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Water Gelation by Small Organic Molecules

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1. Introduction

The discovery and design of small organic molecules capable of gelling aqueous solvents (hydrogelators) is a rapidly expanding area of research, in particular due to their possible practical applications in tissue engineering,[1] vehicles for controlled drug release,[2,3] and pollutant capture and removal.[4] Low-molecular-weight hydrogelators offer several advantages to the currently more prevalent polymer gels. For biological applications, a constant challenge is finding biodegradable polymers to use for controlled drug release.[5] Many small molecule gelators could overcome this problem, since they are derived from biocompatible components and are held together by noncovalent forces, making them easier for the body to degrade. In addition, the diversity of functionality available in the synthesis of gelators opens up the possibility of incorporating the drug directly into the gelling component without needing to capture it.[2]

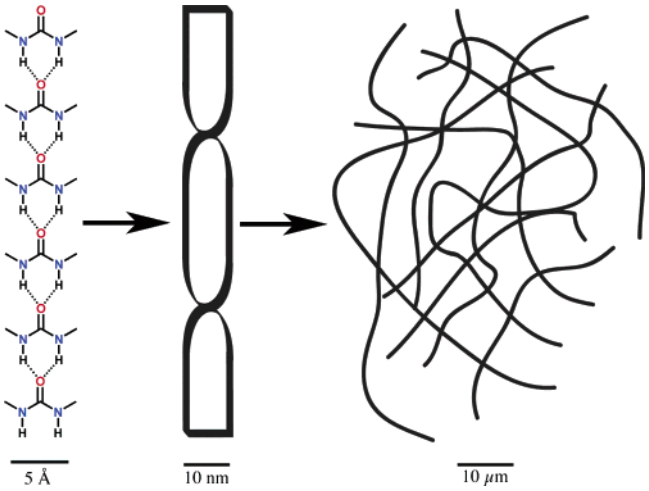

Figure 1. The primary, secondary, and tertiary structure of a self-assembled physical gel.

Flory defined a gel as a two-component, colloidal dispersion with a continuous structure with macroscopic dimensions that is permanent on the time scale of the experiment and is solidlike in its rheological behavior.[6] Usually, gels are formed by dissolving a small amount (usually 0.1−10 wt %) of gelator in hot solvent (water for hydrogels).[7] Upon cooling below the T_{gel} (temperature of gelation), the complete volume of solvent is immobilized and can support its own weight without collapsing (often tested by turning the test tube upside down; if no flow is observed, the solution is said to have gelled).

The phenomenon of gelation is thought to arise from fibers (nano- to micrometer) becoming entangled and trapping solvent via surface tension.[6,8−10] To understand the mechanism of gel formation, a gel can be broken down into a primary, secondary, and tertiary structure, much like a protein (Figure 1).[11,12] The primary structure (angstrom to nanometer scale) is determined by the molecular level recognition

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events that promote anisotropic aggregation in one or two dimensions of the gelator molecules. Assembly of small organic molecules in aqueous solvents into fibrous structures poses interesting challenges in the fields of molecular recognition and self-assembly. To achieve gelation, there must be a balance between the tendency of the molecules to dissolve or to aggregate. Hydrogen bonds, a common driving force for aggregation in organogelators, lose their strength in water unless many are combined in a cooperative manner and protected from solvent.[13] Instead, hydrophobic forces, which lack the precise directing ability of hydrogen bonds, become most important in aqueous environments.[14] A key to the design of organic hydrogelators is the control of hydrophobic interactions. Other contacts can also play a role in gelation, including salt bridges and transition metal coordination.[15]

The secondary structure (nano- to micrometer scale) is defined as the morphology of the aggregates, that is, micelles, vesicles, fibers, ribbons, or sheets, and is directly influenced by the molecular structure (Figure 1). Aggregation of amphiphilic organic molecules in water is a well-developed area of study.[16,17] Multiple morphologies are observed, including micelles, vesicles, lamellae, and amorphous or crystalline precipitates (Figure 2). Micelles are fluid species and form at the critical micellar concentration (CMC), which depends on the structure of the amphiphile. Above this concentration, micelles can convert to ellipsoidal micelles (disks) and then, with further increase in concentration, to cylindrical micellar fibers (rods). These fibers, however, generally precipitate or display viscoelastic behavior at concentrations above the critical micelle concentration without forming a gel, due to electrostatic repulsion of the charged surfaces.[18] Since many of these aggregates exist along with the gel state as part of a continuum controlled by pH, temperature, ionic strength, and other factors, they, too, will be discussed in the course of this review.

Several models have been developed to explain the transition from molecular to primary and secondary structure.[12,14,19,20] For example, Boden and co-workers have modeled the hierarchical self-assembly of rodlike chiral molecules, such as peptides in a β-strand conformation, into ribbons and fibers (Figure 3).[12] They begin with a chiral rodlike monomer functionalized with complementary donor and acceptor groups on opposite sides and chemically different surfaces (in Figure 3a, black = hydrophobic, white = hydrophilic). In solution, the rods first assemble into one-dimensional tapes via recognition of the donor and acceptor groups (Figure 3c). The chirality of the monomer is translated into the twist of the tape, and the two sides of the tape are chemically different, resulting in different affinities for the solvent. This in turn leads to a helical curvature to the tape (Figure 3c′). The tapes can further assemble, due to greater attraction between the hydrophobic (black) faces, into ribbons (Figure 3d). Now both sides of the ribbon are chemically equivalent, resulting in a saddlelike curvature (Figure 3d′). Subsequent aggregation (with increasing concentration) leads to the formation of fibers and then fibrils (Figure 3e,f). The chirality-induced twist leads to fibers and fibrils with well-defined widths dependent on balancing the favorable attractive interactions and unfavored distortion energies from the twisting.

Finally, the tertiary structure of a gel (micro- to millimeter scale) involves the interaction of individual aggregates and ultimately determines whether

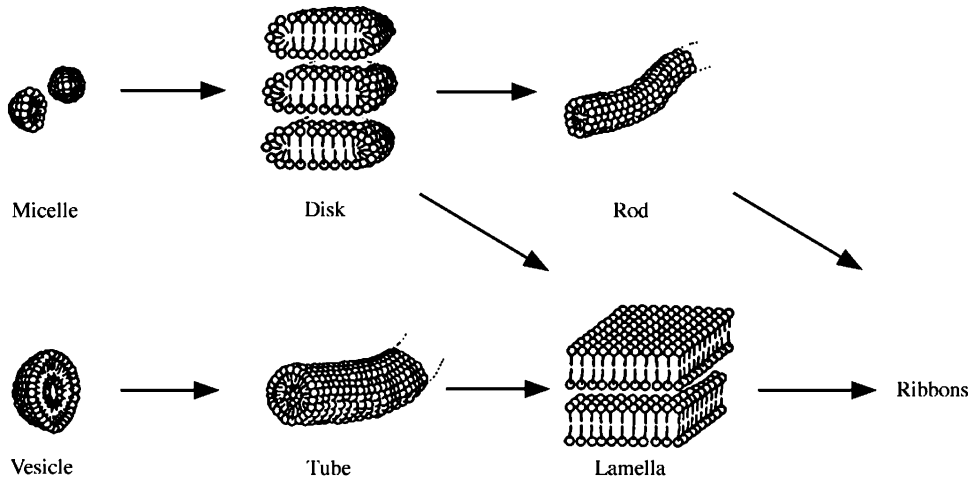


Figure 2. Schematic illustrations of possible aggregates of amphiphilic molecules in aqueous solution. The arrows represent possible interconversion pathways, dependent on concentration and other solution variables (pH, ionic strength, etc.). (Adapted with permission from ref 28, Copyright 1981, American Chemical Society.)

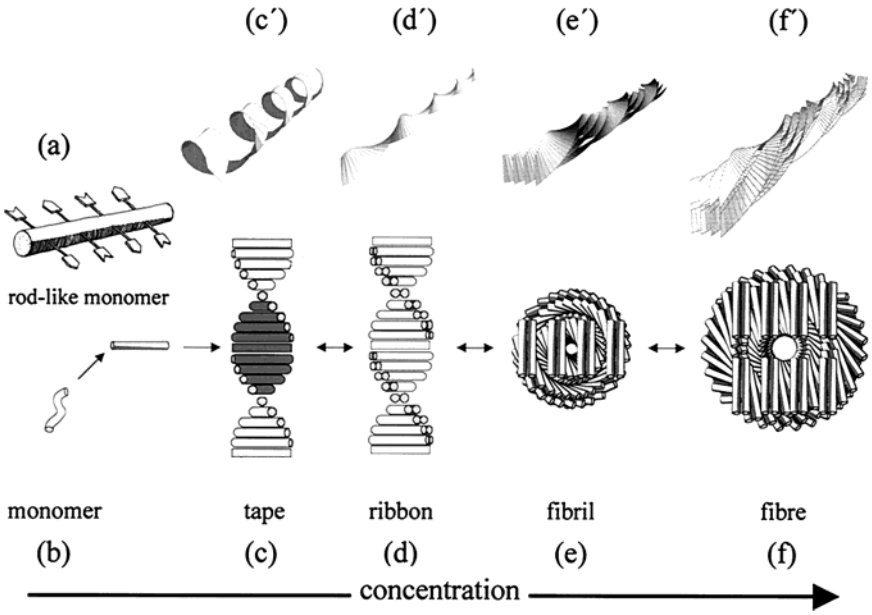


Figure 3. Model of the hierarchical self-assembly of chiral rodlike monomers. (a) The monomer with complementary functionality and chemically different faces. The local arrangements (c−f) and the corresponding global equilibrium conformations (c′−f′) of the structures formed in solutions of the monomer with increasing concentration. See the text for details. (Adapted with permission from ref 12, Copyright 2001, National Academy of Sciences, U.S.A.)

a gel is formed or, instead, fibers (or other aggregates) precipitate from solution rather than trap it (Figure 1). The transition from secondary to tertiary structure is determined by the type of interactions that can occur among the fibers. Gels can be formed by both physically branched fibers (interconnected networks) and entangled fibers. The type of cross-linking often determines the rheological properties of the gel (see Section 2.1). Physically, long, thin, flexible fibers are better able than shorter fibers to trap solvent, leading to gelation (Figure 4).[6] The experimental conditions can be varied to achieve different morphologies and, thus, gels with different physical properties. For example, Liu, Sawant, and co-workers have demonstrated how the presence of an additive can promote branching and, thus, gelation.[21−23] In other systems, the gelation temperature[23] and rate of cooling[24] have been found to alter the properties of the resulting gels. Presumably, such variables affect the rates of nucleation and growth, with an increasing number of branching events at higher temperatures.

Hydrogels formed via the self-assembly of small, organic molecules are related to, but fundamentally different from, both polymer hydrogels[8] and low-molecular-weight organogels.[25−27] Unlike polymer gels, the strands of organic hydrogels are assembled by noncovalent interactions. In addition, the cross-links between fibers are also noncovalent. One consequence of this is that small molecule hydrogels are often thermally reversible. The majority of small molecule gelators are able to gel only aqueous or organic solvents, suggesting that there are distinguishing molecular characteristics that determine their gelation abilities. This review focuses on understanding what determines if a given chemical structure will self-assemble in water to form a gel. For this reason, emphasis is placed on understanding the origins of the primary and secondary structures of the gels discussed. Such knowledge will assist us

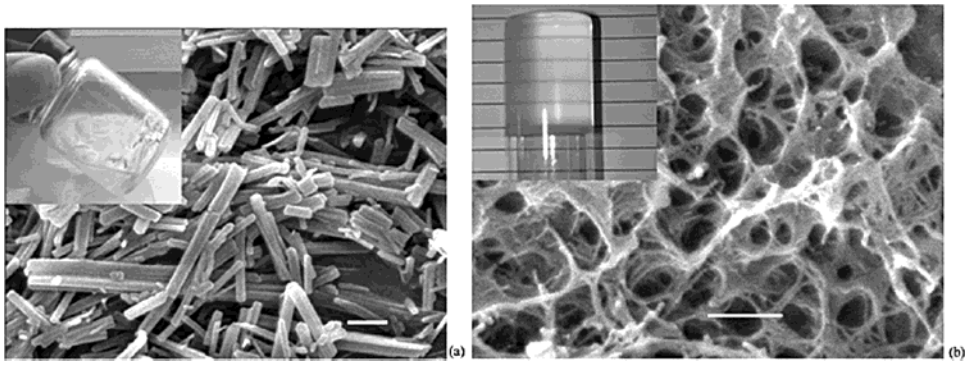


Figure 4. Scanning electron micrographs of fibers formed by L-DHL (lanosta-8,24-dien-3β-ol/24,25-dihydrolanosterol, 56:44 molar ratio) in diisooctylphthalate (DIOP). (a) Short, thick fibers formed by 10 wt % L-DHL/DIOP system give rise to a viscous solution as shown in the upper right corner. (b) Interconnected fiber networks in 10 wt % L-DHL/DIOP system after adding 0.004 wt % EVACP (ethylene/vinyl acetate copolymer) to promote branching. This system is a gel, as shown in the upper right corner. Scale bars: 1 μm. (Reproduced with permission from ref 21, Copyright 2002, American Chemical Society.)

in rationally designing new, effective, small molecule organic hydrogelators. Before discussing the different types of molecules known to form hydrogels, there is a brief section on the techniques used to characterize all of the structural levels of a gel.

2. Techniques

As the number of known gelators increases, the characterization of the resultant gels at both the nanometer and molecular levels has lagged behind. Therefore, before discussing the various classes of organic hydrogelators, an introduction to the techniques currently used to evaluate gel structure will be given. Particular focus will be placed on those techniques that provide the highest resolution description of the molecular assembly processes that lead to gelation. Special attention will also be given to the sample preparation required for the different techniques and how it affects the native gel structure. Methods that retain the native (i.e., solvated) state during characterization are preferred over the more common techniques that require drying or staining of the sample or both. The ultimate aim of any characterization study is to develop a better understanding of the molecular level organization in a gel, from which the ability to rationally develop new families of gelators will emerge.

2.1 Rheology

The macroscopic properties of a gel are derived primarily from the tertiary and, to some extent, the secondary structure. These properties, rheological and thermodynamic, can be investigated using techniques such as differential scanning calorimetry (DSC) and rheometry. Data collected via these methods are useful for comparing structurally diverse gelators and also evaluating the potential for practical applications due to the strength and flexibility of a given gel.[28−33] The temperature of gelation (T_{gel}) is one of the most often reported characterizations of a gel system. Multiple methods can be used to determine this value, including the "dropping ball" experiment in which a small ball bearing is placed on top of a gel while it is being heated. The temperature at which the ball breaks through the gel (the tertiary structure loses its weight bearing capacity) is recorded as the T_{gel}.[34] DSC and various rheometric measurements (see next paragraph) can provide better defined T_{gel}'s that correspond to the breaking of cross-links or molecular rearrangements.

Rheology is the study of flow and provides information about the type of network (tertiary structure) that is responsible for the observed gelation. For example, the type, number, and strength of cross-links can be evaluated with these techniques. There are several types of setups (parallel plates, concentric cylinders, cone-and-plate, etc.) that can be used, but all involve the spreading of a thin layer of gel between a stationary and a movable component. By measuring how the material responds to an applied oscillatory stress, several variables can be determined. The most useful being G* (complex modulus), G′ (storage or elastic modulus), and G″ (loss modulus or viscosity). By plotting these variables against the oscillary frequency, the imposed stress, temperature, and gelator concentration, certain characteristics of the gel system can be ascertained.

Information about the bulk properties of a gel gives little insight into the molecular organization (primary structure) that results in gelation by these small molecules. If the goal is to rationally design molecules capable of gelling a given solvent, we need to understand the molecular recognition events that result in gelation rather than crystallization or solvation. The following sections, therefore, discuss other techniques that can help in determining the primary structure of small molecule gels.

2.2 Spectroscopy

Various spectroscopic techniques have been applied to organic hydrogel systems, including NMR, fluorescence, UV, CD, and IR spectroscopies, all of which can provide information on the molecular organization of the gels. Since many of these techniques are temperature-sensitive, they provide an alternative to the methods discussed above for determining T_{gel}. The melting temperatures determined by spectroscopy will often be different from those determined from rheometry, since they detect changes in primary, rather than tertiary, structure.[34]

Solution-state NMR can be used to identify the formation of hydrogen bonds during gelation.[35−37]

Relaxation time measurements (T1 and T2) can be used to identify those parts of the molecule whose conformational and translational motions slow during gelation.[28,38] Solid-state magic angle spinning NMR has also been used to examine the gelled state and identify chemical shift changes from the solution spectrum, indicating a change in aggregation.[39,40]

The incorporation of spectroscopic probes, such as fluorescent groups,[2,32,41] into gelators has been both an effective design strategy (probably due to the large, flat aromatic surfaces that promote aggregation) and a useful tool for evaluating aggregation geometries of the aromatic groups in the gelled state. Fluorescent probes have also been used to identify the formation of hydrophobic pockets inside hydrogels.[42−45] UV/vis techniques can also be used to detect a change in the hydrophobicity of the surroundings of the reporter group (either part of the gelator molecule or an added probe)[43] and identify $\pi-\pi$ stacking or metal coordination that might result in aggregation, leading to gelation. Often chiral gelators with a weak UV/vis signal will show a significant enhancement of circular dichroism (CD) upon gelation. This can be useful for monitoring gel formation[46] and also provides information similar to that gained from the UV/vis experiments with regard to $\pi-\pi$ stacking.[2,47,48] The absorbance of amide and urea functionalities (200−250 nm) can also be used to follow aggregation.[49,50]

Finally, IR is useful for confirming the presence of H-bonding and determining the protonation state of carboxylic acids.[36,46,51−54] Some peaks of interest (such as the NH stretch) are obscured by the OH stretch of water, and so often these studies, unlike those mentioned above, are done with dehydrated samples. Therefore, the results must be interpreted cautiously, since structural changes may have occurred during removal of solvent.

2.3 Microscopy

Microscopy, depending on the technique, provides insight into the micro- and nanostructure of a given gel. Polarizing light techniques, despite a relatively low resolution (0.2 μm is the theoretical limit due to the wavelength of visible light), do not require manipulation of the sample, allowing the native structure of the aggregates to be observed.[44,49,51,55] In addition, the extinction pattern provides information about the degree of order in the aggregates. Scanning probe microscopies (AFM, STM, etc.) are high-resolution techniques that have the potential to image hydrated samples in situ under high humidity conditions and without dehydration;[9,56] however, to facilitate imaging, the samples are often dried, possibly introducing artifacts.[53,55,57] A benefit of SPM is that it can provide molecular-scale resolution, allowing the imaging of headgroups and alkyl chain packing patterns.[56]

Electron microscopy techniques, both scanning (SEM) and transmission (TEM), allow imaging of features with resolution up to 0.2 nm and, therefore, provide valuable information about the morphology of the aggregates that result in gelation. However, under standard operating conditions (high vacuum), SEM and TEM require complete drying of the sample, resulting in artifacts for gel systems that inherently exist in a solvated state.[58] In addition, TEM requires staining of organic assemblies to improve the image by increasing the electron density. The stains, including phosphotungstate and osmium tetroxide, have the potential of introducing artifacts by interacting with the assemblies in a manner that can change their morphology.[17]

Recently, cryogenic techniques have been applied to gel systems, making nanometer resolution (cryoTEM) images of the native gel state feasible. For cryoTEM imaging, aqueous samples are flash-frozen in liquid ethane at the temperature of liquid nitrogen, creating thin vitrified ice films. This allows the visualization of organic assemblies in what is essentially an aqueous environment.[59] The high viscosity of gel systems makes it difficult to form a film containing well-formed aggregates that is sufficiently thin for complete vitrification. Nevertheless, several groups have successfully used cryo-TEM to visualize the structures of organic hydrogels and related fibrous assemblies.[53,60−69] Other cryotechniques include freeze-fracture TEM in which a frozen sample is fractured, usually splitting bilayers in half, and then making a replica of the fracture surface and imaging it under standard TEM operating conditions.[70,71] There are also cryoSEM techniques, which Menger and co-workers have applied to organic assemblies in aqueous solutions.[33,72,73] Sample preparation is similar to that used for cryoTEM, but instead of thin vitrified films, more substantial samples ($\sim$10 μL) are vitrified in liquid ethane, etched to remove a layer of ice, and then sputter-coated to allow imaging with SEM. While it is more difficult to completely vitrify such large volumes, a potential advantage is that since SEM images secondary electrons emitted from the sample's surface, pseudo-three-dimensional images can be obtained.

2.4 Diffraction

There are two diffraction techniques, SAXS and SANS (small-angle X-ray and neutron scattering, respectively), whose resolution is approximately that of TEM. These have been applied to hydrogels to investigate the suprastructures formed by the fibers (10s of nanometers).[57,68,71,74] Rigorous mathematical analysis is required to interpret the results of these techniques. First, a model is chosen for the type of aggregate, for example, rodlike micelles, and then using the appropriate parameters, the data are fitted to this model. Information on the type of packing (cubic, hexagonal, etc.) of the rodlike aggregates can be determined. In addition, because native gel samples can be examined using SAXS, several authors have used the technique to model the role of solvent molecules in fiber formation in organogels.[10,11,75,76] To do this, they compare the predicted bundle size (from close-packed fibers) to the actual measured size and attribute the difference to interpenetration of solvent molecules between the fibers.

Wide-angle X-ray powder diffraction (XRD) has great potential for elucidating the molecular structure of organogels.[35,37,51,55,64,67,77−79] One of the most useful pieces of information from a powder pattern

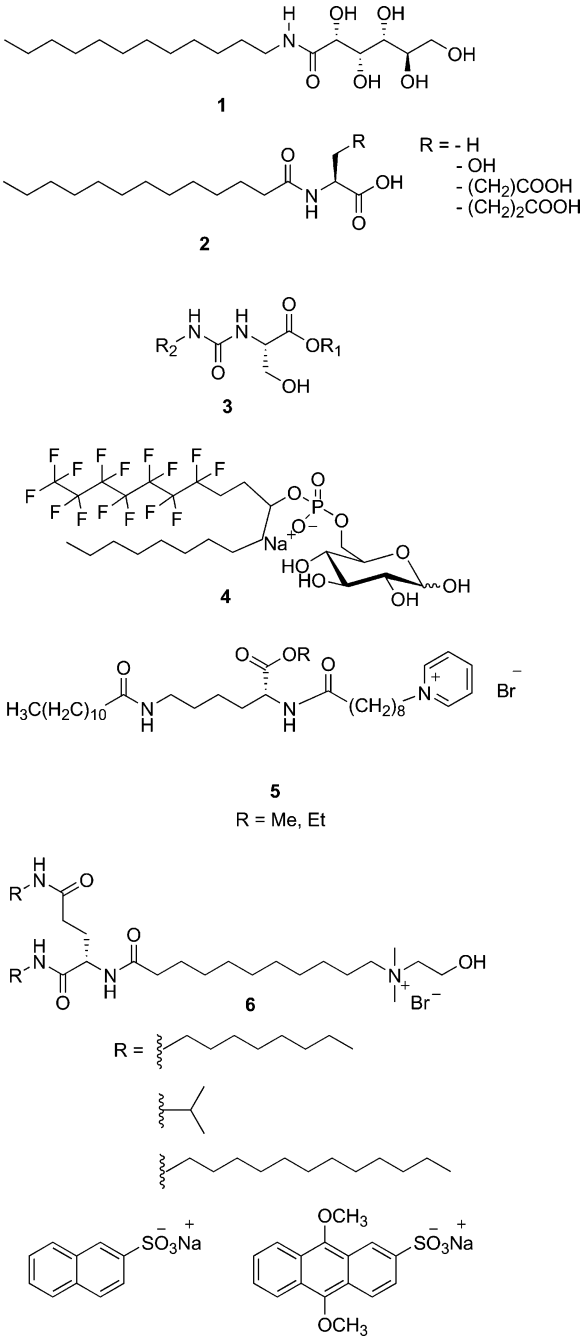
is the long *d* spacing (with a resolvable spacing of >40 Å, depending on the detector) which corresponds to the longest repeat distance in the crystalline structure. By comparing the *d* spacings to molecular dimensions, such factors as the packing of molecules in an extended or bent conformation or the possible interdigitation of alkyl chains can be determined.[35,37,51,55,78,79] The spacing of subsequent peaks can be used to distinguish lamellar (1, 1/2, 1/3) from hexagonal (1, $1/\sqrt{2}$, $1/\sqrt{3}$) packing;[80,81] however, much of this work has been on dried samples, making it difficult to draw direct conclusions about the structure of the gel in its native state.

Crystal structures of related molecules can provide information about molecular order in the gelled state with several caveats.[33,82−87] The ideal situation is to have crystal structure(s) of all possible polymorphs of the gelator molecule itself which can then be compared to the powder diffraction pattern of the gelled material. The closest match is chosen as the structure of the gel.[36,82,87] When this is not possible due to poor crystallinity of the gelators, single crystals of related molecules can be obtained and then compared to the XRD pattern of the gel to develop a possible model of its molecular packing.[83,84,88] In these cases, however, caution should be exercised, since polymorphism is common among gelling molecules, and the very fact that one molecule gels and the other crystallizes points to a difference in molecular assembly. Finally, if no single-crystal structures are available, it is possible to use good quality powder diffraction data,[89−93] complemented by modeling to obtain a molecular level representation of a gel.

2.5 Modeling

Since atomic resolution is often unattainable due to the inherent disorder in gels, it is possible to use modeling, based on data collected from several of the complementary techniques discussed above, to obtain a working picture of the molecular organization in the gel state.[64] Higher level energy minimization and molecular dynamics calculations have also been used to model the primary structure of gels. In this way, possible modes of aggregation for gelators of both aqueous[31,36,94] and organic solvents[83,95−98] have been identified.

Chart 1. Amphiphilic Molecules That Form Aqueous Gels



3. Structural Motifs in Hydrogelators

To further aid in the rational design of new organic hydrogelators, it is helpful to identify common themes among those already in the literature. As discussed in the Introduction, gelation is a balance between crystallization and solubilization, and thus, to gel a given solvent, a molecule requires functionality that will provide both. In water, therefore, amphiphilic molecules with hydrophobic groups to promote aggregation and hydrophilic groups to provide solubility are most likely to be competent gelators. In addition to increasing solubility, charged groups can also provide triggers for gelation via a change in solution pH or ionic strength. Within these general requirements, there are several distinct classes of small molecule organic hydrogelators characterized by the type and placement of the polar groups. In the following sections, these categories will be discussed.

3.1 Conventional Amphiphiles

Conventional amphiphiles contain a polar headgroup and one or two hydrophobic tails. The polar head can be a range of functional groups, including a carboxylic acid, an amino acid, a sugar, a phosphate, or a quaternary amine. Similarly, there is much variation in the number, length, and flexibility (saturation, cyclic, etc.) of the hydrophobic tails. Such molecules are prevalent in nature[99] and are known to form a variety of aggregates in aqueous solutions,[16,17] including hydrogels (Figure 2 and Chart 1).

Table 1. Packing Shapes of Lipids and the Structures They Form Based on the Critical Packing Parameter[14]

critical packing parameter (v/a_0l_c)	critical packing shape	structures formed
<1/3	cone	spherical micelles
1/3−1/2	truncated cone	cylindrical micelles
1/2−1	truncated cone	flexible bilayers, vesicles
~1	cylinder	planar bilayers
>1	inverted truncated cone	inverted micelles

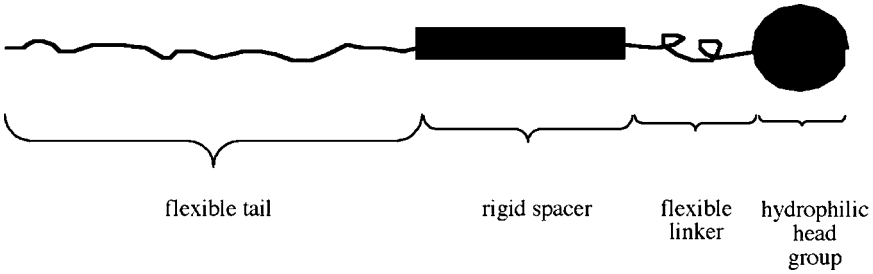


Figure 5. The divisions of an amphiphilic structure that Kunitake used to synthesize a library of 60 molecules through systematic variation of the four components.

Lipids are one type of amphiphile that has been extensively studied.[19,100−104] Much work has been done to elucidate the mechanism of tubule formation by lipids and the origin of different aggregate morphologies.[19,102] Since this work has been reviewed extensively elsewhere,[17,19] it will be only briefly discussed here. A lipid can be described by several variables. The surface area of the headgroup when the lipids are packed so as to maximize the attractive forces and minimize the repulsive forces is defined as the optimal headgroup area, a_0. The hydrocarbon tail is described by two terms: the volume, v, is assumed to be fluid and incompressible, and the critical chain length, l_c, is the maximum effective length the chains can assume. Using these variables, Israelachvili defined a *critical packing parameter* or *shape factor*, v/a_0l_c, that can be used to predict which structures a lipid will assemble to form (Table 1).[14] The headgroup area can be changed by varying the pH and ionic strength, thus explaining why one molecule can assemble into several different structures. Beyond this, it is unclear what determines whether an amphiphile aggregates to form gels rather than vesicles,[105] bilayers (lamellae), rods, or tubes (see Figure 2).

In an early paper, Kunitake and co-workers attempted to identify relationships between aggregate morphology and amphiphile structure.[28] They divided the amphiphilic structure into four parts that can synthetically be varied independently of each other: the flexible tail, a rigid segment, a spacer group, and the hydrophilic headgroup (Figure 5). In some structures, they add another interacting group, such as an ester or amide in the flexible tail, to provide additional hydrogen bonding possibilities. In a survey of over 60 amphiphiles, they identified a number of possible aggregate morphologies, including globules, vesicles, lamellae, rods, tubes, and disks (see Figure 2). By varying the length of the tail, flexible linker, or both, the structure of the aggregate could be changed. They identified the flexible tail, rigid segment, and hydrophilic headgroup as essential elements for stable self-assemblies. Surface curvature (rods and vesicles versus bilayers and sheets) was found to be enhanced by bent rigid segments.

Fuhrhop and co-workers have focused on *N*-alkylaldonamides (**1**) and made great progress in understanding the molecular origins of the aggregate morphology.[39,60,65,66] Using TEM, 3-D image processing, and solid-state NMR techniques, they have developed a molecular-scale model of the quadruple strands of micellar fibers that lead to gelation by *N*-dodecylgluconamide (**1**) (Figure 6). Only enantiomerically pure samples form gels; the racemate quickly precipitates as crystalline sheets. They propose a chiral bilayer effect to explain why the rearrangement of enantiomerically pure micellar fibers to crystals is a slow process, whereas for the racemate, it occurs rapidly.[60] Different diastereomers form different morphologies (helical ropes, twisted bilayer sheets, and ribbons), suggesting that the geometry of the headgroup is responsible for the packing, which is translated into aggregate morphology. While the chemical structure dictates gross morphology, they also emphasize the importance of geometrical rules in determining the finer structure.[65]

Another system, *N*-dodecanoyl-(D- and L-)-serine (**2**), investigated by the same authors, also exhibits the chiral bilayer effect.[62] This work is particularly interesting because they observe the aggregation of the same amphiphile in both aqueous and organic solvents using cryo-TEM (Figure 7). They propose that in both solvents, the molecules go through similar aggregation pathways, beginning with micelles (or reverse micelles), progressing through bilayers (or reverse bilayers), and ending with smooth tubular rods. The biggest difference between the two solvents is how many of the intermediates are observed in each. In water, which is better able to solvate the headgroups, twisted ribbons, a high energy intermediate before closed tubes, are observed. Hydration can stabilize large surface areas, whereas organic solvents cannot.

Imae and co-workers have extensively studied other amino acid surfactants, including those with glutamic acid, aspartic acid, and alanine as headgroups (**2**).[29,57] The carboxylic acid functionality makes the gels formed by these molecules pH-dependent. In addition, the pK_a of the acid can be modulated by

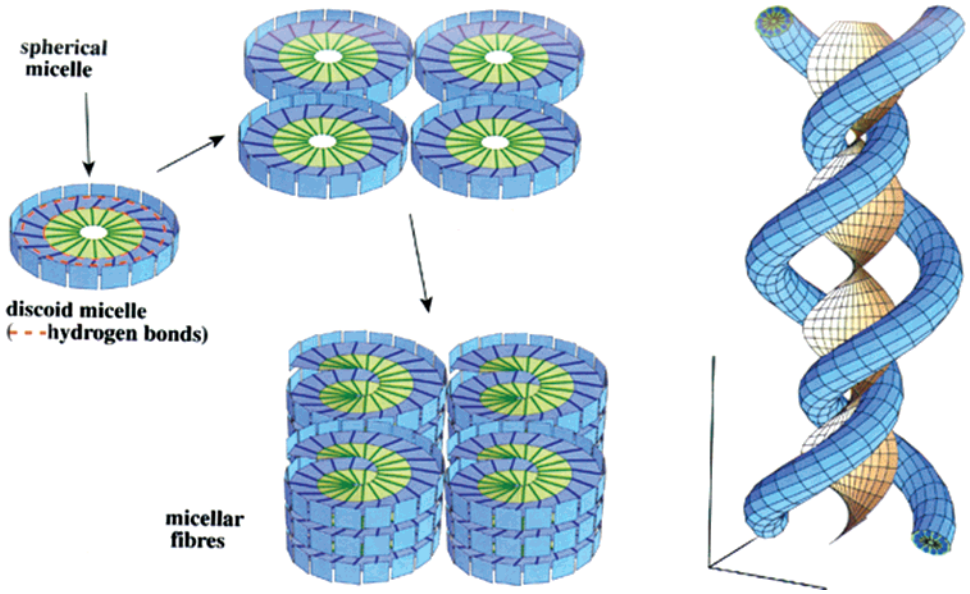


Figure 6. Spherical micelles of *N*-dodecylgluconamide (**1**) transform into micellar disks with hydrophobic surfaces due to the formation of amide hydrogen bonds. The hydrophobic edges promote association of the disks, which then grow into rods. Uneven hydration of the inner and outer surfaces leads to bending of the rods into helices. These helical fibers have a supramolecular dipole moment that repels neighboring helices, causing the observed morphology. (Reproduced by permission from ref 17, Copyright 1994, The Royal Society of Chemistry.)

changing the length of the alkyl chain: with increasing length, the pK_a increases by 2 pH units, most likely due to being buried in a hydrophobic microenvironment that is shielded from the bulk aqueous solution. In addition, the aggregate morphology shows a strong temperature dependence. From the temperature−pH phase diagrams, it is clear that gelation occurs in the transition from carboxylic acid to carboxylate species, suggesting a role for mixed aggregates of the protonated and unprotonated acids (Figure 8).[29] They hypothesize that rodlike micelles are responsible for gelation and have used SAXS and SANS to obtain dimensions of the rods, including the helical periodicity (Figure 8).[57]

Some of the lowest-molecular-weight organic hydrogelators (below 250 Da) are serine-based amphiphiles (**3**).[106] These simple designs do not require any buffer, salt, or other additives for fiber formation and gelation to occur. Those derivatives that contained aromatic groups required lower concentrations for gelation, suggesting a role for $\pi-\pi$ stacking in the aggregation. Further supporting the importance of a balance between hydrophobicity and hydrophilicity for gelation, we found an optimum number of total methylenes were required for gelation. Above this number, the compounds were insoluble in pure water, whereas below, they were soluble.

Fluorocarbons have been used as the hydrophobic component in amphiphiles (**4**), several of which form hydrogels.[71,77] Fluoroalkanes have exceptional properties, including very high surface activities, low critical micelle concentrations, and a tendency to self-assemble in water. This could be due to the added rigidity of a fluorocarbon, as compared to the corresponding hydrocarbon. The "fluorous" effect is also known to be stronger than simple hydrophobic forces.

It is also possible to have a positively charged headgroup, as in the lysine derivatives (**5**) used by Hanabusa et al.[42,54,107] Using a fluorescent probe, they identified a two-step assembly process in which initial aggregates with hydrophobic pockets form and then rearrange into nanofibers with hydrophobic interiors. This mechanism emphasizes the importance of hydrophobic effects as a driving force for the formation of hydrogels by small organic molecules.

Nakashima and Kimizuka recently reported an interesting study on the formation of "light-harvesting" hydrogels that are formed by two-headed amphiphiles (**6**) and anionic fluorescent dyes.[45] Their design was based upon the observation that aqueous dispersions of chiral bilayers formed by the longer-chained derivatives (12 methylenes) develop into fibrous nanoassemblies that do not form gels due to electrostatic repulsion of the positively charged surfaces. Shortening the alkyl chains and introducing hydrophobic, anionic cross-linkers leads to fibers that are able to aggregate to form gels. Interestingly, addition of the anionic dyes to the long-chained amphiphile resulted in precipitation, presumably by destabilization of the bilayer. This design highlights the importance of a balance between charge−charge interactions and hydrophobic effects in the gelation of water by small organic molecules.

3.2 Bolaamphiphiles

Bolaamphiphiles (two-headed amphiphiles) are named after the "bola", which is a South American weapon made of two balls connected by a string. As with conventional amphiphiles, the chemical functionality of the headgroups and linking group can be varied to change the aggregation properties. The structural differences, as compared to conventional amphiphiles, can result in different aggregate morphologies. For example, they can form a "bilayer" that is one molecule thick; thus, vesicles and other bilayer structures are most commonly formed. Depending on

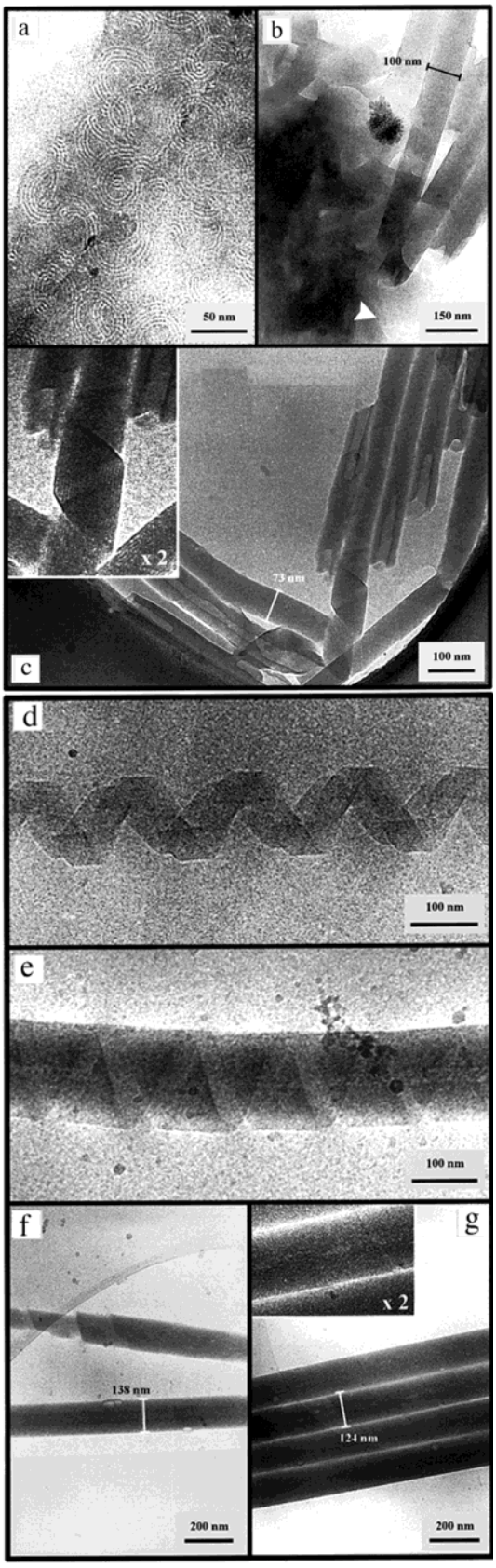


Figure 7. Cryo-TEM images of assemblies of L-dodecanoylserine (**2**) in (a−c) vitrified toluene. (a) Multilamellar vesicles, (b) tubular aggregates, and (c) multilamellar tubules. (d−f) Vitrified water (citrate buffer, pH 6.4), (d) helical ribbons, (e) ribbons progressing to closed tubes, (f) multilamellar tubules, and (g) tubular rods in pH 4.9 acetate buffer. (Reproduced with permission from ref 62, Copyright 2001, American Chemical Society.)

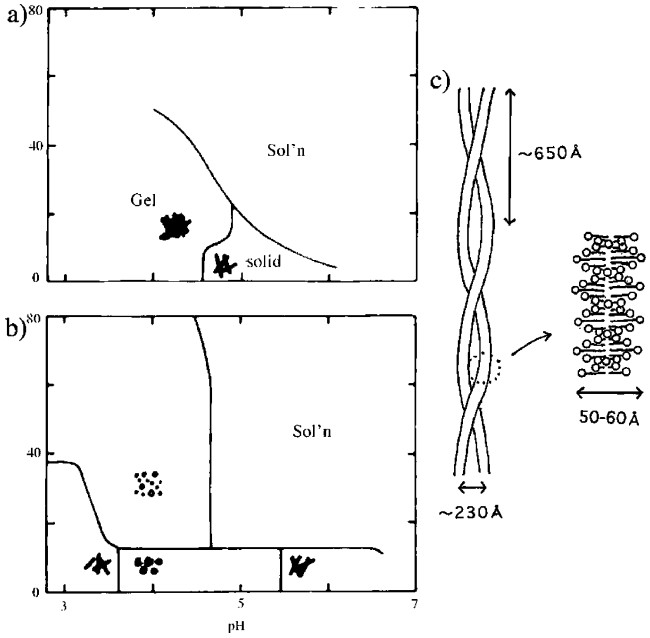


Figure 8. Temperature−pH phase diagram for 1% aqueous solutions of (a) C_{12}Glu and (b) C_{12}Asp. (Reproduced with permission from ref 29, Copyright 1992, American Chemical Society.) A schematic representation of a possible model for C_nAsp fibers showing the distances measured from the SANS and SAXS data. (Reprinted with permission from ref 57, Copyright 2000, Elsevier.)

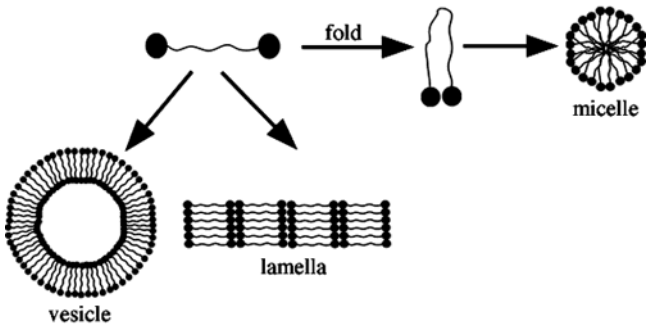
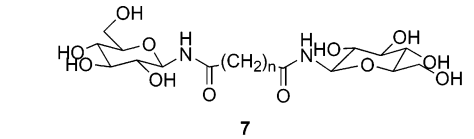


Figure 9. The different types of aggregates that can be formed by a bolaamphiphile.

the length and flexibility of the linker, some bolaamphiphiles can fold in half and form micelles (Figure 9).[30]

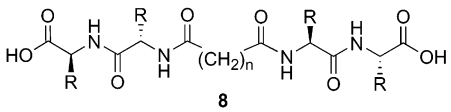
Shimizu and co-workers have thoroughly explored bolaamphiphiles with a variety of headgroups (**7**−**9** in Chart 2 and **14** in Chart 3), including nucleotides,[46,55,78] amino acids,[52,53] and sugars,[40,51] that form both gels and fibers. The amino acid derivatives (**8**), with terminal carboxylic acids, show interesting variation in aggregation with changing pH and have pK_a values that change with the alkyl chain length (similar to Imae's single-chain amphiphiles)(Figure 10a).[52,53] At high pH, the glycylglycine derivatives exist as a solution of rodlike micelles (observed by cryo-TEM). As the pH is lowered, protonation occurs at the fluid surfaces of the micelles, triggering aggregation between charged and uncharged species, which then form microtubes. Further increase in proton concentration protonates all remaining carboxylates, resulting in the precipitation of needlelike microcrystals (Figure 10b).

Chart 2. Bolaamphiphiles That Form Hydrogels



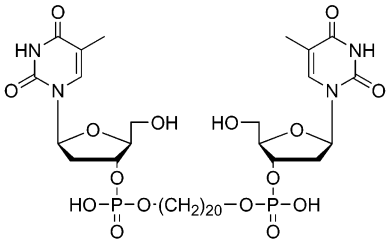
7

n = 6,9,10,11,12,13,14



8

n = 8, 10



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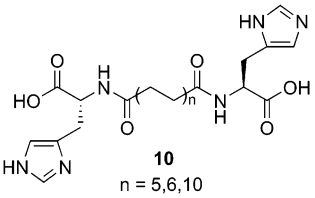
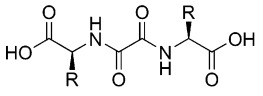


10

n = 5,6,10



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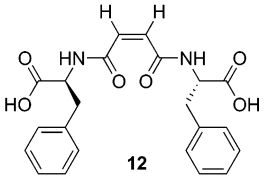

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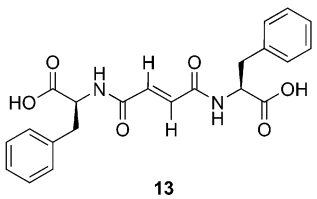
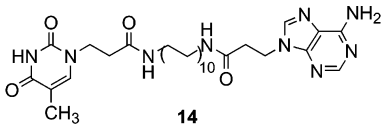


13

The aggregation of the sugar derivatives (**7**) depends strongly on whether the linking chain has an odd or even number of carbons.[40,51] This length-dependence emphasizes the importance of the orientation of the terminal sugar groups in promoting aggregation. The molecular organization of the nucleotide bolaamphiphiles is also controlled by hydrogen bonding of the end groups. It is interesting to note that only the more complex compounds with the solubilizing deoxyribose and phosphodiester groups (**9**) form gels,[46,55] whereas those with simple nucleotide headgroups (**14**) precipitate as crystalline fibers.[78]

Another family of gel-forming amino acid bolaamphiphiles (**10**) has been studied by Franceschi et al.,[30] who showed that depending on the linker length, micelles, vesicles, or fibers are formed. The longer linkers allow the molecule to fold in half, essentially becoming an amphiphile that can assemble into micelles, as discussed above (Figure 9). The molecules

Chart 3. Bolaamphiphiles That Assemble in Aqueous Solution to Form Fibers



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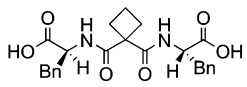

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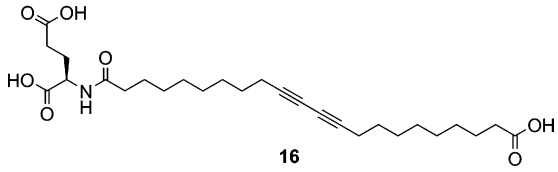

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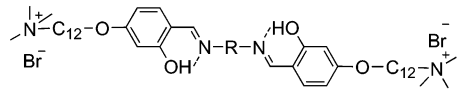

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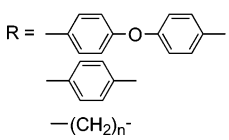


with shorter linkers showed a concentration-dependent transition from vesicles to fibers. Only those bolaamphiphiles with the longest (20 methylene units) linkers showed any appreciable gel formation. The authors suggested that the other derivatives are too soluble (not hydrophobic enough) to gel.

A long alkyl linker is not the only type of hydrophobic core for bolaamphiphiles. Bis(amino acid)-oxalyl amides with bulky (phenyl or isopropyl) side chains (**11**) are effective gelators of both water and organic solvents.[36,41] In water, the hydrophobic interactions of the side chains promote linear aggregation, and then hydrogen bonding of the adjacent carboxylic acids further strengthens the assembly. The primary role of the oxalyl group is the rigid projection of the substituents onto one side of the molecule to allow for the stacking of the hydrophobic groups (Figure 11). The meso compounds do not form gels, presumably because the orientation of the side chains does not allow the necessary stacking to occur. The same authors have recently reported a related set of structures (**12** and **13**) in which gelation is triggered by photoisomerization of the double bond, going from **12** to **13**.[38] Only the trans double bond, **13**, projects the hydrophobic side chains in an orientation similar to the oxalyl group, thus promoting $\pi-\pi$ stacking, fiber formation, and subsequent hydrogelation. The kinetics of isomerization is also an important factor. Gelation occurs only when the isomerization is rapid (UV/Br_2), whereas when it is slow (daylight), crystals are formed, emphasizing the close relationship between gelation and crystallization.

There are several interesting families of bolaamphiphiles that do not form gels but do show interest-

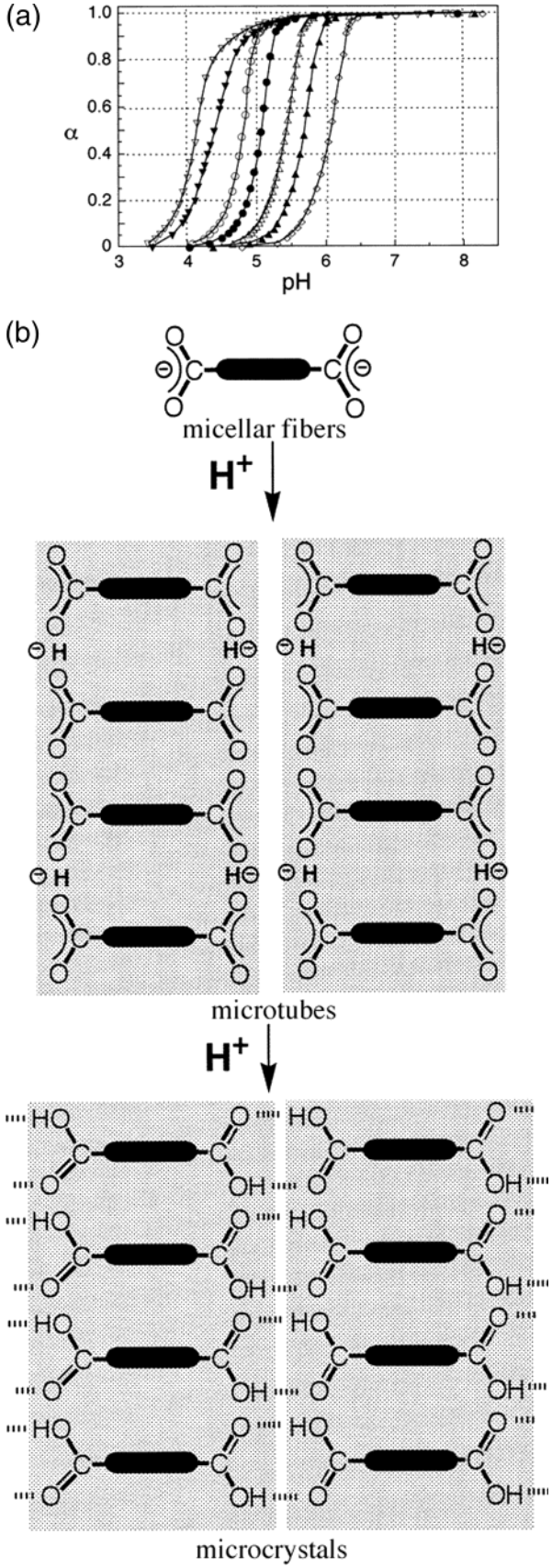


Figure 10. (a) pH dependence of the degree of ionization α of **8** as a function of pH (titration with 1 M NaOH). Moving from left to right, the linker length (*n*) increases incrementally from 6 to 12. (b) Schematic representation of the pH-dependent aggregation of **8**. (Reproduced with permission from ref 53, Copyright 1998, American Chemical Society.)

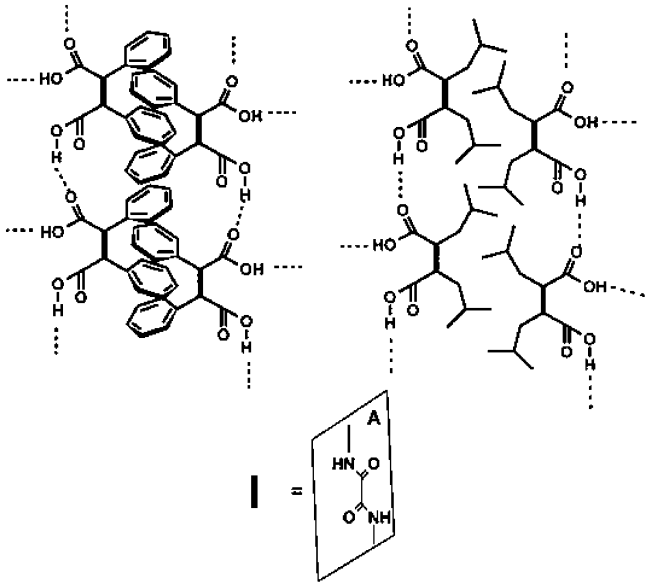


Figure 11. Schematic representation of the organization in hydrogel fibers of **11** based on $\pi-\pi$ stacking and hydrophobic interactions. The bold line represents the oxalyl amide fragment in plane *A*, which is perpendicular to the plane of the drawing. (Reproduced with permission from ref 36, Copyright 2001, Wiley-VCH.)

ing aggregation properties in water (Chart 3). Matsui and co-workers have examined the aggregation behavior of molecules related to Shimizu's amino acid bolaamphiphiles.[108,109] Instead of having a flexible alkyl chain linker, these molecules contain rigid, "twisted" linkers, such as the cyclobutane derivative **15**.[109] The presence of carboxylic acids again results in pH-triggered phase transitions. The twist introduced by the strained ring helps to stagger the hydrogen-bonding functionality in a helical fashion that allows complementary interactions to occur.

Song et al. have synthesized an unsymmetrical bolaamphiphile with a polymerizable linker (**16**).[56] At low pH, the molecules assemble into helical ribbons that turn blue upon polymerization of the diacetylenes. With increasing pH, both the color and morphology change, resulting in red nanofibers. This opens up the intriguing possibility of a color-coded transition between different microstructures that is triggered by outside stimuli (such as pH).

A family of positively charged bolaamphiphiles with a rigid bis-Schiff base connector (**17**) has been synthesized by Wang et al.[79] The effect of changing from a rigid (phenyl or biphenyl) to a flexible (alkyl chain) linker on the morphology of the aggregates formed was examined. The more rigid linkers result in linear aggregates, such as tubules and fibers. The flexible alkyl derivatives form aggregates with high curvature, such as vesicles. Interestingly, a sharp gel-to-liquid-crystalline phase transition was not observed, suggesting that the hydrophobic alkyl chains are loosely packed, with interpenetrated water. The driving force for aggregation likely derives from the stacking of the bis(salicylideneimine) units and not the hydrophobic interactions of the alkyl chains.

3.3 Gemini Surfactants

Gemini surfactants have the general structure shown in Figure 12.[110] Molecules in this family often

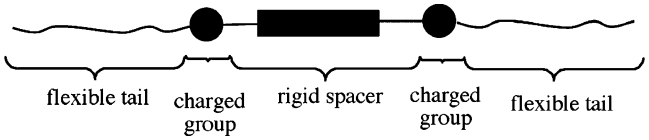


Figure 12. The general structure of a gemini surfactant: flexible tail−ion−linker−ion−flexible tail.

have critical micelle concentrations (CMCs) orders of magnitude lower than the corresponding "simple" surfactant. As with amphiphiles and bolaamphiphiles, the more complex molecular structure of gemini surfactants is translated into a richer diversity of aggregate morphologies.

Menger and co-workers, who coined the term gemini surfactants,[111] have studied this class of surfactants most extensively. In particular, they have found several families that form hydrogels (**18**−**21**).[72,73] Using cryoetch-HRSEM they have visualized the hydrated morphologies of several derivatives. Following a general trend found throughout all classes of small molecule organic hydrogelators, hydrophobicity plays a determinant role in the structure−function relationship of these molecules.[73] As shown in Chart 4, reducing the length of one alkyl chain from 18 methylenes (**19**) to 10 methylenes (**20**) results in the formation of a coaservate (a spongy, water-insoluble mass) rather than a gel. Reducing the length by one more methylene (**21**) eliminates all visible aggregation and results in a free flowing, clear solution.

Oda and Huc have also studied a family of gemini surfactants with chiral counterions (**22**) that form hydrogels.[70,88,112−114] TEM images reveal that the gels are formed from twisted ribbons. Using a variety of techniques, including single-crystal XRD, NMR, UV/CD, and VCD (vibrational circular dichroism), they have developed a model for the origin of this twist. As indicated in Figure 13, the degree of twist varies with enantiomeric excess (ee), beginning with flat ribbons formed by the racemate progressing to a tightly twisted ribbon with pure L-tartrate (the same is observed for D-tartrate, except the twist is of the opposite chirality).[88,114] There are two separate issues to be addressed: (a) the origin of the morphology of the twist and (b) the ability to tune the degree of twisting by changing the ee. The shape of the twist can be explained geometrically. Interlayer coordination favors saddlelike (Gaussian) curvature, which maintains equal contact between all layers, over cylindrical curvature in which the outer

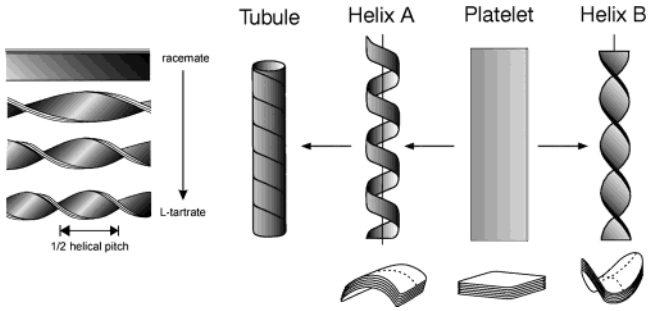


Figure 13. Schematic representation of the multibilayer ribbons formed by **22** in water. The pitch of the ribbons can be tuned upon varying the ee of the anion. (Reproduced with permission from ref 88, Copyright 2002, American Chemical Society.) Different types of ribbons showing cylindrical (helix A) and Gaussian (helix B)-type curvature. The side views show the difference in contact between multiple layers in the two geometries. (Reproduced with permission from *Nature* (http://www.nature.com) and the authors of ref 114, Copyright 1999, Macmillan Magazines Ltd.)

Chart 4. Gemini Surfactants That Form Aqueous Gels

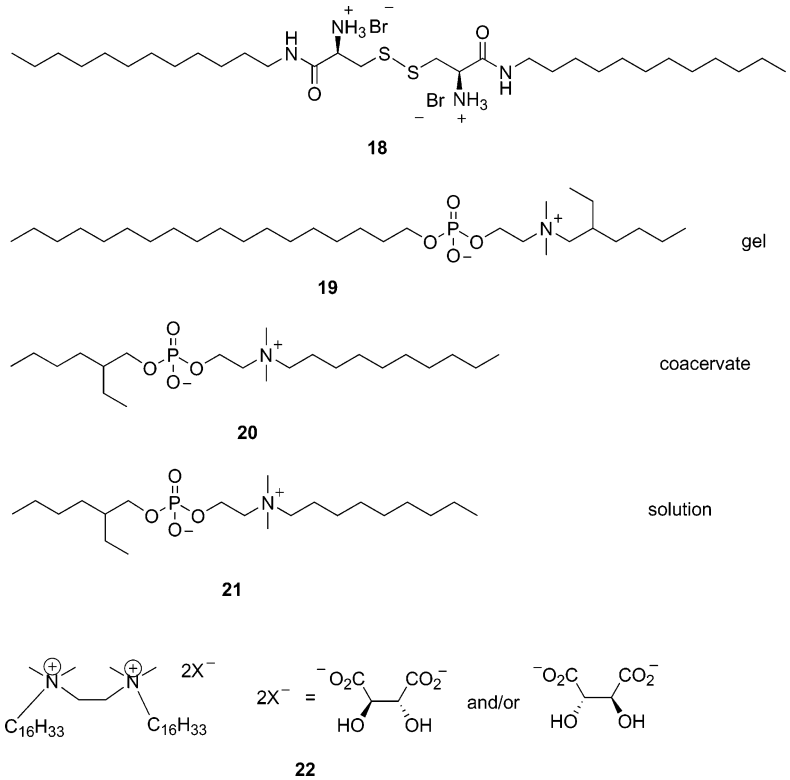
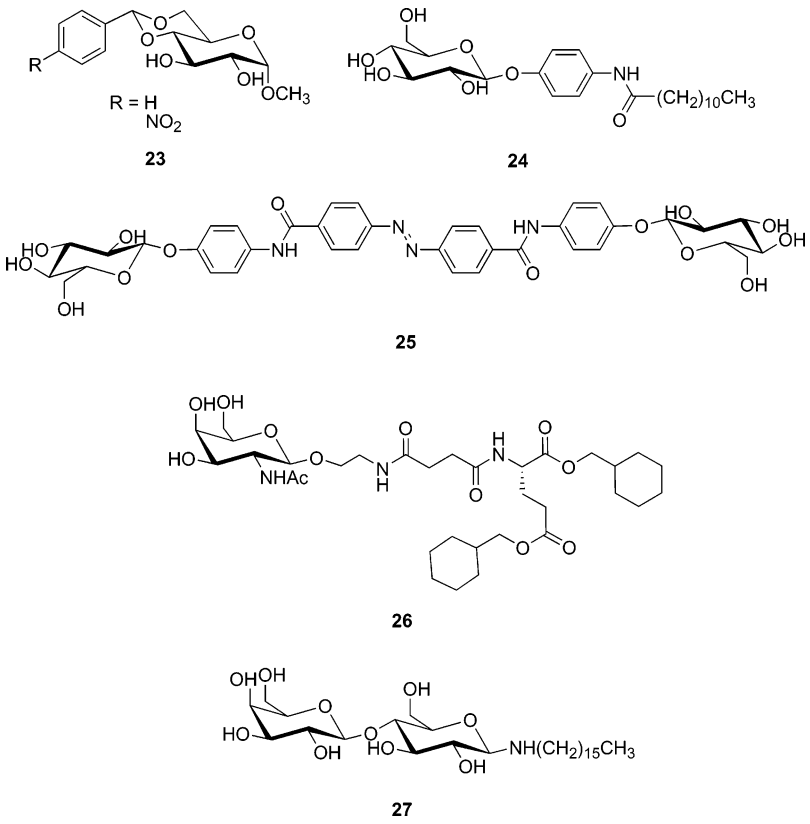


Chart 5. Sugar-Based Hydrogelators



23 **24** **25** **26** **27**

layers have less contact than the inner ones (Figure 13).

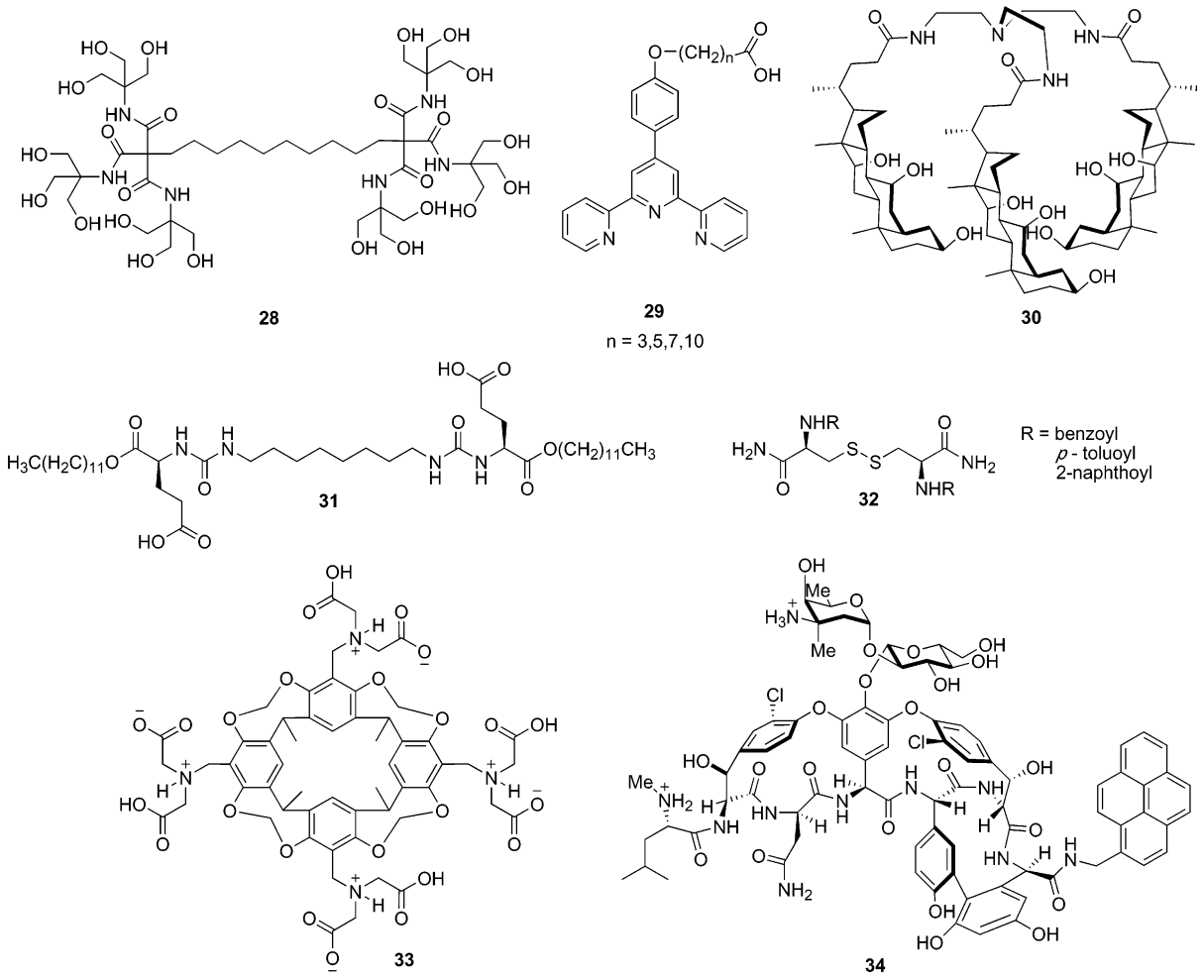
The tunabilty of the twist is a more complicated issue. In the presence of achiral counterions, such as bromide, flat ribbons similar to those formed in the presence of the racemate are observed. This, in addition to the fact that D- and L-tartrate give opposite-handed twists, indicates that the twisting has its origins at the molecular level. The 16-2-16 gemini surfactant **22** can adopt any of seven conformers by rotation about the bonds linking the nitrogens to the spacer carbons. Among these seven, there are three sets of enantiomers and one symmetrical conformer. The single crystal X-ray structure of a related surfactant (dioctadecyl dimethylammonium bromide monohydrate) is a mixture of one pair of enantiomeric conformers. In the presence of achiral counterions, both enantiomers should be equally populated. However, from proton NMR, Berthier et al. showed that there is direct interaction of the dications and chiral tartrate anions, suggesting that the chiral structure of the aggregate may be induced by the chiral anion.[88] It remains to be explained why reducing the ee lowers the degree of twisting rather than resulting in enantiomeric resolution or precipitation of racemate.[60] The dynamic nature of the chirality in the dication means that as the ee is lowered, the efficiency of the chiral induction by the tartrate ions will be reduced. Therefore, the degree of twisting will reflect the global enantiomeric excess. This work is an excellent example of using a variety of complementary techniques and modeling to evaluate a gel system and provide fresh insight into the connection between aggregate morphology and molecular structure.

3.4 Sugar-Based Systems

Carbohydrates provide a rich library of water-soluble, chiral building blocks that have been used successfully in the design of both organo and hydrogelators (Chart 5).[115] Sugars are also biocompatible, which makes them attractive candidates for hydrogels with biological applications. Shinkai and coworkers have made the most extensive use of sugars in their quest for small molecule organic hydrogelators. Three related examples (**23**−**25**) all use a sugar for solubility and an aromatic group to promote $\pi-\pi$ aggregation in water.[35,37,47,48,116−118] Many of these derivatives are able to gel both water and organic solvents, highlighting the versatility of sugar moieties.[35,37,48,117,118] Several of these gelators have been identified via a combinatorial approach.[4,115,117−119] By rapidly synthesizing and screening a library of glycosylated amino acids as potential gelators, **26** was found to have a thermally responsive phase transition.[4,119] This could be useful for the release or capture of drugs or pollutants.[4] Depending on the chemical properties (hydrophobicity versus hydrophilicity), a molecule will be either trapped in the gel (pollutants such as bisphenol A) or released from the gel (DNA) with heating. The authors also show that these glycosylated gelators can stabilize myoglobin in its active state for extended periods (longer than in solution) without significant leakage into buffer.[119]

Bhattacharya and Acharya have examined the hydrogelation abilities of a series of disaccharide amphiphiles (**27**) with both one and two alkyl tails in the presence of alcohol cosolvents.[31] Only the cyclic derivatives form gels, suggesting that the conforma-

Chart 6. Assorted Other Organic Hydrogelators



tional rigidity of sugars is important for directing the intermolecular hydrogen-bonding networks formed by amide N−H and carbohydrate OH groups. The double-chained amphiphiles do not form gels that are as stable in comparison to their monochain equivalents, suggesting again that gelation results from a careful balance of the hydrophobicity and hydrophilicity of these molecules.

3.5 Others

There are several small molecule hydrogelators that defy categorization into any of the previous four groupings. Two classes of significantly larger molecules self-assemble to form hydrogels. Since the gels are still held together via noncovalent interactions, they are not considered polymer gels, despite the high molecular weights. One such family is the arborol or cascade molecules (**28**), designed by Newkome and co-workers, that can be thought of as large bolaamphiphiles in which the hydroxyl headgroups provide solubility and the hydrophobic core promotes aggregation.[44] Related, even larger, structures that gel water at lower weight percentages than the arborols are dendrimers.[120,121]

The sodium salts of terpyridine-containing carboxylic acids (**29**) have been shown to form hydrogels above their CMC, which indicates that the gel is most likely composed of rodlike micelles.[32] If this is the case, these molecules can be characterized as amphiphiles. However, the authors do not account for the role of the terpyridine unit and only note that the di- and monopyridine-containing derivatives do not form gels. Unfortunately, no further structural analysis was performed to elucidate the molecular recognition events leading to gelation.

Facially amphiphilic molecules also have the potential to form hydrogels.[43,122] The tripodal cholic acid derivative (**30**) forms gels in aqueous medium with large hydrophobic pockets that are able to trap organic dyes.[43] By following fluorescence enhancement upon gelation, the authors report that the hydrophobicity within the gel pockets is greater than the interior of β-cyclodextrin. The pockets are thought to be formed by the association of the lipophilic β faces of the cholic acid backbone. The same authors have also recently reported simpler monomeric bile acid gelators.[122]

One way of identifying possible gelators is to look for molecules that crystallize within a strongly anisotropic arrangement, which suggests possible fibrous behavior. Using this approach, Menger and coworkers synthesized derivatives of aroyl-L-cystines and evaluated them for hydrogelation ability.[33] They found several structures (**32**) that formed very dilute and thermally stable gels.

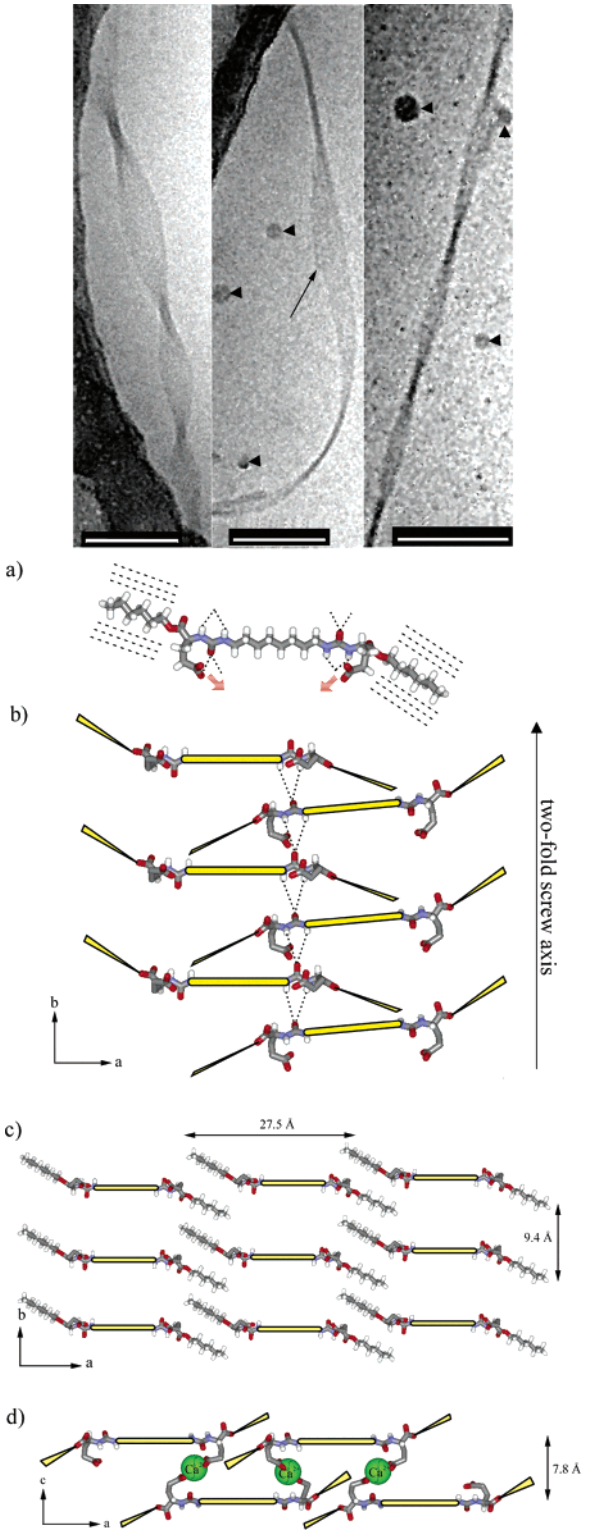


Figure 14. Cryo-TEM images of a gel of **32**. Round dark circles (marked by arrowheads) are ice crystals. The long arrow indicates a step in an untwisted portion of the ribbon. Scale bars: 100 nm. (a) A molecular model showing the different structural motifs leading to aggregation: hydrophobic interactions of the alkyl ester chains, hydrogen bonding of the ureas, and calcium−carboxylate coordination. (b) The hydrogen bonding motif between molecules related by the 2-fold screw axis, *b*. (c) The stacking between the alkyl ester side chains of molecules related by translation. (d) The packing along the *c* axis through Ca^{2+}−bis(carboxylate) interactions, which are located on a 2-fold screw axis. (Reproduced with permission from ref 64, Copyright 2003, Wiley-VCH.)

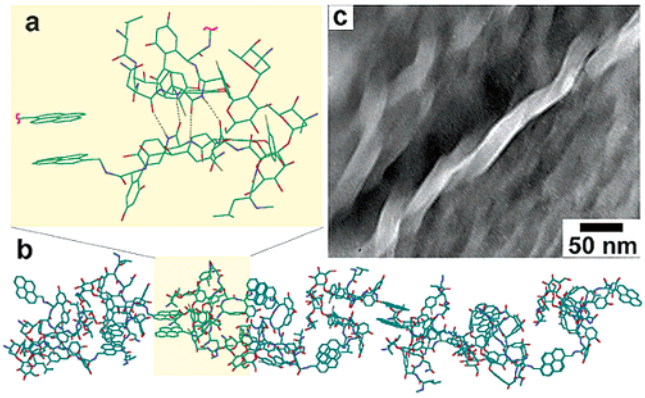


Figure 15. (a) Schematic of the $\pi-\pi$ stacking of the pyrene units and dimerization of the vancomycin, resulting in polymerization of **34**. (b) Possible conformation of a helix of **34**. (c) TEM micrograph of the dried hydrogel. (Reproduced with permission from ref 2, copyright 2002, American Chemical Society.)

The family of bis(urea) dicarboxylic acids (**31**) is a mix between an amino acid bolaamphiphile and a gemini surfactant.[49,64] They were found to self-assemble to form hydrogels, at very low (0.3 wt %) concentrations, dependent on both pH and ionic strength.[49] In addition to gels, molecules in this family also form giant vesicles (at low pH) and precipitate as fibers (at higher pH values). The aggregate morphology was also found to depend strongly on the hydrophobicity of the molecule, with lower-molecular-weight molecules gelling water at lower pH values. The organic hydrogel of **31** was characterized using cryo-TEM and X-ray diffraction in order to gain more information about the atomic scale organization.[64] There are three structural motifs that contribute to the aggregation: the hydrophobic alkyl esters, the ureas capable of hydrogen bonding, and the carboxylates that are available for cation coordination. The diffraction pattern of the gel suggested that there was ordering in only two dimensions. We propose that a structural mismatch between the linker and tail lengths results in disorder in the third dimension and, thus, gel formation rather than precipitation (Figure 14).

Another example of a pH-triggered gelator is the resorcinarene (**33**) recently reported by Haines and Harrison.[123] Gelation occurs only below pH 2.5, which corresponds to the pK_a value for the protonation of one of the carboxylates, at which point the molecule is neutral. In the presence of divalent cations, in particular Cu^{2+}, gelation is inhibited, presumably due to strong interactions of the iminodiacetate ligand and cation.

In a recent communication, Xing et al. report the first example of an antibiotic hydrogel formed by a vancomycin−pyrene derivative (**34**).[2] Vancomycin is known to dimerize via the formation of multiple hydrogen bonds. The large, flat, hydrophobic surface of pyrene is also known to promote aggregation. When combined into one structure, the molecules aggregate to form helical, gelating ribbons (Figure 15). This derivative retains its antibiotic activity, opening up the possibility of a gel that can be applied topically to wounds.

4. Conclusion

From this review of the small molecule organic hydrogelator literature over the past 20 years, a picture begins to emerge of the features necessary for effective gelation. While there appears to be no general rule for how to balance the hydrophobicity and hydrophilicity of a given molecule, such a distribution is essential for gelation to be preferred over fiber precipitation. Within families of structures, predictions can be made about the number of carbons per polar unit that are required to observe gel formation. Charged groups greatly facilitate gel formation and also provide a convenient trigger via pH modulation.

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