# Review
# Hydrogen-bonded supramolecular polymers:
# A literature review

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Supramolecular polymer science has matured into a technology ready for industrial application. This review begins with an overview of the principles underlying self-assembly of supramolecular polymers. Polymers developed over the past decade are discussed, with emphasis placed on stable hydrogen bonded structures that exhibit useful material properties. The commercial potential of such supramolecular polymers is also considered.
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## 1. Introduction: Principles of supramolecular chemistry

Among the many significant advances within the field of supramolecular chemistry over the past decade, perhaps the development of so-called 'supramolecular polymers' is of most direct relevance to materials science. Defined as "chemistry beyond the molecule ... the chemistry of tailor-shaped intermolecular interaction" [1], supramolecular chemistry is concerned with preparing assemblies of molecules using a combination of secondary chemical interactions rather than covalent bonding. The comparatively simple molecules used in these assemblies are driven to spontaneously self-assemble, and then hold together, via such non-covalent interactions as hydrogen bonds, metal coordination sites and van der Waals forces. To better understand the factors that promote the self-assembly of these polymers in more detail, it is first necessary to examine the underlying principles of supramolecular chemistry.

The underlying concepts of self-assembly have long been known: Fischer's lock-and-key theory of enzyme activity, first proposed in 1894, may be considered as their foundation stone because it recognised the central role of shape and geometry in molecular interactions [2]. In fact, self-assembly processes are vital to biosynthesis in nature because they allow large, complicated structures to form quickly.

Within the field of supramolecular chemistry, Lehn [3] distinguished between 'supermolecules' and 'molecular assemblies'. Supermolecules were considered to be oligomers composed of a few components assembled via specific intermolecular associations; examples of these are discussed in Section 2. By compar-

ison, in molecular assemblies, large numbers of components assemble spontaneously into a structure that has reasonably well defined microscopic organisation and displays characteristics typical of macromolecules, e.g., rheology, fibre formation, glass and melting transitions, chain entanglement and high property/weight ratios [4–6]. It is because they exhibit these typical properties that extended-chain molecular assemblies are frequently referred to as 'supramolecular polymers'. The non-covalent interactions that hold these molecular assembly together must be specific and directional so that the assembly forms as intended, and reversible so that the finished assembly may be annealed or undergo self-healing of defects. The individual non-covalent interactions in question have low bond energies compared to covalent bonding. Whereas covalent bonds typically have energies of 250–800 kJ·mol$^{-1}$, the strongest hydrogen bonds have energies of 210 kJ·mol$^{-1}$, with 12–25 kJ·mol$^{-1}$ being more usual for OH···O and NH···N bonds [7]. In contrast, the bond energy of a van der Waals force is typically less than a kilojoule.

Lehn [3] and Lawrence *et al.* [8] considered the advantages offered by self-assembly in the context of synthetic chemistry and biological systems, respectively. Compared with synthesis via covalent bonds, self-assembly offers:

1. Ready synthesis of the required end product due to rapidly formed non-covalent interactions.
2. Fewer structural errors because faulty subunits are rejected during synthesis. Lehn described this behaviour as an "error filter", arguing that it facilitated synthesis by avoiding the formation of unwanted side products.

3. Synthetic economy—complex man-made systems can be prepared from a few relatively simple repeat units. Likewise, in an organism, one gene sequence can code for producing a single repeat unit, which is then used over and over to give the desired end structure. In both cases, fewer steps are needed to convert starting materials to end product.

Equally, there are some recurring problems encountered in preparing and characterising molecular assemblies. These include:

1. Many molecular assemblies are formed in solution. It must be possible to isolate the product to prevent the assembly dissociating back to its components, and to determine sufficient structural information to confirm that an assembly has indeed formed.

2. Determining the shape of the assembly has sometimes proven difficult. Even though Nuclear Magnetic Resonance (NMR) spectroscopy allows the relative position of atoms in solution to be determined, many assemblies are composed of the same unit over and over.

3. If each component can exist in solution in more than two different states, it is not possible to estimate the relative stoichiometry of the assembly. Given the relative stoichiometry of an assembly, its molecular weight must be known to determine the absolute stoichiometry. Loosely co-ordinated structures may not be stable enough to provide a molecular ion for mass spectroscopy. In such cases, techniques such as light scattering and vapour phase osmometry have proven useful.

Though the advantages of self-assembly over conventional synthesis are offset by the dynamic nature of the end product and the difficulties in characterising it, structurally dynamic assemblies may prove advantageous in certain applications. For example, it has been suggested that they should exhibit self-healing of defects, and be able to adjust to changes in harsh environments [3, 9]. Indeed, supramolecular polymers are of particular interest not because they mimic conventional materials, but because of the unique combination of properties they offer.

Despite the variety of supramolecular polymers reported in the literature, most work to date has been concerned with their chemistry (demonstrating that hydrogen bonding arrays form as anticipated) rather than investigating the resulting assembly's suitability for use as a novel material [10]. Notable reviews of the synthesis and chemistry of supramolecular polymers include those by Zimmerman *et al.* [11], Sijbesma and Meijer [9] and Sherrington and Taskinen [10]. Lawrence *et al.* [8] conducted an extensive review of self-assembled structures, with emphasis placed on supermolecules, as defined in Section 3. Comparing these reviews reveals that the designation of any given structure as "supramolecular" or not still remains somewhat arbitrary between workers. Also, numerous polymer systems are known which avail of secondary interactions in their structure (e.g., hydrogen bonding in aromatic polyamides such as Du Pont's *Kevlar* and *Nomex*, and van der Waals interactions between polyethylene chains). Therefore, the present review will focus on systems that depend primarily on secondary interactions—especially hydrogen bonding—to form extended chain structures of high 'virtual' molecular weight which exhibit novel material properties.

To set these systems in context, the factors that influence self-assembly processes will be considered first. Next, examples representing the principal classes of molecular assembly are reviewed in order to outline the development of the concepts underlying supramolecular chemistry. Then, the preparation and properties of supramolecular polymers are examined, with emphasis placed on those systems which promise to broaden and enhance the range of applications macromolecules currently enjoy. In conclusion, the implications of these advances and their future potential is discussed.

## 2. The self-assembly process

Strong, highly directional, reversible interactions are required to form linear supramolecular polymers with high degrees of polymerisation ($D_p$) [11]. Otherwise, the polymer gels or forms microphase-separated structures. For successful self-assembly, the repeat units of the molecular assembly must only interact with their intended partners. Being a multi-stage process, the relative orientation of adjacent repeat units during assembly is important, because each will assume a fixed orientation with respect to its neighbours provided the bonding is strong enough to give directionality. Also, Lehn [3] considered reversible bonding necessary so that the completed molecular assembly would be capable of undergoing annealing and self-healing of defects.

Due to the limited strength of individual interactions, additional stabilisation (e.g., crystallisation or liquid crystallinity) is often needed to obtain useful material [9–11]. Although the interactions in question are weak when considered individually, if combined carefully they give rise to a bonding system that is sufficiently strong and long-lived to be considered a reasonable alternative to covalent bonds. Hydrogen bonding has proven especially suitable for supramolecular polymer synthesis because it is easier to control the direction of hydrogen bonds than ionic interactions, and though metal co-ordination bonds are highly directional, their shape changes with each new bond formed. Examining the polymerisation of ionomers, for example, shows the potential extent of these difficulties [12].

In hydrogen-bonded supramolecular polymer systems where there is no anisotropy, single- or double-hydrogen bonds are not sufficiently stable to allow self-assembly occur. However, if unspecific aggregation is avoided, a high level of control can be exerted over the polymer network as the degree of association, degree of branching, and distance between crosslinks (if present) can all be tuned by modifying the spacers chemically or by varying the hydrogen-bonding functionality. High purity monomers must be used in preparing supramolecular polymers because monofunctional impurities or unreacted repeat units cap the growing polymer chain. Also, high $D_p$ values are only obtained at high monomer concentrations [13, 14].
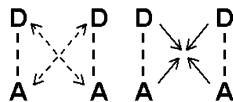
Figure 1 Attractive and repulsive secondary interactions arising between adjacent bond donor (*D*)/acceptor (*A*) sites in a double hydrogen bond array vary depending on whether the sequence is *D/D* or *D/A*. Attractive forces are denoted by dashed arrows; repulsive forces are denoted by solid arrows. The dotted lines represent hydrogen bonds.



Figure 3 Adamantante-1,3,5,7,-tetracarboxylic acid.

## 2.1. Dimerization rate and its significance

Murray and Zimmerman [15] have shown that the sequence of hydrogen bond donor and acceptor sites in triply hydrogen-bonded repeat units has a marked effect on $K_{dim}$, the rate of dimerization. As $K_{dim}$ indicates how quickly the repeat units interlink, it determines the rate at which hydrogen bonded polymer chains can grow. The net effect of the attractive and repulsive forces that arise between adjacent hydrogen bond donor and acceptor sites is such that all possible sequences of donor and acceptor sites give rise to distinctive $K_{dim}$ values [16, 17]. Fig. 1 illustrates these forces for the example of a double hydrogen bond. As an example, computer modelling [16] showed that whereas repeat units with the sequence acceptor-donor-acceptor/donor-acceptor-donor (ADA·DAD) had $K_{dim} \sim 10^2$ M$^{-1}$, two types of repeat units having the sequence DDA·AAD had $K_{dim} \sim 10^4$ M$^{-1}$. This difference was attributed to the different arrangement of the hydrogen bonding sites and the different secondary electrostatic interactions that arise as a result because the primary hydrogen bonds were comparable in each system studied. Murray and Zimmerman noted that the pattern may also be due to changes in primary hydrogen bond strength, differential solvation or alignment of molecular dipole moments.

## 3. Supermolecules

For their investigation of crown ethers, Cram, Pendersen and Lehn shared the 1987 Nobel Prize. The chance discovery of the first crown ether, dibenzo [18] crown-6, by Pendersen in the early 1970s may be considered as supramolecular chemistry's starting point. This oligo-ethylene glycol ether, shown in Fig. 2, was found to behave as a ligand, capturing ions in the hole at the centre of the molecule [1, 18]. If the crown ether could capture ions, then by synthesising a suitably shaped molecule containing a charge centre, it should be possible to promote self-assembly between both complementary species. From this starting point, approximately 5000 crown compounds have been reported. These may form cyclic structures ("coronands") or adopt open-chain structures ("podands"), which have found use as ligands in coordination chemistry.
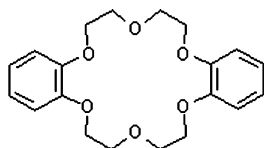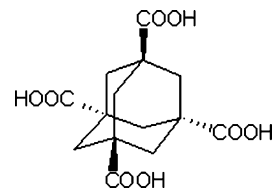
Whereas much of the early efforts in supramolecular chemistry addressed supermolecules or discrete systems, the concept of bonding repeat units using strong, specific, directional intermolecular interactions is equally applicable to the synthesis of network and extended structures. In an early demonstration of these ideas, Ermer [19] showed that adamantane-1,3,5,7,-tetracarboxylic acid, illustrated in Fig. 3, self-assembled via hydrogen bonding between its carboxylic acid functions to form a diamond-like network. The cavities in these networks were observed to be large enough to accommodate guest molecules.

Wuest and co-workers extended these concepts by showing how simple organic repeat units such as those shown in Fig. 4 could be made to self-assemble into a variety of open solids, including zeolite-type structures, all using hydrogen bonding [20, 21]. The resulting networks have large spaces between adjacent repeat units, typically 6–9 Å, up to 14 Å, comparable to the biggest zeolites and large enough to accommodate molecules. Therefore, these networks showed promise for use in separations and Wuest proposed that, were it possible to incorporate catalytic sites into the repeat units, reactions could be made to occur inside the network. However, the hydrogen-bonded structures were not found to be especially rigid, particularly at the high temperatures zeolite catalysts operate at.

Inspired by a tennis ball, Rebek and co-workers produced a spherical dimeric complex from self-complementary repeat units as an alternative approach to preparing supermolecules [22]. The dimer, shown in Fig. 5, self-assembled reversibly in solution to give a closed shell held together by eight hydrogen bonds and was large enough to encapsulate chloroform or methane molecules. Larger analogues of the tennis ball dimer have also been prepared [23] but whereas the dimer was found to be extremely soluble in organic solvents, the larger dimers dissociated to their component monomers under acidic conditions.
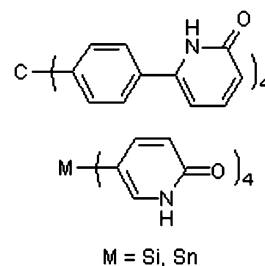


Figure 2 Dibenzo [18] crown-6, the first reported crown ether.



Figure 4 Repeat units used by Wuest and co-workers in the preparation of self-assembled networks.
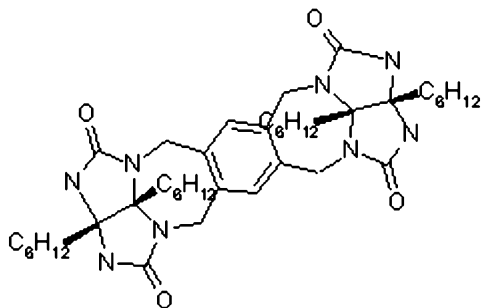
*Figure 5* Repeat unit synthesised by Rebek and co-workers to prepare the 'tennis ball' spherical dimeric complex.
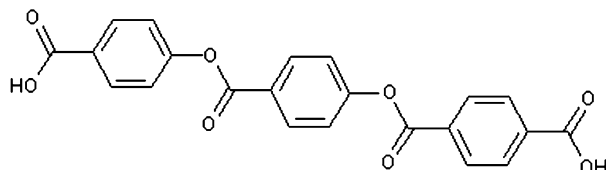


*Figure 6* Aromatic ester triad mesogen capable of hydrogen bonding.

## 4. Molecular assemblies & supramolecular polymers

A first step towards the rational synthesis of supramolecular polymers was taken as far back as 1984. In studying the liquid crystalline behaviour of polymeric glycols, Lenz and co-workers prepared dicarboxylic acid derivatives of glycol polymers [24], hoping to obtain liquid crystals by varying the position of mesogenic groups and flexible spacers along the polymer chain. Upon placing carboxylic acid groups at the ends of these chains (cf. Fig. 6), adjacent acid groups were found to hydrogen bond, doubling the length of the mesogenic groups and giving stiffer, more anisotropic, liquid crystals.

The first truly *supramolecular* polymer was reported by Lehn and co-workers at the College de France in 1990 [3, 25]. The polymer consisted of a molecular assembly composed of an equimolar mixture of repeat units bearing uracil (A) and 2,6 diaminopyridine (B) groups, which associated via triple hydrogen bonding as shown in Fig. 7. This polymer adopted a well-defined structure and displayed physical properties similar to conventional polymers, ad discussed in Section 5.1. In addition, no complications have been reported

regarding its long-term stability. For these reasons, it has become a benchmark in the field of supramolecular polymer chemistry.

Since then, increasing interest has developed in extended self-assembled structures such as one-dimensional chains, two-dimensional sheets and three-dimensional networks. Much research into supramolecular polymers has been concerned with preparing liquid crystalline molecular assemblies that display similar characteristics to that prepared by Lehn *et al.* (Fig. 7) but which are easier to synthesise. Liquid crystals are 'mesophases', ordered liquids that occur at the transition state between solids and liquids, and are anisotropic i.e., their physical properties are direction-dependent [26]. The development of liquid crystalline molecular assemblies stemmed from attempts to stabilise anisotropic phases of small molecules: increasing the axial ratio (length/diameter) of a liquid crystal improves the mesophase's stability, which could be achieved by synthesising liquid crystals from small molecules using non-covalent interactions [11]. Section 5 addresses key advances in this field supramolecular polymer chemistry.

Among attempts to develop molecular assemblies which display polymeric behaviour without the need for liquid crystallinity, the family of materials originally reported by Meijer and co-workers [27, 28] all based on the ureidopyrimidinone hydrogen-bonding motif have proven especially successful. Representative examples of these materials are shown in Fig. 8; note that the aspect of the polymer depends on the choice of spacer between the ureidopyrimidinone functions. These are discussed in more detail in Section 6.4.

## 5. Liquid crystalline supramolecular polymers
### 5.1. Tartaric acid bis-ether liquid crystals

The first reported supramolecular polymer, shown in Fig. 7, was assembled from repeat units consisting of long-chain derivatives of tartaric acid onto which either 2,6 diaminopyridine or uracil motfis were condensed [3, 25]. When equimolar amounts of the repeat units were combined, these diaminopyridine and uracil groups associated via triple hydrogen bonding to yield the extended-chain polymer.

Though the individual repeat units did not display liquid crystalline behaviour, the resulting polymer gave
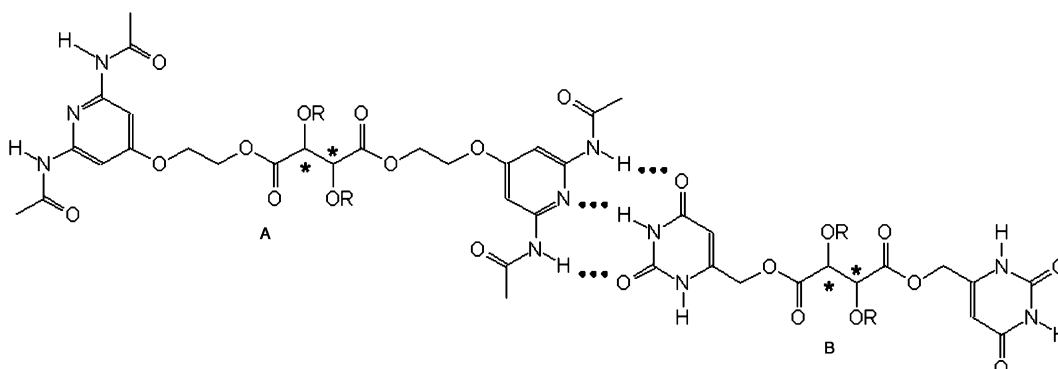


*Figure 7* Lehn's diaminopyridine (A)-uracil (B) molecular assembly. The hydrogen bonds between repeat units are indicated by dotted lines and chiral centres are marked*.
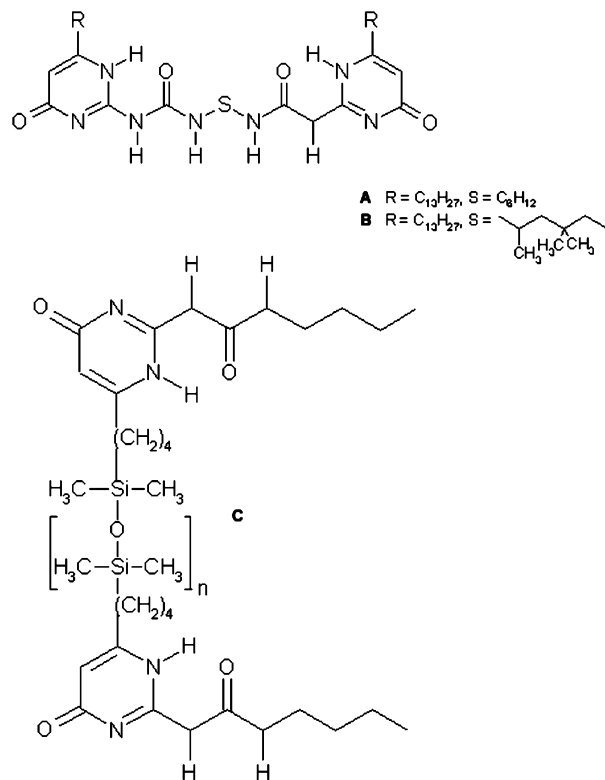
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*Figure 8* Ureidopyrimidinone supramolecular polymer structures having alkyl (A), methyl-substituted (B) and siloxane (C) spacers.

a theromotropic mesophase stable from room temperature to over 200°C. The exact temperature at which the nematic—isotropic transition occurred depended on whether the repeat units contained L-, D- or meso-tartaric acid backbones. In all cases, the polymer stacked to produce a hexagonal columnar structure [3]. This stacking also served to pre-organise the repeat units to promote hydrogen bonding between them. The stacking mechanism compared closely with that of base pairing in double-stranded DNA. Microscopy revealed that this supramolecular polymer had the aspect of birefringent glue. If a film of the polymer was spread across a surface, it formed fibres, just as a conventional polymer would. It was also found that if repeat units were prepared from a mixture of tartaric acid's stereoisomers, the assembly process brought about spontaneous resolution of the racemic mixture. Furthermore, the final assembly was observed to be chiral, still a unique feature among supramolecular polymer liquid crystals.

Subsequently, the diaminopyridine—uracil triple hydrogen-bonding motif has been used to synthesise supramolecular rigid rods [3, 29]. By grafting the uracil or diaminopyridine groups described above onto a rigid core (cf. Fig. 9) via imide functions, a molecule results
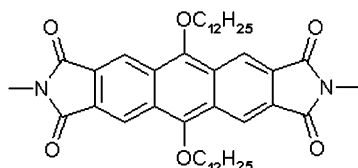


*Figure 9* Imide backbone used by Kotera *et al.* to synthesise supramolecular rigid rods.

in which rotation about any of its bonds is impossible. Upon mixing equimolar quantities of these repeat units, they self-assembled to form rigid linear rods which presented a lyotropic meosphase and were found to be reasonably soluble in common organic solvents.

Though the chemistry underlying their synthesis is straightforward, preparing useful quantities of these supramolecular polymers must be considered a painstaking task. Starting from commercially available reagents, twelve steps are necessary to produce each repeat unit shown in Fig. 7; an overall yield of 25% may be expected for each synthesis [25, 30–32]. Preparing the rigid rod repeat units is equally taxing [29]. Two component systems require that exact stoichiometric quantities of both components be combined for successful assembly, which can prove difficult to obtain in practice. As a result, more recent work has sought to find simpler routes to prepare polymers with comparable properties.

## 5.2. Acid/pyridyl liquid crystalline polymers

Several groups have studied hydrogen-bonded complexes involving benzoic or carboxylic acid and pyridine (See refs. 11 and 33 for examples). Because these complexes can form no more than two hydrogen bonds between repeat units, the resulting polymers inevitably depend on liquid crystallinity to align the repeat units so that self-assembly can occur. In many cases, small molecules have been grafted onto a conventional preformed polymer main chain via hydrogen bonds to give, or modify, liquid crystalline properties. Of greater relevance to this review are those systems which use hydrogen bonding alone to form the polymer chain.

As Lehn's group announced their first supramolecular polymers, Kato and Frecht sought to prepare well-defined liquid crystalline polymers using single or double hydrogen bonds [33–36]. Benzoic acid and 2-aminopyridines (without ortho-substituents) were used to prepare 1:1 complexes via double hydrogen bonds, as illustrated by Fig. 10A. These 1:1 complexes had sharp melting transitions, indicating that they behaved as single molecules, and displayed liquid crystallinity—monotropic smectic B mesophases—not observed for the individual components. Similarly, 2-aminopyridine groups were grafted onto a polyacrylate main chain polymer via double hydrogen bonds to give a supramolecular side-chain liquid crystal (Fig. 10B). Kato also suggested that applying the principles of self-assembly to polymer blends could help to improve their miscibility. For example, the formation of single hydrogen bonds between pyridine side chains on a thermotropic polyester chain and the phenol groups of non-mesogenic poly(4-vinylphenol) gave rise to a mesomorphic polymer blend. Finally, it proved possible to form a network polymer by the self-assembly of a star-shaped repeat unit (Fig. 10C) whose functionalised terminal groups were linked via small bifunctional molecules such as 1,2-di(4-pyridyl)ethylene (Fig. 11A).

Using similar chemistry, Lee and co-workers [37] prepared liquid crystals by reacting molten dipyridine (Fig. 11B) and dicarboxylic acid (Fig. 11C) monomers
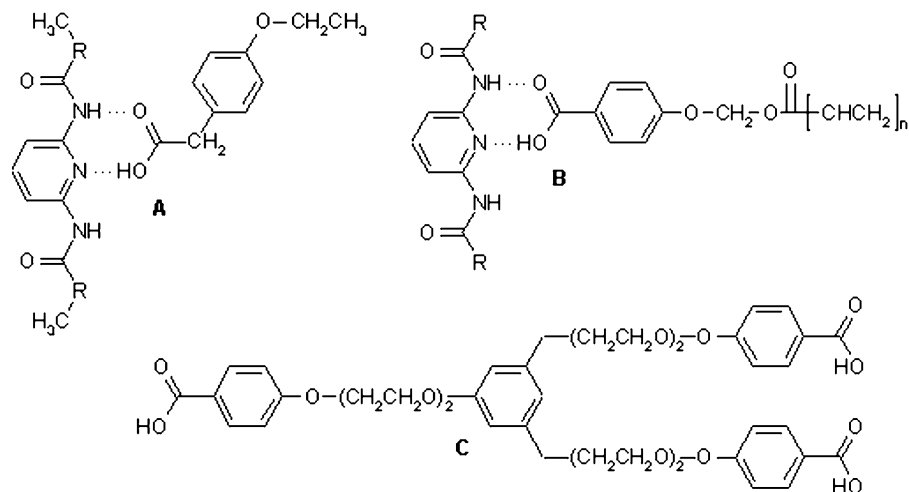
*Figure 10* Liquid crystalline polymers prepared by Kato and Frecht—1:1 liquid crystalline complex (A), side chain liquid crystalline polymer (B) and network polymer (C).
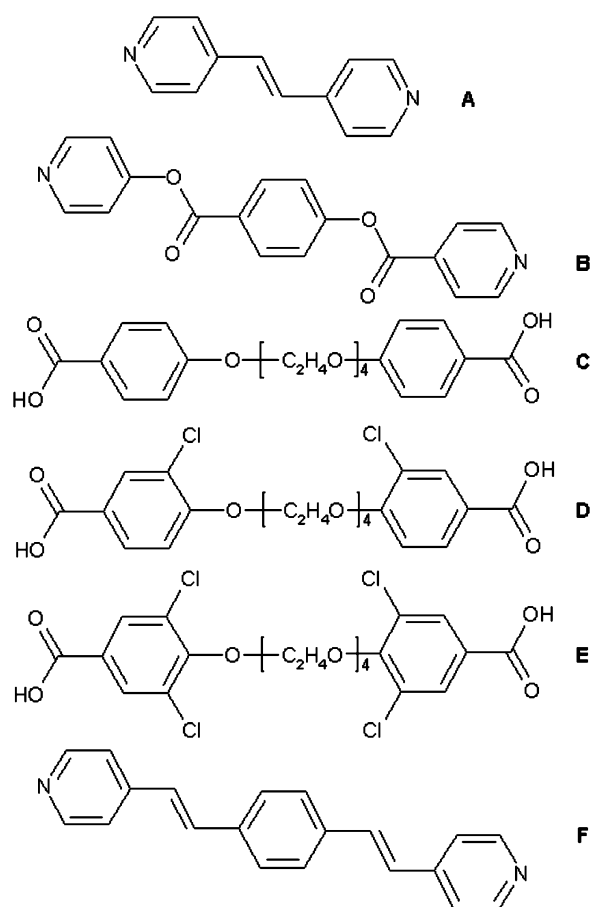


*Figure 11* Monomers that form liquid crystals via single hydrogen bonds.

Fig. 11), also underwent a change in its smectic phase on the second and subsequent heat/cool cycles. In both liquid crystals, new peaks at 2500 and 1900 cm$^{-1}$ in their infrared (IR) spectra resulted from hydrogen bond formation between the monomers. Variable-temperature IR spectroscopy showed that these strong hydrogen bonds remained intact until the liquid crystals reached their melting point.

## 5.3. The influence of crystallisation rate

Lee and Griffin [38] reported that it was often difficult to prove such acid/pyridyl liquid crystals to be polymeric because, at low $D_p$ and high temperatures, they tended to crystallise as oligomers. Repeat units were synthesised bearing substituted rings to reduce the polymer's tendency to crystallise (cf. Fig. 11D and E), effectively reducing their axial ratio. It was proposed that, if the liquid crystals prepared from these repeat units exhibited a glass transition and formed fibres, the liquid crystals could be considered polymeric.

These liquid crystals formed oligomers at high temperatures where the hydrogen bonds were too weak to promote self-assembly effectively. It proved essential to retard crystallisation to obtain polymeric behaviour, so that the material could cool to ambient temperature, allowing hydrogen bonding to occur and a mechanically coherent extended polymer chain to form. Lee and Griffin found that lateral substitution successfully retarded crystallisation by adding a 'carbuncle' to the polymer chain, which restricted close packing of adjacent chains. The 'carbuncled' polymer, containing equimolar amounts of monomers E and F, Fig. 11, gave a glassy nematic phase from which fibres could be drawn. On cooling from the melt, the polymer did not give distinct transitions between liquid crystalline phases, but did exhibit a glass transition at 34°C. When heated again, it underwent a glass transition at 37°C. Such behaviour is also seen in conventional polymer liquid crystals. On annealing the polymer at room temperature for four days, the glass transition decreased to 32.3°C. From this, the authors concluded that the 'carbuncled' polymer could only assume a crystalline structure with difficulty.

in the isotropic phase. Two reaction times were used: 10 min, and no more than 2 min, with the longer reaction time giving rise to broader solid—nematic and nematic-isotropic phase transitions in the resulting polymer. Repeated heating and cooling of the short-reaction-time liquid crystal caused it to show the same thermal properties as the long-reaction-time one; the difference in thermal properties was attributed to a cross reaction between the monomers which led to the formation of covalent crosslinks. A second liquid crystal, prepared from monomers incapable of cross-reaction (A and C,
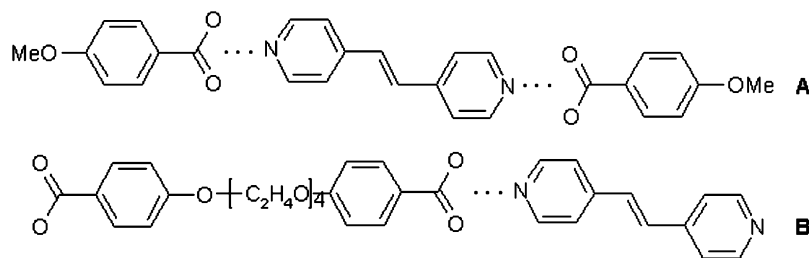
*Figure 12* p-Methoxybenzoic acid—1,2-di(4-pyridyl)ethylene 2:1 complex (A) and tetraethyleneglycoxy bis(4-benzoic acid)—1,2-di(4-pyridyl)ethylene 1:1 liquid crystalline complex (B). Intermolecular hydrogen bonds between adjacent carboxylic acid and pyridyl groups are represented by dotted lines.

## 5.4. Hydrogen bond stability

Drawing on Kato and Frecht's use of small molecules to prepare liquid crystals, St Pourçain complexed benzoic acid derivatives with trans-1,2,bis (4-pyridyl) ethylene to determine their hydrogen bond stability [39]. IR spectroscopy confirmed that a complex was formed; it was previously known [37] that complexation causes the OH absorption between 3500 and 3000 cm$^{-1}$ to be replaced by two peaks at 2500 and 1900 cm$^{-1}$. St Pourçain proposed that double minimum bonds would form whenever the difference between the pKa values of the acid and pyridyl was less than 3.75, so the range 3.51–5.00 was used. The intensity of the C=O peak in eight complexes was correlated with the pKa value of the benzoic acid derivative with a correlation coefficient of 0.93.

This correlation implied that the hydrogen bonds in each complex were in similar environments and that the differences in C=O absorption were due to the electron withdrawing or donating effects of the substituents on benzoic acid. Therefore, the bond strength was controlled primarily by substitution. Having proven that the hydrogen bonds in all eight complexes studied were comparable, the bond stability was determined by variable temperature IR spectroscopy. The spectra of each complex continued to show peaks at 2500 and 1900 cm$^{-1}$ with no broadening observed between 3500 and 3000 cm$^{-1}$ until they reached their melting points. Broadening began after melting, proving that, irrespective of bond strength, the benzoic acid derivatives remained completely complexed until all other intermolecular forces were overcome.

Thermal analysis of the acid-dipyridyl model complex A shown in Fig. 12 revealed that the complex underwent degradataion as a single species [40]. Contrary to expectations, $E_{act}$ for the degradation process was determined to be 127 kJ·mol$^{-1}$, appreciably higher than the typical bond energy of a single hydrogen bond. The underlying cause of this result was not entirely clear, though it was suggested that the complex's tendency to form a liquid-crystalline mesophase may be a contributing factor. The polymeric analogue of 12A, 1:1 complex 12B remained thermally stable until 230°C. As these complexes can also be compression moulded [37, 38], the acid-dipyridyl motif may prove useful as a structural material in applications where the liquid-crystallinity necessary to pre-order the hydrogen-bonding sites is acceptable.
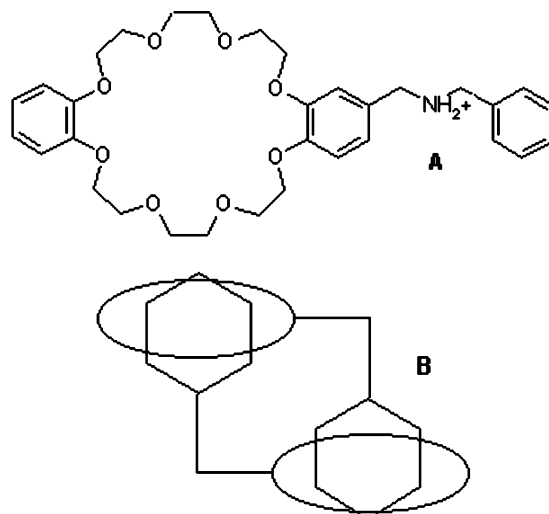


*Figure 13* Self-complementary hybrid molecule formed by grafting a secondary ammonium ion to a crown ether ring (A). X-ray crystallography showed that the resulting monomer self-assembled into a dimer (B).

## 6. Alternative approaches to self-assembly
## 6.1. Daisy chains

By grafting a secondary ammonium ion onto dibenzo [24] crown-8 as illustrated Fig. 13, Stoddart and co-workers [41] prepared a self-complimentary monomer (A) which ought to thread together forming either macrocycles or extended chains. The geometry of the monomer was such that it was impossible for the crown ether and ammonium ion to interact with each other and form an intramolecular complex. Therefore, the monomer could complex with its neighbours to afford either cyclic dimers, trimers etc. or extended liner chain oligomers. X-ray crystallography revealed that it formed the smallest possible cyclic structure, a head-to-tail dimer (Fig. 13B), stabilised by N$^{+}$-H···O hydrogen bonds.

Stoddart concluded that to prepare a supramolecular polymer through these threading interactions would require a very strong recognition motif based on crown ethers possessing more than one site capable of binding secondary ammonium ions. Fig. 14 is a schematic
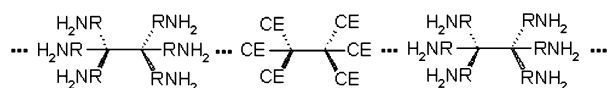


*Figure 14* Schematic of a supramolecular polymer assembled via threading interactions.
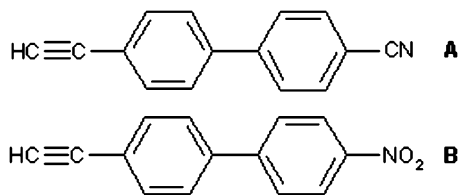
*Figure 15* Repeat units chosen by Langley *et al.* for crystal engineering.

of self-complementary monomers based on this principle. It will be appreciated that the synthesis of these repeat units would be challenging, and preparation of the target supramolecular polymer complicated by the need for a stoichiometric mixture of both monomers. While the organic chemistry involved is impressive, such an approach does not fulfil the aspiration for easy synthesis set out in the introduction to this review.

## 6.2. Crystal engineering

Seeking to prove that it was possible to predict the assembly of a molecular assembly, Langley and co-workers [42] investigated the potential of the $C\equiv C$-$H\cdots O_2N$ hydrogen-bonding motif. At the time of their study, this motif had not been examined before, but analogous systems were known. The repeat units shown in Fig. 15 were prepared and both did indeed form centrosymmetric crystal structures. The second polymer also formed crosslinks between $C-H\cdots O$ and $C\text{-}H\cdots(C\equiv C)$. As the $(C\equiv)C-H$ IR stretching frequency increased from 3265 to 3302 cm$^{-1}$ when spectra were recorded in deuterated chloroform solution rather than potassium bromide discs, it was concluded that there was significant hydrogen bonding between the repeat units. Only limited structural information could be obtained about this system, but crystals of 15A and 15B both emitted green light in response to laser irradiation at 1064 nm. This behaviour was attributed to second harmonic generation, which the authors believed arose from disordered orientation in the crystal structure. It was proposed, therefore, that these finding opened the possibility of engineering crystals possessing novel nonlinear optical properties via supramolecular chemistry [43, 44].

## 6.3. Pyridones

2-pyridone is a hydrogen bonding motif which may exist in lactam or lactim tautomers, yet remains capable of hydrogen bonding in each tautomeric form [45]. Fig. 16 shows that both of these tautomers are self-complementary and may form homodimers A and B; however, because the spacing between hydrogen bond donor and acceptor sites is similar in both tautomers, the lacatam and lactim tautomers may also associate to form a heterodimer C.

Wuest and co-workers synthesised dipyridones linked by a variety of spacers, which readily formed dimers, even in dilute chloroform solutions of <1 mmol [46, 47]. Seeking to overcome the limitations
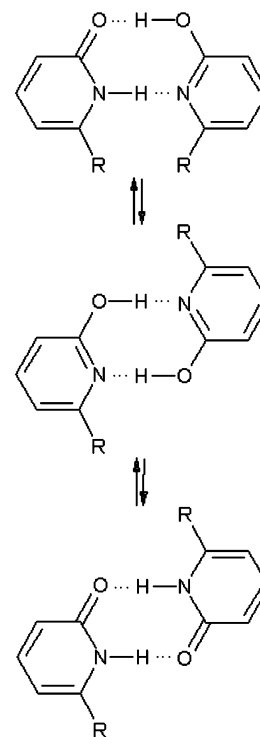


*Figure 16* Homodimers of the lactam (A) and lactim (B) tautomers of 2-pyridone. The lactam and lactim tautomers may also assemble to form a heterodimer (C).
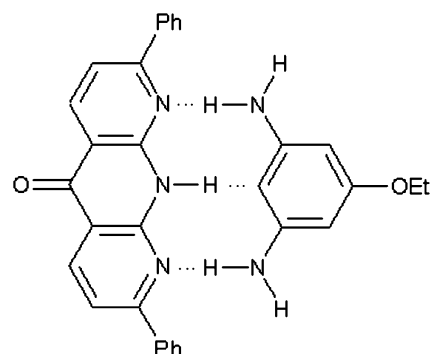


*Figure 17* Pyridone heterocycle capable of forming triple hydrogen bonds.

imposed by weak interactions mentioned previously, Zimmerman and co-workers took the 2-pyridone dimer as a starting point in preparing heterocycles capable of forming multiple hydrogen bonds [15, 45]. These motifs were intended to self-assemble without the need for liquid crystallinity and to be capable of hydrogen bonding irrespective of changes in tautomerism. Having prepared a series of triply hydrogen-bonded dimers such as that illustrated in Fig. 17 (used in the study of dimerization rates discussed in Section 2.1) a pyrimidin-4-one derivative bearing four hydrogen bond donor and acceptor sites was synthesised. This derivative was found to remain capable of forming dimers in each of its three conformations—illustrated in Fig. 18—with $K_{dim} > 10^7$ M$^{-1}$. The same pyrimidin-4-one motif has been used successfully to functionalise dendrimers, allowing them self-assemble into hexamers [48].
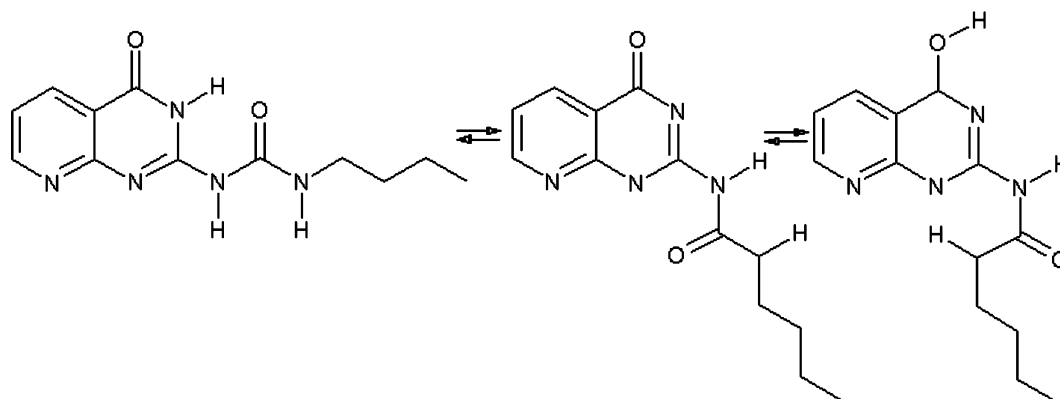
*Figure 18* Pyrimidin-4-one—derived heterocycle that dimerizes via quadruple-hydrogen bonds in each of its three tautomeric forms.

## 6.4. Ureidopyrimidinones

Meijer and co-workers designed derivatives of the ureidopyrimidinone motif for use as an associating end-group to overcome the limitations imposed by weak interactions mentioned previously. Ureidopyrimidinones offer strong, directional hydrogen bonding, and have been shown to form dimers following a predictable recognition and assembly process. The ureidopyrimidinone motif is more readily synthesised [28] than the majority of hydrogen bonding motifs and, because it is self-complementary, the problem of preparing stoichiometric mixtures of repeat units is avoided.

Polymers derived from ureidopyrimidinones may also have potential for preparing soft materials whose flow properties can be accurately controlled. Viscoelasticity in polymers arises from entanglements between chains. While conventional high molecular weight polymers are elastic, they have long relaxation times. Cates has proposed a model [49] for the rheological behaviour of 'living' polymers having reversible bonds which has been shown to be applicable to model ureidopyrimidinone polymers [27, 50]. For example, these supramolecular polymers offer the possibility that the structure can adapt to changing environmental stresses after synthesis [9, 27]. They would be expected to exhibit low melt viscosity typical of organic compounds at elevated temperatures but display the mechanical properties of conventional polymers upon returning to room temperature [51], behaviour which should offer considerable advantages during processing.

The simplest ureidopyrimidinone, 2-butylureido-6-methyl-4-pyrimidinone (cf. Fig. 19) dimerizes via four hydrogen bonds in chloroform solution or in the solid state [27, 28]. Infrared spectroscopy has shown that, in both cases, no free NH groups remain in the dimer. An intramolecular hydrogen bond between the NH group of the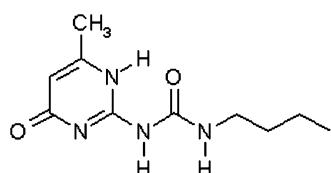 pyrimidinone and the adjacent C=O of the urea pre-organises the molecule into a linear conformation suitable for dimerization. Also, the pattern of hydrogen bond donor and acceptor sites in these dimers is donor, donor, acceptor, acceptor (DDAA), which is a particularly stable arrangement because it gives rise to fewer repulsive secondary interaction between adjacent donor/acceptor pairs (cf. Section 2 for a discussion of the effect of secondary interactions in hydrogen bonding motifs). Thermal analysis showed that dimeric 2-butylureido-6-methyl-4-pyrimidinone remained stable to higher temperatures than commonplace conventional engineering polymers [52]—the dimer did not degrade until heated beyond its melting point of 225°C, although once the degradation process began, it proceeded rapidly.

The ureidopyrimidinone structure is prone to keto-enol tautomerism, as illustrated in Fig. 20, and the dimers formed by monofunctional ureidopyrimidinones may adopt at least three crystal structures, all with similar dimer geometry [27, 28]. All three crystal structures pack in layers, differing mainly in the position of the layers with respect to each other. These dimers have high $K_{\text{dim}}$ and each exists in solution as a single tautomer. $K_{\text{dim}}$ is higher for keto tautomers than enol and is also a function of the solvent. $K_{\text{dim}}$ for the ureidopyrimidinone motif has been estimated [53] at $6 \times 10^7$ M$^{-1}$ in chloroform solution at 298 K; the value of $K_{\text{dim}}$ was found to increase tenfold in toluene solution and decrease sixfold in water-saturated chloroform. Such behaviour is to be expected as apolar toluene should favour hydrogen bonding whereas water molecules could bond to the free hydrogen bonding sites on the motif, competing with the dimerization reaction.

The potential of the ureidopyrimidinone motif to yield extended chain supramolecular polymers having promising material properties was first demonstrated by
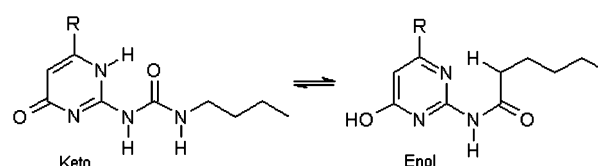


*Figure 19* 2-Butylureido-6-methyl-4-pyrimidinone, which dimerizes via quadruple hydrogen bonds in solution and the solid state.



*Figure 20* Keto (left) and enol (right) tautomers of the ureidopyrimidinone structure.

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synthesising bifunctional repeat units which had urei-dopyrimidinone end-groups grafted to alkyl (cf. Fig. 8A and B) or siloxane (8C) spacers [27, 49, 54]. 8A was a crystalline solid, but substituting the spacer with methyl groups (8B) resulted in an elastomeric material. Both 8A and C formed viscous solutions in chloroform. It was found that their solution viscosity was highly temperature-dependent, exhibiting behaviour that would be expected of a reversible covalently-bonded polymer. In contrast, the solution viscosity of 8B was found to be strongly concentration dependent. Below 0.1 mol·dm$^{-3}$ in chloroform solution, cyclic structures predominate; above 0.1 mol·dm$^{-3}$ repeat units assemble of 8B preferentially into an extended chain linear polymer causing a sharp increase in solution viscosity. This concentration dependence was explained as follows: whether bifunctional ureidopyrimidinones form cyclic or linear structures depends on the ability of the spacer in the molecule to fold [55]. Due to the methyl substitution on its spacer, 8B may adopt cyclic or extended chain conformations that exist in equilibrium with each other; the equilibrium shifts in favour of the extended chain conformation above 0.1 mol·dm$^{-3}$. However, it was also noted that these polymers showed history-dependent properties, tending to crystallise over time.

Whereas siloxane-based 8C exhibited shear thinning similar to poly(dimethyl siloxane), the precursor of this repeat unit exhibited Newtonian shear behaviour. This implies that the polymer-like rheology observed for this ureidopyrimidinone was a result of intermolecular hydrogen bonding between the repeat units, and not simply the presence of siloxane groups. Adding a mono-functional species (Fig. 21A) to chloroform solutions of these polymers caused a sharp decrease in $D_p$ because 21A could bond to the ureidopyrimidinone end-groups on the growing supramolecular polymer chain, acting as a chain stopper. Folmer and co-workers confirmed these observations via photo-induced depolymerisation [56]. Precursor 21B was synthesised such that it degraded upon irradiation with UV light to produce chain stopper 21A. Adding 0.1 equivalents chain stopper to 9.9 mM 8A in chloroform solution caused a sharp decrease in relative viscosity, from 13.16 to 1.92. Adding 0.1 equiv. precursor caused a negligible drop, from 13.16 to 10.79, but irradiation of the solution caused a sharp drop in relative viscosity comparable to that observed upon addition of 21A. These experiments confimred that $D_p$ depends strongly on the presence of chain stoppers and, therefore, that high purity repeat units are essential to prepare supramolecular polymers of high molecular weight. $D_p$ may be predicted from
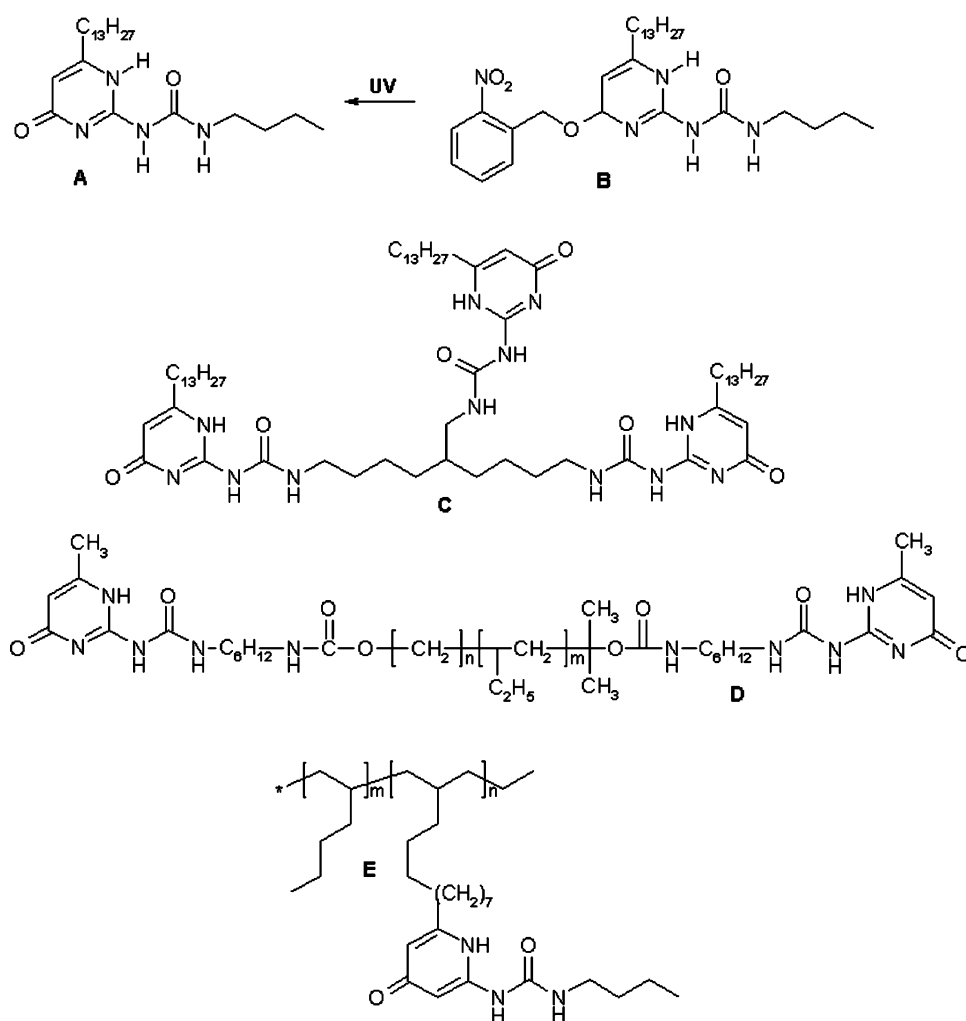


*Figure 21* Ureidopyrimidinone structures. A: 2-Butylureido-6-tridecyl-4-pyrimidinone; B: Precursor which degrades upon UV irradiation to yield A; C: Trifunctional repeat unit; D: Ureidopyrimidinone functionalised telechelic poly(ethylenebutylene); E: Ureidopyrimidinone functionalised poly(1-hexane) copolymer.

the equation:

$$D_\mathrm{p} = \frac{2([R] + [S])}{[S] - \frac{1}{4K_\mathrm{dim}} \left[1 - \sqrt{1 + 8K_\mathrm{dim}([S] + 2[S])}\right]}$$

where $R$ = repeat unit and $S$ = chain stopper [27].

The model compounds 8A–C all demonstrated macromolecule-like rheology which was confirmed to arise from self-assembly of the ureidopyrimidinone groups, thus confirming that the motif was a valuable addition to supramolecular polymer chemistry. Lange and co-workers sought to extend the use of the motif to preparing network supramolecular polymers. They synthesised a trifunctional repeat unit (21C) bearing 2-ureido-4[1H]pyrimidinone groups which were expected to self-assemble to form the polymer network [50]. The network polymer obtained was found to be soluble in organic solvents and exhibited viscoelastic behaviour comparable to that already reported for model ureidopyrimidinone extended chain polymers. Like the model polymers, it formed more viscous solutions in non-polar solvents. Its relative viscosity in solution decreased sharply upon adding chain stopper to the solution. Similarly, adding 11% water to 21C caused its viscosity to fall by two orders of magnitude, from $2.6 \times 10^4$ Pa·S to $2.6 \times 10^4$ Pa·S. The viscosity of solutions of 21C also decreased rapidly upon dilution; Lange and co-workers attributed this observation to a shift in the equilibrium of the hydrogen bonding, which is known to be concentration dependent. The network polymer also underwent a clearly discernible glass transition, determined to be $-53°C$ by differential scanning calorimetry (DSC).

Recently, ureidopyrimidinone motifs have also been incorporated into conventional polymers to advantage, resulting in remarkable changes in the properties of these polymers. Folmer and colleagues [57] grafted the motif to telechelic polyol oligomers (e.g., 21D) which assembled into chains of high virtual molecular weight, while Coates and co-workers [58] synthesised a polyolefin copolymer (21E) with a random branched architecture bearing $\sim2\%$ ureidopyrimidinone side chains. These acted as reversible crosslinks. Both preparations were straightforward and used starting materials known from the chemical literature. The synthesis of 21D has the further advantages that the reagents are commercially available and that it has been successfully scaled up to produce kilogram-scale batches in good yield [59]. Both 21D and E self-assembled to give clear elastic solids that displayed similar rheological and mechanical properties to 21C and also 8A, B and C.

The relative viscosity of polyolefin copolymer 21E in toluene increased exponentially with concentration, with gelation occurring above 20 g·dm$^{-3}$. Adding three equivalents of monofunctional ureidopyrimidinone eliminated the crosslinking effect of the ureidopyrimidione side chains completely. Coates and co-workers suggested that this finding indicated that the ureidopyrimidinone moieties did not form clusters as the introduction of the monofunctional species ought not to have such a pronounced effect on clusters of hydrogen bonds. Tensile tests were conducted to compare the mechanical properties of 21E with a homopolymer analogue. Low molecular weight homopolymer displayed tensile properties typical of a viscous liquid: after initial deformation to uncoil the polymer chains, minimum stress was required to elongate the polymer. However, low molecular weight 21E displayed elastomeric properties: after initial deformation, the stress required to continue deformation increased dramatically. At high molecular weight, both 21E and the homopolymer exhibited similar behaviour, but at higher stresses and with greater elongation at rupture. These differences were attributed to the increased intermolecular interaction of the longer polymer chains.

Whereas the polyol from which it was synthesised was a viscous liquid, telechelic 21D adopted the aspect of an elastic solid which formed highly viscous solutions in chloroform. The sharp decrease in viscosity caused by adding trifluoroacetic acid (which disrupts hydrogen bonds) to these solutions indicated that the change in aspect resulted from the self-assembly of the ureidopyrimidinone motifs. DSC revealed that 21D underwent a glass transition at $-57°C$; dynamic mechanical thermal analysis showed a glass transition at $-50°C$ (at 1 Hz) and a rubber plateau of $5 \times 10^6$ Pa at room temperature. The polymer was fully amorphous: no melting transition was detected. Dynamic oscillatory shear experiments revealed strongly frequency-dependent viscoelastic behaviour. The zero-shear viscosity was determined to be $2 \times 10^6$ Pa·S at $40°C$ at low frequency, with a storage modulus of $\sim10^6$ Pa at high frequency. A particularly promising feature of 21D was that its zero-shear melt viscosity decreased fourfold upon heating from 40 to $50°C$. This remarkable property was in keeping with McLeish's predictions on the viscoelastic properties of supramolecular polymers. Such strongly temperature-dependent rheology should make telechelic 21D very easy to process compared to conventional polymers.

## 7. Conclusions

The developments discussed in this review show that supramolecular polymer science has matured into a technology ripe for industrial use. Synthetic methods are available to produce supramolecular polymers in good yield using straightforward chemistry. In the case of ureidopyrimidinones, these methods have already been scaled up to kilgoram scale successfully. Compared to conventional engineering polymers, acid-pyridyl liquid crystals and ureidopyrimidinones exhibit high thermal stability, while self-assembled crystals (cf. Section 6.2) exhibiting non-linear optical properties should enjoy significant commercial advantage over existing NLO materials. Also, the principles of self-assembly can also be exploited to enhance conventional polymers, leading to valuable improvements in their material properties, e.g., side-chain polymer liquid crystals (e.g., Fig. 10B), telechelic polyols (Fig. 21D) and polyolefins (Fig. 21E).

However, some new factors remain to be considered in selecting supramolecular polymers for any given

application. For example, exposure to water in service may affect hydrogen bond strength or exposure to heat may cause creep due to their temperature-dependent viscoelastic behaviour. The majority of supramolecular systems reported to date have been synthesised and processed in non-polar solvents. It is thought that if supramolecular polymers are to be adopted in industry, the potential problems associated with the use of solvent-based systems to maximise hydrogen bonding must be overcome. This may require the development of novel non-solvent processing techniques or modification of the materials for use in water.

Few obstacles should be expected to using hydrogen-bonded supramolecular polymers with existing polymer processing equipment. These materials have been proven to exhibit temperature-dependent viscoelastic properties, which ought to allow for easy processing, while the acid-pyridyl liquid crystalline polymers considered in Section 5.2 were amenable to compression moulding. At the time of writing, in fact, members of the Meijer Group are actively involved in SupraPolix, a new company founded by Eindhoven Technical University to commercialise the ureidopyrimidinone-based technology developed there [60].

## Acknowledgements

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