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LOW MOLECULAR WEIGHT GELATORS FOR ORGANIC SOLVENTS

From serendipity towards design

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1 Introduction

Everyone knows what a gel is, but from a scientific point of view the term gel encompasses chemically very diverse systems. Well known gel systems include, for instance, dilute solutions of polymers, proteins, and surfactants in water and organic solvents. These gel systems are important in medicine, biology, chemistry, and physics, and find many applications in the photographic, cosmetics, food, and petroleum industries [1]. However, as D. Jordan Lloyd already wrote in 1926: 'The colloidal condition, the "gel", is one which is easier to recognise than to define,...'. And although an exact definition of a gel is still a problem, from a topological point of view gels can be defined as dilute mixtures of at least two components, in which both components form a separate continuous phase throughout the system [2]. This definition includes not only gels composed of a solid-like and a liquid phase, but also those composed of a solid and a gas phase (so called aerogels). For most gels a solid-like phase is the minor component which forms a three dimensional network structure within the fluid or gas phase. For solid-fluid gels it can be said that the network structure prevents the fluid from flowing, whereas the liquid phase prevents the network from collapsing [3]. The coexistence of a solid network structure together with a liquid phase distinguishes gels from pure solid, liquid crystalline, or fluid materials and gives gels their unique elastic properties.

Often gels are divided into two groups depending on the type of interactions which hold the network structure together. In chemical gels, both the individual filaments of which the network consists, as well as the connections (junction zones) between the filaments to form the network, are created through the formation of covalent bonds. Cross-linked polymer gels belong to this class of gels, but also many gels composed of inorganic oxides, like vanadium pentoxide and silica. The properties of

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chemical gels can be as different as their constituents, but they have in common that their formation is irreversible. Opposed to chemical gels are the physical gels. In this type of gels the network structure is build up from small molecular subunits, which are held together by non-covalent interactions. The attractive forces between the molecular subunits can be very specific, like hydrogen bonding or π - π stacking, but also solvophobic and entropy effects play an important role. Because the non-covalent interactions stabilizing the network are orders of magnitude weaker than covalent bonds and comparable to the thermal energy ($RT \approx 0.6$ kcal/mol at 300 K), physical gels exhibit a characteristic reversible transition from the gel phase to a solution at moderate temperatures. Many gels containing mineral clays, polymers and proteins belong to this class. Properties of physical gels like thermal stability and viscoelastic behavior are therefore the result of a delicate balance between the properties of their constituents and the interactions between them.

Also certain low molecular weight organic compounds are capable of forming gels. Whereas with macromolecular gels the smallest molecular entity has at least a size of several kDa, the size of most of these compounds, often called organogelators, ranges from 300-1000 Da. Gelation of solvents by organogelators is the subject of increasing attention, not only because of the numerous applications of gels, but in particular because these compounds represent a class of gelators that exhibit striking properties with respect to self-assembly phenomena [4]. Although many aspects of the mechanism of gelation are unclear and there is a great variety in the structure of low molecular weight gelators it appears that these compounds have certain features in common. Gelation of a solvent by organogelators occurs through self-assembly of the gelator molecules into elongated fiber like structures, which then form an entangled network in the solvent [4]. In these networks, the fibers consist of infinite arrays of small molecules, solely held together by non-covalent interactions. Organogels thus belong to the physical gels. Despite impressive achievements of supramolecular chemistry in the controlled self-assembly of small molecules [5,6,7], most low-molecular weight gelators so far have, however, been found by serendipity rather than design. The control of gelation phenomena induced by small organic molecules and the design of new gelators are challenging goals, and it has only been recently that a number of successes have been reported.

Because the literature on organogelators till 1996 has been covered in an excellent review by Terech and Weiss[4], we will give in the following section only a brief overview with some representative examples of the older literature. In the next sections we discuss some of the background and principles used for the design of organogelators, and give an overview of our work on the design of novel organogelators. Finally we will briefly discuss the development of functional organogelators, which is an area of large potential and whose development only has become possible through a better understanding of organogels. It should be stressed, however, that the field of organogelators, although still in its infancy, only has developed to what it is nowadays thanks to the work of a limited number of research groups, including Weiss, Rabolt, Terech, Hanabusa, Shinkai, and ours, who recognized in an early stage the large potential of organogels.

2 Examples of Organogelators

2.1 INTRODUCTION

The group of low molecular weight organogelators consists of a great number of very different compounds, which have in common that they self-assemble into fiber-like structures, which in turn form a three dimensional network in the solvent. The non-covalent interactions which provide the driving force for the self-assembly process include ion-ion and dipole-dipole electrostatic interactions, hydrogen bonding, π -stacking interactions, and van der Waals interactions. It is therefore tempting to classify organogelators according to the nature of interaction responsible for self-assembly. However, in most cases it is not well understood what kind of structure a specific organogelator forms nor what the contribution is of each kind of interaction. It is even more likely that the often very efficient aggregation of organogelators is the result of several forces acting in a cooperative way. Therefore we classified the organogelators according to their chemical constitution, in similar way as has been done by Terech and Weiss [4].

2.2 FATTY ACID AND SURFACTANT TYPE GELATORS

Most of the earlier reports on organogelators deal with compounds that are derived from fatty acids or surfactants. A few examples are given in Figure 1. Compound **1** is an example of a fatty acid type of organogelator [8]. It forms thixotropic gels with organic solvents like benzene or chloroform. According to FT-IR measurements the gels are stabilized by intermolecular hydrogen bonds. The gels form a lyotropic mesophase and exhibit a supramolecular helical structure. Fluorocarbon-hydrocarbon diblock compounds **2** form gels with saturated and aromatic hydrocarbon solvents, whereas inverted micelles were formed in fluorinated solvents. The gelating capability and surfactant like behavior is contributed to the mutual solvophobicity of the hydrocarbon and fluorocarbon moiety [9,10]. The organogelator **3** is clear example of gelation of organic solvents by surfactant type of molecules [11,12]. A wide range of solvents can be gelled by this type of compounds and some of these compounds show polymorphic behavior.

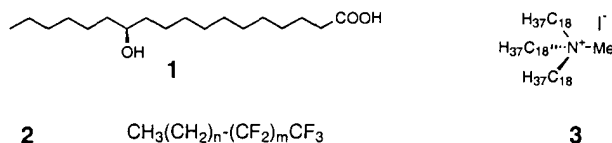


Figure 1 Fatty acid and surfactant type organogelators.

2.3 ANTHRACENE, ANTHRAQUINONE, TETRALINE AND STEROID DERIVATIVES

A well-studied group of organogelators are derived from anthracene and anthraquinone (**4,5**) [13], or steroids (**6**) [14], and include also compounds which contain both groups linked via a spacer (**7,8**) [15,16]. Other organogelators of this type are an azobenzene-steroid derivatives (**9**) [17] and a chiral tetraline derivative (**10**) [18]. Aggregation of these compounds is based upon π - π stacking and solvophobic effects. Figure 2 presents some examples.

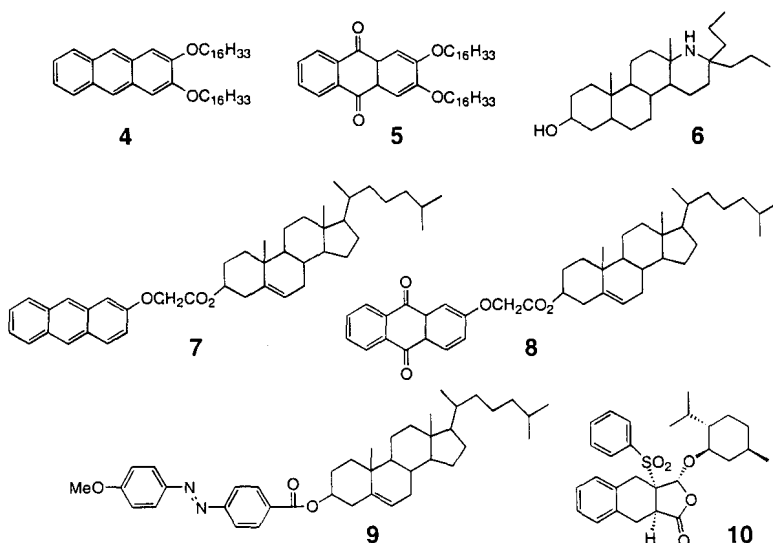


Figure 2 Anthracene, anthraquinone, tetraline, and steroid based organogelators.

Compound **5** forms thermoreversible gels in various aliphatic alcohols and amines at low concentrations. A three dimensional network is formed, which consists of assembled head-to-tail aggregates of the aromatic component with the solvent. The organization mainly depends on dipolar forces and π - π stacking. This compound is of special interest because of its photochromic properties.

The steroid derivative **6** was found to gelate only a few hydrocarbons. It aggregates into helical fibers, which intertwine at the junction zones thus forming a three dimensional network.

Compounds **7** and **8** are members of a family of gelators (ALS) in which an anthryl or anthraquinonyl group (A) is connected to a steroid (S) via a linker (L). Both form thermoreversible gels with a wide range of organic solvents. The stability of these gels depends on the concentration and structure of the gelator, as well as the properties of the solvent. The gel network consists of long intertwined fibers, which are built from several stacks of molecules. In these molecular stacks the anthryl or anthraquinonyl groups overlap. Some of their derivatives form luminescent gels.

Another steroid derivative is the azobenzene **9**, which is able to gelate a large variety of organic solvents. The thermoreversible gels are built from helical intertwining fibers. Furthermore, it was possible to switch reversibly from the gel to the sol phase by means of light. This transition could be read-out by means of CD-spectroscopy.

The chiral compound **10** was found by accident in our laboratory. It is able to gelate a series of alkanes and alcohols via π - π stacking. X-ray analysis indicated the formation of helical fibers, which formed a three dimensional network through the fluid as was shown by electron microscopy (EM).

2.4 METAL-BASED ORGANOGELOTORS

This class contains compounds for which gelation is induced by the formation of coordination complexes. Two examples are shown in Figure 3, however more compounds are known [19].

Compound **11** forms a gel with cyclohexane at room temperature. From small-angle neutron scattering (SANS) measurements it was found that the molecules are stacked on top of each other linked by axial copper-oxygen coordination bonds. The stacks consist of a polar core (copper and oxygen) surrounded by a hydrophobic shell (aliphatic tails). These stacks in turn are part of the three dimensional network which forms the gel.

Compounds **12a** and **12b** were found to gelate solvents like tetrahydrofuran, toluene and methanol at low concentrations [20]. The ligand itself does not gelate any solvent. Transmission electron microscopy proved that the gels consist of (helical) fibers. These fibers in turn can self-assemble into super helices.

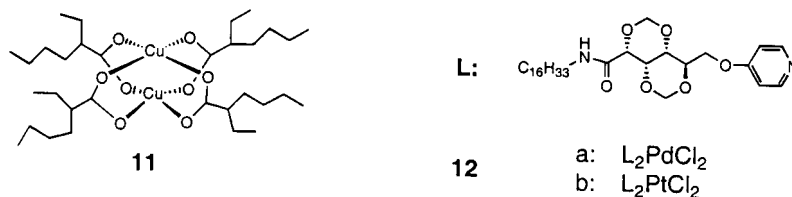


Figure 3 Metal-based gelators: **11** is a binuclear copper(II)-tetra(2-ethyl hexanoate) complex; **12a** and **12b** are Pd(II) or Pt(II) bis-gluconamide complexes, respectively.

2.5 AMIDE AND CARBOHYDRATE CONTAINING GELATORS

The gelators for which aggregation is best understood are those which are able to form highly directional hydrogen bonds. Among these are amino acid, amide and urea derivatives. A few examples are shown in Figure 4.

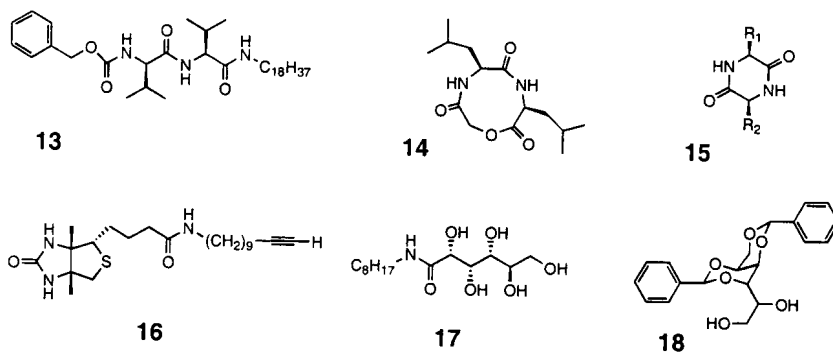


Figure 4 Amide and carbohydrate containing gelators

Compound **13** is a long-chain alkyl-amide derivative, which was found to gelate a wide range of solvents at low concentrations [21]. Infrared measurements proved that in the

gel the amide groups are intermolecular hydrogen bonded. It was found that some important factors for gelation are: the structure of the amino acid residue, optical activity and the balance between the hydrophilic amino acid residue and the lipophilic tail. From transmission electron microscopy (TEM) it was found that the gel consists of a network of fibers.

The depsipeptide **14** was found to gelate a few solvents, among which polar (MeCN) and apolar (Et₂O) solvents [22]. Because **14** does not dissolve in these solvents, a pre-solubilization step with a droplet of methanol is required. Recently it was found that the gelating structure was not the cyclic compound but its ring opened form.

The cyclic dipeptide **15** [23] contains two self-complementary hydrogen bonding sites and gelate a wide range of solvents. Many different R-groups are tolerated but optimal gelating properties were observed when R₁ and R₂ are different.

Compound **16** was found by chance to gelate a few organic solvents [24]. Several other derivatives were synthesized but the range of gelled solvents remained quite small. From ¹H-NMR spectroscopy it was found that gelation was induced by the formation of hydrogen bonds. For surfactant **17** the only organic solvent known to be gelled is *o*-xylene [25]. In these gels long fibers were observed, which consist of multiple concentrically stacked sheets. The fibers were stabilized by amide hydrogen bonds and solvophobic effects.

The benzylidene-sorbitol derivative **18** is one of the oldest organogelators known, and is capable of gelating many different organic solvents, ranging from heptane to DMSO and glycerol [26]. Recent investigations showed that only the pure enantiomer forms gels whereas the racemate crystallizes, and that both hydrogen bonding and π -stacking interactions are important for gelation [27]. In addition, D-glucose, D-galactose and D-mannose-benzylidene derivatives have recently been reported as potent organogelators [28], as well as a number of other compounds which gelate organic solvents via intermolecular hydrogen bonds [29,30,31,32, 33, 34].

2.6 TWO COMPONENT SYSTEMS

Some systems have been reported in which two different components are needed to obtain gelation (Figure 5).

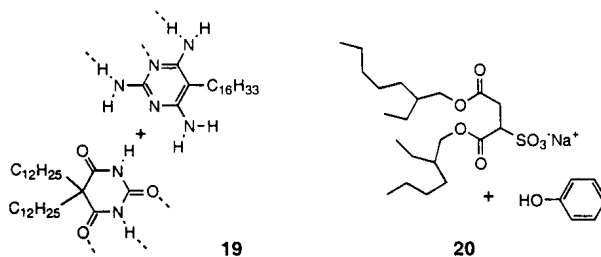


Figure 5 Two types of two component systems: **19** is an equimolar mixture of 5-hexadecyl-2,4,6-triaminopyrimidine with 5,5-didodecylbarbituric acid; **20** is an equimolar mixture of sodium bis(2-ethylhexyl)sulfosuccinate (AOT) with phenol.

System **19** forms gels with organic solvents resulting from the formation of hydrogen bonds between both molecules [35]. Long fibers are formed, which assemble into a three dimensional network through the fluid. Crystallization is avoided due to the flexibility of the long alkyl chains.

During investigations on reversed micelles of the surfactant AOT, system **20** was found to gelate organic solvents into completely clear gels [36]. Interestingly, these gels melt upon exposure to a trace of moisture. Also for this system formation of the gel results from hydrogen bond formation between the different molecules.

3 Design of Organogelators

3.1 DESIGN PRINCIPLES

For most compounds whose gelating properties have been accidentally discovered, the structure of the aggregates and mode of aggregation remains obscure. Many attempts to improve the performance of these gelators or to alter characteristics as solvent compatibility by structural modification of these gelators have failed, and have often been hampered by synthetic difficulties. In a different approach one can design new gelators for organic solvents, starting from criteria derived from some common features of known gelators [4]. In a proper design the geometry of the building blocks and the spatial arrangement and nature of the intermolecular bonds will determine the structure and properties of the supramolecular aggregate [6]. A priori knowledge of the possible modes of aggregation of the designed compounds offers a working model with which one can explain the successes and failures of gelation experiments and with which one can design new compounds.

In order to develop molecular design criteria one should consider the events and intermolecular interactions which occur during the process of gelation (Figure 6).

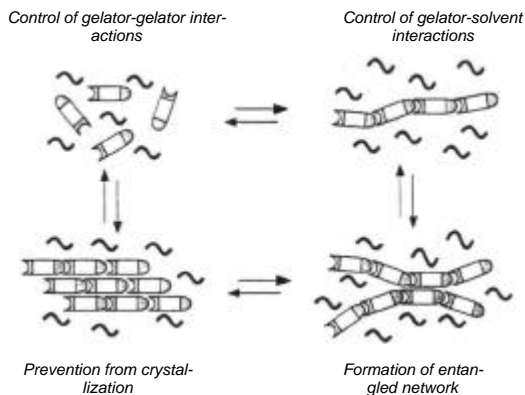


Figure 6 Schematic view of gelation of organic solvents by small organic molecules

The first step in the gelation process is most likely the self-assembly of the gelator molecules into extremely elongated and perhaps even one-dimensional aggregates [4]. These elongated or one-dimensional strands of gelator molecules subsequently assemble into fiber like structures, which in turn assemble into the three dimensional network in the liquid. The latter processes of fiber and network formation reflect a delicate balance between gelator-gelator interactions and gelator-solvent interactions: stronger gelator-gelator interactions induce stronger contacts between fibers which may lead to a more

dense network or even crystallization, whereas stronger gelator-solvent interactions might prohibit aggregation of strands into fibers and network.

Critical factors in the design of low molecular weight gelators are therefore [see also 37,38]: (i) fiber formation by control of an anisotropic growth process. Predominant self-assembly along one direction can be controlled by employing highly directional intermolecular interactions, like hydrogen bonding, π -stacking of arene moieties, and metal-ligand interactions. Simultaneously, self-assembly in the other directions should be less favorable. This can be achieved by using solvent-like moieties, *e.g.* aliphatic chains for hydrocarbon solvents. In an optimal case, such molecules will self-assemble into aggregates in which the strongly interacting groups are exposed at one face, whereas the solvent-interacting groups are exposed at the remaining interface of the fiber. As a result the interfacial free energy of the fiber will be highly anisotropic, which under kinetically controlled growth conditions will boost the one-dimensional shape of the fibers. (ii) Intertwining of the aggregates to form a three dimensional network. A few types of linking nodes have been distinguished [39], *e.g.* (pseudo)crystalline microdomains, entanglements or spatially limited organised microdomains. The formation and stability of such junctions zones are governed by a delicate balance between fiber-fiber and fiber-solvent interactions, and its understanding requires a detailed knowledge of the structure of the junction zones. It remains therefore the most difficult factor in the design of novel gelators. As an alternative, one can consider the use of non-covalent crosslinker molecules, which would allow a more direct control of the stability and number of the junctions via the nature and amount of the cross-linker. (iii) Crystallization of the self-assembled aggregates has to be precluded and therefore a delicate balance between order and disorder has to be found. Although it is obvious that a certain degree of (one-dimensional) order is required to achieve self-assembly in one direction, the packing should be far from ideal. Prevention of crystallization remains a little obscure in the design of new gelators and approaches that are used are to frustrate crystallization by certain peripheral groups, *e.g.* by the introduction of flexible or branched alkyl chains or to introduce (deliberately) a tendency to form polymorphic structures [23].

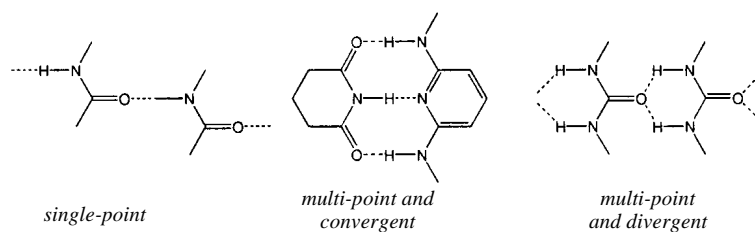


Figure 7 Topography of hydrogen bonded assemblies formed by an amide group, the complementary couple barbituric acid-diaminopyrimidine, and urea moieties.

There are numerous approaches to design molecules with self-complementary binding groups that can assemble into one, two or three-dimensional constructs [5,40]. The nature, orientation and the number of the interacting subunits present is essential for the size and shape that is found. Particular successful was the use of multiple hydrogen bonding in the self-assembly of macromolecule-like fibers [41,42], sheets [43,44], ribbons and rosettes [45,46,47], cages [48,49], and nanotubes [50]. Arrays of multiple hydrogen

bonds were obtained by employing *e.g.* amides, urea, guanines, barbiturates, and ureidopyrimidones. Some examples of amide and urea moieties with specific single- and multi-point interactions are shown in Figure 7.

Pertinent examples related to our work of control of molecular aggregation by the design of self-complementary sub-units involving multiple hydrogen bonds are shown in Figure 8. Hamilton and co-workers obtained linear rod-shaped structures in the solid state by triple hydrogen bonded interactions of the cyclohexane-1,3,5-triamide **21** [51]. Cyclohexane bis- and tris-alkylamide derivatives **22** and **23** were found by Hanabusa to be excellent gelators [37,52]. Compounds **22** and **23** are able to gelate a wide range of organic solvents into completely clear gels. Electron microscopy revealed that the gels exist of long fibers with a width of 40-70 nm. From FT-IR and molecular modelling studies it was deduced that the molecules form intermolecular hydrogen bonds which forces them to stack right on top of each other, most likely very similar to the hydrogen-bonded arrays in crystals of **21**. In gels of **23** close packing of the alkyl chains significantly enhances the stability of the hydrogen-bonded stacks, which makes this compound also a potent gelator for polar solvents.

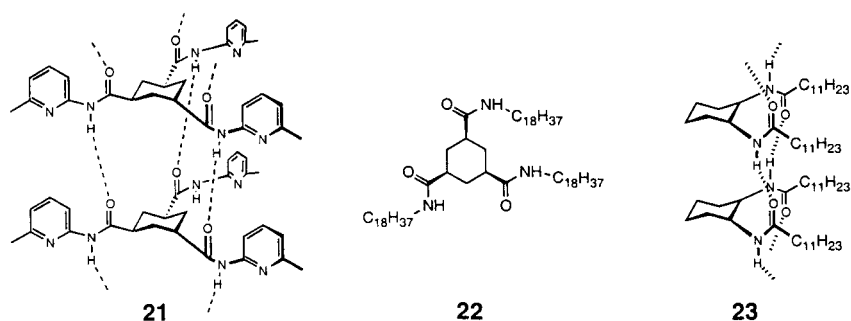


Figure 8 Hydrogen bonded stacks formed by cyclohexyl-amide derivatives.

3.2 LINEAR BIS-UREA GELATORS

A class of compounds particularly known to form extended one dimensional networks of hydrogen bonds are ureas. For instance, the hydrogen bond directed (co-)crystallization of diaryl-urea to form linear arrays has been demonstrated by Etter et al. [53]. A comparison of 27 crystal structures of simple urea compounds deposited in the Cambridge Structure Database revealed that urea groups preferentially form infinite hydrogen bonded arrays, the structure of which is very well maintained in the different crystals (Figure 9). The arrays have a planar structure with the carbonyl moieties all lying in one line.

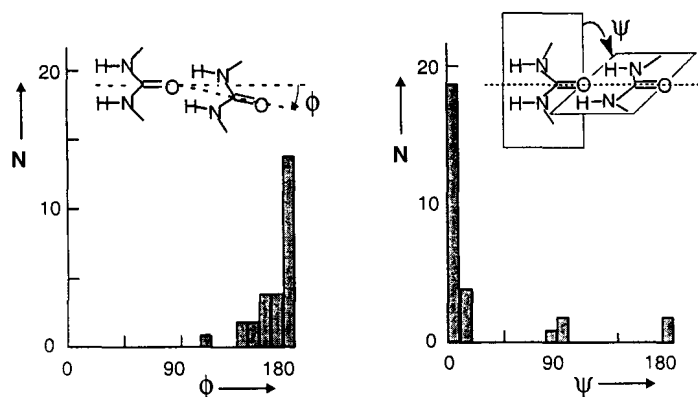


Figure 9 Geometry of hydrogen-bonded arrays of urea groups in crystal structures.

The well-defined geometry of aggregated ureas makes it an ideal group to be used as the main and highly directional interacting unit in the new gelators. An additional advantage is that substituted urea compounds can easily be prepared in high yields by the addition of amines to isocyanates (Figure 10) [54]. Many isocyanates are commercially available or are readily accessible from, for instance, carboxylic acids via the Curtius rearrangement of the corresponding azides.

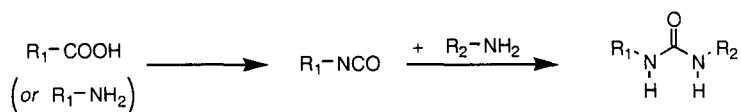


Figure 10 Synthesis of urea compounds

The capacity of urea groups to form extended chains of hydrogen bonds was explored by Hanabusa [55] and our group [38] in a new approach to design gelators and self-assembled nanosize structures. First we examined the gelating ability of some mono- and bis-urea compounds and quickly established that the presence of two urea groups in one molecule is a sufficient condition to enforce aggregation in dilute solutions of a range of organic solvents. When N-benzyl mono-urea **24** and N-benzyl bis-urea **25** and **26**, containing a long alkyl chain or alkyl spacer, respectively, are compared the advantage of the introduction of a second urea group becomes clear.

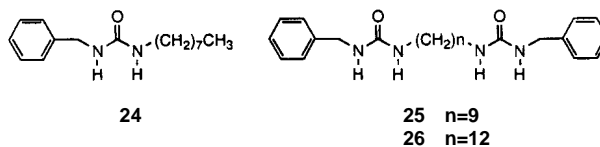


Figure 11 Mono- and linear bis-urea compounds tested for gelation.

Only in the case of **24** in hexadecane a gel was obtained. In all other solvents precipitation occurred after cooling of the solutions to room temperature. On the other hand the bis-urea compounds **25** and **26** are potent gelators for a wide range of solvents

(Table 1). Although sparingly soluble at room temperature they gradually dissolve upon heating and form gels upon cooling. Notable features are: (i) these gels are stable for at least weeks when stored at room temperature; (ii) gel formation is completely reversible; (iii) only very low amounts are needed for gelation (typical critical gelation concentrations are <1 (w/v)%); (iv) decreasing the spacer length between the urea groups to $n=3, 4$ or 6 makes solutions of these compounds less susceptible to gelation.

The concept of aggregation of bis-urea appears to be quite general and extremely powerful in the design of new self-assembled fibers, tapes and networks. General structural features are two urea units connected by a spacer and decorated with pending groups on each side. Upon aggregation a linear strand of bis-urea can be formed in which each molecule can form up to eight hydrogen bonds with neighboring groups in the aggregates (Figure 12).

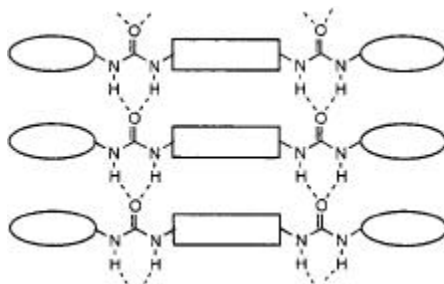


Figure 12 Schematic representation of hydrogen bonded stack of linear bis-urea gelators.

Figure 13 shows a number of bis-urea compounds, that were prepared from the corresponding isocyanates and bisamines, which are not only capable of aggregation but are also illustrative for the possibility to tune the assembly process via simple structural modifications [38]. The ability of the bis-urea compounds to act as gelators is shown in Table 1. The minimum gelation concentration for a typical example like **28** is remarkably low ($3\text{mg}\cdot\text{ml}^{-1}$) and is independent of the solvent that is gelled. When the dodecyl side chain is replaced by a more sterically demanding group or the alkyl linker is replaced by a shorter or a more rigid linker the gelating abilities change.

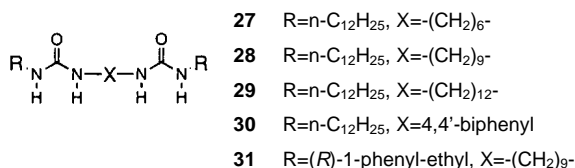


Figure 13 Linear bis-urea compounds

Some characteristic features of these gels need to be emphasized. The bis-urea form transparent gels with aromatic solvents like *p*-xylene or tetralin but with other solvents turbidity is observed. Although the gels formed by these linear bis-urea compounds are stable for months they are irreversibly disrupted by mechanical agitation. The gelation process is however thermoreversible. The melting temperatures of the gels increase with increasing concentration but level off at higher concentrations. FTIR spectra of dried gels of **28** and **29** show amide bands at 1616 cm^{-1} and 1575 cm^{-1} and a NH stretch

vibration at 3337 cm^{-1} which are characteristic of the presence of hydrogen bonded urea groups [56]. A broad endotherm with a maximum at 125°C for the same gel, measured by differential scanning calorimetry, points to a less cooperative phase transition.

TABLE 1 Gelating capability of linear bis-urea compounds [a]

	hexadecane	p-xylene	1-octanol	n-butyl acetate	cyclohexanone	tetralin
25	i	g(10)	g(10)	p	g	g(7)
26	i	p	g(10)	-	-	g(6)
27	p	p	p	p	p	g
28	g(3)	g(3)	p	g(3)	g(3)	g(3)
29	g	g	p	p	g	g
30	i	g	p	p	p	g
31	p	p	p	p	p	g

[a] The following abbreviations are used: g: gelation (minimum gelation concentration at 20°C in mg compound / ml solvent); i: insoluble at solvent reflux temperature; p: precipitate.

The structures of the aggregates depend on the type of gelator and the solvent. Figure 14 shows typical light microscopy photographs of the entangled networks of fiber-like structures present in gels of **28** and tetralin and butyl acetate, respectively. The fibers are only $2\text{-}5\ \mu\text{m}$ thick but can be as long as $300\text{-}400\ \mu\text{m}$. The strong birefringence of the fibers indicate that they consist of well-ordered arrays of molecules. Furthermore the elongated shape of the fibers must be the result of a strong anisotropic growth again pointing to well ordered molecular aggregation. The single fibers show repetitions of strong birefringent regions indicating that the fibers are highly twisted. Both the width of the fibers and the degree of twisting depend on the structure of the gelator as well as the solvent. For instance fibers of **29** are somewhat broader than those formed by **28** and fibers in butyl acetate are more strongly twisted than those in tetralin.

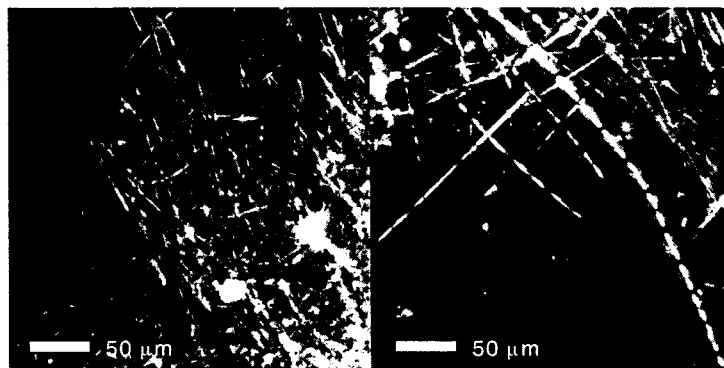


Figure 14 Light-microscopy of a gel of **28** in tetralin (left) and butyl acetate (right).

Further information on the organization within the fibers was obtained by electron microscopy (EM) and X-ray powder diffraction. Figure 15a shows an EM picture of a gel of **28** in tetralin clearly indicating that the fibers have a multilayered structure.

Typically 5-20 sheets are stacked in a single fiber. Based on EM data the thickness of a single sheet was estimated to be approximately 5 nm. Powder diffraction of gels of **28** and **29**, after most of the solvent was removed, confirmed a lamellar structure with spacings of 3.65-3.89 nm. Figure 15b shows a single fiber in a gel of **28** in hexadecane. It is clearly seen that the twisted structure observed in the light micrographs is a single turn of the sheets along the long axis of the fiber. Twisting has been observed in other fiber type aggregates, but the mechanism that is responsible for the formation of the twists in the fibers is not clear [25,57]. Most likely the formation of twists is driven by a reduction of the interfacial free energy, in which view a preferred screw sense can be explained by an anisotropy of the interfacial free energy in aggregates of chiral molecules. Obviously, such a preference for left- or right-handed twists was not observed for fibers of non-chiral bis-urea molecules as shown here.

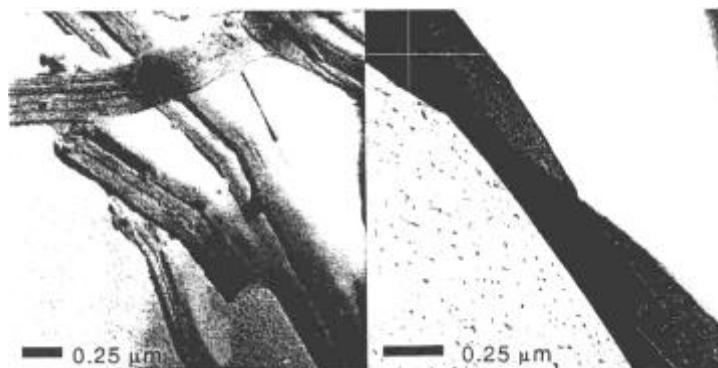


Figure 15 Electron microscopy of a gel of **28** in tetralin (left) and *n*-hexadecane (right).

A schematic view of the molecular arrangement of the bis-urea gelators, based on cumulative evidence as summarized above, is given in Figure 16. In this model the bis-urea molecules aggregate through hydrogen bond formation into strands or ribbons which assemble into sheets. Several sheets stack to form the twisted long thin fibers observed by light microscopy. It should be noted that in the sheets the ribbons are tilted.



Figure 16 Proposed arrangement of linear bis-urea compounds in sheets and fibers.

Scanning tunneling microscopy (STM) provides a powerful tool to study the two dimensional organization of molecules physisorbed on a conductive surface [see for instance 58]. The structure of layers of the bis-urea gelators deposited on graphite was studied to gain a more detailed information on the organization on the molecular level. Monolayers of linear bis-urea physisorbed at the graphite/octanol interface imaged by

STM revealed a closely packed arrangement on the graphite surface with sub-molecular resolution [38a,59]. Figure 17 shows a typical STM image of an ordered monolayer of **27** and a two dimensional packing model with the ribbons formed by linear aggregation of bis-urea molecules.

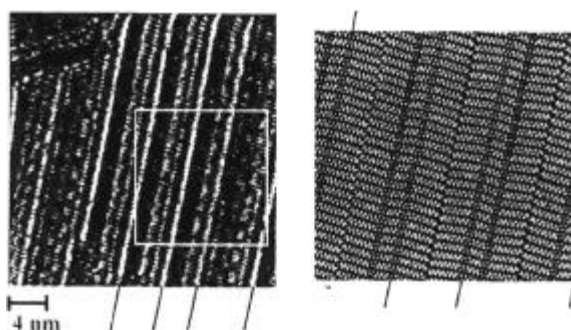


Figure 17 STM micrograph of **27** physisorbed on graphite (left) and molecular packing model of the square region (right).

A more detailed arrangement of the bis-urea molecules is seen in Figure 18. Within one ribbon the darker region corresponding with the hexyl-spacer is flanked by urea moieties but with distinct contrasts. One chain of urea appears as bright spots whereas the other chain appears as a row of relatively dark spots. Realizing that a bis-urea with a spacer containing an *even number* of methylene groups, *i.e.* **27** with a hexyl spacer, in an *all-trans* configuration adopt a kinked structure on the surface, the difference in contrast points to an antiparallel orientation of the urea groups in a single ribbon. This means that on the molecular level a distinction can be made between two similar functional groups which have a different orientation in self-assembled aggregate.

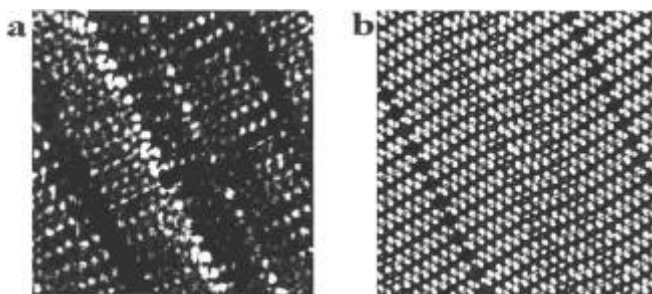


Figure 18 STM micrograph of **27** physisorbed on graphite (a) and molecular packing model (b).

Fascinating is also the observation at the molecular level of a change in organization upon subtle change in the structure of the bis-urea compound. In Figure 19 the STM image of bis-urea **28** with a nonane spacer is shown. Again ribbons are seen as well as defects in the two dimensional pattern. Some ribbons are characterized by bright spots of both urea moieties whereas in other ribbons the urea groups appear almost as dark as the alkyl groups. The different types of ribbons appear to coexist randomly, but within one

ribbon the two chains of urea groups always have the same contrast. This is in perfect agreement with an all-trans minimum energy conformation of two urea groups separated by an odd number of methylene groups, *i.e.* as in **28** with a nonane spacer, in which both carbonyl groups point in the same direction and the molecule adopt a bend shape. A bend structure was indeed observed. Comparison of ribbons with opposite contrast with regard to the urea groups show that the ribbons are mirror images with the urea groups pointing in opposite directions. The distance of 0.462 ± 0.005 nm between two neighboring molecules within a ribbon corresponds very well with the distances found for hydrogen bonded urea moieties. The width of a ribbon (5.0 ± 0.1 nm) corresponds with the length of a single bis-urea molecule.

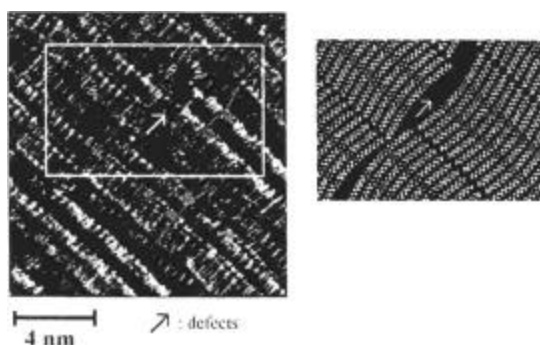


Figure 19 STM micrograph of **28** physisorbed on graphite (left), and molecular packing model of the rectangular region (right).

It should be emphasized that on comparison of the width of the ribbons on graphite (5.0 nm based on STM) with the thickness of the sheets observed in the gels (3.65 nm based on X-ray diffraction) of the same bis-urea compound that these are related but not identical structures. A rationale is provided by a model (Figure 16) in which a sheet consist of a stack of ribbons which are tilted by approximately 45° . Further support for the arrangement shown in Figure 16 came from molecular dynamics simulations. Figure 20 shows a snapshot taken from a 200 ps molecular dynamics simulation of a rectangular box with 64 molecules of **28** arranged in 8 parallel stacked ribbons. The simulations converged to a structure in which a sheet has a thickness of 4.1 nm and the ribbons are spaced by 0.4 nm and make a tilt angle of 54° with the surface of the sheet. This arrangement is in good agreement with X-ray data.

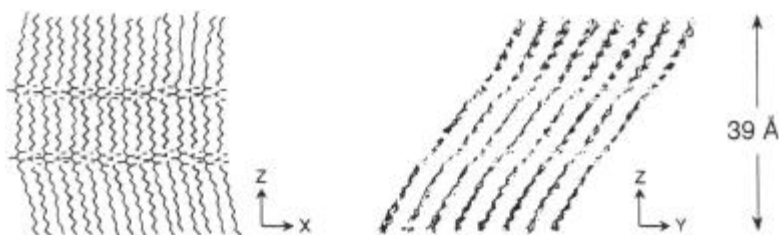


Figure 20 Snapshot from a 100 ps MD simulation (300 K, NPT) of a box containing 64 molecules of **28**, showing two ribbons each consisting of 8 molecules of **28** (left, view along y-axis, the other ribbons are omitted for clarity), and a stack of 8 ribbons forming a sheet (right, view along x-axis).

Our studies clearly show the potential of linear bis-urea in the control of molecular assemblies. For instance the intermolecular organization in a tape can be controlled by the spacer whereas the width of the tape and the interaction between different tapes might be governed by the flanking moieties, providing thus an excellent framework for the spatial organization of functional entities.

3.3 CONFORMATIONALLY CONSTRAINED BIS-UREA GELATORS

Structural studies on the micrometer long fibers of bis-urea, in which the urea groups are connected by linear alkyl spacers, indicate that in addition to hydrogen bonding the regular packing of the alkyl chains causes the formation of the well ordered structures. When the packing of the alkyl chains is distorted as in the case of non-symmetric bis-urea (Figure 21a, $R_1 \neq R_2$) less regular two dimensional structures are obtained. This behavior can be related to the conformational flexibility of the linker between two urea moieties allowing each urea group to aggregate in a particular direction.

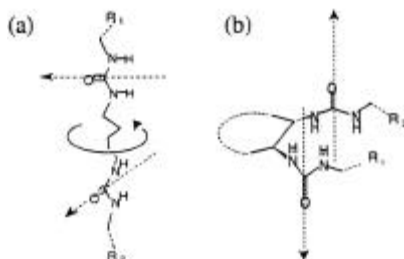


Figure 21 Hydrogen bonding directionality of bis-urea compounds with a flexible linker (a) and with a conformationally constrained linker (b).

When the conformational flexibility of the linker is reduced as shown in Figure 21b the urea groups can have a coplanar orientation and aggregation along one direction is enforced. Semi-rigid bis-urea based on *trans*-1,2-bis(ureido)cyclohexane, 1,2-bis(ureido)benzene and a geminal bis(ureido)-compound are shown in Figure 22. The antiparallel orientation of the urea groups and the different geometries due to the change in bridging unit are evident.

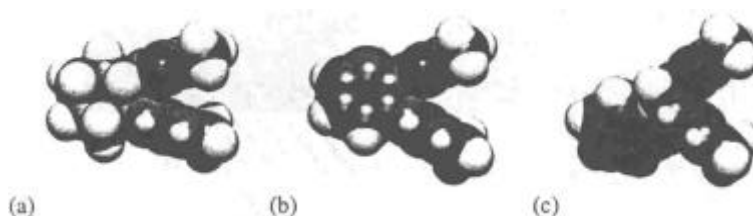


Figure 22 CPK models of 1,2-*trans*-bis(3-methylureido)cyclohexane (a), 1,2-bis(3-methylureido)benzene (b), and 1,1-bis(3-methylureido)-1-phenyl-methane (c).

One of the three main conformations of (*S,S*)-*trans*-1,2-bis(methylureido)cyclohexane, obtained by molecular modeling studies, is shown in Figure 23. The urea groups have a coplanar orientation but the urea groups point in opposite directions (antiparallel

conformation). Based on docking experiments it was established that the preferred sites of interaction are located above and below the urea groups (Figure 23b) [60]. Apparently, non-covalent interactions (hydrogen bond formation) between these molecules are highly anisotropic in accordance with our expectations based on the design of these systems and therefore aggregation along one direction is highly favored over other directions.

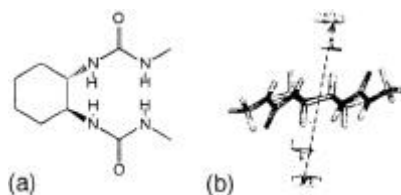


Figure 23 Structure of the model compound *trans*-1,2-bis-(*N*-methylureido)-cyclohexane (a), and energy minimized conformation of *trans*-1,2-bis-(*N*-methylureido)-cyclohexane with an antiparallel orientation of the urea groups (b). The shaded areas in (b) are the contour levels for a interaction energy of -80 kJ/mol with a second molecule of 1,2-bis-(*N*-methylureido)-cyclohexane.

The line through the most favorable sites of interaction defines the primary axis along which one dimensional aggregation most likely will take place. Molecular modeling revealed that indeed the formation of one dimensional aggregates is strongly favored by 108-122 kJ/mol relative to the most stable monomer conformation (Figure 24). In the aggregates the molecules are translated by 4.4-4.5 Å. The antiparallel conformer of the bis-urea give a translational aggregate that is stabilized by the maximum number of eight hydrogen bonds for each monomer. Surprisingly, a comparable stability was found for the screw-axis aggregate formed from the monomer with a parallel conformation of the urea groups, despite the lower stability for the parallel orientation of the urea groups in the monomer.

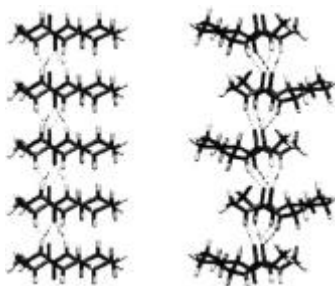


Figure 24 Two possible hydrogen bonded aggregates of *trans*-1,2-bis-(*N*-methylureido)-cyclohexane: (a) translational aggregate with urea groups antiparallel, and (b) screw axis or glide plane aggregate with urea groups parallel.

An important result from the modeling studies is that replacement of the methyl groups on the urea groups with longer or even branched alkyl chains does not distort the hydrogen bonding pattern which stabilizes the one-dimensional aggregates. Similar

molecular modeling experiments with 1,2-bis(methylureido)benzene gave comparable results and again one dimensional aggregates are relatively stable.

A variety of cyclohexyl- and phenyl- bis-urea compounds were indeed found to be potent gelators of organic solvents [60]. Typical examples of these gelators are shown in Figure 25 and some gelation properties and minimum gelation concentrations are given in Table 2. It is clear that a wide range of apolar and polar organic solvents can be gelled. The cyclohexyl-based compounds readily gelate aliphatic and aromatic hydrocarbons, but except for **32**, are not effective in the gelation of solvents that strongly compete for hydrogen bond formation like lower alcohols and DMSO in accordance with results from Hanabusa [55]. The gelating capability does not seem to depend much on the peripheral R- groups both for the cyclohexyl- and the phenyl- based systems.

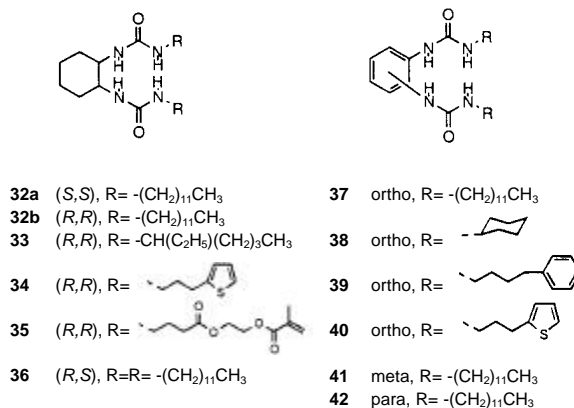


Figure 25

Again it is seen that the geometry of the bis-urea is essential for the self-assembly process as the cis-cyclohexyl analogue, with two adjacent urea moieties in an axial and equatorial orientation (in the chair conformation), does not lead to gelation. Similar the ortho-bis-ureido-phenyl moiety is essential for gelation whereas the meta- and para-substituted analogues fail to gelate any of the investigated solvents.

Furthermore there are some clear differences between cyclohexyl-based and phenyl-based gelators. Whereas gels of the first class are stable for months without any deterioration gels of the latter class show only limited stability. Similar trends are seen when solvent compatibility and minimum gelation concentrations are compared. The cyclohexyl-based compounds gelate a wider range of solvents and in most cases the minimum gelation concentrations required are lower. Again these gels are fully thermoreversible. A fascinating property of many gels of these bis-urea compounds is that they are thixotropic; a process that appears also to be fully reversible.

Infrared, DSC and small angle X-ray scattering (SAXS) studies on these gels reveal that aggregation is accompanied by the formation of hydrogen bonded networks, that highly cooperative and less cooperative phase transitions can occur prior to melting of the gels and that thermotropic polymorphism depends on the gelator-solvent combination.

TABLE 2A Gelation properties of cyclohexyl bis-urea derivatives [a]

<i>solvent</i>	32 ^[b]	33	34	35	36
hexadecane	<10	<2	<2	p	p
cyclohexane	<2	<2	p	<2	vs
toluene	<2	<2	<10	<2	vs
p-xylene	<5	<2	<10	<2	vs
n-butyl acetate	<10	<2	p	<2	p
cyclohexanone	<2	<5	<10	<2	s
1,2-dichloroethane	<2	<2	<2	<20	p
dimethyl sulfoxide	<5	<10	s	p	p
ethanol	<2	s	s	p	s
2-propanol	<2	s	s	p	s

TABLE 2B Gelation properties of phenyl bis-urea derivatives [a]

<i>solvent</i>	37	38	39	40	41	42
hexadecane	<2	p	<10	p	<2	I
cyclohexane	<2	I	i	i	p	I
toluene	<2	<10	<2	<5	p	I
p-xylene	<2	p	<5	p	p	I
n-butyl acetate	p	p	p	p	p	I
cyclohexanone	s	<10	s	s	p	p
1,2-dichloroethane	p	<2	<5	<5	p	I
dimethyl sulfoxide	<5	s	s	s	p	p
ethanol	p	s	s	s	p	p
2-propanol	s	s	s	s	p	p

[a] The following abbreviations are used: gelation: g(minimum gelation concentration in mg compound /mL solvent); insoluble at solvent reflux temperature: i; precipitate: p; soluble at room temperature (solubility > 20 mg/mL): s; viscous solution: vs. [b] The same results were obtained for **32a** and **32b**.

Long thin fibers which form entangled networks are observed for both types of gelators by EM. The morphology show a regular shape with an extreme aspect ratio which must arise from a strong anisotropic growth process and indicating that the fibers have a well ordered molecular packing. From the pictures in Figure 26 it is clear that structural differences have a large effect on the morphology. Compound **32** forms in p-xylene untwisted thin but highly flexible straight fibers. Fibers of **33** have a less regular structure and are strongly twisted but both types of fibers are flat and consist of stacks of smaller fibers. The diameter of the smallest entity which can be distinguished is 30-50 nm and 15-25 nm, respectively, which is an order of magnitude larger than the molecular dimensions of **32** and **33**. The phenyl-bis-urea **37** and **39** also form fibers but now many thin fibers can be distinguished with diameters as small as 2-4 nm, which are comparable to the molecular dimensions. Small fibers also appear to fuse to form sheets which stack into layered structures. The calculated thickness of a single sheet was approximately 3-5 nm. There is also a clear change in morphology of the fibers depending on the solvent. Since X-ray diffraction points to the same molecular

arrangement in the fibers, the different morphologies should originate from differences in interfacial energy or attachment energies in the various solvents.

From the EM micrographs in Figure 26 it is clear that both type of gelators form entangled networks and many intertwined and fused fibers are observed. Similar structural features are often observed as junction zones in gels of (bio)-polymers [39]. It has been argued that thixotropy is related to reversible disruption and formation of junction zones [61]. Their presence might therefore explain the thixotropic behavior found with these gelators. In contrast, intertwined structures were not observed in gels of linear bis-urea and in accordance with the rational given above gels of linear bis-urea are not thixotropic and are easily irreversible destroyed by mechanical agitation.

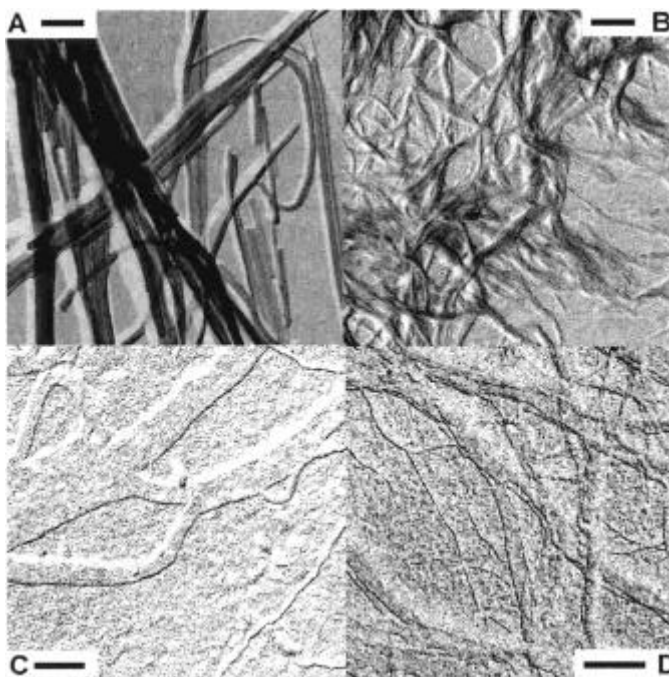


Figure 26 Electron micrographs of **32a** in *p*-xylene (A, 3 mg/mL, Pt shadow 45°, bar = 500 nm), **33** in *p*-xylene (B, 3 mg/mL, Pt shadow 45°, bar = 500 nm), **37** in *p*-xylene (C, 3 mg/mL, Pt shadow 10°, bar = 100 nm), and **39** in toluene (D, 3 mg/mL, Pt shadow 10°, bar = 200 nm).

The chirality of the gelator molecules is an intriguing aspect in view of the organization in self-assembled aggregates. The cyclohexyl-based bis-urea gelators have two stereogenic centers but rather to our surprise, the chirality is expressed at the supramolecular level only in a few cases. Only for gels of in ethanol a clear twist of the fibers is observed in the electron micrographs. Thus for (*S,S*)-**32** right handed helices are observed whereas for (*R,R*)-**32** left-handed helices are found (Figure 27). Apparently the screw-sense of the helices is related to the handedness of the gelator molecules but the pitch is not regular. This indicates that the twists do not arise from a helical arrangement at the molecular level but more likely are the result of the anisotropy of the interfacial energy.

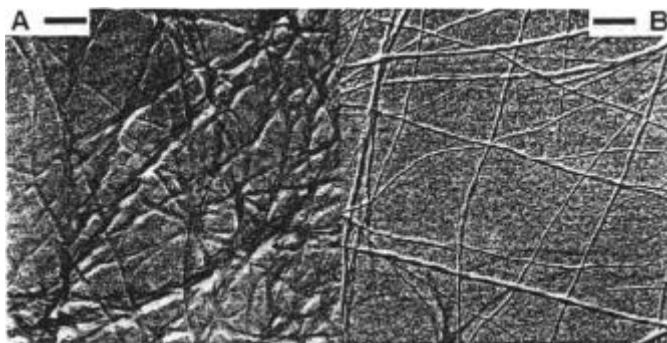


Figure 27 Electron micrographs of **32a** in ethanol (A, 3 mg/mL, Pt shadow 45°, bar = 200 nm) and of **32b** in ethanol (B, 3 mg/mL, Pt shadow 45°, bar = 500 nm).

X-ray diffraction measurements showed that many of the 1,2-cyclohexyl- and 1,2-phenyl-bis-urea based gels have a lamellar structure. This is in excellent agreement with the electron microscopic observations (*vide infra*), which showed that the fibers are build up of sheets with a thickness which nicely corresponds to the spacing of the lamella. As has been discussed above, the electron micrographs have revealed that the sheets consist of thin strands of only 2–4 nm thick, and the long axis of the strands runs parallel with the fiber long axis. Apparently, the fibers consist of closely packed hydrogen bonded arrays of bis-urea gelators. Within such an arrangement, however, different molecular packings are possible, as SAXS measurements of **37** and **40** provide clear evidence of polymorphism. Polymorphism can be related to different packings of strands of the gelator molecules, e.g. in a rectangular lattice or a hexagonal lattice, but it can also be the result of different arrangements of the bis-urea gelator molecules in each strand. For instance, in crystals of **40**, the two urea moieties in each molecule have a parallel orientation, and the hydrogen bonded aggregate is build up by a glide plane. Molecular modeling showed, as already has been discussed above, that other arrangements, *i.e.* translational or screw aggregate of the parallel conformation of the 1,2-bis(ureido)benzene moiety, or aggregates built up from the antiparallel conformation of 1,2-bis(ureido)benzene via translation or inversion operations, are equally stable within a window of 8 kJ/mol. For gelators **37–40**, based on the data yet available, we cannot determine which of these arrangements dominate in gels of these compounds, and probably two or more of these structures coexist in gels.

For the 1,2-bis(ureido)cyclohexane based gelators the number of possible arrangements is limited, because these molecules are *chiral* and *non-racemic*, and therefore aggregates can only be constructed by application of translation or screw axis operations. Molecular modeling studies showed that translational aggregates built up from molecules with the urea groups in an antiparallel conformation and screw axis constructed from molecules with the urea groups in a parallel conformation are equally stable (see Figure 24). Two possible lamellar arrangements of molecules of **32** are depicted in Figure 28. In the translational aggregate, hydrogen bonding between the two 1,2-bis(ureido)cyclohexane moieties allows for a close packing of the alkyl chains. For the screw axis aggregate close packing can only be achieved by intercalation. The experimentally observed spacing of lamella of **32** (31.5 Å) does however, neither fit with a single layer structure nor with an intercalated structure. A more likely arrangement of molecules of **32** in lamella is in a double layered structure (Figure 28) in which a tilt of

the molecules can explain the discrepancy between the theoretical width of 42 Å and the observed spacing of 31.5 Å, although other arrangements can not be excluded.

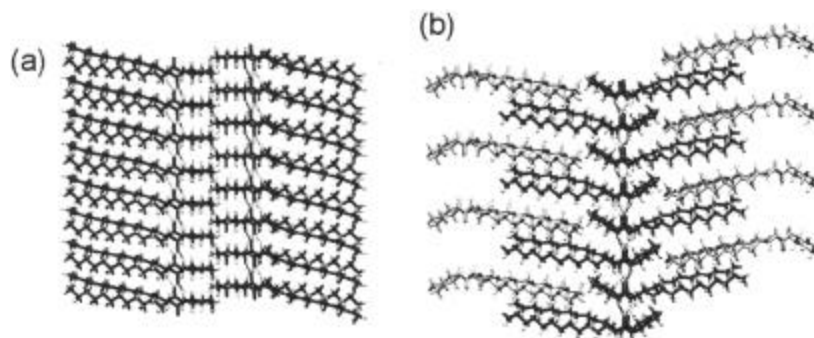


Figure 28 Tentative arrangement of **32** in a double layer structure, constructed from translational aggregates (a), and an intercalated layer structure constructed from screw aggregates (b).

It is evident that starting from molecules which preferentially self-assemble in one dimension, we have succeeded in the design of new gelators for organic solvents. The derivatives of 1,2-bis(ureido)benzene and trans-1,2-bis(ureido)cyclohexane presented here are very potent gelators for a wide range of organic solvents. Although the morphology of the fibrous network within the gels depends both on the nature of the substituents on the urea groups and on the solvent, the molecular arrangement of these bis-urea compounds is dominated by intermolecular hydrogen bond formation between the urea moieties. These one dimensional strands of hydrogen bonded bis-urea compounds assemble into sheets and lamella, which in turn stack into fiber like structures. To what extent this secondary assembly process has taken place is determined by the interfacial energy of the strands, which mainly depends on the nature of the substituents and on the solvent. As a result, these bis-urea compounds display a rich variety of morphologies.

The bis-urea compounds presented have many properties in common with other gelators. They are, however, very easy to synthesize, and many structural variations are possible without losing the gelating ability. For these reasons, the bis-urea compounds are not only excellent model compounds to study gelation phenomena in more detail, but also are excellent building blocks for the development of functional gels.

4 Towards Functional Organogelators

Many applications of gels are based on the coexistence of a three dimensional network structure and a liquid phase [1,3]. For instance, gels with a well-defined pore size are used in separation processes, and the limited diffusion in gels has been exploited for drug delivery systems. Gels with entrapped catalysts or receptors are receiving much interest in catalysis and sensor technology [62]. An exciting new development are 'smart gels', *i.e.* gels which respond to external stimuli by a change of their elasticity, size, or shape [63]. Most of these applications requires the incorporation of functional entities into the gels. In macromolecular gels this is often achieved via less selective methods,

such as physical entrapment within the porous network structure or via covalent linkage of the active species to the polymer backbone. Organogels, however, have some unique features that clearly distinguish them from other gel systems: (i) the gelation process, starting with self-assembly in an isotropic solution of the gelator, up to the formation of a network structure, is completely reversible, and (ii) the self-assembly process leads to well ordered arrays of molecules, up to a length scale of micrometers, whereby the precise molecular arrangement is determined by the molecular structure of the individual molecules. These special features of organogels make them excellent systems for the development of functional gels. It is obvious that smart gels or responsive gels will greatly benefit from the dynamic and reversible formation of organogels. Also many applications will have great advantage from a well-defined spatial arrangement of the functional species within the gels. For instance, the selectivity of recognition processes will increase if receptor sites are embedded in a well-ordered matrix, and signal transduction chains will only function if the individual segments are properly aligned.

Very recently, a peptide consisting of a 24 amino acid sequence with a high propensity to form a β -sheet structure was found to form temperature and pH responsive gels in aqueous solution [64]. The first report on responsive organogels was, however, from Shinkai's group [17,65]. They prepared cholesterol-based organogelators with covalently attached azo-benzene (**9**) or crown ether moieties as light or metal responsive functions (Figure 29). The azobenzene containing organogelator **9** forms thermoreversible gels with a range of organic solvents, including aliphatic hydrocarbons, esters, alcohols, and amides, at concentrations well below 1 (w/v)%. For crown-ether containing compound **43** the gelating capability is limited to some aliphatic hydrocarbons. It was, however, found that the thermal stability of the gels strongly depend on cation complexation by the crown-ether moiety, and thus in principle represent a cation-responsive gel system. Compound **9** is not only a much better gelator, it was also found that the thermal stability of gels strongly depend on the conformation of the photo-isomerizable azo unit: gels of *trans*-**9** have a gel-sol transition temperature of 16°C whereas the melting temperature of gels of *cis*-**9** is well below 2°C. Most interestingly, by alternate irradiation at 10°C with UV and visible light a reversible switching between a gel of *trans*-**9** and a solution of *cis*-**9** has been achieved.

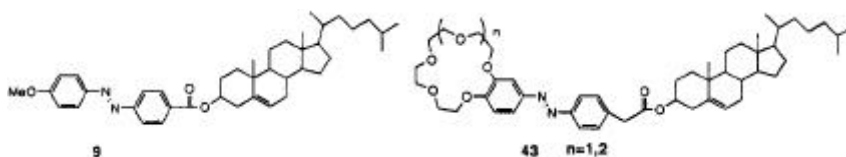


Figure 29

Other examples of functional organogel systems include for instance mesogenic derivatives of cyclohexyl bis-amide **23** which form novel liquid crystalline materials with nematic liquids [66], and the tetraoctadecylammonium bromide (like **3**) and the metal-containing gluconamides **12** which were able to gelate monomers as styrene and methacrylates and were used to prepare nanoporous membranes and for polymer imprinting [67,20].

A novel approach to polymerized gel systems has been followed by our group. Based on the design principles described in the previous section, we successfully prepared a new polymerizable bis-urea gelator **35**, which is capable of gelating a many different organic solvents [68]. On the other hand, the bis-amide derivative does not gel

any of the solvents investigated, indicating that the stronger hydrogen bonding urea groups are essential for gelation. Before polymerization, **35** forms thermoreversible gels which melt at temperatures below 100°C. Effective polymerization of gels of **35** was achieved by UV irradiation in the presence of a photo-initiator. Electron microscopy showed that the polymerized gels consist of a network of very thin fibers, which occasionally fuse and intertwine (Figure 30). Remarkably, after polymerization the gels are now stable up to at least 135°C, at which temperature the gels still did not show any sign of melting or shrinking. The solvent can be removed by freeze drying without causing collapse of the gel, yielding a white brittle material with a very low density, having all the characteristics of an organic aerogel.

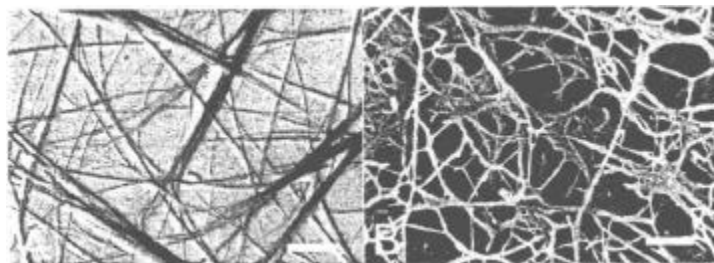


Figure 30 Transmission electron micrograph of a butyl acetate gel of **35** before polymerization (A, 5 mg/ml, Pt shadowed, bar = 1 μm), and scanning electron micrograph of a benzene gel of **35** after irradiation for 1 h (B, 5 mg/ml, Pt coated, bar = 0.4 μm).

5 Concluding remarks

During the last decade, the field of organogelators has rapidly developed from being guided by serendipity, towards a rich area of science, in which principles from supramolecular chemistry, macromolecular science, and colloid physics merge together. It has become clear that the gelation of organic solvents by low molecular weight organic compounds is an example of supramolecular organization par excellence. A better understanding of the structure of organogels and the mechanism of gelation will facilitate their application and will allow the development of new gelators with novel properties. Many applications of functionalized gels in catalysis, sensors, molecular electronics and material science are within reach, and especially switchable organogelators offers exciting prospects for the development of responsive (smart) gel systems.

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