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CRITICAL REVIEW

Supramolecular polymeric hydrogels†

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The supramolecular crosslinking of polymer chains in water by specific, directional and dynamic non-covalent interactions has led to the development of novel supramolecular polymeric hydrogels. These aqueous polymeric networks constitute an interesting class of soft materials exhibiting attractive properties such as stimuli-responsiveness and self-healing arising from their dynamic behaviour and that are crucial for a wide variety of emerging applications. We present here a *critical review* summarising the formation of dynamic polymeric networks through specific non-covalent interactions, with a particular emphasis on those systems based on host–guest complex formation, as well as the characterisation of their physical characteristics. Aqueous supramolecular chemistry has unlocked a versatile toolbox for the design and fine-tuning of the material properties of these hydrogels (264 references).

1 Introduction

Polymeric hydrogels are 3D networks of crosslinked macromolecules that can entrap substantial amounts of water, typically through surface tension and capillary forces.^{1–5} Since their introduction in the late 1950s,⁶ synthetic polymeric

hydrogels have defined a remarkable research area, mainly on account of their wide range of applications, including super-absorbent materials, matrix chemistry and biology, media for storage and delivery of substances in biomedicine and as highly promising scaffolds to reconstitute artificial extra-cellular matrix environments.^{2,4,7–15} These materials have also shown promising applications in biomedical related research on account of their good biocompatibility^{16,17} and ability to selectively mimic the viscoelastic properties of human tissues.^{2,4,7–10}

Polymeric hydrogels can be classified in several ways depending on the nature of the polymer chains (neutral or ionic) or their structural characteristics, but a particularly useful classification

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Eric A. Appel was born in Long Beach, California, USA. He received his BS in Chemistry and MS in Polymers and Coatings Science from the California Polytechnic State University in San Luis Obispo. He performed his MS thesis research on the synthesis of biodegradable polymers of unique architectures under the direction of Dr Robert D. Miller and Dr James L. Hedrick at the IBM Almaden Research Center in San Jose, California. He is

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Jesús del Barrio

Jesús del Barrio was born in Tudela, Navarra (Spain). He received his PhD degree (Chemistry, 2010) from the University of Zaragoza with a thesis on photosensitive polymers for optical applications under the direction of Dr Luis Oriol and Dr Carlos Sánchez. He then moved to the United Kingdom to work on supramolecular materials at the University of Cambridge with Dr Oren Scherman. Since 2011, he has been a Marie Curie Post-

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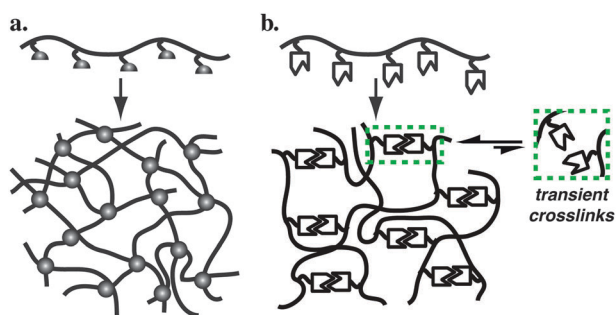


Fig. 1 Schematic representation of (a) covalent crosslinking of functional polymer precursors to form static hydrogels and (b) supramolecular crosslinking of functional polymer precursors to form transiently crosslinked hydrogels.

consists on the type of crosslinking present in the network, which can be either covalent or non-covalent in nature (Fig. 1).¹⁸ Chemically crosslinked hydrogels consist of polymer chains interconnected by permanent non-reversible bonds, which often makes them rather brittle, poorly transparent and unable to self-heal once the network is broken.¹⁹ They have been fabricated using numerous covalent reactions including Michael type addition,^{20,21} Schiff base formation,^{22,23} photopolymerisation of thiol and terminal alkenes,²⁴ free radical chain growth photopolymerisation,²⁵ enzyme-catalysed reactions^{26,27} and 1,3-dipolar cycloaddition between azides and alkynes.²⁸ Chemical crosslinking can be easily tuned in order to adequately alter the mechanical properties of the final material and it has been commonly utilised when tough and stable hydrogels are required.²⁹

However, the applicability of these systems may be limited by the utilisation of metal catalysts, photoinitiators, ultraviolet light to induce hydrogel formation, or the incomplete conversion

of reactive functional groups.³⁰ Additionally, a poorly-defined structure associated with network defects and large equilibrium volume swelling have also hampered *in vivo* material performance. In contrast, physical hydrogels rely on the formation of transient crosslinks between polymer chains. Physical hydrogel formation can be induced in aqueous media and is driven by molecular self-assembly, thereby not requiring additional crosslinking reagents, and their transition from solution to gel occurs without significant volume change. However, physical crosslinking often leads to weaker gels more susceptible to shearing by mechanical forces. Nevertheless, their dynamic nature can be regarded as an advantageous characteristic as it is the basis for both shear-thinning (viscous flow under shear stress) and self-healing (time dependant recovery upon relaxation) properties, two desirable characteristics for a variety of important applications.^{31–33}

Physical crosslinking arises from either entanglements between dynamic macromolecular species or non-covalent supramolecular interactions between polymer chains (Fig. 1).^{34–37} Myriad small molecules exist which self-assemble into long fibers, whose entanglement subsequently leads to hydrogel formation, an excellent example of which is the series of amphiphilic peptides developed by Stupp and coworkers.³⁸ Several review articles exist covering many aspects of the former method.^{39–44} Polymeric supramolecular hydrogels occur where specific and dynamic non-covalent interactions are used as the structural crosslinks between polymer chains, thereby coupling many of the exceptional qualities of polymer-based hydrogels with the diversity and orthogonality of supramolecular chemistry.

Many examples of physical polymeric hydrogels exist, typically based on biopolymers or polyelectrolytes, whereby crosslinking occurs in a non-specific manner, which can potentially hinder the available diversity of their physical properties.



Xian Jun Loh

Xian Jun Loh graduated with a PhD in 2009 under the supervision of Prof. Li Jun at the National University of Singapore (NUS). He was awarded the National Science Talent Search Award in 1999, Agency for Science, Technology and Research (A*STAR) National Science Scholarship in 2002 (undergraduate studies) and A*STAR Graduate Scholarship in 2007 (postgraduate studies). He obtained a B.Appl.Sc. (1st Class Hons) in Applied Chem-

istry from NUS in 2006. After a one year attachment stint at IMRE, he continued his PhD studies in 2007. He is currently a postdoctoral researcher in the Melville Laboratory for Polymer Synthesis. In 2011, he was elected into the Fellowship at Fitzwilliam College, Cambridge. His main interests are in the design of stimuli-responsive polymers and hydrogels for biomedical applications. Currently, he is the author and co-author of 40 journal papers and 4 patents, publishing mainly in the area of biomaterials.



Oren A. Scherman

Oren Scherman graduated from Cornell University in Ithaca, New York with a BA in Chemistry in 1999. He then went on to complete a PhD under the supervision of Professor Robert H. Grubbs at the California Institute of Technology (Caltech) in Pasadena, California in 2004. After finishing his PhD in the area of olefin metathesis and controlled polymerisation, he moved to the Netherlands to work on supramolecular polymers, at the Eindhoven Uni-

versity of Technology (TU/e), with Professors E. W. (Bert) Meijer and Rint P. Sijbesma. In 2006, he moved to Cambridge to take an academic position where he is now a University Reader in Supramolecular and Polymer Chemistry and Next Generation Fellow in the Melville Laboratory for Polymer Synthesis in the Department of Chemistry at the University of Cambridge. Oren and his research group are interested in studying supramolecular polymers, hydrogels and composite materials and their dynamics of assembly in an aqueous environment.

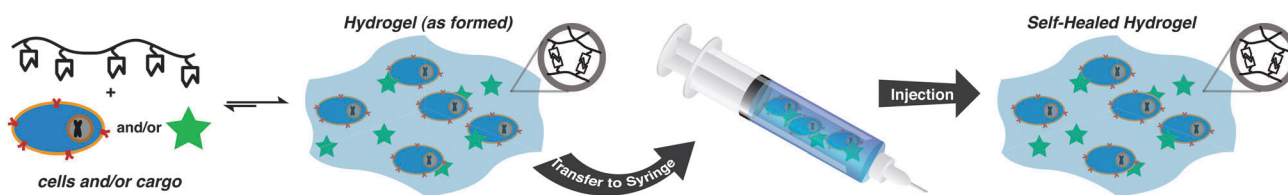


Fig. 2 Schematic representation of the utilisation of shear-thinning capability of supramolecular polymeric hydrogels for facile and minimally invasive delivery of the hydrogels *in vivo* for a variety of biomedical applications.

However, specific and directional ‘dynamic chemistries’, where a specific bond can be broken and reformed under certain environmental stimulus, have emerged as an attractive and increasingly viable option for the preparation of a broad variety of materials, including aqueous polymeric networks. These type of materials rely on highly specific non-covalent binding motifs which tie the polymer chains together. The resultant hydrogel combines the characteristics of both chemical and physical networks and their mechanical properties can be readily tuned by modifying the crosslink density and composition of the polymeric material. Drawing from the precedence of supramolecular polymers⁴⁵ it is clear that only very few specific and directional non-covalent systems exist that function in aqueous medium.^{46,47} Typical supramolecular binding motifs capable of operating in aqueous media that have been employed in the preparation of non-covalent polymer hydrogels include host–guest, multivalent ionic, metal–ligand and ‘biomimetic’ interactions, as well as hydrogen bonding and formation of stereocomplexes. These highly specific and directional binding motifs have a wide range of binding strengths and dynamics and are generally highly orthogonal, allowing researchers to unlock a diverse toolbox for the design and manipulation of the properties of the hydrogels (Fig. 3). For example, binding strength of cyclodextrins with different guests can be tuned over 3 orders of magnitude whereas for cucurbit[*n*]urils, the specific host–guest interactions can be tuned over an impressive 10 orders of magnitude! The dynamic and specific interactions between two orthogonal motifs can be exploited for the design of a wide variety of hydrogel materials.⁴⁸

In particular, these types of materials have displayed exceptional utility within the field of biomedicine, in part on the fact that they do not require surgical or implantation procedures since they can be pre-formed *ex vivo* and then delivered in a minimally invasive manner *in vivo* by applying shear stress when injected through a syringe (Fig. 2). Upon application of a shear stress, a drop in the

modulus of the gel allows it to flow during injection, followed by recovery of the elastic modulus after shear by reformation of the physical crosslinks. This method for implantation has been demonstrated to provide for more uniform distributions of cells or other therapeutic cargo in the injected gel⁴⁹ and greater control over placement of the material *in vivo*.⁵⁰ A recent review³² has discussed in detail many examples of these types of ‘shear-thinning’ injectable hydrogels.

In this contribution, we review the most important and recent results dealing with the preparation of aqueous transient polymeric networks formed through supramolecular crosslinking of polymer chains, with an emphasis on those based on host–guest inclusion complexes. We discuss the variety of supramolecular interactions which exist, including a discussion of binding thermodynamics, binding mode and molecular dynamics. Finally, we highlight some of the important applications for these types of materials and the current status of physical characterisation of the role of supramolecular interactions in determining the bulk material behaviour.

2 Supramolecular interactions

2.1 Historical perspectives

Despite extreme initial skepticism facing macromolecular science in the early 20th century, the development of polymers over the past century has had a dramatic and indispensable impact on human life. Polymer science is continuing to grow rapidly as increasing knowledge in chemistry and physics drives the development of more complex polymeric materials. Over the past century, covalent polymer chemistry has focused heavily on the development of synthetic strategies for the preparation of polymers progressing on two major fronts: chemical composition and topology. However, as the field of supramolecular chemistry has grown, and particularly the

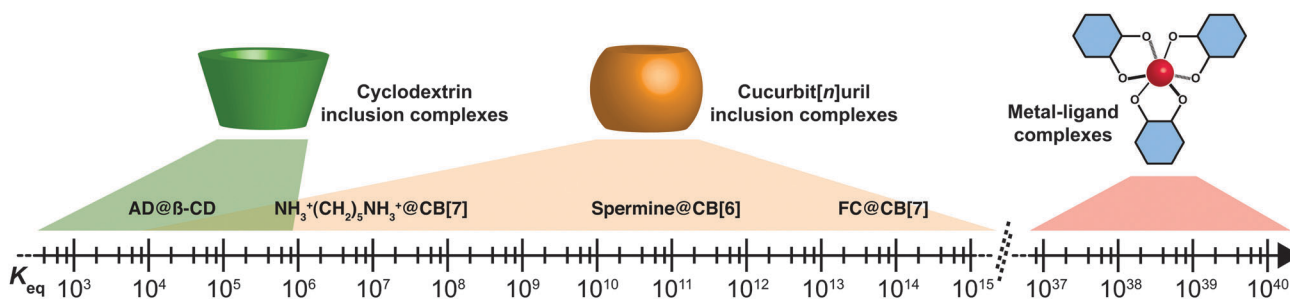


Fig. 3 Schematic representation of some selected examples of supramolecular binding motifs – cyclodextrin (left) and cucurbit[*n*]uril (middle) inclusion complexes together with catechol–iron complexes (right) – which have been utilised in the preparation of supramolecular polymeric hydrogels and the range of their typical equilibrium binding constants (AD = adamantane, FC = ferrocene).

incredible progress in synthetic self-assembling molecules,^{51–53} a paradigm shift has recently occurred through the application of directional, non-covalent interactions in polymer science, expanding the range of applications for polymeric materials immensely. The importance of supramolecular interactions within polymer science has been understood for a long time as the materials properties of many important covalent polymers (e.g. nylons, kevlar, etc.) result mainly from cooperative non-covalent interactions (hydrogen bonding in both cases mentioned). The major shift, however, has been through the development of specific, directional non-covalent interactions leading to programmed structure formation of polymeric architectures.

Supramolecular chemistry^{54–56} is an extremely fast growing field, which focuses greatly on the concept of self assembly on the molecular level. The term ‘self-assembly’ has been used to describe a seemingly infinite variety of systems in a wide range of scientific fields with enormous elasticity of definition, requiring that a more limiting definition be made. Whitesides and Grzybowski have defined self-assembly as processes arising from reversible association of distinct entities out of a disordered system that can be controlled by the rational design of those entities.⁵⁷ The concept is one of great interest and potential as it describes the appearance of order from disorder and provides a way of understanding emergent properties of chemical systems, that is, properties found in collective behavior and not exhibited by individual subunits. These properties arise from the assembly or aggregation of physically similar subunits, therefore providing the means to pursue the connection between reductionistic simplicity and perceived emergence in science.⁵⁸ When specifically considering self assembly leading to the formation of transiently crosslinked polymer-based materials, the design parameters (i.e. thermodynamics and molecular dynamics) of the supramolecular moieties are important in determining the physical characteristics and macroscopic behaviour of the resultant materials.^{59,60}

The majority of the published research coming from the interface of polymer science and supramolecular chemistry has been aimed at the preparation of ‘supramolecular polymers’. When the covalent bonds holding monomeric units in a polymer together are replaced by directional non-covalent interactions, linear main-chain supramolecular polymers are formed.^{45,61–64} These polymers are similar to traditional covalent polymers in that they are formed *via* specific mechanisms that mimic those of covalent polymerisations and can be similarly classified. However, linear main-chain supramolecular polymers differ greatly from their covalent counterparts because they are stimuli-responsive as the repeat units are reversibly associated with association strengths dependent on many environmental parameters such as solvent, temperature, ionic strength, pH, etc. Direct control over the physical properties exhibited by these polymeric materials is theoretically possible through variation in the external environment with respect to the non-covalent interactions built into the monomeric units, potentially providing access to new materials properties not available to traditional macromolecules.^{61,62}

In addition to this work, and the focus of the present review, is the considerable effort made towards incorporation of strong, directional non-covalent interactions with functional covalent polymers to develop self-assembled polymer-based hydrogels.

Additionally, a wide range of supramolecular motifs have been developed which include orthogonal chemistries. Supramolecular materials, therefore, which utilise multiple, orthogonal non-covalent motifs in concert, allow for the preparation of controlled, selective, multi-stimuli responsive hydrogels materials.

2.2 Design considerations

Over the past two decades a wide variety of specific, directional non-covalent moieties have been developed utilising hydrogen bonding, metal–ligand coordination, host–guest complexation and ionic interactions. The non-covalent interactions between these moieties are realised through various binding mechanisms, equilibrium association constants (K_{eq}), and binding dynamics, defined by the rate of association (k_a) and dissociation (k_d) of the moieties, and are important when designing a supramolecular hydrogel. Generally, the equilibrium constant directly affects the *degree* of association of the supramolecular moieties, whilst the kinetics directly affect the *dynamic nature* of the crosslinking between polymer chains. Moreover, the concentration of the functionality in question, c , is also intimately connected to *degree* of association. Within dynamically crosslinked materials exists a complex interplay between each of these parameters, in addition to more traditional parameters affecting covalent hydrogels, which typically include polymer molecular weight, crosslink density, and polymer concentration. Even when considering the same general type of interaction (e.g. hydrogen bonding), each of these specific parameters must be considered in order to develop a system taking full advantage of the specific non-covalent interactions used (*vide infra*).

2.2.1 Binding mode. A typical model for the preparation of supramolecular polymeric hydrogels is based on the use of side-chain functional polymers bearing supramolecular moieties capable of dynamically crosslinking the polymer chains *via* ‘self-complementary’ or ‘complementary’ binding motifs (Fig. 4). Self-complementary motifs (Fig. 4a) binding either through an A:A or A:B motif, the latter class generally consisting of ‘double-sided’ discotic molecules capable of associating through π - π -stacking or hydrogen bonding (i.e. urea stacking). Complementary motifs (Fig. 4b and c) can be either two-component, binding through an A:B motif, or three-component, whereby a

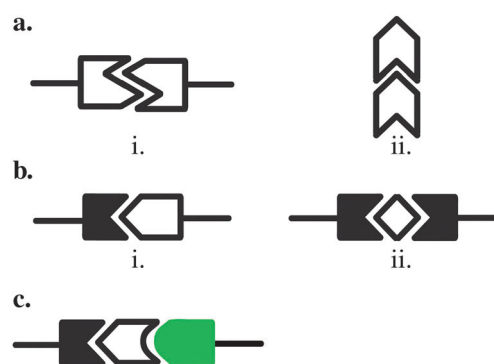


Fig. 4 General modes of binding for directional supramolecular motifs. (a) Self-complementary motifs containing either (i) A:A or (ii) A:B interactions. (b) Complementary motifs formed from (i) A:B or (ii) or A:B:A systems. (c) Three-component A:B:C complementary binding interactions.

third moiety is required for association of the complementary binding motifs (Fig. 4c). The highly studied quadruple hydrogen bonding unit 2-ureido-4-[1H]pyrimidone (UPy) is particularly interesting because it is capable of homodimerising with exceptionally high equilibrium association constants ($K_{\text{dim}} = 6 \times 10^7 \text{ M}^{-1}$ in chloroform),⁶⁵ yet can also undergo tautomerisation to selectively form an A:B complementary binding pair with 2,7-diamido-1,8-naphthyridine (NaPy; $K_{\text{eq}} = 5 \times 10^6 \text{ M}^{-1}$ in chloroform).^{66,67} In some cases metal–ligand complexation would constitute a three-component binding (Fig. 4b(ii)) whereby two of the same moiety (*e.g.* terpyridine ligands) are complexed by a single metal ion. Indeed the terpyridine ligand has been widely exploited and affords facile synthesis of supramolecular polymers through an A:B:A three component binding motif whose properties are determined by the choice of metal ion (*vide infra*). The two motifs mentioned, UPy and terpyridine, have proven to be very popular for several reasons including their facile synthesis and high association constants. The three component complementary binding motif demonstrated in Fig. 4c is rather unique and reflects the ternary complex formation of the macrocyclic host molecule cucurbit[8]uril (*vide infra*).

Judicious choice of binding motif is most relevant in that a system employing complementary binding motifs bound to separate polymer chains generally promotes *interchain* crosslinking, while self-complementary binding motifs can easily form *intrachain* rings. For example, a self-associative unit is much more prone to the formation of rings rather than truly ‘active’ physical *interchain* crosslinks. It has also been shown that complementary binding motifs, when bound to the same polymer chain, promotes *intrachain* ring formation.

This picture is rather simple and easily applied to linear supramolecular polymers, however, the role of the associative mechanism is more complicated in three-dimensional crosslinked networks. For example, Weck *et al.* studied the impact of the type and strength of hydrogen-bond crosslinking on the mechanical strength of supramolecular networks.^{68,69} These investigations revealed that the relationship between the hydrogen-bond equilibrium association constant and the network strength was not trivial. In these studies the authors demonstrated that intrinsically weak triple hydrogen-bonding interactions that assemble into multi-point hydrogen bonded arrays demonstrated a high degree of network chain connectivity, whereas intrinsically strong sextuple hydrogen bonding arrays only capable of standard complementary binding interactions led to a much lower network chain connectivity. Therefore, the assembly mechanism of supramolecular crosslinks has an important role in determining the elasticity of the resulting networks in addition to the strength of the specific supramolecular motif itself, which will be covered below.

2.2.2 Equilibrium association constants. The *degree* of association of supramolecular moieties is strongly affected by both their concentration in solution and their equilibrium constant, and is proportional to $(K_{\text{eq}}c)^{1/2}$, as illustrated in Fig. 5.⁷⁰ Hydrogel formation in a given system will occur at a particular ‘gelation transition’ whereby a contiguous network is formed through evolution of a percolated structure at a critical concentration. This quality is particularly useful in that facile targeting of

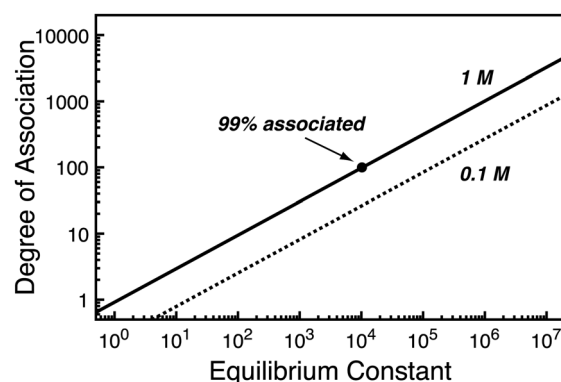


Fig. 5 Theoretical relationship between the degree of supramolecular association between two moieties and their equilibrium association constant, K_{eq} , demonstrated at various concentrations. Image reproduced from ref. 70.

specific crosslink densities in supramolecular polymer hydrogels can be accomplished provided the K_{eq} and concentration of the non-covalently associating moieties are known. In contrast, crosslinking in covalent systems can only be determined in some instances through experimental methods after the crosslinking reactions occur.

Several methods are widely used to determine K_{eq} values, including a variety of spectroscopic methods, such as nuclear magnetic resonance, infra-red, UV-visible and fluorescence spectroscopy. Isothermal titration calorimetry (ITC) is a powerful physical technique for measuring solution binding thermodynamics and stoichiometry and has been utilized previously to measure K_{eq} values in supramolecular systems in water.^{71–75} Complete thermodynamic data can be extremely useful for understanding the driving forces for association and dissociation when correlating molecular dynamics with hydrogel network mechanics (*vide infra*).

2.2.3 Binding dynamics. Another important characteristic in supramolecular polymers is the timescale upon which the supramolecular associations exist and the rate of association–dissociation of the supramolecular moieties. True dynamic supramolecular polymers must be reversible (breaking and recombining) on experimental time scales (*e.g.* NMR time scale). Fig. 6 displays a typical example of a two-component complementary binding motif and its corresponding reaction kinetics. When considering the supramolecular networks shown in Fig. 1b above, it is clear that the associated complex will represent an ‘active’ crosslink within a hydrogel, while the

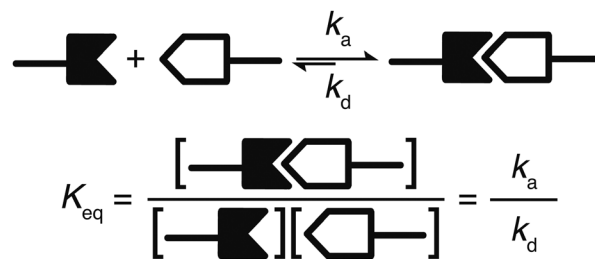


Fig. 6 Schematic illustration of the association reaction between two motifs demonstrating the relationship between the reaction kinetics and equilibrium association constant.

dissociated complex will represent an 'inactive' crosslink. The interchange between 'active' and 'inactive' crosslinks can have a very large impact on the overall behaviour of the hydrogels (*vide infra*). Moreover, the overall lifetime of a bound complex is implicated in 'active' crosslinking.⁶⁵

Building an understanding of the role of the specific molecular dynamics in determining the behaviour of bulk hydrogel networks requires an understanding of the driving forces for association and dissociation of the crosslinks, and the thermodynamic parameters governing these processes, for a particular supramolecular system. Particularly important parameters are the activation energies (E_a) for association and dissociation processes. Eyring theory relates reaction rates of chemical kinetics to temperature and can give a wide variety of important information for a given reaction, including the Gibbs free energy, enthalpy and entropy of activation, and is written below in eqn (1), where ΔG^\ddagger is the Gibbs free energy of activation, k_B is Boltzmann's constant, and h is Planck's constant. This equation is easily rewritten to give eqn (2), where ΔH^\ddagger and ΔS^\ddagger are the enthalpy and entropy of activation, respectively. The Arrhenius relationship is somewhat similar in that it also relates reaction rates to temperature and is written in eqn (3), where A represents the pre-exponential factor and R is the universal gas constant.

$$k = \frac{k_B T}{h} \exp\left(-\frac{\Delta G^\ddagger}{RT}\right) \quad (1)$$

$$k = \frac{k_B T}{h} \exp\left(-\frac{\Delta S^\ddagger}{R}\right) \exp\left(-\frac{\Delta H^\ddagger}{RT}\right) \quad (2)$$

$$k = A \exp\left(-\frac{E_a}{RT}\right) \quad (3)$$

An in-depth understanding of the behaviour of supramolecular moiety can be extremely powerful when designing supramolecular hydrogels to exhibit certain macroscopic properties. In the next section we will review examples of the multitude of supramolecular moieties that have been successfully applied to the non-covalent crosslinking of polymer chains to form supramolecular polymeric hydrogels.

3 Preparation of supramolecular polymeric hydrogels

Supramolecular polymeric hydrogels have been prepared using a wide variety of supramolecular motifs, including H-bonding, metal–ligand coordination, host–guest complexation, ionic and 'biomimetic' interactions. Several important examples of each type are discussed below.

3.1 Hydrogen bonding

Hydrogen bonding as the main driving force for assembly of molecules (or between two portions of the same molecule) is vital to a number of important biological and synthetic supramolecular systems. For example, it is responsible for the three dimensional assembly of DNA and RNA on account of the specificity and directionality of the interactions between hydrogen bonding motifs found in their nucleobases along

with their ability to function cooperatively and orthogonally, as multiple base pairs together along with π – π stacking make it possible to overcome competition by water. They hold a prominent place in supramolecular chemistry in general.^{47,76,77} These 'bonds' are relatively weak when considering bond energies of non-covalent interactions (10–65 kJ mol⁻¹).⁷⁸ However, on account of their their directionality and specificity, facile design and synthesis of units capable of accepting or donating (or both) multiple hydrogen bonds simultaneously, greatly increasing overall association constants through multi-valency is possible. As with single H-bonds, the strength of the resulting interactions is affected by several factors: (a) the nature of the donors and acceptors (*i.e.* angle between donor and acceptor, 180° providing maximum association, and whether H-bonding moiety is aromatic or alkyl), (b) the solvent and (c) the configuration of the donor–acceptor sites (*e.g.* donor (D) and acceptor (A) arrays of DAAD *vs.* DADA provide differing binding strengths through secondary interactions). Additionally, multiple-hydrogen bonding motifs can be designed with specific bonding arrays which allow for use in complex, multi-component systems on behalf of the orthogonality provided by these recognition units.

One downside of the H-bonding is the ability for polar solvent molecules, including water, to compete for binding sites, decreasing equilibrium association strengths. As mentioned above, one particularly important example of an H-bonding motif used in polymer science is the quadruple hydrogen bonding unit UPy, developed by Meijer and coworkers, which has an acceptor–acceptor–donor–donor (AADD) array and is easily synthesised in one step from commercially available isocytosines.^{65,80} An early study by Meijer and coworkers used poly(propylene oxide-*co*-ethylene oxide) three-arm star polymers with UPy functional termini.⁸¹ The materials were determined to be viscoelastic in nature and were easily degraded through addition of a monovalent small molecule and addition of only a small amount of water led to large decreases in mechanical properties through competitive H-bonding with the UPy units. For this reason, UPy, although utilised extensively in organic systems, especially in the preparation of linear supramolecular polymers,^{62,70,82–85} has not been widely used in aqueous systems.

Recently, however, Meijer *et al.* have reported the preparation of UPy-terminated telechelic poly(ethylene glycol) (PEG) chains containing a hydrophobic linker between the UPy moieties and the main PEG chain.⁸⁶ The ABA structures assemble into 'flower'-type polymeric micelles that aggregate to form micrometer-long nanofibers, resulting in shear-thinning injectable hydrogel formation. The authors observed that the macroscopic properties could be tuned by modifications in the molecular structure of the hydrophobic end-groups, making use of the control of the association and dissociation rate constants through molecular design.

There has also been much work on the preparation of hydrogels using several natural polysaccharides, including cellulose, guar gum, zanthan gum, starch, and dextran, which forms hydrogels through strong hydrogen-bonding interactions between highly hydroxyl-functional chains.⁸⁷ Rowan and coworkers exploited crystalline cellulose 'nanowhiskers' to prepare gels using a specially designed method that mimicks the stimuli-responsive nature of sea cucumber dermis (Fig. 7).^{79,88–91}

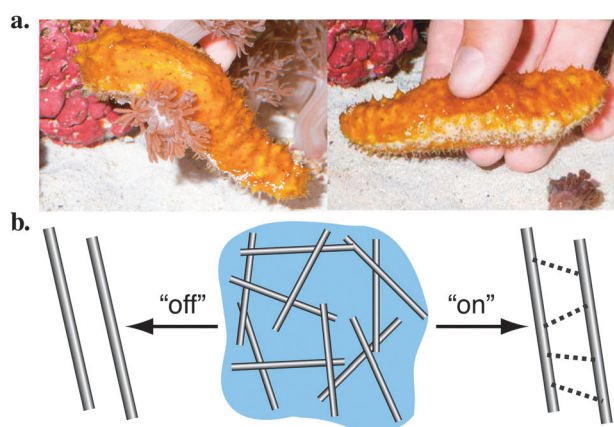


Fig. 7 (a) Image of the sea cucumber, whose dermis is a nanocomposite that has the ability to rapidly alter its modulus from soft to rigid upon application of a stimulus. (b) Schematic representation of the role of H-bonding in turning 'on' the interactions between the cellulose nanowhiskers, leading to nanocomposite formation.⁷⁹

The nanowhiskers-based materials (the nanowhiskers are harvested from a variety of natural sources) gel *via* strong hydrogen-bonding interactions through a slow solvent exchange of a strong (*i.e.* water) and a weak (*i.e.* acetone) hydrogen-bonding solvent. These materials are strong and stable, and composite materials are formed upon subsequent exchange of the solvent with a weak hydrogen-bonding polymer such as poly(vinyl acetate) from a solution of a nonsolvent (*i.e.* toluene).

Lehn and co-workers described reversible pH responsive hydrogels formed from the potassium-stabilised association of a bis-guanine telechelic (PEG) oligomer.⁹² These oligomers form linear supramolecular polymers; however, the potassium cations promote aggregation of the dimerised guanine end groups to form G-quartets, the cross-linking motif of the network. Reversible binding and release of the potassium ions by cryptand[2.2.2] undergoing deprotonation–protonation promotes gel-to-sol and sol-to-gel transitions. The authors demonstrated several cycles of reversibility in the hydrogel formation–deformation.

3.2 Metal–ligand complexation

Metal–ligand complexation has been used in aqueous as well as organic media in a variety of systems where crosslinks are formed when two or more ligands each donate a non-bonding electron pair to empty orbitals in a transition metal ion. Some metal–ligand coordination does not display dynamic character on experimental time-scales as some metal ions (such as those of Ru(II)) are essentially inert and therefore cannot be considered 'supramolecular' on account of their exceptional stability.⁹³ This feature is, however, interesting as it can be used to make materials with properties very similar to traditional covalently crosslinked systems, only with latent, chemically responsive functionality.

With this form of interaction in particular it is necessary to make judicious choices when designing a system as the choice of metal ion and ligand has a drastic affect on lability and responsiveness as binding energies are highly variable (0–400 kJ mol⁻¹).⁷⁸ The most common metal ions used in

metal-based supramolecular systems are Mn, Fe, Ru, Os, Co, Ir, Ni, Pt, Cu, Ag, Zn, Cd, and Hg and all are normally used in low oxidation states.⁹⁴ It was determined by Schubert *et al.* that supramolecular polymers utilising terpyridine ligands complexed by Fe(II) are thermally stable to 160 °C,⁹⁵ whereas Ru(II) complexes were stable well above 250 °C.⁹⁶ Additionally, it was observed that Zn(II) complexes with the same ligands are easily degraded in both acidic and basic media while Ni(II) complexes were completely insensitive to pH changes.⁹⁶ Side-chain functional polymers bearing terpyridine units^{97,98} multi-arm star polymers bearing tripyridine units at their termini,⁹⁹ and small molecule trivalent bipyridine ligands¹⁰⁰ have demonstrated the formation of gelled and elastomeric materials upon addition of various metal ions.

Because of their high stability and rates of formation, coordination-based crosslinks have been proposed to endow certain biological structures with a number of desirable material properties, including triggered self-assembly, increased toughness, self-repair, adhesion, high hardness in the absence of mineralisation, and mechanical tenability. Rowan *et al.* have reported several systems of stimuli-responsive metallo-supramolecular polymers and organogels that clearly demonstrate the utility of such metal–ligand complex formation in supramolecular materials.^{101–107} Moreover, Tong and coworkers identify one of the major advantages of metal-based systems in describing a poly(acrylic acid)-based hydrogel formed through complexation of the polymer with Fe(III) ions.¹⁰⁸ Simple addition of Fe(III) to a polymer solution forms strong yet reversible hydrogels. Upon irradiation with light in the absence of O₂, the metal is reduced to Fe(II) which no longer binds the acid-functional polymer, thereby destructing the gel network. Reintroduction of O₂ in the dark oxidizes the metal ion to Fe(III) and the hydrogel reforms in a completely reversible process.

Messersmith and co-workers described a strategy for introducing bis- and/or tris-catechol Fe(III) crosslinks into a synthetic polymer network which displayed high elastic moduli and self-healing properties.¹⁰⁹ Tris- and bis-catechol Fe(III) complexes possess some of the highest known stability constants of metal–ligand chelates (K_{eq} up to 10⁴⁰ M⁻¹; Fig. 3).¹¹⁰ Additionally, the stoichiometry of these complexes can be controlled by pH. Neutral or higher pH is required to stabilise the bis- and tris-complexes. The authors incorporated 3,4-dihydroxyphenylalanine (DOPA) moieties at the chain ends of a 4-arm PEG star polymer (10 kDa) which formed a reversible aqueous polymeric network in the presence of Fe(III) cations. Polymer–FeCl₃ mixtures at pH < 5 displayed a purely viscous response in dynamic oscillatory rheology, whereas the bis- and tris-catechol–Fe(III) crosslinked gels at pH > 8 behaved increasingly elastically. The hydrogels displayed near covalent stiffness at high strain rates supporting the idea that Fe(III) coordinate bonds can provide significant strength to bulk materials despite their transient nature, given that the pH is high enough to ensure crosslink stability on experimentally relevant time scales.

Moreover, a wide variety of natural systems have been reported including self-assembled chitosan-based hydrogels that can be formed at high pH,¹¹¹ and alginate-based hydrogels crosslinked by multivalent cations (*e.g.* Ca²⁺ and Ba²⁺) in a mild gelling reaction.¹¹² These materials are outside the scope of the present review and will not be covered at length here.

3.3 Macrocyclic host–guest complexation

Macrocyclic host–guest complexation is another interesting and widely exploited non-covalent interaction. A wide variety of macrocycles have been synthesised over the past three decades and classes of compounds include crown ethers, cyclophanes, catenanes, cavitands (such as cyclodextrins, calix[n]arenes and cucurbit[n]urils), porphyrins, cryptophanes and carcerands.^{47,78} For the purposes of this review, only the cavitands will be considered here. The cavitands form inclusion complexes where a guest molecule is locked within the cavity of the host. In these cases, the ‘host’ typically has external features that interact with solvent and internal features that foster binding of a ‘guest’ through either a specific shape or a favourable environment. This is especially seen in cases where stronger binding occurs between a hydrophobic guest sequestered into the hydrophobic inner cavity of a host, such as cyclodextrins (α -, β - and γ -CD) or cucurbit[n]urils (CB[n], $n = 5$ –8 and 10), in water through favourable solvophobic interactions. For comparison, simple host molecules, such as crown ethers, have demonstrated K_{eq} values between 10^2 to 10^4 M^{-1} in polar organic solvents and are highly dependent on solvent and temperature.⁵⁴ The highly studied CD host family^{113–116} report higher K_{eq} values of up to 10^5 M^{-1} in water (*vide infra*).¹¹³ The CB[n] host family are capable of using multiple non-covalent interactions in concert and exhibit much higher K_{eq} values of up to 10^{15} M^{-1} in water (*vide infra*).¹¹⁷ As CB[n] and CD hosts are nontoxic and biocompatible and are primarily useful in water, they provide an excellent platform for many biological applications and are considered in more depth below.

3.3.1 Cyclodextrins (CDs). Cyclodextrins (CDs), also known as cycloamyloses, cyclomaltooses or Schardinger dextrins, are cyclic oligosaccharides composed of D-glucose repeating units coupled through α -1,4-glucosidic linkages (Fig. 8).^{118,119} Commonly used CDs are α -, β -, γ -CDs which are composed of 6, 7, and 8 D-glucose repeating units, respectively, although larger CDs have been reported as well. Their 3D structure can be represented as a truncated cone with the secondary and primary hydroxyl groups on the smaller cone rim exposed to the solvent. This particular arrangement makes the interior of the macrocycle less hydrophilic relative to the aqueous media and favours the hosting of hydrophobic molecules. Thus the main driving forces behind the formation of CD host–guest inclusion complexes are

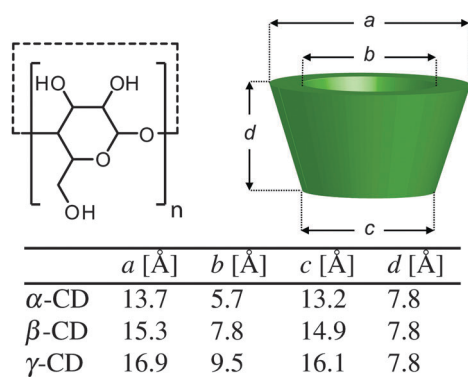


Fig. 8 Schematic representation of the cyclodextrin (CD) family.

hydrophobic and van der Waals interactions, although other factors also play a role and include the release of CD ring strain, changes in solvent–surface tensions, and hydrogen bonding with CDs hydroxyl groups.^{113,120,121} The formation of the inclusion complex alters the physical and chemical properties of the guest molecule, which normally shows enhanced water solubility. On account of their low price, good availability and the capability of forming inclusion complexes with high water solubility, CDs have been proven to be very useful compounds in a wide range of areas including analytical science, pharmacy, improved separation techniques, catalysis, as well as in the food, textile and cosmetic industries.^{119,122–129}

The inclusion complex formation capability of CDs has only recently been utilised as a non-covalent binding motif for the development of a wide variety of dynamic polymeric networks and assemblies in aqueous media.^{118,119} These polymeric systems have been frequently investigated in terms of pharmaceutical and biomedical applications including sustained and targeted release of bioactive substances, biocompatible scaffolds for tissue engineering and medical diagnostics. The following section is an overview of the different polymeric systems which incorporate CDs in order to induce hydrogel formation. From a topological point of view it is possible to differentiate two families of non-covalent CD polymeric hydrogels: (a) poly(pseudo)rotaxane hydrogels containing CDs threaded onto one or two polymer chains and (b) hydrogels in which the polymer chains are held together by host–guest inclusion between CDs and small organic guest moieties. Research in supramolecular CD polymeric hydrogels has been broadly developed since the 1990s and, since it has been reviewed in several occasions,^{113,122} the following sections will only cover a few selected investigations on CD-based polymeric hydrogels.

Hydrogels prepared through *in situ* formation of a poly(pseudo)rotaxane *via* threading of CDs onto non-functional polymer PEG chains were first reported by Harada and coworkers in 1994 (Fig. 9a).¹³⁰ Crosslinking in these cases occurs from reversible H-bonding interactions between the exteriors of bound cyclodextrin units and the formation of crystalline domains. The authors later extended the system to the use of poly(ϵ -caprolactone) and other aliphatic polyesters.¹³¹ Tonelli and coworkers reported the use of poly(vinyl alcohol).¹³² A system developed by Hadziioannou and coworkers uses a crosslinker containing two α -CDs bound by a divinyl sulfone

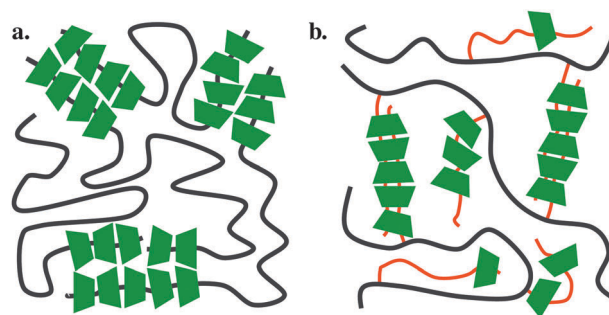


Fig. 9 Schematic representation of poly(pseudo)rotaxane formation utilising CD-based interactions with either (a) polymer chains or (b) grafted polymer chains from graft copolymers as the driving force for hydrogel preparation.

linker that form rotaxanes with PEG.¹³³ These are aptly named ‘sliding gels’ as the crosslinkers are capable of ‘sliding’ along the polymer chain like beads on a line. Wang *et al.* reported the preparation of dual-stimuli responsive gels using the complexation of α -CD onto PEG grafts present in random copolymers of poly(ethylene glycol)methacrylate (PEGMA) and 2-(dimethyl-amino)ethyl methacrylate (DMAEMA), as demonstrated in Fig. 9b.¹³⁴ The α -CD slides onto the PEG side-chains of the polymer allowing for gel formation at high pH, while the pendant dimethylamino-functionality allows for pH sensitivity leading to disruption of the hydrogel structure at low pH.

Gels combining supramolecular and covalent crosslinking have been developed by Tonelli *et al.* where PLA-PEG-PLA triblock copolymers bearing methacryloyl-functional endgroups were non-covalently crosslinked by addition of CD to the polymer solution followed by subsequent polymerisation of the methacryloyl units *in situ* by photopolymerisation.¹³⁵ Similarly, Larsen and coworkers crosslinked PEG using CD modified with vinyl units that were subsequently photopolymerised *in situ*.¹³⁶ These materials demonstrated promising drug release profiles. Additionally, several other studies have investigated the delivery potential of these types of hydrogels for either multi-drug delivery¹³⁷ or protein delivery¹³⁸ applications.

In the case of γ -CD, two polymer chains can thread simultaneously through the cavity leading to very strong entanglements.¹³⁹ These, however, are not easily reversible as a polymer chain must completely dethread in order to disrupt crosslinking. To address this the authors developed a reversible, redox-responsive, disulfide-based covalent polymer backbone to impart reversibility to the system.¹⁴⁰

Several hybrid hydrogel systems have been reported using gold¹⁴¹ and silica¹²⁰ nanoparticles. In the first case, thiolated cyclodextrins were used as ligands for gold nanoparticles that were subsequently crosslinked through addition of polymer which includes in the CD cavity, trapping the nanoparticles within the hydrogel structure. Similarly, β -CD bound to the surface of silica nanoparticles non-covalently binds an adamantane-terminal PEG polymer that is subsequently cross-linked upon addition of α -CD and pseudorotaxane formation.

As mentioned above, several attempts have also been made to develop hydrogels from CDs by covalently attaching a CD host to a polymer chain and mixing with a similarly functionalised guest-containing polymer (Fig. 10a).^{142–145} In each of

these cases, adamantane@ β -CD inclusion complex formation has been utilised. Multivalent PEG multi-arm star polymers functionalised with either a cholesterol or CD unit have been reported.^{138,146} As briefly mentioned above, appending the CD-host and an appropriate guest moiety to the same polymer chain leads to *intrachain* folding and collapse instead of *interchain* crosslinking.¹⁴⁷ Ritter *et al.* also demonstrated that a guest-functional polymer could be crosslinked in a similar fashion by employing a CD-dimer (Fig. 10b).¹⁴⁸

The abovementioned polymer networks are sensitive to external stimuli such as mechanical forces and temperature by virtue of the non-covalent nature of the crosslinks. Nevertheless, when designing and fabricating new supramolecular constructs, the realisation of reversibility is particularly important as it could enable these materials to be superior to more conventional ones. The host–guest supramolecular chemistry of CDs allows for controlled binding under other stimuli different than heat, shearing or the presence of competing guest. Several investigations have exploited this point and have demonstrated pH, redox potential and light responsive sol–gel transition. The most common strategy implies the preparation of water-soluble polymers bearing selected guest molecules which can change their binding affinity for CD upon application of an external stimulus. Among the different investigated stimuli, light is particularly interesting as it is a remote stimulus that can be controlled spatially and temporally with great ease and convenience.

Stoddart and coworkers have recently developed a photo-responsive hydrogel system that takes advantage of specific binding interactions between azobenzene with a β -CD unit bearing a pendant deoxycholate unit.¹⁴⁹ The authors prepared azobenzene side-chain functional poly(sodium acrylate) copolymers bearing 8% loading of azobenzene units. The azobenzene units are indirectly responsible for hydrogel formation as the *trans* form binds β -CD, displacing the pendant deoxycholate unit from the CD cavity, allowing for strong hydrophobic and H-bonding interactions between deoxycholate units to promote gel formation. Isomerisation of the azobenzene unit from the *trans* to the *cis* conformation by irradiation with UV light at 355 nm causes displacement of the *cis* conformer from the β -CD cavity by *intramolecular* binding of the deoxycholate unit, breaking the *intermolecular* interactions between deoxycholate moieties and disrupting the hydrogel structure. As the isomerisation is fully reversible upon irradiation with visible light at 450 nm, a sol-to-gel transition occurs whereby the gel structure is reformed. Several similarly photoresponsive systems have been prepared by Harada and coworkers.^{150–152}

Besides the photoresponsive systems mentioned above, other studies have reported physical hydrogels based on CDs that are responsive to pH.^{153–158} Yui and co-workers have developed a system where α - or β -CD containing poly(lysine) are combined with 3-(trimethylsilyl)propionic acid (TPA) analogs.¹⁵³ The addition of TPA to an aqueous solution of the CD polymer lead to hydrogel formation on account of simultaneous formation of host–guest complexes between α -CD and the TPA trimethylsilyl group, and ionic interactions between the negatively charged carboxylic acid group of TPA and the positively charged amines of the poly(lysine).¹⁵⁵ The combination of both ionic and host–guest interactions makes

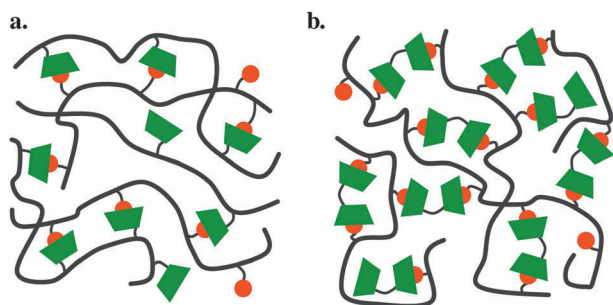


Fig. 10 Schematic representation of some selected types of hydrogel structures that can be prepared utilising functional polymers bearing good guests for CD complex formation and either (a) CD-functionalised polymers or (b) small molecule CD dimers.

the system responsive to temperature as well as pH. The amino groups of the poly(lysine) are negatively charged at neutral pH and the ionic interaction with the CD-bound TPA hold together the polymeric network. At pH > 8, repulsive ionic interactions between the negatively charged carboxylic acid groups of the TPA and the polymer chains induces gel disassembly.

Harada and co-workers have also shown recently that redox-responsive self-healing materials can be created based on FC@CD host-guest interactions.¹⁵⁹ In this investigation, a transparent supramolecular hydrogel was formed by mixing poly(acrylic acid) modified with β -CD as a host polymer with ferrocene-containing poly(acrylic acid). Both chemical and electrochemical redox stimulus were found to induce a sol-gel phase transition in the supramolecular hydrogel (a 35% decrease in the storage modulus was observed after electrochemical reduction, which was fully recovered after heating at 50 °C). Furthermore, the self-healing ability of the system was clearly demonstrated through the macroscopic re-adhesion of two cut surfaces of a hydrogel sample, which could be controlled by redox reactions. Again, this is an excellent example where non-covalent interactions are used to create simple, reversible stimuli-responsive materials.

3.3.2 Cucurbit[*n*]urils (CB[*n*]s). Cucurbit[*n*]urils (CB[*n*], $n = 5-8, 10$), named after the genus *cucurbita* (genus in the gourd family *cucurbitaceae*) because of its structural resemblance, are macrocyclic oligomers based on repeating monomer units of glycoluril.¹⁶⁰⁻¹⁶⁴ The common characteristic structural features of CB[*n*]s are the hydrophobic cavity and the polar carbonyl groups surrounding the portals (Fig. 11). They have a cavity size ranging from 4.4–8.8 Å (for CB[*n*], $n = 5-8$) and a portal diameter ranging from 2.4–6.9 Å. This corresponds to a cavity volume range of 82–479 Å³, which results in discernible features in the host-guest chemistry of the different CB[*n*] homologues.¹⁶⁵ The water solubility of CB[*n*]s varies across the family in an odd-even fashion, presumably on account of the altered arrangement of H-bonding water clusters between the homologues in aqueous solution, a feature similar to that of linear (oligo)ureas.¹⁶⁶ CB[5] and CB[7] show relatively high solubilities of 20–30 mM in neutral water, whereas CB[6] and CB[8] have much lower solubilities of 0.018 and <0.01 mM, respectively.¹⁶⁵ All CB[*n*]s are soluble in acidic

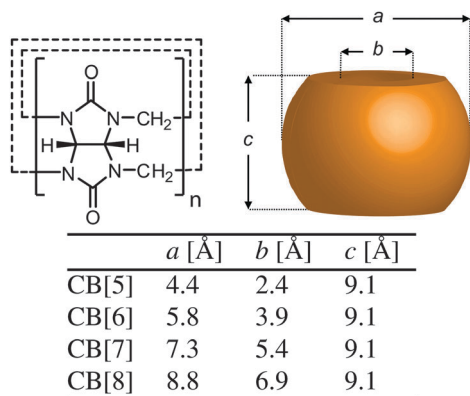


Fig. 11 Schematic representation of the cucurbit[*n*]uril (CB[*n*]) family.

water, as well as in aqueous solutions of alkali metals on account of protonation or coordination of the metal ions to the carbonyl oxygen atoms. The solubility of CB[*n*]s in common organic solvents is less than 10⁻⁵ M, and therefore the host-guest chemistry of CB[*n*]s has primarily been studied in aqueous media.

There have been few examples of singly or multiply substituted CB[*n*]s being synthesised in order to modify their solubility to a range of solvents as well as to increase aqueous solubility. An additional potential gain is to provide a route to more complex structures.¹⁶⁷⁻¹⁷⁰ Substitution on a CB[*n*]s at this point in their development is defined as where the methine carbon of the glycoluril moiety (at the CB[*n*]s equator) bears a group, which can be either an alkyl radical or an oxy radical. CB[*n*]s homologues can be synthesised through the condensation of any suitably substituted glycoluril bearing a group(s) at either or both carbons of the fuse junction of the two imadazolone rings. This approach has met with limited success as the predominant homologues are CB[5]s with only small amounts of CB[6]s. The alternative method for the introduction of substitution is through direct oxidation of the regular CB to introduce an oxy radical. In 2003, Kim *et al.* reported an oxidative method to introduce hydroxyl moieties at the equatorial positions of CB[6],¹⁷⁰ which were used in a range of supramolecular systems from synthetic pores to surface-modified vesicles.¹⁷¹ Although multivalent CB[6] has great potential, devising a straightforward procedure to introduce a single point of chemical attachment on the parent CB molecule would guarantee a high level of control over molecular structures and topologies on the nanoscale. The synthesis of monohydroxylated CB[6] from regular CB[6] in aqueous solution using host-guest interactions to control the oxidation mechanism has been recently reported.¹⁷² Alternatively, methylene bridged glycoluril hexamer can be prepared, which can form monofunctionalised cucurbituril derivatives in a subsequent step.¹⁷³

Several concerted intermolecular interactions promote the binding of guests by CB[*n*]s. On one hand, hydrophobic effects are present in a similar way to CDs. However, there is an important interplay between the release of 'high-energy' water molecules upon inclusion of nonpolar organic residues and concomitant differential dispersion interactions inside the cavity and in bulk water. Ion-dipole interactions between metal or organic cations and the ureido-carbonyl rims come into play while hydrogen-bonding interactions prevail less frequently. The preference of CB[*n*]s to bind cationic species and its reluctance to complex anions can be rationalised on the negative electrostatic potential of the carbonyl rims and the inner cavity.^{174,175} This feature clearly differentiates CB[*n*]s from CDs, which preferentially bind to neutral or anionic guest. Higher order CB[*n*]s also exhibit a degree of flexibility in their binding and they are known to create an induced fit, constrictively binding sterically bulky guests.^{176,177} Variation of the number of repeating units and therefore sizes of both the inner cavity and the portals results in different molecular recognition properties with the CB[*n*]s family. The smallest, CB[5], can encapsulate a variety of gas molecules including krypton, xenon, nitrogen, oxygen, argon, nitrous oxide, nitric oxide, carbon monoxide, carbon dioxide, methane, ethylene and ethane as well as small solvent molecules such as methanol

and acetonitrile inside its cavity.^{167,169,178–181} They can also bind simultaneously two cations (alkali, alkali-earth, NH_4^+ , Pb^{2+} , Cd^{2+}) through electrostatic interactions with the ureido carbonyl groups, fully occupying the two portals.¹⁸²

CB[6] can not only bind alkali-metal, alkaline-earth, transition-metal, lanthanide cations and several gas molecules but also a large variety of positively charged and neutral organic guests on account of its larger inner cavity.^{165,183–186} CB[6] forms remarkably stable complexes with protonated aminoalkanes as the hydrophobic oligomethylene chain can partially fill the cavity while the ammonium cation can be simultaneously bounded to one of the portals through strong ion–dipole interactions. In particular, CB[6] tightly binds protonated polyamines such as 1,6-diaminohexane or spermine yielding highly stable 1:1 host–guest complexes (K_{eq} up to 10^{12} M^{-1}).¹⁷⁴

CB[7] forms strong 1:1 complexes with positively charged amphiphilic guests including adamantane, ferrocene, *p*-xylylene and trimethylsilyl derivatives containing one or two amino groups, as well as viologen derivatives.^{187–189} CB[7] exhibits association constants for some selected guests that reach and even surpass that of avidin/biotin interaction ($K_{\text{eq}} = 10^{15} \text{ M}^{-1}$) and represent the strongest non-covalent interactions for a synthetic system. In 2005, Isaacs and co-workers reported the equilibrium association constant of the rimantadine@CB[7] complex to be on the order 10^{12} M^{-1} .¹⁷⁷ Two years later, Kaifer, Gilson, Kim, Inoue and co-workers reported a $K_{\text{eq}} = 3.0 \times 10^{15} \text{ M}^{-1}$ for the 1,1'-bis(trimethylammoniomethyl)ferrocene@CB[7] pair.¹⁸⁷ The groups of Kim, Inoue and Gilson reported the record-breaking affinity of $K_{\text{eq}} = 5.0 \times 10^{15} \text{ M}^{-1}$ for 1-(2-aminoethylamino)-adamantane@CB[7].¹⁸⁹ Kim *et al.* have recently developed yet another class of molecule, bicyclo[2.2.2]octane derivatives, that bind to CB[7] with K_{eq} above 10^{15} M^{-1} .¹⁸⁸ The extremely high affinities of these complexes, with rigid, near-perfect complementary structures, are traceable to a large enthalpic gain, originating from the tight fit of the guest to the rigid CB[7] cavity, assisted by the entropic gain arising from the dehydration of the CB[7].

CB[8] also displays remarkable binding affinities towards positively charged and relatively large guests such as AD derivatives, cyclen and cyclam macrocycles (as well as their doubly charged Cu and Zn complexes) and long alkylammonium aliphatic chains. In contrast to CB[5–7], the cavity of CB[8] is large enough to accommodate two organic guests simultaneously thus forming highly stable ternary complexes. In 2001, Kim and co-workers reported the formation of a stable ternary complex between CB[8] and two doubly-charged 2,6-bis(4,5-dihydro-1*H*-imidazol-2-yl)naphthalene molecules.¹⁶² This group has also reported the selective formation of a 1:1:1 complex between CB[8], viologen (paraquat) and 2,6-dihydroxynaphthalene, which results in enhanced charge–transfer complex within the complex.^{169,190} The ternary complex motif using CB[8] has been expanded broadly and the ability to bind two guests simultaneously (K_{eq} up to 10^{14} M^{-2})⁷⁵ has been utilised for the reversible assembly of supramolecular diblock copolymers and polymer–protein conjugates, as well as supramolecular glycopolymers *via* dynamic side-chain conjugation.^{186,191–197}

Although in its infancy, the supramolecular chemistry of CB[*n*]s have attracted a widespread attention during the past twelve years and their recognition properties have enabled the preparation of a large variety of stimuli-responsive

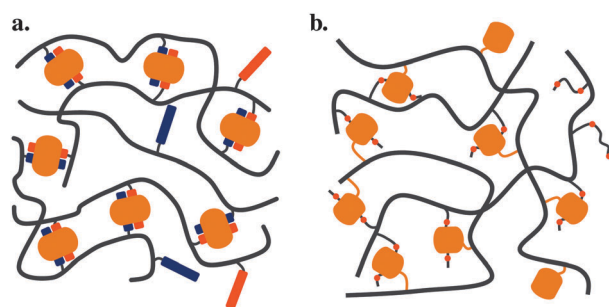


Fig. 12 Schematic representation of the types of hydrogel structures that can be prepared utilising CB[*n*]-based complex formation. (a) Hetero-ternary CB[8] binding and (b) binary CB[6] complexes utilising functionalised CB[6] derivatives.

self-organised molecular constructs with interesting properties. Nowadays, there is an increasing interest in the utilisation of the unique properties of CB[*n*]s in the implementation of materials for advanced applications such catalysis, sensing, cell culture or the controlled delivery and release of specific substances. Moreover, several recent studies have demonstrated that the CB[*n*] family are non-toxic, opening them up for potential application in a wide variety of biomedically related fields.^{198,199} The following section is an overview of the different hydrogel systems which incorporate CB[*n*] binding motifs and the reported applications of this new type of transient polymeric networks. Two different strategies have been devised to produce CB[*n*]-based hydrogels: (a) three-component systems cross-linked by ternary CB[8] inclusion complexes (Fig. 12a) and (b) two-component systems based on CB[6]@alkylammonium ion host–guest pairs (Fig. 12b) and we discuss them in turn.

Scherman and co-workers reported in 2010 the first example of a supramolecular polymeric hydrogel based on CB[*n*] host–guest inclusion complexes.²⁰⁰ By employing a pair of multivalent side-chain functional polymers bearing either viologen (a good first guest) or naphthoxy (a good second guest) derivatives, the authors demonstrated that the presence of CB[8] induced supramolecular cross-linking and subsequent hydrogel formation (Fig. 12a). No hydrogel formation was observed when all polymeric materials are dissolved together. It is only upon addition of CB[8] that the pendant guest molecules can interact to form a cross-linked network. Rheological characterisation of the viscoelastic polymeric networks allowed for the determination of the dissociation kinetics of the ternary complex with $k_{\text{d}} = 1200 \text{ s}^{-1}$. The materials exhibited intermediate mechanical properties at around 5 wt% in water (plateau modulus = 350–600 Pa and zero-shear viscosity = 5–55 Pa s), for systems with a crosslink density in the 2.5–10.0% range (percentage of monomer units participating in crosslinking and determined by the molar equivalent of CB[8] added to the material). The authors also demonstrated that the facile control over crosslink density through the addition of CB[8] to the system allowed for control over the microstructure as changes in the pore sizes measured cryo-dried samples of the hydrogels using SEM were proportional to the crosslink density of the network. For comparison, when both guests are present on the same polymer chain, even at very high molecular weights, single-chain polymeric nanoparticles can be formed at sufficiently low concentrations that demonstrate stimuli-responsive transitions

between 'natured' and 'denatured' states, similar to many biomacromolecules.^{201,202}

In a follow-up investigation, Scherman and co-workers prepared extremely high water-content (up to 99.75% water), self-assembled polymeric hydrogels derived from renewable cellulosic derivatives.^{203,204} The hydrogels had highly tunable mechanical properties (spanning three orders of magnitude), controlled simply by the relative loadings of the three components, and they displayed responsiveness to a multitude of external stimuli including temperature, chemical potential and competing guests. Moreover, with this study the authors demonstrated that the extremely rapid dynamics of the CB[8] ternary complex lead to instantaneous recovery of the mechanical properties after shear-induced deformation. The shear-thinning and fast recovery properties, in addition to the demonstrated biocompatibility of the hydrogels, makes these materials very exciting candidates for use as 'shear-thinning' materials in various biomedical and industrial applications, as mentioned above. The simple preparation process, their availability from inexpensive renewable resources, and the tunability of their mechanical properties are important for a wide variety of applications. Furthermore, the authors displayed the extremely sustained release of bovine serum albumin (BSA) and lysozyme (used as a model protein for protein therapeutics) from supramolecular hydrogels containing only 1.5 wt% polymeric constituents. Indeed BSA was released over the course of 160 days. In addition, the bioactivities of the proteins were maintained, showing the utility of the materials for sustained delivery of protein therapeutics.

Kim *et al.* have demonstrated the utility of CB[6] for the preparation of hydrogels by utilising a hydroxy-functional CB[6] moiety with alkylammonium guests derived from 1,6-diaminohexane (DAH) and spermine (SPM).^{205,206} On one hand, the authors prepared CB[6]-containing hyaluronic acid (around 6 mol% of functionalised repeating units) by grafting (allyloxy)₁₂CB[6] to a thiol-functionalised hyaluronic acid through a thiol-ene reaction (although both CB and hyaluronic acid have multiple reactive sites, it is not clear whether the CB molecules are only attached to one or several polymer chains). The mixing of solutions of the CB[6]-containing polymer and an DAH-containing hyaluronic acid (around 50 mol% of functionalised repeating units) produced a hydrogel after 2 min. The addition of excess of SPM to the hydrogel resulted in a phase transition from gel to sol within 10 min, suggesting that the crosslinks of the polymer network indeed resulted from the specific host-guest interactions. Storage moduli as high as 3.4 kPa were measured for a hydrogel composed of a mixture of spermine and CB[6]-functionalised hyaluronic acid (2 wt%). Cytocompatibility studies demonstrated the high cell viability, enzymatic degradability and negligible cytotoxicity of gels. The most interesting feature of the system is that the presence of free alkylammonium guest in the polymeric network allows for further functionalisation of the gel with biorelevant motifs attached to CB[6]. The authors demonstrated the incorporation of functional tags, including FITC, rhodamine B derivatives and RGD-based adhesion peptides, through covalent conjugation to a functional CB[6], which could then simply be mixed into the precursor solutions. The authors even demonstrated the *in situ* formation of the hydrogel under the skin of mice by sequentially injecting

solutions of the complementary polymers, CB[6]- and DAH-containing hyaluronic acid. The hydrogel was formed within a few minutes after the injection and was stable for longer than 2 weeks. It was even possible to modify the hydrogels *in vivo* by injection of a solution of FITC-CB[6]. The preparation of physical hydrogel that can either be injected after formation or generated *in situ* has proven to be of great importance as these materials may act as effective and modular platforms for a wider variety of biomedical applications including the delivery of specific substances or the scaffolding of cell structures.

3.4 Ionic interactions

Hydrogels prepared *via* electrostatic (ionic) interactions clearly demonstrate the capacity of strong, multivalent non-covalent interactions to form extremely strong (as well as stimuli-responsive) materials. There are several recent examples of polymeric hydrogels prepared *via* electrostatic interactions between multivalent polymers. Mixing two aqueous solutions of oppositely charged polyelectrolytes generally leads to phase separation.²⁰⁷ However, the addition of a neutral hydrophilic block to the polyelectrolyte chain can result in hydrogel formation by preventing macroscopic phase separation.

Aida and coworkers reported the preparation of high-water-content (96–98% water) hydrogels prepared with poly(sodium acrylate) (ASAP) treated clay nanosheets (Laponite XLG) and telechelic PEG polymers bearing multivalent guanidinium dendritic endgroups (Fig. 13).^{208,209} A PEG ($M_n = 10$ kDa) precursor was functionalised with dendrimers of various generations (G1–G3) bearing varying numbers of guanidine hydrochloride groups (two, four and eight for G1, G2 and G3 dendrons, respectively). These cationic 'binder' materials quickly form crosslinks with the anionic faces of the silicate-based clay nano-sheets to form hydrogels with exceptional mechanical strength (G' up to 10^6 Pa) and rapid self-healing. They were easily mouldable into transparent, shape-persistent, free-standing objects. Moreover, the gel materials demonstrated the ability to transport biological activity as a myoglobin-containing hydrogel retained its catalytic capacity relative to free myoglobin.

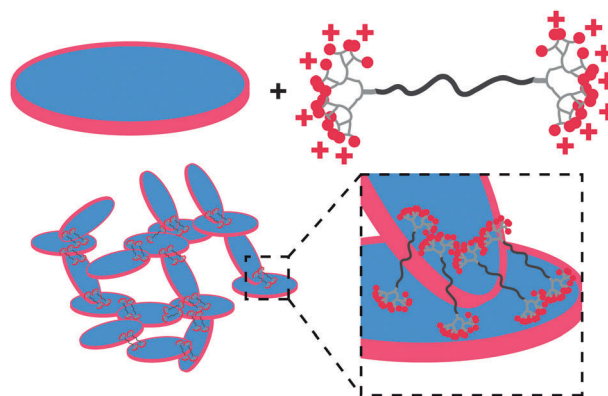


Fig. 13 Schematic representation of hydrogels prepared by stabilisation of clay nanosheet-based crosslinked networks with an ABA triblock copolymer bearing guanidinium-functional generation-3 dendrimers as the end-groups of PEG chains. The cationic edges (red) of the clay associate with the anionic faces (blue), which also interact strongly with the cationic dendritic end-groups of the polymers.²⁰⁸

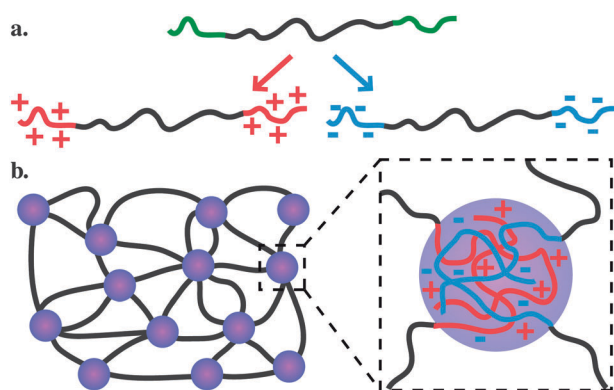


Fig. 14 (a) Schematic representation of hydrogels prepared by Hawker *et al.* through functionalisation of ABA triblock copolymers with cationic and anionic groups. (b) Self-assembly of the triblock copolymers led to formation of coacervate domains connected by PEG chains.²¹¹

Cohen Stuart and co-workers reported a novel class of multiresponsive reversible gels based on the co-assembly of a triblock copolymer having two negatively charged end blocks with a positively charged homopolymer. The authors showed that the hydrogel consisted of a network of interconnected polyelectrolyte complex micelles stabilised by a corona of neutral solvophilic blocks. The gel responded not only to changes in temperature and concentration but also to ionic strength, cationic–anionic composition and, if weak polyelectrolytes are used, pH value.²¹⁰

Utilising a similar strategy, Hawker and co-workers reported the formation of well-defined hydrogels by mixing ionic ABA triblock copolymers (Fig. 14).²¹¹ Four types of ionic functional groups including sulfonate, carboxylate, ammonium and guanidinium, representing a range of different pK_a values were incorporated from a parent ABA triblock copolymer containing a central PEG block (M_n 10–35 kDa) and varying numbers of reactive sites in the terminal A blocks. These materials were particularly interesting in that they displayed extremely high moduli (G' up to 10^4 Pa) through the formation of non-solvated coacervate domains, which the authors characterised using small angle X-ray scattering (SAXS). This class of non-covalent interaction can be extremely sensitive to ionic strength of the aqueous media and often to changes in pH and therefore, as expected, an increase in G'' and a corresponding decrease in G' was observed with increasing amounts of sodium chloride.

3.5 Biomimetic interactions and stereocomplex formation

Many interesting biomimetic and bioinspired non-covalent motifs have been utilised for hydrogel formation. The well

known and widely utilised biotin@streptavidin binding motif, in many ways mimicking the host–guest systems discussed above, is extremely strong and representative of a wide range of biological substrate–receptor interactions. Likewise, many protein–protein interactions exist, including the ‘leucine zipper’, whereby leucine-rich peptide fragments, which form coiled-coil motifs based on hydrophobic interactions, very strongly associate in a dynamic fashion (*vide infra*). Moreover, many synthetic polymers exist that are able to form strong stereo-complexes through association of two opposite optically active stereoregular polymer chains. Below we will cover only select examples of these types of interactions for development of supramolecular polymeric hydrogels.

3.5.1 Biomimetic interactions. Tirrell and co-workers reported a system of biofunctional physical hydrogels designed from telechelic proteins²¹² in which coiled-coil end blocks are joined by a flexible biopolymer linker (Fig. 15). Artificial proteins were readily prepared by biosynthetic methods whereby the amino acid sequence of interest was encoded into an artificial gene and the protein was expressed in an appropriately transformed bacterial host. The flexibility of the recombinant DNA technology allowed for systematic investigation of structure–property relationships and provided the potential for incorporating biological information, including cell binding domains and enzyme recognition sites into the engineered hydrogels. Leucine zippers constitute a subcategory of coiled-coil domains found widely in nature and play critical roles in biological functions ranging from muscle contraction to transcriptional control.²¹³ These ‘zippers’ are typically characterised by repeating units designated as abcdefg, where the a and d positions are occupied by hydrophobic residues such as leucine and the e and g positions are occupied by charged residues. These domains assemble into amphiphilic helices and hydrophobic interactions drive association of the helices into clusters.²¹⁴ When these domains are connected *via* a flexible biopolymer linker, association leads to hydrogel formation, where the leucine zipper bundles serve as junction points.²¹² These hydrogels are reversible in response to pH and temperature and the associations can be turned ‘off’ under conditions of high pH or high temperature, where the leucine zipper domains are denatured.²¹²

The coiled-coil motif has been exploited in both telechelic^{215–218} and graft polymers^{219–221} to produce a wide variety of protein hydrogels. Moreover, the authors have demonstrated that protein engineering allowed for control of the coiled-coil association multiplicity in the hydrogel network junctions and that changes in the coiled-coil sequence^{216,218} and midblock molecular weight^{215,222} could be used to vary the modulus of the hydrogel.

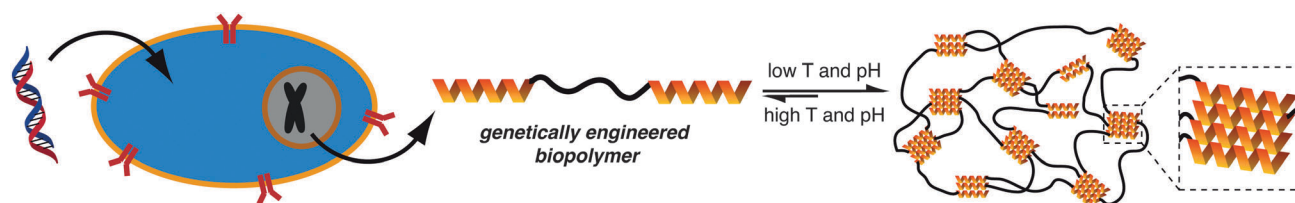


Fig. 15 Genetically engineered biopolymers with ABA triblock structure containing ‘leucine zipper’ coiled-coil peptides as the A-endgroups self-assemble into artificial protein hydrogels through hydrophobically driven association of the end-groups into clusters.²¹²

Tirrell *et al.* extended the system to prepare a disulfide-stabilised version of these hydrogels, whereby judicious engineering of the artificial proteins to place cystine moieties into the end-blocks led to self-assembled hydrogels with disulfide-stabilisation within the bundled junction points between polymer chains.²²³ Moreover, functional sequences such as the RGD cell binding domain can be incorporated into the midblock through genetic engineering without affecting the physical properties of the materials.

Gel structures based on similar design paradigms have been reported for block copolypeptides,²²⁴ elastin-mimetic triblock copolymers,^{225–227} and telechelic proteins that use collagen-like blocks to form associating helical domains.^{228,229} Li and coworkers have also produced hydrogels utilising the ‘leucine zipper’ binding concept.²³⁰

Burdick and coworkers described injectable shear-thinning hydrogels prepared with a self-assembling ‘dock-and-lock’ mechanism utilising genetic engineering techniques.²³¹ One biopolymer precursor derived from the RII α subunit of cAMP-dependent kinase A was engineered as a telechelic protein with end groups that dimerize, which the authors called ‘docking’. The second component was derived from the anchoring domain of A-kinase anchoring protein (AD) and was attached to multi-arm crosslinker polymers and binds to the docked proteins to ‘locking’ the crosslinking. When mixed, these two components form robust physical hydrogels instantaneously and under physiological conditions. The authors demonstrated that the mechanical properties and erosion rates of the hydrogels could be tuned through the genetic engineering, the concentration and ratio of each component, and the number of ‘arms’ on the crosslinking polymer. These hydrogels displayed complete and immediate recovery after deformation and demonstrated resistance to yields at strains as high as 400%. Moreover, the authors demonstrated that Mesenchymal stem cells mixed in into the hydrogels and injected through a ne needle remained highly viable (>90%) during the encapsulation and delivery process, and that encapsulated large molecules could be released from the hydrogels with profiles corresponding to gel erosion.

Kiick *et al.* have prepared a variety of hydrogels utilising the complexation of low molecular weight heparin (LMWH) with heparin-binding peptides (HBP).^{232–237} By appending LMWH and HBP on 4-armed PEG-based star polymers, the non-covalent interactions of heparin and heparin-binding peptides support hydrogel formation and delivery of growth factors from such hydrogels can be regulated based on the erosion profile of the hydrogel. The authors also demonstrated that heparin-binding growth factors (VEGF) can crosslink the heparin-functional polymers themselves, conferring to the resulting hydrogels erosion behaviour that is responsive to the presence of the VEGFR-2 receptor (KDR). Moreover, the targeted delivery of VEGF to its relevant receptors on cells and subsequent erosion was demonstrated to occur automatically, without the need for external stimuli such as enzymatic degradation.²³⁸ Hydrogels could also be prepared using PEG-based materials containing heparin only.^{239,240}

Uragami and coworkers reported the use of antigen–antibody binding as the driving force for crosslinking between polymer chains.²⁴¹ Antigens and antibodies were functionalised with

acrylamide monomer moieties that could be copolymerised with acrylamide and the resulting polymers formed hydrogels when mixed that were tunably antigen-responsive. Supramolecular hydrogels have also been developed using the natural receptor–ligand pair streptavidin with biotin (S@Av),^{242,243} which displays an extremely high binding affinity ($K_{eq} = 10^{13–15} \text{ M}^{-1}$).

3.5.2 Stereocomplex formation. Non-covalent interactions are highly diverse and many times multivalency of relatively weak interactions can have an enormous effect on macromolecular self-assembly. This is true in the case of protein folding and in many other biomacromolecule *inter-* and *intra-*molecular interactions, as well as the self-assembly of synthetic macromolecules into well-defined architectures, *e.g.* stereocomplex formation in optically active polymers such as PMMA or PLA. The stereocomplex formation between blocks of P(D)LA and P(L)LA is particularly interesting for the production of hydrogels on account of the high biocompatibility of and biodegradability of PLA polymers. Stereoregular blocks of PLA form helices that associate through multivalent van der Waals interactions.

In one study, Park *et al.* demonstrated the utility of PLA-based stereocomplex formation to bolster the interactions present in Pluronic-based thermogelling polymers. The resultant physically crosslinked Pluronic hydrogels exhibited significantly altered solution to gel phase transition behaviour with much lower critical hydrogel formation concentrations and temperatures, compared to the uncomplexed multi-block or Pluronic homopolymer hydrogels.²⁴⁴ The stereocomplexed hydrogels also led to increased mechanical strength with high resistance to erosion.

Hennink *et al.* reported the conjugation of stereoregular PLA oligomers to dextran polymers and their self-assembly into hydrogels.²⁴⁵ The authors later investigated their hydrolytic degradation and release of protein therapeutics.²⁴⁶

4 Physical characteristics of supramolecular polymer networks

A physical model developed by Cates *et al.* in 1987 predicts many of the viscoelastic properties of supramolecular polymer interactions as a function of the strength and molecular dynamics of the non-covalent interactions in the system.^{247–249} Although initial studies focused on worm-like micelles, the model has been demonstrated to successfully describe the behaviour of a wide variety of non-covalently crosslinked materials.⁸⁰ Often the most interesting and informative examples of the role of the strength and molecular dynamics of the non-covalent interactions in determining material behaviour have been demonstrated in supramolecular systems that function in organic media. As the physical characteristics of these systems can often be directly applied to the characterisation of hydrogels, the following section will therefore consider several important examples that describe supramolecular crosslinking of polymeric materials in general. A thorough review on this topic has recently been published, so only a brief discussion will appear here.⁴⁸

4.1 The role of molecular dynamics

Supramolecular polymer networks are characterised by two important timescales: (a) that of the association–dissociation

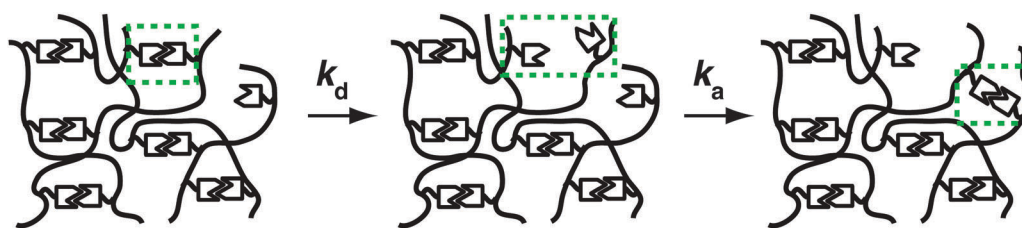


Fig. 16 Schematic representation of relaxation of stress through the dissociation of a supramolecular crosslink, determined by the dissociation rate constant (k_d) of the supramolecular moiety. This is followed by re-association to form a new crosslink, determined by the association rate constant (k_a) of the supramolecular moiety.

of the supramolecular crosslinks (molecular dynamics; demonstrated in Fig. 16) and (b) that of the relaxation of chains or chain segments as understood by classical polymer physics. One difficulty in addressing the issue of the role of molecular dynamics in determining the time-dependent micro- and macroscopic material properties has been that independent control of the molecular dynamics and equilibrium thermodynamics of a supramolecular motif is difficult.

In 2005, Craig and coworkers published a seminal study demonstrating the use of metallo-supramolecular interactions to form crosslinked poly(4-vinylpyridine) (PVP) networks.^{250,251} The authors developed a simple bis-metallic pincer molecule that utilises small variations in steric hindrance between *methyl* and *ethyl* substituents on the pincer to elicit large changes ($\Delta k_{\text{ex}} = 10^2 \text{ s}^{-1}$) in the exchange kinetics of the bound metal to the pendant pyridine moieties in the PVP, without significantly altering the binding thermodynamics.^{250–253} Two metals, palladium and platinum, were used in the study and demonstrated large differences in binding thermodynamics ($K_{\text{eq}} = 10^1$ and 10^3 M^{-1} , respectively) while retaining the same Δk_{ex} between the *methyl* and *ethyl* pincer variants. The influence of the crosslinking kinetics could therefore be studied independent of the equilibrium association constant.

The remarkable study clearly identified that the bulk material properties in both dynamic and steady shear rheological characterisation scaled exactly with the dissociation rate constant, k_d , regardless of the K_{eq} or the binding thermodynamics. A master curve of the frequency-dependent storage and loss moduli could be prepared by simply scaling the frequency of perturbation with k_d , as determined by small-molecule NMR studies. Moreover, a master curve of the frequency-dependent viscosities of the transient networks could also be prepared by scaling with k_d . Characterisation of the four bis-pincer molecules scaled exactly, regardless of the platinum variants having a K_{eq} two orders of magnitude lower than their palladium counterparts, demonstrating little to no dependence of primary bulk properties on K_{eq} or binding thermodynamics. A broadly applicable principle from this study was ‘strong means slow’,^{250,251} meaning that slow dissociation lead to strong crosslinking. This study identifies an important and striking influence on bulk properties as the number of ‘active’ crosslinks (thermodynamics) does not dominate over the timescale each crosslink remains ‘active’ (dissociation kinetics) in determining material properties. The dynamic nature of the supramolecular interactions is responsible for observed properties and for the comparative differences between transient non-covalent and covalent crosslinks in a network.

These observations have been supported by independent studies using the UPy H-bonding motif⁸⁰ and the CB[8] ternary complex.²⁰⁰ Meijer and coworkers found that application of a simple Maxwell model to describe the viscoelastic behaviour of the H-bonded system yielded a single relaxation time that agreed well with the lifetime of the UPy dimer as measured independently by NMR spectroscopy.⁸⁰ Scherman and coworkers also applied a simple Maxwell model to their CB⁸ crosslinked system and were able to determine the CB[8] ternary complex kinetics for the first time.²⁰⁰ Moreover, systems that consist of multiple types of crosslinks have been shown to exhibit discrete contributions from the dynamics of each supramolecular motif.^{253–256}

In a similar fashion, Tirrell and coworkers found a strong correlation between the exchange kinetics of leucine zipper domains in genetically engineered biopolymer-based hydrogels and the macroscopic dynamic behaviour of the hydrogels.²⁵⁷ The rate of leucine zipper strand exchange was found to be sensitive to inter-strand electrostatic interactions, the relaxation behaviour of the artificial protein hydrogels could be systematically engineered through genetic programming of the amino acid sequence of the zipper domains.

However, there are some systems where these simple explanations break down. A recent study by Hawker, Kramer and coworkers describe transient networks from UPy-functionalised polymers prepared by post-polymerisation modification of either a random copolymer or an ABA triblock copolymer prepared *via* ATRP.²⁵⁸ Here the A blocks were copolymers of *n*-butylacrylate and amine functional acrylate monomer that provided a handle for conjugation of the UPy moiety, while the B block was purely *n*-butylacrylate, providing separation between the UPy pendant blocks. These materials were described by the Rubinstein–Semenov model whereby the effective relaxation time is much longer than the relaxation time of the dynamic crosslinks, and that it increases with increasing number of UPy units. The authors determined that by concentrating the UPy functionality near the ends of the polymer chain in the case of the ABA triblock copolymers, the plateau modulus remains essentially equal to the random copolymer, but the crossover frequency of the storage and loss moduli decreased dramatically ($-\Delta G' > 10^2 \text{ Hz}$). Consequently, the triblock materials show solid-like behavior over much longer time scales than the corresponding random copolymer materials. This study clearly determined that overall network relaxation timescales can be controlled by the distribution of supramolecular moieties throughout the polymer backbone through controlled synthetic techniques, whereas the plateau modulus of the material is determined primarily by the average chain composition.

4.2 Non-linear mechanics

When supramolecular polymer systems are probed at high deformation, non-linear behaviour is observed that is not currently well understood. As mentioned previously, shear-thinning in hydrogels is of particular importance for a variety of applications. The formation of hydrogels with beneficial biological properties and linear mechanics has been extensively investigated, however, the non-linear rheology that leads to shear-thinning and injectability is less well understood. In some cases, supramolecular polymer networks exhibit shear-thinning, whereas in other cases, they show shear-thickening. These observations are complicated further by the fact that both shear-thinning and shear-thickening has been observed on the same system, depending on the experimental conditions. Dissociation of the physically associating groups under shear is clearly implicated in shear thinning behavior,^{32,49,50,259} however, the flow profiles and mechanisms of thinning are often unknown.

Craig and co-workers observed both shear-thinning and shear-thickening on the same metallo-pincer crosslinked PVP networks mentioned above.^{260,261} They attributed the shear-thinning, which is usually observed in systems with fast dissociation of the dynamic crosslinks, to shear induced disentanglement of rapidly associating and dissociating network chains. By contrast, shear-thickening, which is usually observed in systems with slower crosslinking kinetics, was attributed to network reorganization under shear, whereby 'inactive' *intrachain* crosslinks are converted into 'active' *interchain* crosslinks (Fig. 17). The authors observation that shear-thickening is substantially enhanced above a critical shear rate, which directly relates to the lifetime of the metal-complexes. Scherman *et al.* later applied this same explanation to account for shear-thickening and shear-thinning observed in CB[8] ternary complex cross-linked supramolecular networks.²⁰⁰

In a recent study,²⁶² Xu and Craig extended their original work to systems in the semidilute entangled regime, revealing even more complex behaviour whereby various types of shear-thinning and shear-thickening characteristics were observed. The authors found that if the network chain relaxation occurs *faster* than the reconnection of an unassociated crosslink, shear-thickening occurs on account of the transformation of 'inactive' *intramolecular* to *intermolecular* crosslinks (Fig. 17). No shear-thickening is observed in these systems when network relaxation occurs *slower* than the reconnection of an unassociated crosslink.

Furthermore, it has been extensively demonstrated that for a wide variety of entangled systems, including polymer melts and wormlike micellar solutions, inhomogeneous flow profiles may occur on account of instabilities in the stress-strain curve.²⁶³ These instabilities are manifest as shear bands, areas of high deformation rate where the entanglements are preferentially

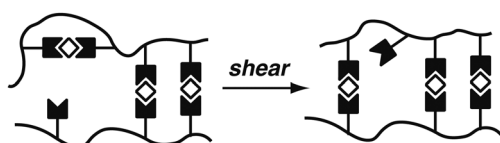


Fig. 17 Mechanism of shear-thickening in supramolecular cross-linked polymer networks as suggested by Craig *et al.*²⁶¹

disrupted, that accommodate the majority of the strain applied to the system. This was observed in injectable hydrogels from artificial proteins reported by Tirrell and coworkers.²⁶⁴ The authors found that shear-thinning behaviour was related to yielding within the bulk of the hydrogels consistent with a shear-banding mechanism for yielding. The shear-banding mechanism was shown to localise deformation during flow into narrow regions of the gels, which was found to allow for a very large proportion (>95%) of encapsulated cells to survive the high shear rates during injection through narrow gauge needles.

5 Conclusion and outlook

This review has treated the main research that is ongoing in the field of supramolecular polymeric hydrogels, which is a remarkable new class of soft and responsive materials. Different from conventional covalent crosslinking methods, the combination of polymer chains and selective and strong supramolecular crosslinks presents an attractive platform from which one can readily modify structural parameters such as the polymeric backbone, the strength and dynamics of crosslinking interactions, directionality, multiple-responsiveness and tunable degradability in a modular fashion. Supramolecular crosslinks allow for dynamic behaviour: structural error correction, shear-thinning, self-healing properties, elasticity and mouldability. Some of these properties are fundamental for the fabrication of performance materials, fault-tolerant products and components encompassing a range of industries including coatings, electronics, transportation, and energy. Many of the existing studies presented here were particularly focused on synthesis of supramolecular polymeric hydrogels. However, only very few studies have been emerging to describe completely and quantitatively the relationship between the fundamental parameters guiding self-assembly of the supramolecular crosslinking motifs and the macroscopic behaviour of the resulting materials. Therefore, a need still exists to develop systematic studies on this complex relationship and the structure and dynamics of these supramolecular polymeric hydrogels. Nevertheless, the use of supramolecular chemistry in the assembly of networked structures has been demonstrated to allow the spatiotemporal control of the macroscopic viscoelastic properties of these hydrogels, which could have implications in biomedical applications, particularly in shear-thinning injectable materials. The current developments in this field have provided us with a toolbox from which we can utilise to build customisable structures and these advances bode well for the future development of improved supramolecular polymeric hydrogels.

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