presence of $CuCl_2$ enhanced chiral order and resulted in the formation of a fibrillar network. With $CoCl_2$ and $ZnCl_2$, however, a decrease in helicity was

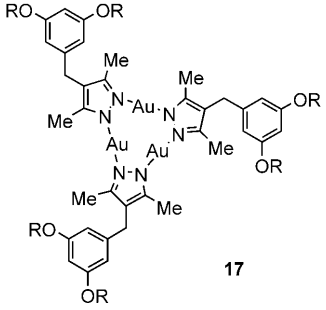


Scheme 10. Isoquinoline-based gelator that on the addition of metal ions forms gels with chiral and morphological modifications.

observed, rendering the aggregated state effectively achiral. This exciting work indicated that self-assembly was controlled by the geometric preference of the metal ion. Copper(II) has a strong preference for square-planar coordination. However, the different preference of Co^{II} and Zn^{II} appears to disrupt the chiral organisation of gelator building blocks.

Metal coordination has also been exploited as a tool for directing self-assembly and gelation by Král, Dražar and co-workers.[35] Cholic acid was used as the self-assembling unit, and it was covalently connected to phenanthroline, which acted as the metal-binding subunit. This compound formed a one-component translucent gel in 1:1 methanol/water mixtures. SEM revealed that this one-component gelation process was underpinned by a fibrous network with fibre diameters ~0.5 μm and lengths of 5–20 μm. The Zn^{II} complex in the same solvent formed a white translucent gel. Imaging by means of SEM revealed a morphological change in the self-assembled state, with a globular structure of 0.5–3 μm diameter being formed. On standing, this gel was transformed to a transparent, low-viscosity liquid. The presence of Zn^{II} therefore controls the hierarchical self-assembly process with the relatively sterically demanding phenanthroline–metal-ion interaction perturbing the mode of self-assembly, which is directed by π–π stacking, hydrogen-bonding and lipophilic interactions of the steroid.

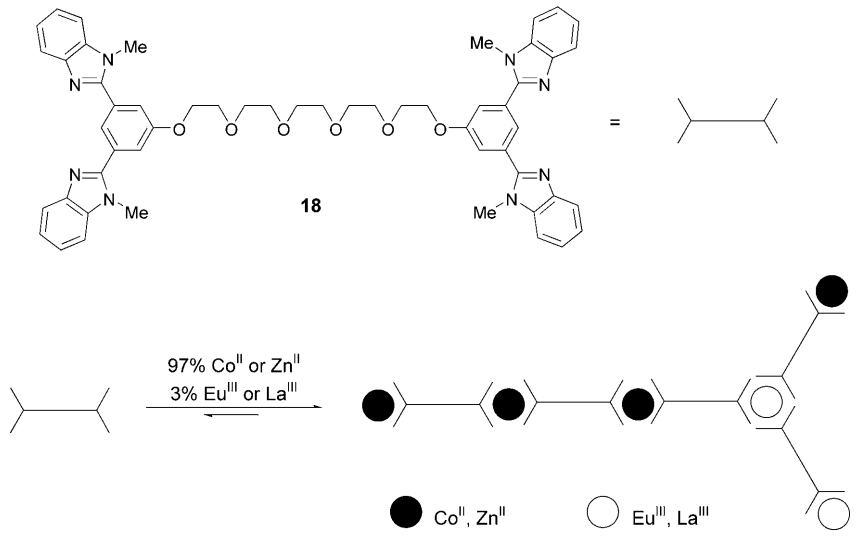
Aida and co-workers have also reported what is effectively a two-component approach to a fibrous (columnar) assembled nanostructure.[36] They synthesised dendritic ligands with a pyrazole unit at the focal point. The pyrazolate anion is an exobidentate ligand capable of binding Group 11 univalent metal ions (Cu^{I}, Ag^{I} and Au^{I}) to form a triangular complex (**17**). Appropriately functionalised pyrazoles are therefore capable of forming metal–pyrazolate coordination triangles. Heating a paraffin suspension of the dendron–



metal complexes at 200 °C and then cooling gave rise to a fibrous precipitate. In this case, the material did not show gel-phase properties due to its poor solubility in paraffin. It was argued that metal–metal interactions were responsible for holding the assembled superstructure together. The fibres were intensely luminescent, and the dendritic ligand was capable of acting as an antenna and transferring energy to the interior metal-ion cluster. On dissolution in CH_2Cl_2, the characteristic luminescence disappeared as the fibre became dissociated into individual metallacycles.

Aida and co-workers have recently extended this concept and reported the first phosphorescent organogels formed through metal–metal interactions, by using a trinuclear Au^I–pyrazolate complex with long C_{18} alkyl chains at the periphery (these enhance the solubility and begin to favour gelation rather than precipitation).[37] This complex self-assembled in hexane to form a red luminescent organogel ($\lambda_{ex}=$ 284 nm, $\lambda_{em}=640$ nm). Doping the organogel with a small amount of Ag^+ resulted in a blue luminescence ($\lambda_{ex}=$ 370 nm, $\lambda_{em}=458$ nm) without disruption of the gel, whilst removal of Ag^+ with cetyltrimethylammonium chloride resulted in complete recovery of the red luminescent gel. Furthermore, heating the doped organogel above the T_{gel} value reduces metal–metal interactions, generating a green solution ($\lambda_{ex}=370$ nm, $\lambda_{em}=501$ nm).

Beck and Rowan have reported an excellent system that exploits the reversibility of metal–ligand interactions.[38] They synthesised dumbbell-shaped compound **18** with an ethylene oxide chain connecting two ligating groups (Scheme 11). Co^{II} or Zn^{II} ions (added in 97%) are bound by two ligands, and therefore act as "chain-extension" units. Meanwhile La^{III} or Eu^{III} ions (added in 3%) are bound by three ligands and therefore act as "cross-linking" agents. Therefore this combination of metals enabled gelation. The resultant gel exhibited thermal and mechanical responses, as well as light-emitting properties. Given the wide range of metal ions, counterions and possible ligand structures, a wide variety of environmentally responsive metallosupramolecular materials may be envisaged.



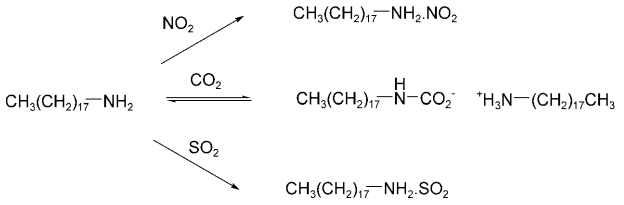
Scheme 11. A dumbbell-shaped ligand can form a cross-linked supramolecular polymer on the addition of a mixture of metal ions with different programmed geometric requirements.

In an recent paper,[39] Kimizuka and co-workers reported a ligand with a triazole head group that formed gel-phase materials in the presence of cobalt(II). Most interestingly, the blue gel was only obtained at temperatures above 25 °C; below this temperature a pink solution was obtained. This striking feature is the first example of a supramolecular two-component gel to exhibit thermally induced gelation; that is, assembly was triggered by heating not by cooling. It was argued that below 25 °C, the geometry about the metal ion changes from tetrahedral to octahedral, and that the gel-phase material only results if tetrahedral Co^{II} complexes are present. As such, this result indicates how two-component gels can access truly new types of materials behaviour.

Reversible chemical reactions: In addition to using intermolecular interactions as described in the preceding sections, it is also possible to use reversible chemical reactions for the formation of responsive two-component gel-phase materials. A good example of this is provided by the rapid uptake of CO_2 by solutions composed of a primary or secondary aliphatic amine and an organic liquid; this leads to in situ chemical transformation to the corresponding alkylammonium alkylcarbamate based gels (Scheme 12).[40] The ionic interactions, initiated as part of the chemical transformation, are the major driving force to generate thermally stable gels. Furthermore, in each case, the thermal stability of the gels was enhanced with longer alkyl chains, indicative that van der Waals forces are also important in the self-assembly process. Chemical reversibility was demonstrated by the removal of CO_2 from the gels by using gentle heating in the presence of nitrogen.

This work was extended[41] to assess the impact of different neutral triatomic molecules, i.e., CO_2, NO_2, SO_2 and CS_2, on the gelation properties (Scheme 12). The gelation properties of the products were observed to depend primarily on the nature of the triatomic molecule added to the amine and the length of the alkyl chain: alkylammonium alkylcarbamates were better gelators than the salts formed from other triatomic molecules, and the efficiency within one family of salts increased with increasing alkyl-chain length. However, only CO_2 gave rise to truly reversible gel-phase materials.

Suzuki and co-workers investigated the in situ formation of gel-phase materials by using a two-component "covalent reaction" approach.[42] Interestingly,



Scheme 12. Latent gelators formed on chemical reaction between two-components. The gel formed with CO_2 is a truly reversible system and reverts to the precursors on heating in the presence of nitrogen gas.

they illustrated that a mixture of an appropriate isocyanate and an alkylamine in toluene underwent a reaction at room temperature to yield a product capable of acting as a one-component gelator. Hence, in situ organogelation, although not yielding a truly reversible two-component gel, offers the advantages that the heating process is omitted and the gelation time is reduced.

Two-component hydrogels: There is intense current interest in hydrogels as a consequence of their potential applications in drug delivery and as biocompatible scaffolds for tissue engineering.[43] Xu and co-workers have employed the affinity of vancomycin antibiotic for D-Ala-D-Ala to yield an intriguing class of new materials.[44] Hydrogels based on a small library of Fmoc-protected (Fmoc = *N*-fluorenylmethoxycarbonyl) dipeptides (i.e., alanine, glycine, serine and threonine) were synthesised and their response to the addition of vancomycin investigated. Since the dipeptides bind to vancomycin with different affinities, the materials properties of the gels were dramatically different. In certain cases, vancomycin had no effect on gelation, whilst in other cases vancomycin acted as a gel–sol "trigger".

This strategy was taken a step further in order to improve the mechanical strength of the supramolecular hydrogels.[45] Xu and co-workers showed that the addition of vancomycin to an appropriate D-Ala-D-Ala derivative (**19**) led to a dramatic rise in the mechanical strength of the gel (Figure 3). Using small amplitude oscillating shear measurements, they estimated that the molecular recognition between the two-components provided a 10^5-fold increase in the storage modulus of the material.

Investigations with SEM suggested that the addition of vancomycin modulated the microstructure that underpins gelation, transforming a self-assembled one-dimensional linear superstructure to a highly cross-linked two-dimensional sheet. Again replacing the D-Ala-D-Ala derivative with its enantiomer or a close structural analogue resulted in only a small or moderate increase in mechanical strength on the addition of vancomycin. Overall, this work highlights the way in which a specific biomolecular recognition event can be used to control the mode of hydrogel self-assembly and the resultant materials properties.

Furthermore, Xu and co-workers have illustrated that by using a combination of two Fmoc-protected amino acids (**20** and **21**), hydrogels could be formed.[46] Interestingly, neither component formed a hydrogel independently due to their

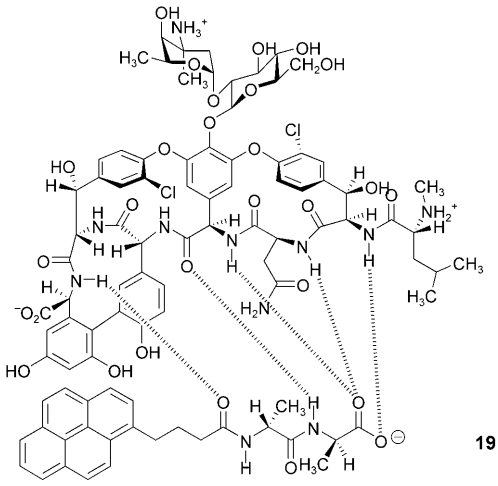
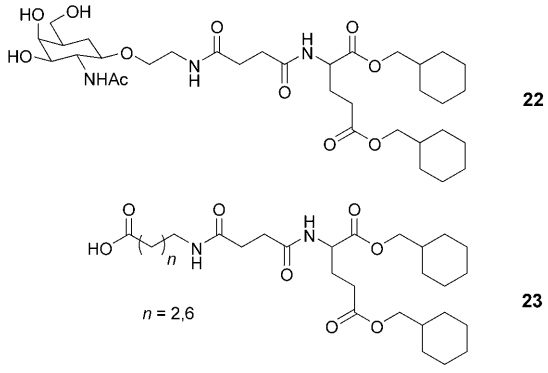


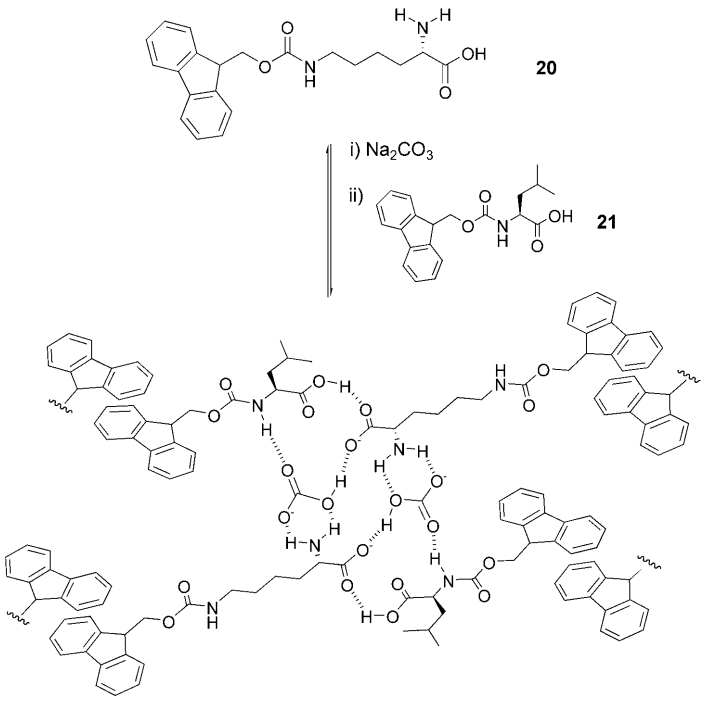
Figure 3. Structural illustration of the complex formed between vancomycin and pyrene functionalised D-Ala-D-Ala (**19**). Complexation to vancomycin significantly increases the mechanical strength of the gel that is formed.

limited water solubility. Addition of Na_2CO_3 (1 equiv) to a suspension of either component lead to the formation of a solution. The use of the same procedure with the two-component mixture produced a clear gel that underwent a gel–sol transition at pH > 11.4.

By using CD and fluorescence spectroscopy it was shown that Na_2CO_3 aided the self-assembly process, promoting a superhelical arrangement of the fluorenyl groups, which stacked in an antiparallel fashion. The π–π stacking interactions between fluorenyl groups provide part of the interaction strength required for forming extended chain structures, complemented by a hydrogen bonded network as shown in Scheme 13. These gels offer an anti-inflammatory function and may additionally act as a drug delivery vehicle. Specifically, an antineoplastic agent was successfully incorporated into the gel.

A pH-responsive character has also been conferred onto a supramolecular hydrogel by mixing a hydrogelator with related small acidic molecules to generate what is effectively a supramolecular copolymer.[47] The resultant hydrogel displayed pH-responsive shrinkage or swelling. Compound **22** induces the structuring of an aqueous environment, whilst **23** confers the pH responsiveness. As such this is effectively a mixed gelation system (like the example by van Esch and





Scheme 13. Proposed mode of self-assembly of a supramolecular hydrogel driven by hydrogen bonding and π–π interactions when the molar ratio of **20**/**21**/Na_2CO_3 was 1:1:1.

co-workers[27] described above) rather than a true two-component gel. The pH–volume change was exploited as a drug release mechanism, releasing water-soluble B_1, B_6 and B_{12} vitamins. Conversely, relatively hydrophobic flavone derivatives, for example, myricetin and quercetin, were less effectively released, in spite of gel shrinkage. Therefore, controlled release could be performed by using this system.

Conclusions and Prospects

It is clear that the study of supramolecular gel-phase materials has led to a revolution in the ability of chemists to engineer nanoscale structures that have macroscopic soft-materials properties. This article has described the way in which two-component gels, by inserting an additional level of hierarchical control into the self-assembly process, offer highly tunable and controllable forms of materials behaviour.

It is relatively straightforward to vary the structure of one or both of the two individual components. This enables the incorporation of functionality and switchability (e.g., pH triggers, light triggers etc.) into the materials. This also enables chemists to develop a deeper understanding of the molecular recognition pathways that underpin gelation, and it is clear that this level of understanding will be of deep significance in the rapidly emerging field of nanochemistry. Furthermore, it is also possible to vary the ratio of the two components, and it has been demonstrated that this additional level of control—impossible with a one-component gelator—can enable the controlled assembly of completely new nanostructured morphologies.

It is the opinion of the authors that as the understanding of gelation and other self-assembly processes becomes increasingly refined, researchers will be able to develop self-assembling systems that employ increasingly complex mixtures of components in order to generate materials with truly new, synergistic forms of behaviour.

Acknowledgements

This work was supported by a Leverhulme Trust fellowship (A.R.H.) and the EPSRC (EP/C520750/1).

[1] For general text-books dealing with supramolecular chemistry see: a) P. D. Beer, P. A. Gale, D. K. Smith, *Supramolecular Chemistry*, Oxford University Press, Oxford, (UK), **1999**; b) J. W. Steed, J. L. Atwood, *Supramolecular Chemistry*, Wiley, Chichester (UK), **2000**; for recent articles providing an overview of nanoscale self-assembly processes see: c) G. M. Whitesides, B. Grzybowski, *Science* **2002**, *295*, 2418–2421; d) I. W. Hamley, *Angew. Chem.* **2003**, *115*, 1730–1752; *Angew. Chem. Int. Ed.* **2003**, *42*, 1692–1712; e) J. A. A. W. Elemans, A. E. Rowan, R. J. M. Nolte, *J. Mater. Chem.* **2003**, *13*, 2661–2670; f) M. A. Mateos-Timoneda, M. Crego-Calama, D. N. Reinhoudt, *Chem. Soc. Rev.* **2004**, *33*, 363–372; g) C. A. Schalley, A. Lützen, M. Albrecht, *Chem. Eur. J.* **2004**, *10*, 1072–1080; h) D. K. Smith, A. R. Hirst, C. S. Love, J. G. Hardy, S. V. Brignell, B. Huang, *Prog. Poly. Sci.* **2005**, *30*, 220–293.

[2] For good review articles dealing with organogel assembly see: a) P. Terech, R. G. Weiss, *Chem. Rev.* **1997**, *97*, 3133–3159; b) O. Gronwald, E. Snip, S. Shinkai, *Curr. Opin. Colloid Interface Sci.* **2002**, *7*, 148–156; c) J. H. van Esch, B. L. Feringa, *Angew. Chem.* **2000**, *112*, 2351–2354; *Angew. Chem. Int. Ed.* **2000**, *39*, 2263–2266; d) R. Oda, I. Huc, S. J. Candau, *Angew. Chem.* **1998**, *110*, 2835–2838; *Angew. Chem. Int. Ed.* **1998**, *37*, 2689–2691; e) D. J. Abdallah, R. G. Weiss, *Adv. Mater.* **2000**, *12*, 1237–1247; f) T. Shimizu, *Polym. J.* **2003**, *35*, 1–22.

[3] K. Hanabusa, T. Miki, Y. Taguchi, T. Koyama, H. Shirai, *J. Chem. Soc. Chem. Commun.* **1993**, 1382–1384.

[4] T. Bauer, R. Thomann, R. Mülhaupt, *Macromolecules* **1998**, *31*, 7651–7658.

[5] a) K. Inoue, Y. Ono, Y. Kanekiyo, T. Ishi-I, K. Yoshihara, S. Shinkai, *J. Org. Chem.* **1999**, *64*, 2933–2937; b) S. W. Jeong, S. Shinkai, *Nanotechnology* **1997**, *8*, 179–185.

[6] S. Yagai, M. Higashi, T. Karatsu, A. Kitamura, *Chem. Mater.* **2004**, *16*, 3582–3585.

[7] a) M. Numata, S. Shinkai, *Chem. Lett.* **2003**, *32*, 308–309; b) K. Sugiyasu, M. Numata, N. Fujita, S. M. Park, Y. J. Yun, B. H. Kim, S. Shinkai, *Chem. Commun.* **2004**, 1996–1997.

[8] a) X. Xu, M. Ayyagari, M. Tata, V. T. John, G. L. McPherson, *J. Phys. Chem.* **1993**, *97*, 11350–11353; b) M. Tata, V. T. John, Y. Y. Waguespack, G. L. McPherson, *J. Am. Chem. Soc.* **1994**, *116*, 9464–9470; c) M. Tata, V. T. John, Y. Y. Waguespack, G. L. McPherson, *J. Phys. Chem.* **1994**, *98*, 3809–3817; d) B. A. Simmons, C. E. Taylor, F. A. Landis, V. T. John, G. L. McPherson, D. K. Schwartz, R. Moore, *J. Am. Chem. Soc.* **2001**, *123*, 2414–2421; e) B. Simmons, S. C. Li, V. T. John, G. L. McPherson, C. Taylor, D. K. Schwartz, K. Maskos, *Nano Lett.* **2002**, *2*, 1037–1042.

[9] Y. Y. Waguespack, S. Banerjee, P. Ramannair, G. C. Irvin, V. T. John, G. L. McPherson, *Langmuir* **2000** *16*, 3036–3041.

[10] K. S. Partridge, D. K. Smith, G. M. Dykes, P. T. McGrail, *Chem. Commun.* **2001**, 319–320.

[11] A. R. Hirst, D. K. Smith, *Langmuir* **2004**, *20*, 10851–10857.

[12] A. R. Hirst, D. K. Smith, M. C. Feiters, H. P. M. Geurts, *Langmuir* **2004**, *20*, 7070–7077.

[13] A. R. Hirst, D. K. Smith, *Org. Biomol. Chem.* **2004**, *2*, 2965–2971.
[14] For a review of dendritic gelators see: A. R. Hirst, D. K. Smith, *Top. Curr. Chem.* **2005**, *127*, DOI: 10.1007/b107178.
[15] a) C. S. Love, A. R. Hirst, V. Chechik, D. K. Smith, I. Ashworth, C. Brennan, *Langmuir*, **2004**, *20*, 6580–6585; b) B. Huang, A. R. Hirst, D. K. Smith, *J. Am. Chem. Soc.* **2005**, *127*, 7130–7139.
[16] A. R. Hirst, D. K. Smith, M. C. Feiters, H. P. M. Geurts, *Chem. Eur. J.* **2004**, *10*, 5901–5910.
[17] a) A. R. Hirst, D. K. Smith, M. C. Feiters, H. P. M. Geurts, *J. Am. Chem. Soc.* **2003**, *125*, 9010–9011; b) A. R. Hirst, D. K. Smith, unpublished results.
[18] J. G. Hardy, A. R. Hirst, D. K. Smith, I. Ashworth, C. Brennan, *Chem. Commun.* **2005**, 385–387.
[19] K. Nakano, Y. Hishikawa, K. Sada, M. Miyata, K. Hanabusa, **2000**, 1170–1171.
[20] M. Ayabe, T. Kishida, N. Fujita, K. Sada, S. Shinkai, *Org. Biomol. Chem.* **2003**, *1*, 2744–2747.
[21] a) A. Ballabh, D. R. Trivedi, P. Dastidar, *Chem. Mater.* **2003**, *15*, 2136–2140; b) D. R. Trivedi, A. Ballabh, P. Dastidar, *Chem. Mater.* **2003**, *15*, 3971–3973.
[22] J. H. Jung, Y. Ono, S. Shinkai, *Tetrahedron Lett.* **1999**, *40*, 8395–8399.
[23] S. Kawano, N. Fujita, S. Shinkai, *Chem. Commun.* **2003**, 1352–1353.
[24] G. M. Dykes, D. K. Smith, *Tetrahedron* **2003**, *59*, 3999–4009.
[25] H. M. Willemen, T. Vermonden, A. T. M. Marcelis, E. J. R Sudhölter, *Langmuir* **2002**, *18*, 7102–7106.
[26] T. Gerkensmeier, B. Decker, M. Schwertfeger, W. Buchheim, J. Mattay, *Eur. J. Org. Chem.* **2002**, 2120–2125.
[27] M. de Loos, J. van Esch, R. M. Kellogg, B. L. Feringa, *Angew. Chem.* **2001**, *113*, 633–636; *Angew. Chem. Int. Ed.* **2001**, *40*, 613–616.
[28] U. Maitra, P. V. Kumar, N. Chandra, L. J. D'Souza, M. D. Prasanna, A. R. Raju, *Chem. Commun.* **1999**, 595–596.
[29] P. Babu, N. M. Sangeetha, P. Vijaykumar, U. Maitra, K. Rissanen, A. R. Raju, *Chem. Eur. J.* **2003**, *9*, 1922–1932.
[30] A. Friggeri, O. Gronwald, K. J. C. van Bommel, S. Shinkai, D. N. Reinhoudt, *J. Am. Chem. Soc.* **2002**, *124*, 10754–10758.
[31] T. Ishi-i, R. Iguchi, E. Snip, M. Ikeda, S. Shinkai, *Langmuir* **2001**, *17*, 5825–5833.
[32] J. H. Jung, S. J. Lee, J. A. Rim, H. Lee, T.-S. Bae, S. S. Lee, S. Shinkai, *Chem. Mater.* **2005**, *17*, 459–462.
[33] K. Hanabusa, Y. Maesaka, M. Suzuki, M. Kimura, H. Shirai, *Chem. Lett.* **2000**, 1168–1169.
[34] H. Ihara, T. Sakurai, T. Yamada, T. Hashimoto, M. Takafuji, T. Sagawa, H. Hachisako, *Langmuir* **2002**, *18*, 7120–7123.
[35] M. Dukh, D. Šaman, J. Kroulík, I. Černý, V. Pouzar, V. Král, P. Drašar, *Tetrahedron* **2003**, *59*, 4069–4076.
[36] M. Enomoto, A. Kishimura, T. Aida, *J. Am. Chem. Soc.* **2001**, *123*, 5608–5609.
[37] A. Kishimura, T. Yamashita, T. Aida, *J. Am. Chem. Soc.* **2005**, *127*, 179–183.
[38] a) J. B. Beck, S. J. Rowan, *J. Am. Chem. Soc.* **2003**, *125*, 13922–13923; b) Y. Q. Zhao, J. B. Beck, S. J. Rowan, A. M. Jamieson, *Macromolecules* **2004**, *37*, 352–3531; c) S. J. Rowan, J. B. Beck, *Faraday Discuss.* **2005**, *128*, 43–53.
[39] K. Kuroiwa, T. Shibata, A. Takada, N. Nemoto, N. Kimizuka, *J. Am. Chem. Soc.* **2004**, *126*, 2016–2021.
[40] a) M. George, R. D. Weiss, *J. Am. Chem. Soc.* **2001**, *123*, 10393–10394; b) M. George, R. D. Weiss, *Langmuir* **2002**, *18*, 7124–7135.
[41] M. George, R. D. Weiss, *Langmuir* **2003**, *19*, 1017–1025.
[42] M. Suzuki, Y. Nakajima, M. Yumoto, M. Kimura, H. Shirai, K. Hanabusa, *Langmuir* **2003**, *19*, 8622–8624; M. Suzuki, Y. Nakajima, M. Yumoto, M. Kimura, H. Shirai, K. Hanabusa, *Org. Biomol. Chem.* **2004**, *2*, 1155–1159.
[43] L. A. Estroff, A. D. Hamilton, *Chem. Rev.* **2004**, *104*, 1201–1217.
[44] Y. Zhang, H. Gu, Z. Yang, B. Xu, *J. Am. Chem. Soc.* **2003**, *125*, 13680–13681.
[45] Y. Zhang, Z. Yang, F. Yuan, H. Gu, P. Gao, B. Xu, *J. Am. Chem. Soc.* **2004**, *126*, 15028–15029.
[46] Z. Yang, H. Gu, Y. Zhang, L. Wang, B. Xu, *Chem. Commun.* **2004**, 208–209.
[47] S.-L. Zhou, S. Matsumoto, H.-D. Tian, H. Yamane, A. Ojida, S. Kiyonaka, I. Hamachi, *Chem. Eur. J.* **2005**, *11*, 1130–1136.

Published online: June 20, 2005

