Tetrahedron 66 (2010) 5962–5971

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis and characterization of D-glucosamine-derived low molecular weight gelators

Navneet Goyal [1], Sherwin Cheuk [1], Guijun Wang *

Department of Chemistry, University of New Orleans, New Orleans, LA 70148, USA

ARTICLE INFO

Article history:
Received 21 April 2010
Accepted 17 May 2010
Available online 1 July 2010

Keywords:
Hydrogelator
Organogelator
Glucosamine
Carbohydrate
Self-assembling

ABSTRACT

Carbohydrate-based low molecular weight gelators are an interesting class of molecules with many potential applications. Previously, we have found that certain esters and carbamates of 4,6-*O*-benzylidene-α-D-methyl-glucopyranoside are low molecular weight gelators for a variety of solvents, including water. In order to obtain effective and robust sugar-based organogelators and understand the structure and gelation relationship, we extended our studies using 4,6-*O*-benzylidene-α-D-methyl-2-deoxy-2-amino-glucopyranoside as the headgroup. A series of amides and ureas were prepared from the protected D-glucosamine and the corresponding isocyanates or acid chlorides, in good yields. The self-assembling properties of these compounds were studied in several solvents, including water and aqueous solutions. Comparing to the ester and carbamate derivatives previously prepared from D-glucose, the amides and urea derivatives afforded more robust gels at lower concentrations typically. Most of these compounds were found to be efficient low molecular weight hydrogelators (LMHGs) for aqueous solutions at concentrations lower than 0.5 wt %. The preparation and characterization of these compounds are reported here.

1. Introduction

In recent years, low molecular weight gelators (LMWGs) have gained great attention because of their potential applications as advanced soft materials. LMWGs are small molecules that are able to form reversible gels in organic solvents or aqueous solutions. These compounds are able to self-assemble and form three-dimensional networks by solely non-covalent forces, such as hydrogen bonding, π–π stacking, hydrophobic interactions, etc. The resulting gels are usually called supramolecular gels or physical gels to differentiate from polymer gels. There has been much effort in discovering effective LMWGs and understanding the gelation phenomenon.[1–5] LMWGs encompass broad structure classes and are often discovered by serendipity. Carbohydrates are naturally abundant renewable resources, which are useful in the preparation of chiral intermediates and advanced materials. The dense chiral hydroxyl groups present in carbohydrates can be regioselectively functionalized to form interesting self-assembled supramolecular structures including LMWGs. Sugar-based organogelators have been found to be versatile materials for drug delivery, enzyme immobilization, etc.[6–10]

The modification of simple carbohydrate derivatives to obtain effective low molecular weight hydrogelators and organogelators is of great interests to us.[11–14] Previously, we had found that various derivatives of 4,6-*O*-benzylidene-methyl-α-D-glucopyranose exhibited good gelation properties.[11–13] A series of esters and carbamates were synthesized and studied systematically, and we found that certain structural features are important for forming gels in aqueous solutions of DMSO or ethanol. For example, compounds with the general structure **1** exhibited good gelation in polar solvents when the R group is a short alkyl chain with terminal acetylene function.[11] In monoesters **1**, the free hydroxyl group can function as hydrogen bond donor and facilitates the self-assembling. The carbamate derivatives **2** were more efficient gelators compared to the esters and the R group tolerated a broader range of functional groups, typically these compounds were able to form gels at lower concentrations. We also synthesized several carbamate derivatives with the general structure **3**, these compounds generally showed gelation capability in aqueous mixtures. The improved gelation efficacy for carbamates is attributed to the additional hydrogen bonding donor NH group (Fig. 1).[14]

The carbamates **3** were synthesized using the protected D-glucosamine **4** as the headgroup.[15,16] Based on the improved gelation for carbamates, it is reasonable to expect that other types of derivatives of compound **4** such as amides and ureas may offer even better gelation results. Urea derivatives have been studied extensively as organogelators. Much of their gelation ability stems from the one-dimensional hydrogen bonding array formed by the urea functional groups.[17–37] This allows the molecules to self-assemble in a highly ordered fashion. Though they are not as extensively studied

* Corresponding author. Tel.: +1 504 280 1258; fax: +1 504 280 6860; e-mail address: gwang2@uno.edu (G. Wang).

[1] The two authors, Goyal N. and Cheuk S. contributed equally.

0040-4020/$ – see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.tet.2010.05.071

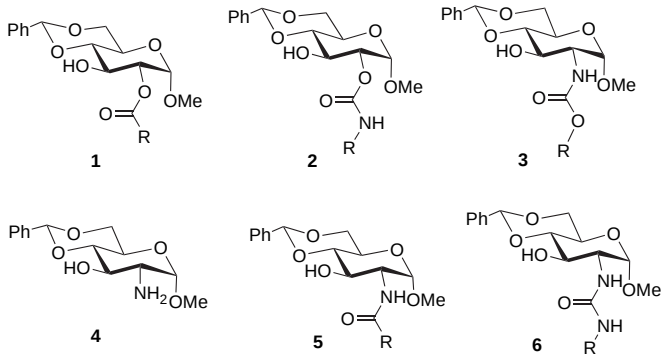


Figure 1. General structures of several D-glucose and D-glucosamine derivatives.

as the ureas, amides can also form hydrogen bonding arrays, and are also used often in the design and synthesis of low molecular weight gelators.[38–42] Therefore, with the proper selection of alkyl groups, the amide and urea derivatives **5** and **6** are expected to be good hydrogelators or organogelators. The structure information obtained from our studies of the glucose-based gelators **1**, **2**, and **3** can help us to select suitable substituents for the amino group.

2. Results and discussions

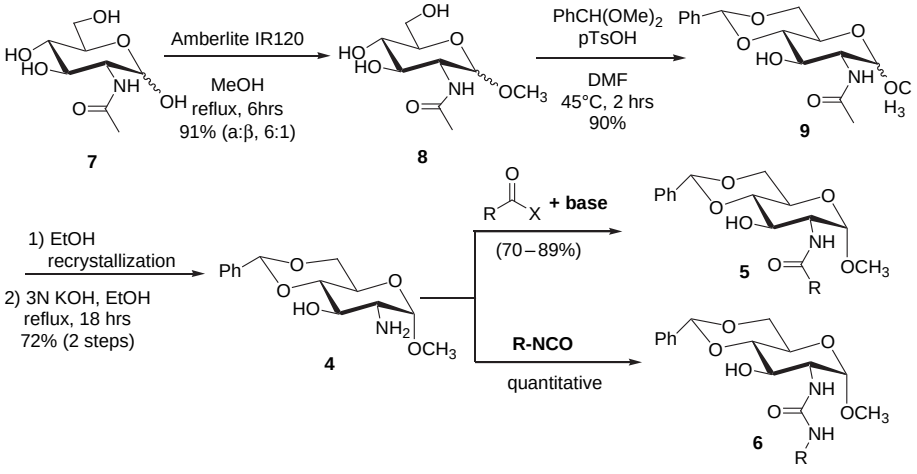
In order to understand the structure requirements for the glucosamine derivatives to form stable and efficient hydro/organogels at lower gelation concentrations, we synthesized and characterized two new series of compounds, the amides **5** and ureas **6**. These compounds can be synthesized readily using the headgroup glucosamine derivative **4**, which was obtained in a few steps from *N*-acetyl-glucosamine **7** as shown in Scheme 1.[16] First, *N*-acetyl-D-glucosamine **7** was methylated in the presence of acidic resin, giving a mixture of anomers with the α anomer as the major product. The resulting intermediate **8** was converted to the acetal **9** using benzylidene dimethyl acetal. The major isomer was separated via recrystallization in ethanol, followed by hydrolysis using KOH to afford the headgroup **4**.

2.1. Preparation of amides and gelation properties

The amides **5** were prepared by the method shown in the last step of Scheme 1. The amino group from **4** was typically functionalized with an acid chloride in the presence of pyridine or triethylamine to give the amide in good yield. The structures of the amides synthesized and their gelation properties in several solvents are summarized in Table 1. These functional groups were chosen partially based on the structural information obtained from the ester derivatives. We expected that the additional hydrogen bonding unit would allow a wider range of the hydrophobic tail R groups to afford gels because of the potential for enhanced hydrogen bonding interactions. Therefore, a broader series of acyl groups were selected here. These include the straight chain analogs with 5–8 carbons **10**–**13**, compounds with terminal acetylene functional groups **14**–**17**, compounds with alkene groups **18** and **19**, compounds with halogens **20** and **21**, and aromatic derivatives **22** and **23**. After their preparation, these compounds were screened for their gelation properties (Table 1).

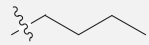
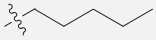
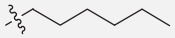
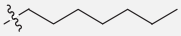
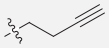
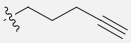
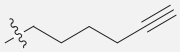
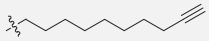
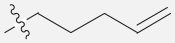
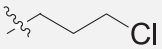
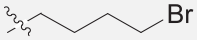
From Table 1, most of the compounds were able to form stable gels in 33% aqueous solutions of DMSO or ethanol at concentrations lower than 5.0 mg/mL. Several compounds also formed gels in ethanol and fewer formed gels in hexane or water. These results are different than the ones obtained from the glucose ester derivatives, in which a majority of the alkynyl 2-esters were able to gelate both hexane and water.[11] The presence of the amide bonds, especially the NH bond, is important in the formation of the self-assembled networks. Similar to the glucose ester derivatives, the alkyl chain plays an important role in gelation. We found that amides containing chains that were 6–8 carbons in length formed very stable gels at relatively low concentrations. Typically, the amides formed robust and translucent gels (Figure S1). For example, the hexyl amide formed gels that were stable for several months in closed containers. The gels can be reformed repeatedly by reheating and sonication of the solution phases. The ability of these various amides to form stable gels in aqueous mixtures might arise from a hydrogen bonding interaction of the amide bonds with the solvents. Ethanol and DMSO can aid in self-assembly by solvating the hydrophobic regions of the LMOGs, disrupting the crystalline packing, and thus forming gels. In addition, the compounds and the solvents have a certain 'matched' hydrophobicity and hydrophilicity, in that ethanol and DMSO can help to stabilize the gels by interacting with both regions in the amides.

For the aliphatic derivatives, the amides with saturated alkyl chains (**10**–**13**) are quite versatile and efficient LMOGs that are able to efficiently gelate a range of solvents, including hexane and aqueous mixtures of ethanol and DMSO, but not pure water. The compounds with 6–8 carbon chains (**11**–**13**) are the most efficient gelators. The alkynyl derivatives exhibit a similar trend, in that a longer chain is somewhat more favorable than a shorter chain; compounds **15**–**17** are good gelators for aqueous solutions of DMSO and EtOH. The hexynyl compound **16** proved to be the most efficient, forming stable gels in ethanol/water at 0.7 mg/mL. For the



Scheme 1. Synthesis of the amides and ureas from *N*-acetyl-D-glucosamine.

Table 1
Library of amide derivatives of **4** and their corresponding minimum gelation concentrations (MGCs) in mg/mL

	R=	Hexane	Water	EtOH	Water:DMSO (2:1)	Water:EtOH (2:1)	THF	*i*-PrOH	DCM
10		I	I	G 5.0	G 4.0	4.0	S	S	S
11		C	C	S	G 1.3	G 1.3	S	S	S
12		G 1.7	I	S	G 1.0	G 2.0	S	S	S
13		P	I	S	G 1.2	G 1.6	S	S	S
14		C	I	G 10.0	G 10.0	G 5.0	S	G 20	S
15		C	I	S	G 5.0	G 2.2	S	G10	S
16		C	C	S	G 2.0	G 0.7	C	C	S
17		G 4.0	I	S	G 1.7	G 1.2	P	C	S
18		C	I	S	C	G 10	S	S	S
19		C	I	G 10	G 5	G 2.5	P	S	S
20		C	I	G 10	G 6.6	G 5.0	S	S	S
21		I	I	G 20	G 5	G 20	S	S	S
22		I	G 2	S	G 5.0	G 3.3	C	S	S
23		C	I	S	C	G 10	C	S	S

G, gel at room temperature; the numbers in the table are the minimum gelation concentrations in mg/mL; I, insoluble; C, crystallization; S, soluble at ~20 mg/mL; P, precipitation.

alkenyl derivatives, the pentenyl derivative **19** is a versatile gelator, but the methacrylate derivative **18** is less efficient. The halogenated compounds **20** and **21** also showed positive results. For the two aryl derivatives, the phenyl amide **22** formed stable gels in water, and aqueous DMSO and ethanol, while the naphthyl amide **23** only formed gels in aqueous DMSO at higher concentrations.

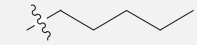
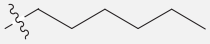
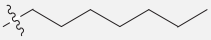
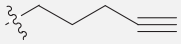
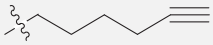
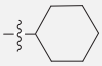
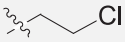
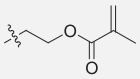
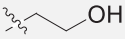
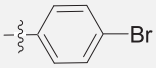
2.2. Preparation of ureas and gelation properties

Several urea derivatives were prepared by reacting compound **4** with a stoichiometric amount of the corresponding isocyanate in THF. For the compounds with terminal acetylenes, terminal alkynyl acids were converted to the corresponding isocyanates in situ by Curtis rearrangement using DPPA and triethylamine. The reactions generally proceeded with close to quantitative yields, and the products can be purified on silica gel by flash chromatography using a polar solvent. The structures of the ureas synthesized and their gelation properties are shown in Table 2. The selection of the R groups is based on the results from the carbamate and amide series and the availability of starting materials. These include compounds **24**–**26**, with saturated 5–7 carbon alkyl chains, and **27** and **28**, which are 5–6 carbon terminal alkynyl derivatives. The cyclohexyl urea **29**, several compounds with terminal substituents **30**–**32**, and aryl ureas **33**–**35** were also prepared. The gelation test results are shown in Table 2. From the screening of the gelation results of these compounds, we can determine how the structure of the alkyl or aryl groups affects self-assembling.

For the sugar derivatives here, the urea analogs showed gelation tendencies similar to the amides, with the aliphatic derivatives with 5–7 carbons being most versatile gelators for aqueous mixtures. Compounds **24**–**27** formed gels in EtOH/water and DMSO/water at concentrations lower than 0.2 wt %. The presence of a terminal acetylene group does not seem to affect gelation, and the compounds with the same chain length as their saturated counterparts gave similar gelation results. Interestingly, the chloroethyl and methacryloylethyl ureas (**30**, **31**) were also able to form gels in aqueous solutions, while the carbamate and ester analogs were not able to form gels in these solvents. The methacrylate **30** can form gels in water at 10 mg/mL. After hydrolysis of the methacrylate, the alcohol **32** can also form stable clear gels in water (Figure S1 in Supplementary data). Aromatic ureas are somewhat less effective for aqueous solutions compared to the aliphatic ureas; this may be due to the extra rigidity in the molecule. The aromatic urea derivatives **33**–**35** contain hydrogen bonding functions plus the aromatic rings necessary for $\pi-\pi$ stacking. These aromatic interactions reinforce the molecular packing and result in stronger intermolecular forces. Therefore, they tend to be insoluble or crystallize in polar solvents.

We analyzed several gels in their gel states using optical microscopy, in an attempt to reveal the supramolecular assembly of the gels with the solvents still trapped inside. The dried xerogels were also studied by optical microscopy and scanning electron microscopy. These results are shown in Figures 2–5. The optical micrographs of the wet gels formed by compounds **17** and **19** are

Table 2
Library of urea derivatives of **4** and corresponding MGCs (mg/mL)

	R=	Hexane	Water	EtOH	Water:DMSO (2:1)	Water:EtOH (2:1)	THF	*i*-PrOH	DCM
24		I	I	S	G 1.2	G 1.3	S	S	S
25		I	I	S	G 1.0	G 1.5	S	S	S
26		I	P	G 10	G 1.0	G 1.6	S	G20	S
27		P	I	G 6.6	G 2.8	G 1.2	S	G20	S
28		C	I	S	G 2.8	G 1.3	P	S	S
29		I	I	G 10	G 3.3	G 1.3	S	S	S
30		I	I	S	G 10	G 10	S	S	S
31		P	G 10	S	G 6.7	G 2.2	S	S	S
32		I	G 2.2	G 20	G 10	G 4.0	S	G20	S
33		I	I	G 10	G 5	G 20	S	S	S
34		I	I	I	G 2.5	G 2.0	C	S	S
35		I	I	G 15	G 2.2	P	S	S	S

G, stable gel at room temperature, the numbers are the minimum gelation concentrations in mg/mL; I, insoluble; C, crystallization; S, soluble at ~20 mg/mL, P, precipitate.

shown in Figures 2 and 3. The gel of **17** in ethanol/water showed bundled fibrous assemblies, as shown in Figure 2A–C. At lower magnification (200×), we can see the long fibers floating in the gel solvent matrix. Figure 2C is a picture of the bundled fibers in 2B at a higher magnification, and it is evident that the dark regions are composed of many tubular types of aggregates and smaller, softer, feather like fibers spanning from the center. In DMSO/water solutions, we also observed tubular types of structures, as shown in Figure 2D–F. The fibers or tubules emerged from the gel media or were trapped in the gel media (Fig. 2D and E). At higher magnification (500×), we can observe the embedded fibrous network at the surface of the gel droplet (Fig. 2F).

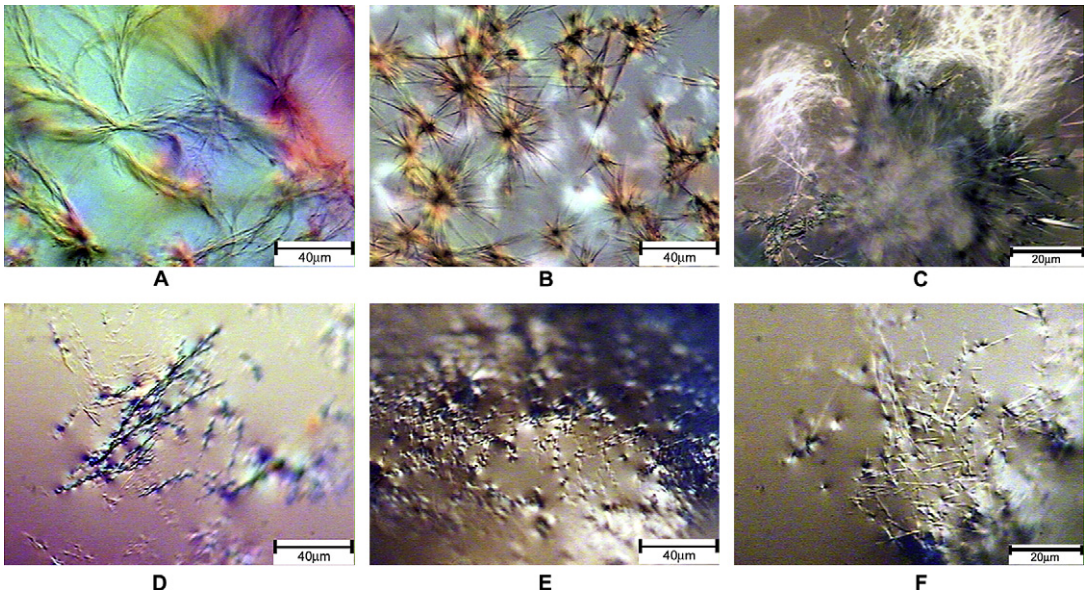


Figure 2. Optical micrographs of the gels formed by compound **17** in wet gel state. A–C are gels in EtOH/H_2O (1:2) at 3 mg/mL; D–F are gels in DMSO/H_2O (1:2) at 2 mg/mL. A, B, D, and E are obtained at 200× magnification, C and F are at 500× magnification.

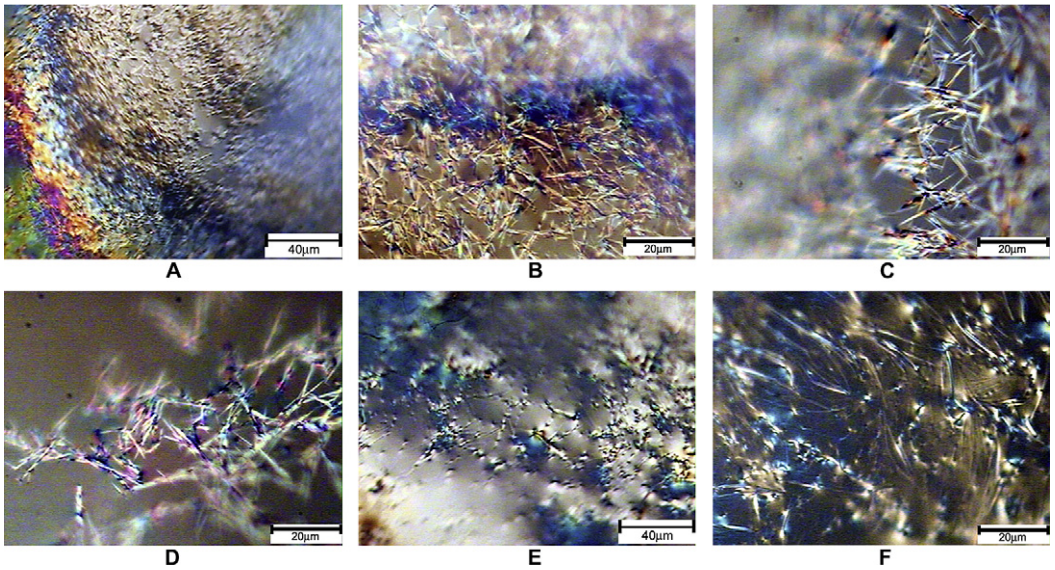


Figure 3. Optical micrographs of the gels formed by compound **19** in wet gel state. A–D are gels in EtOH/H_2O (1:2) at 2.5 mg/mL; E and F are gels in DMSO/H_2O (1:2) at 3 mg/mL. These images were obtained under crossed polarizers in phase contrast mode. A and E are 200×, B, C, D, and F are at 500× magnification.

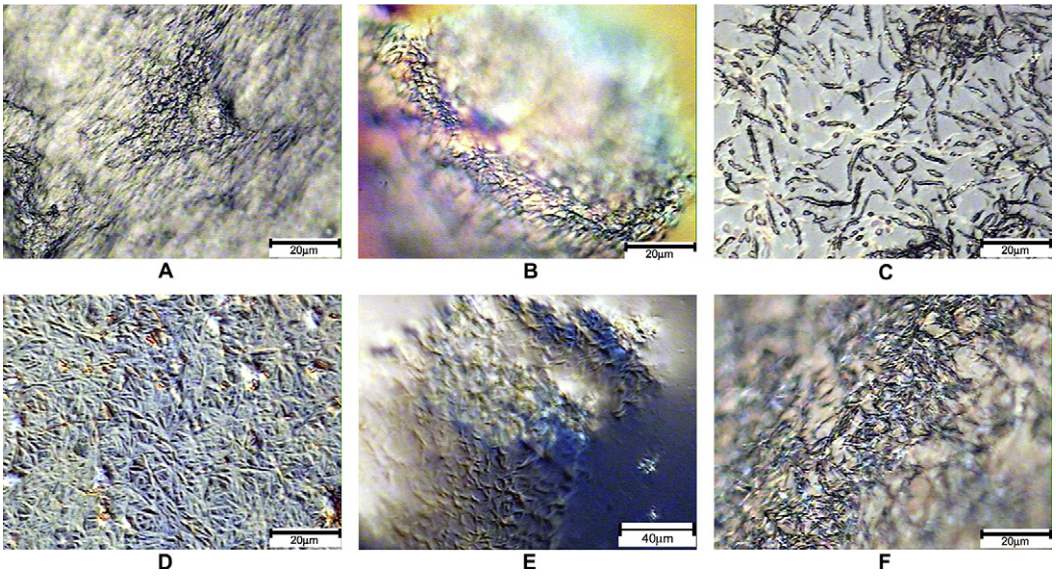


Figure 4. Optical micrographs of the gels formed by compounds **24** and **28** in gel phases. A, gel by **28** in EtOH/H_2O (1:2) at 1.5 mg/mL; B, gel by **28** in DMSO/H_2O (1:2) at 3.0 mg/mL; C and D, gel by **24** in EtOH/H_2O (1:2) at 1.5 mg/mL; E and F, gel by **24** in DMSO/H_2O (1:2) at 1.2 mg/mL. Magnification for E is 200×, and for the rest is 500×.

The gels formed by compound **19** also showed somewhat similar morphologies, as shown in Figure 3. In EtOH/H_2O, we can clearly observe the fibrous assemblies at low magnification (Fig. 3A), while at higher magnification, more detailed features of the fibrous networks can be observed (Fig. 3B–D), including birefringent fibers and tubules. In DMSO/water, long fibers were also the predominant morphologies observed in the gel (Fig. 3E and F). These were more difficult to image since the gel is three-dimensional. In many regions, we were only able to focus on one slice of the gels. Changing the focus on the microscope allowed us to observe the gels at different depths and some of these images are shown in Figure S2 in Supplementary data section.

We also obtained the optical micrographs of the ureas in the gel phase, and these are shown in Figure 4. They formed somewhat different morphologies compared to those of the amides. Compound **28** formed a stable gel in ethanol/water (1:2). The gel surface was smooth and contained some contiguous fibrous assemblies, though it was difficult to obtain better-quality pictures since, typically, they were not isolated fibers (Fig. 4A). In DMSO/water (1:2), it formed a similar morphology, and a slice of the gel showed some intertwined fibrous networks (Fig. 4B). The gel formed by compound **24** showed different morphologies as well. In EtOH/H_2O, in thinner regions, we could observe the soft tubular networks (Fig. 4C), while in the denser regions, when the solvent evaporated, we were able to observe densely packed fibrous structures (Fig. 4D). In DMSO/H_2O, we again were able to see some continuous intertwined fibrous assemblies at low magnification (Fig. 4E) and the tubular fibrous networks were observed more clearly at higher magnifications (Fig. 4F). Again, it was difficult to obtain the images of the gels since they are -three-dimensional, so we obtained the micrographs of different cross-sections of the gels. These images showed that at different surfaces of the gels, similar features of the fibrous assemblies can be observed (Figure S3 in Supplementary data).

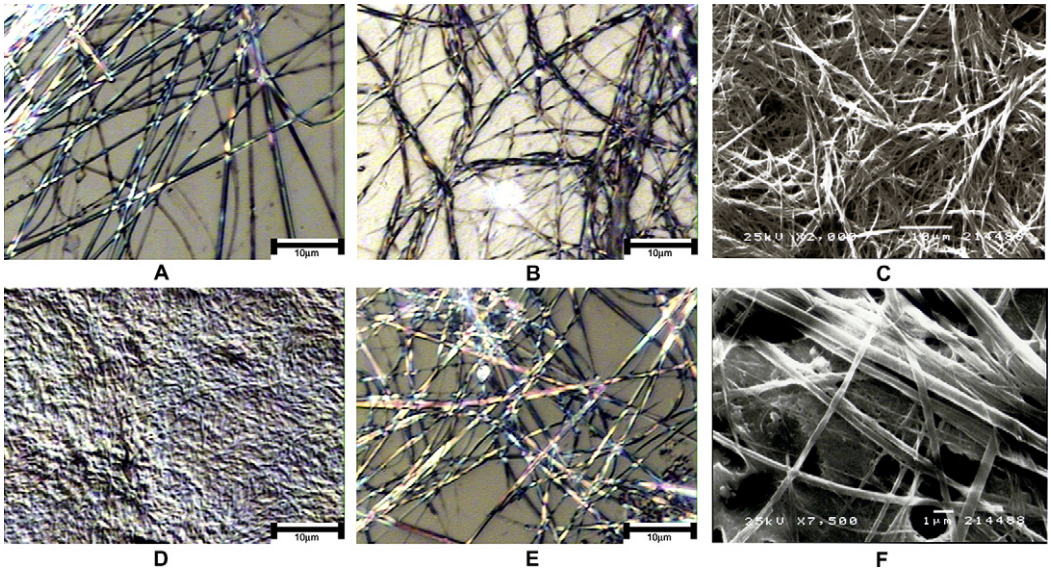


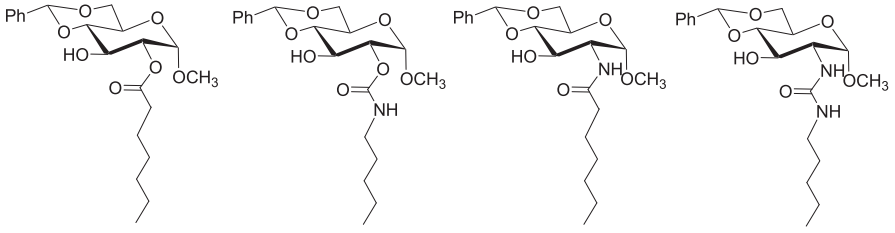
Figure 5. Optical micrographs (A, B, D, E) and scanning electron micrographs (C, F) of several dried gels. A, gel of compound **16** in EtOH/H_2O (1:2) at 0.7 mg/mL, B and C, gel of compound **12** in hexane at 1.7 mg/mL; D, gel formed by compound **11** in DMSO/H_2O (1:2) at 1.0 mg/mL, E and F, gel formed by compound **32** in water at 2.5 mg/mL. Magnifications for A, B, C, and E are1000×.

For the dried gels, it was easier to obtain their morphologies using OM or EM, and several of these are shown in Figure 5. The gels exhibit different morphologies, depending on their structures. The optical microscopy of the dried gels revealed that flexible fibers lead to more effective gelators, and that the derivatives with straight alkyl chains (as opposed to aromatic groups) tend to form these morphologies, especially in aqueous solvents. The gel formed by **16** in ethanol/water showed long uniform fibrous features (Fig. 5A). The gel of compound **11** in DMSO/water showed presence of very thin fibrous network structures (Fig. 5D). Both the OM and SEM of the gel formed by heptyl amide **12** in hexane showed the formation of entangled fibrous networks (Fig. 5B and C). The urea derivative **32** also formed fibrous or tubular type of structures (Fig. 5E and F). The SEM indicated that the tubular structures typically have diameters less than 1 μm.

From Tables 1 and 2, we can compare the gelation properties of amides and ureas containing similar alkyl chain derivatives. The compounds containing similar alkyl chain lengths are shown in Table 3, where the headgroup linkages are ester **36**, carbamate **37**, amide **12**, or urea **24**. The gelation ability of the compounds increases with the addition of an NH hydrogen bond donor.

The solvents also affect the results, since hydrophobic forces are dominant in hydrogels, whereas hydrogen bonding is the primary force in organogels. In aqueous solutions of DMSO and ethanol, the presence of organic soluble components makes the hydrogen bonding somewhat more important and the hydrophobic interactions less important. The notable difference in the gelation ability between the ester and carbamate derivatives of compound **4** indicates that the −NH is essential. This hydrogen bond donor is likely involved in the formation of a one-dimensional hydrogen bonding network. When the hydrogen bond donor NH group is closer to the sugar pyranoside ring as in compounds **13** and **17**, the gelation capabilities are similar to that of the carbamates. Few of the 2- or 3- monoesters of 4,6-*O*-benzylidene-methyl-α-D-gluco-pyranoside (**1**) formed gels in water or in aqueous solution. From esters to carbamates, amides, and ureas, the number of hydrogen bond donors in the molecules increases. It seems that the increase in intermolecular interactions is necessary to extend the network. Typically, the amides and ureas formed more robust gels than the esters. However, there is not much difference between the classes of amides and ureas. We also carried out IR studies for two representative compounds amide **17** and urea **24** in their solid and gel states (in EtOH/H_2O), respectively. The results are shown in Figures S4 and S5 in the Supplementary data section. In the gel states, both compounds exhibited similar patterns with their corresponding solid forms except for the region from 2500 to 3500 cm^{-1}, at which

Table 3
Comparing LMOGs with similar alkyl chain lengths. Positive gelation results are noted in mg/mL; P, precipitate; I, insoluble.



Compounds	**36**	**37**	**12**	**24**
H_2O	I	20	I	I
H_2O:DMSO 2:1	P	3.0	1.0	1.2
H_2O:EtOH 2:1	P	1.4	2.0	1.3

the gels' IR spectra showed broad and strong absorptions. This clearly indicates the presence of hydrogen bonds of the gelator molecules with the solvents.

3. Conclusions

A series of amide and urea derivatives of the protected D-glucosamine **4** were prepared and analyzed for their self-assembling properties in several solvents. They were synthesized via straightforward reactions with high yields in general. We found that the amides and ureas with alkyl chains are excellent gelators for solutions of aqueous ethanol and aqueous DMSO, while the aryl derivatives studied are also gelators for some polar solvents. In comparison to the esters with similar acyl functional groups, the amides and ureas showed enhanced gelation due to the presence of extra hydrogen bond donors. Optical microscopy and scanning electronic microscopy studies revealed that typically the aqueous gels are composed of self-assembled fibrous networks. Therefore, the glucosamine derivative **4** is a good building block for synthesizing effective low molecular weight gelators, and the correlation of the structure and gelation can be used for the design of other functional organo/hydrogelators. These simple sugar-derived LMWGs are expected to be useful in a variety of applications, such as in entrapping large biomolecules including enzymes, and providing a good media for enzymatic reactions.

4. Experimental section

4.1. General methods

4.1.1. Gelation testing. The compounds were tested in a 1 dram vial with a rubber lined screw cap from Kimble. A starting concentration of 20 mg/mL was used. The mixture was heated and sonicated until the sample was fully dissolved. Typically the mixture was heated in a closed container at lower temperature than the boiling points of the solvents used. The solution was then left at room temperature for 20–30 min. The vial was then examined by visual observation; if it appears as a homogenous liquid/solid, the vial is inverted, and if no solvent flows while the gel is inverted or gently shaking then it is called a stable gel. If the semi-solid like material falls apart during inversion and by gentle shaking, then it is called an unstable gel or self-supporting solids depending on the appearance. If a stable gel is formed, serial dilution is performed until the resulting gel is no longer stable. The concentration prior to formation of the unstable gel was recorded as the minimum gelation concentration (MGC).

4.1.2. Optical microscopy. The slides were prepared after a stable gel was formed. A small amount of the gel was placed on a clean glass slide and observed immediately while the solvent is still present. For DMSO aqueous solutions, since the solvent evaporates very slowly, the gels were observed within 2 h typically. For the dried gels, the slides were air dried for hydrogels and in a desiccator for organogels for overnight or longer. The gels were observed with an Olympus BX60M optical microscope using a DSP Color Hi-Res EXvision camera and an Olympus U-TV1X lens. The program used to acquire and store the photos was Corel Photo-Paint 7.

4.1.3. Scanning electron microscopy. Samples were prepared by drying the gel on an aluminum pellet in a desiccator under reduced pressure for several days. A thin layer of platinum was deposited on to the pellet by a Denton Vacuum (model Desk II) at a reduced pressure of ~30 mtorr and a current of 45 mA for 60 s. The sample was analyzed using a JEOL JSM 5410 scanning microscope.

4.2. General procedure for the synthesis of amides

4,6-*O*-Benzylidene-2-amino-2-deoxy-methyl-α-D-glucopyranoside **4** and pyridine or DIEA (2 equiv) were mixed in anhydrous THF at 0 °C. The corresponding acyl halide (1.1 equiv) was added dropwise. After 4–6 h the reaction was diluted with DCM and washed with H_2O and then dilute HCl (~0.1 N). The organic layer was dried with anhydrous Na_2SO_4. The crude products were purified using flash chromatography on silica gel with a solvent gradient of hexane and acetone or DCM with 1–2% MeOH.

4.2.1. General procedure for the synthesis of ureas. The urea library was synthesized by mixing compound **4** and the corresponding isocyanate in stoichiometric quantities in anhydrous THF. The solution was stirred at rt for 6–8 h. The crude products were purified by flash chromatography on silica gel if the ^{1}H NMR spectrum indicates the product is not pure. Typically DCM/MeOH gradient solvent system is used for the chromatography separation, if needed.

*4.2.2. Pentyl amide **10**.* The compound was obtained as a white solid at a yield of 88%, mp 195.2–196.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) 7.47–7.54 (m, 2H), 7.32–7.40 (m, 3H), 5.83 (d, 1H, *J*=8.1 Hz), 5.57 (s, 1H), 4.72 (d, 1H, *J*=4.0 Hz), 4.20–4.33 (m, 2H), 3.90 (dt, 1H, *J*=3.3, 9.5 Hz), 3.78 (m, 2H), 3.59 (m, 1H), 3.41 (s, 3H), 3.13 (d, 1H, *J*=3.3 Hz, OH), 2.26 (t, 2H, *J*=7.3 Hz), 1.64 (m, 2H), 1.36 (sext, 2H, *J*=7.3 Hz), 0.92 (t, 3H, *J*=7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 137.1, 129.1, 128.2, 126.3, 101.8, 98.8, 82.0, 70.7, 68.8, 62.3, 55.3, 54.0, 36.3, 27.6, 22.2, 13.7. HRMS calcd for $C_{19}H_{28}NO_6$ $[M+H]^+$ 366.1917, found 366.1920.

*4.2.3. Hexyl amide **11**.* The hexyl amide was obtained as a white solid at a yield of 86%, mp 192.3–193.1 °C. ^{1}H NMR, (400 MHz, $CDCl_3$) δ (ppm) 7.47–7.52 (m, 2H), 7.33–7.39 (m, 3H), 5.85 (d, 1H, *J*=8.4 Hz), 5.57 (s, 1H), 4.72 (d, 1H, *J*=3.7 Hz), 4.19–4.32 (m, 2H), 3.91 (ddt, 1H, *J*=9.7 Hz), 3.74–3.83 (m, 2H), 3.59 (m, 1H), 3.41 (s, 3H), 2.25 (t, 2H, *J*=7.3), 1.65 (p, 2H, *J*=7.3 Hz), 1.32 (m, 4H), 0.90 (t, 3H, *J*=7.2 Hz). ^{13}C NMR, (100 MHz, $CDCl_3$) δ (ppm) 174.9, 137.0, 129.1, 128.2, 126.2, 101.8, 98.9, 82.0, 69.7, 68.7, 62.4, 55.2, 53.8, 36.3, 31.2, 25.1, 22.2, 13.8. HRMS calcd for $C_{20}H_{30}NO_6$ $[M+H]^+$ 380.2073, found 380.2071.

*4.2.4. Heptyl amide **12**.* The product was obtained as a white crystalline solid at a yield of 87%, mp 197.8–198.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44–7.51 (m, 2H), 7.30–7.38 (m, 3H) 6.08 (d, 1H, *J*=8.8 Hz), 5.54 (s, 1H), 4.69 (d, 1H, *J*=3.7 Hz), 4.25 (m, 1H), 4.15 (d, 1H, *J*=3.7, 9.9 Hz), 3.83 (t, 1H, J=9.7 Hz), 3.69–3.78 (m, 2H), 3.55 (m, 1H), 3.37 (s, 3H), 2.13–2.26 (m, 3H), 1.60 (m, 2H), 1.27 (s, 6H), 0.85 (t, 3H, *J*=6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 137.0, 129.1, 128.2, 126.2, 101.9, 98.9, 82.1, 70.0, 68.8, 62.4, 55.3, 53.8, 36.5, 31.4, 28.7, 25.5, 22.4, 14.0. HRMS calcd for $C_{21}H_{32}NO_6$ $[M+H]^+$ 394.2230, found 394.2237.

*4.2.5. Octyl amide **13**.* The product was obtained as a white crystalline solid at a yield of 88%, mp 183.8–185.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46–7.52 (m, 2H), 7.33–7.39 (m, 3H), 5.85 (d, 1H, *J*=8.8 Hz), 5.57 (s, 1H), 4.72 (d, 1H, *J*=4.0 Hz), 4.28 (m, 1H), 4.23 (m, 1H), 3.90 (t, 1H, *J*=9.5 Hz), 3.74–3.83 (m, 2H), 3.59 (m, 1H), 3.41 (s, 3H), 3.15 (br s, 1H), 2.25 (m, 2H), 1.64 (m, 2H), 1.19–1.40 (m, 8H), 0.87 (t, 3H, *J*=7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.7, 137.0, 129.2, 128.2, 126.3, 101.9, 98.8, 82.1, 70.9, 68.8, 62.3, 55.3, 54.0, 36.6, 31.7, 29.1, 29.0, 25.6, 22.6, 14.0. HRMS calcd for $C_{22}H_{34}NO_6$ $[M+H]^+$ 408.2386, found 408.2395.

*4.2.6. 4-Pentynyl amide **14**.* The compound was obtained as a white solid at a yield of 79%, mp 180.0–180.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) 7.46–7.53 (m, 2H), 7.32–7.40 (m, 3H), 6.04 (d, 1H, *J*=8.4 Hz), 5.57(s, 1H), 4.72 (d, 1H, *J*=4.0 Hz), 4.22–4.33 (m, 2H), 3.91 (t, 1H, *J*=9.5 Hz), 3.73–3.85 (m, 2H), 3.59 (m, 1H), 3.41 (s, 3H), 2.99

(br s, 1H), 2.52–2.59 (m, 2H), 2.45–2.50 (m, 2H), 2.02 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 136.9, 129.1, 128.1, 126.2, 101.8, 98.8, 82.6, 81.9, 69.5, 69.2, 68.7, 62.4, 55.2, 53.9, 35.0, 14.7. HRMS calcd for $C_{19}H_{24}NO_6$ $[M+H]^+$ 362.1604, found 366.1604.

4.2.7. 5-Hexynyl amide ***15***. Flash chromatography (CH_2Cl_2:MeOH 9.3:0.7) was used to obtain the product in 70% yield as a white solid, mp 176.1–177.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) 7.47–7.52 (m, 2H), 7.33–7.40 (m, 3H), 5.92 (d, 1H, *J*=8.8 Hz), 5.57 (s, 1H), 4.72 (d, 1H, *J*=3.7 Hz), 4.20–4.31 (m, 2H), 3.90 (dt, 1H, *J*=3.3, 9.9 Hz), 3.73–3.83 (m, 2H), 3.59 (m, 1H), 3.41 (s, 3H), 3.06 (d, 1H, *J*=3.3 Hz), 2.41 (t, 2H, *J*=7.1 Hz), 2.28 (m, 2H), 1.99 (t, 1H, *J*=2.6 Hz), 1.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 137.0, 129.2, 128.3, 126.3, 101.9, 98.8, 83.4, 82.0, 70.8, 69.3, 68.8, 62.3, 55.3, 53.9, 34.9, 23.9, 17.6. HRMS calcd for $C_{20}H_{26}NO_6$ $[M+H]^+$ 376.1760, found 376.1756.

4.2.8. 6-Heptynyl amide ***16***. The compound was isolated as a white solid, 70%, mp 174.4–175.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) 7.47–7.53 (m, 2H), 7.33–7.40 (m, 3H), 5.85 (d, 1H, *J*=8.4 Hz), 5.57 (s, 1H), 4.72 (d, 1H, *J*=3.7 Hz), 4.29 (m, 1H), 4.24 (ddd, 1H, *J*=3.7, 4.0, 8.8 Hz), 3.90 (dt, 1H, *J*=3.3, 9.5 Hz), 3.74–3.85 (m, 2H), 3.59 (m, 1H), 3.41 (s, 3H), 3.03 (d, 1H, *J*=3.3 Hz), 2.29 (t, 2H, *J*=7.3 Hz), 2.22 (dt, 1H, *J*=2.6, 7.0 Hz), 1.96 (t, 1H, *J*=2.6 Hz), 1.79 (m, 2H), 1.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 137.0, 129.1, 128.2, 126.3, 101.8, 98.8, 84.0, 82.0, 70.6, 68.8, 68.6, 62.3, 55.3, 53.9, 35.9, 27.7, 24.6, 18.1. HRMS calcd for $C_{21}H_{28}NO_6$ $[M+H]^+$ 390.1917, found 390.1917.

4.2.9. 10-Undecynyl amide ***17***. The product was obtained as a white solid at a yield of 84%, mp 184.5–185.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46–7.52 (m, 2H), 7.32–7.39 (m, 3H), 5.92 (d, 1H, *J*=8.4 Hz), 5.54 (s, 1H), 4.71 (d, 1H, *J*=3.7 Hz), 4.26 (m, 1H), 4.20 (ddd, 1H, *J*=3.7, 4.0, 8.8 Hz), 3.87 (t, 1H, *J*=9.6 Hz), 3.71–3.82 (m, 2H), 3.57 (t, 1H, *J*=9.0 Hz), 3.38 (s, 3H), 2.22 (m, 2H), 2.16 (dt, 2H, *J*=2.6, 7.1 Hz), 1.93 (t, 1H, *J*=2.6 Hz), 1.62 (m, 2H), 1.50 (pentet, 2H, *J*=7.0), 1.37 (m, 2H), 1.29 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.6, 137.1, 129.1, 128.2, 126.3, 101.8, 98.8, 84.6, 82.0, 70.5, 68.7, 68.1, 62.3, 55.2, 53.9, 36.5, 29.1, 29.0, 28.8, 28.5, 28.3, 25.5, 18.3. HRMS calcd for $C_{25}H_{36}NO_6$ $[M+H]^+$ 446.2543, found 446.2524.

4.2.10. Methacrylamide ***18***. The compound was obtained as a white solid at a yield of 85%, mp 187.2–187.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) 7.45–7.55 (m, 2H), 7.30–7.42 (m, 3H), 6.21 (d, 1H, *J*=8.4 Hz), 5.76 (s, 1H), 5.56 (s, 1H), 5.39 (s, 1H), 4.76 (d, 1H, *J*=3.7 Hz), 4.23–4.33 (m, 2H), 3.94 (t, 1H, *J*=9.5 Hz), 3.72–3.84 (m, 2H), 3.60 (t, 1H, *J*=8.8 Hz), 3.40 (s, 3H), 3.29 (s, 1H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 139.2, 137.1, 129.1, 128.2, 126.3, 120.7, 101.8, 98.8, 82.0, 70.6, 68.8, 62.3, 55.3, 54.1, 18.5. HRMS calcd for $C_{18}H_{24}NO_6$ $[M+H]^+$ 350.1604, found 355.1588.

4.2.11. 5-Hexenyl amide ***19***. The compound was obtained as a white solid at a yield of 76%, mp 178.1–179.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) 7.46–7.52 (m, 2H), 7.33–7.39 (m, 3H), 5.86 (d, 1H, *J*=8.4 Hz), 5.77 (m, 1H), 5.56 (s, 1H), 5.03 (d, 1H, *J*=17.9 Hz), 4.99 (d, 1H, J=10.6 Hz), 4.71 (d, 1H, *J*=3.7 Hz), 4.28–4.19 (m, 2H), 3.88 (t, 1H, *J*=9.5 Hz), 3.77 (m, 2H), 3.58 (m, 1H), 3.40 (s, 3H), 3.19 (br s, 1H), 2.25 (t, 2H, *J*=7.5 Hz), 2.10 (q, 2H, *J*=7.0 Hz), 1.76 (pentet, 2H, *J*=7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 137.8, 137.1, 129.2, 128.2, 126.3, 115.5, 101.9, 98.8, 82.0, 70.8, 68.8, 62.3, 55.3, 54.0, 35.7, 33.0, 24.5. HRMS calcd for $C_{20}H_{28}NO_6$ $[M+H]^+$ 378.1917, found 378.1899.

4.2.12. 4-Chlorobutyl amide ***20***. The compound was obtained as a white solid at a yield of 89%, mp 195.2–196.1. °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) 7.46–7.53 (m, 2H), 7.34–7.40 (m, 3H), 5.89 (d, 1H, *J*=8.4 Hz), 5.57 (s, 1H), 4.72 (d, 1H, *J*=4.0 Hz), 4.21–4.34 (m, 2H), 3.91 (dt, 1H, *J*=2.9, 9.9 Hz), 3.73–3.84 (m, 2H), 3.55–3.68 (m, 3H), 3.42 (s, 3H), 2.91 (d, 1H, *J*=2.9 Hz), 2.46 (t, 2H, *J*=7.0 Hz), 2.14 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 136.9, 129.0, 128.1, 126.1, 101.7, 98.8, 81.8, 69.3, 68.7, 62.4, 55.2, 53.8, 44.2, 33.0, 27.9. HRMS calcd for $C_{18}H_{25}NO_6Cl$ $[M+H]^+$ 386.1370, found 386.1355.

4.2.13. 5-Bromopenyl amide ***21***. The compound was obtained as a white solid at a yield of 80.5%, mp 169.2–170.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) 7.45–7.52 (m, 2H), 7.33–7.39 (m, 3H), 5.88 (d, 1H, *J*=8.4 Hz), 5.56 (s, 1H), 4.72 (d, 1H, *J*=4.0 Hz), 4.28 (m, 1H), 4.22 (m, 1H), 3.89 (ddt, 1H, *J*=9.7 Hz), 3.77 (m, 2H), 3.58 (m, 1H), 3.41 (t, 2H, *J*=6.6 Hz), 3.40 (s, 3H), 2.38 (t, 2H, *J*=7.1 Hz), 1.90 (m, 2H), 1.81 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 136.9, 129.0, 128.1, 126.1, 101.7, 98.8, 81.8, 69.2, 68.6, 62.4, 55.1, 53.8, 44.2, 32.9, 27.9. HRMS calcd for $C_{19}H_{27}BrNO_6$ $[M+H]^+$ 444.1022, found 444.1014.

4.2.14. Benzoyl amide ***22***[43]. The product was obtained as a white crystalline solid at a yield of 89%, mp 247.2–247.8 ^{1}H NMR (400 MHz, $CDCl_3$/MeOH), δ (ppm) 7.74 (d, 2H, *J*=8.1 Hz), 7.40–7.47 (m, 3H), 7.33–7.38 (m, 3H), 7.26–7.32 (m, 3H), 5.52 (s, 1H), 4.78 (d, 1H. *J*=3.7 Hz), 4.27 (dd, 1H, *J*=3.3, 10.3 Hz), 4.22 (m, 1H), 3.91 (t, 1H, *J*=9.5 Hz), 3.70–3.82 (m, 2H), 3.57 (t, 1H, *J*=8.8 Hz), 3.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$/MeOH) δ (ppm) 168.7, 137.0, 133.6, 131.8, 129.0, 128.4, 128.1, 127.0, 126.1, 102.1, 99.1, 81.9, 69.1, 68.7, 62.5, 55.2, 54.4. HRMS calcd for $C_{21}H_{24}NO_6$ $[M+H]^+$ 386.1604, found 386.1595.

4.2.15. Naphthyl amide ***23***. The compound was obtained as a white solid at a yield of 84%, mp 206.8–207.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$, CD_3OD), δ (ppm) 8.34 (d, 1H, *J*=8.1 Hz), 7.93 (d, 1H, *J*=8.4 Hz), 7.88 (d, 1H, *J*=7.3 Hz), 7.67 (d, 1H, *J*=7.0 Hz), 7.43–7.59 (m, 5H), 7.32–7.40 (m, 3H), 6.38 (d, 1H, *J*=8.8 Hz), 5.60 (s, 1H), 4.93 (d, 1H, *J*=3.7 Hz), 4.53 (m, 1H), 4.31 (m, 1H), 4.02 (m, 1H), 3.75–3.88 (m, 2H), 3.63 (t, 1H, *J*=9.2 Hz), 3.41 (s, 3H), 3.25 (d, 1H, *J*=3.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, CD_3OD) δ 170.7, (170.6 minor rotamer), 136.9, 133.6 (133.62, minor rotamer), 133.4, 130.6, 129.8, 129.0, 128.1, 128.06, 127.0, 126.2, 126.1, 125.1, 124.9, 124.6, 101.7, 98.9, 81.9, 69.1, 68.7, 62.5, 55.2, 54.4 (54.5, minor tautomer). HRMS calcd for $C_{25}H_{26}NO_6$ $[M+H]^+$ 436.1760, found 436.1742.

4.2.16. Pentyl urea ***24***. The compound was obtained as a white solid at a yield of 96%, mp 186.2–187.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.41–7.49 (m, 2H), 7.34–7.41 (m, 3H), 6.06 (t, 1H, *J*=5.5 Hz), 5.79 (d, 1H, *J*=8.8 Hz), 5.59 (s, 1H), 5.21 (d, 1H. *J*=5.1 Hz), 4.61 (d, 1H, *J*=3.7 Hz), 4.16 (dd, 1H, *J*=4.8, 9.9 Hz), 3.63–3.77 (m, 2H), 3.41–3.62 (m, 3H), 3.28 (s, 3H), 2.95 (q, 2H, *J*=6.3 Hz), 1.35 (pentet, 2H, *J*=7.0 Hz), 1.24 (m, 4H), 0.85 (t, 3H, *J*=6.6 Hz). ^{13}C NMR, (100 MHz, DMSO-d_6) δ (ppm) 158.1, 137.8, 129.0, 128.1, 126.5, 101.0, 99.6, 82.0, 68.6, 68.1, 62.6, 54.8, 54.7, 39.2, 29.6, 28.7, 21.9, 14.0. HRMS calcd for $C_{20}H_{31}N_2O_6$ $[M+H]^+$ 395.2182, found 395.2196.

4.2.17. Hexyl urea ***25***. Isolated as a light yellow solid in quantitative yield, mp 183.8–185.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.42–7.49 (m, 2H), 7.34–7.41 (m, 3H), 6.07 (t, 1H, *J*=5.5 Hz), 5.80 (d, 1H, *J*=8.4 Hz), 5.60 (s, 1H), 5.22 (br s, 1H), 4.62 (d, 1H, *J*=3.7 Hz), 4.17 (dd, 1H, *J*=4.8, 9.9 Hz), 3.73 (t, 1H, *J*=10.3 Hz), 3.69 (dd, 1H, *J*=3.7, 8.8 Hz), 3.55–3.62 (m, 1H), 3.49 (m, 2H), 3.30 (s, 3H), 2.98 (q, 2H, *J*=6.2 Hz), 1.35 (m, 2H), 1.25 (br s, 6H), 0.86 (t, 3H, *J*=6.8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 157.9, 137.7, 128.8, 127.9, 126.3, 100.8, 99.5, 81.9, 68.5, 68.0, 62.4, 54.6, 54.55, 39.1, 31.0, 29.8, 26.0, 22.0, 13.8. HRMS calcd for $C_{21}H_{33}N_2O_6$ $[M+H]^+$ 409.2339, found 409.2355.

4.2.18. Heptyl urea ***26***. Isolated as an off white solid in quantitative yield, mp 201.3–202.2 °C. ^{1}H NMR (400 MHz, DMSO) δ (ppm) 7.40–7.46 (m, 2H), 7.32–7.39 (m, 3H), 6.04 (t, 1H, *J*=5.5 Hz), 5.78 (d, 1H, *J*=8.4 Hz), 5.58 (s, 1H), 5.21 (d, 1H, *J*=5.1 Hz), 4.60 (d, 1H, *J*=3.2 Hz), 4.15 (dd, 1H, *J*=4.6, 9.8 Hz), 3.63–3.74 (m, 2H), 3.57 (m, 1H), 3.42–3.51 (m, 2H), 3.28 (s, 3H), 2.96 (q, 2H, *J*=6.2 Hz), 1.33 (m, 2H), 1.23 (br s, 8H), 0.84 (t, 3H, *J*=6.4 Hz). ^{13}C NMR (100 MHz,

DMSO) δ 157.8, 137.7, 128.8, 127.9, 126.3, 100.8, 99.4, 81.9, 68.4, 68.0, 62.4, 54.6, 54.5, 39.1, 31.2, 29.9, 28.4, 26.3, 22.0, 13.9. HRMS calcd for $C_{22}H_{35}N_2O_6$ $[M+H]^+$ 423.2495, found 423.2500.

4.2.19. 4-Pentynyl urea ***27***. The compound was obtained as a white solid at a yield of 90.5%, mp 210.0–211.0 °C. ^{1}H NMR (400 MHz, DMSO), δ (ppm) 7.42–7.48 (m, 2H), 7.34–7.41 (m, 3H), 6.13 (t, 1H, *J*=5.6 Hz), 5.78 (d, 1H, *J*=8.8 Hz), 5.60 (s, 1H), 5.20 (d, 1H, *J*=5.5 Hz), 4.62 (d, 1H, *J*=3.7 Hz), 4.17 (dd, 1H, *J*=4.8, 9.9 Hz), 3.73 (m, 1H), 3.69 (m, 1H), 3.59 (dt, 1H, *J*=4.8, 9.9 Hz), 3.44–3.55 (m, 2H), 3.30 (s, 3H), 3.04 (pseudo q, 2H, *J*=6.0 Hz), 2.78 (t, 1H, *J*=2.6 Hz), 2.15 (dt, 2H, *J*=2.6, 7.0 Hz), 1.54 (pentet, 2H, *J*=7.0 Hz), ^{13}C NMR (100 MHz, DMSO) δ 157.8, 137.7, 128.8, 127.9, 126.3, 100.8, 99.4, 83.9, 82.0, 71.3, 68.5, 68.0, 62.4, 55.6, 54.5, 38.2, 28.8, 15.2. HRMS calcd for $C_{20}H_{27}N_2O_6$ $[M+H]^+$ 391.1869, found 391.1855.

4.2.20. 5-Hexynyl urea ***28***. The compound was obtained as a white solid at a yield of 87%, mp 212.0–213.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) 7.47–7.52 (m, 2H), 7.33–7.39 (m, 3H), 5.58 (s, 1H), 4.72 (d, 1H, *J*=3.7 Hz), 4.62–4.81 (m, 2H), 4.28 (m, 1H), 3.84–3.96 (m, 2H), 3.73–3.83 (m, 2H), 2.53–3.61 (m, 1H), 3.40 (s, 3H), 3.21 (m, 2H), 2.22 (dt, 2H, *J*=2.6, 6.9 Hz), 1.96 (t, 1H, *J*=2.6 Hz), 1.51–1.68 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$–one drop of CD_3OD) δ 159.2, 137.0, 129.0, 128.1, 126.2, 101.8, 99.5, 84.1, 82.0, 70.5, 68.8, 68.5, 62.4, 55.2, 54.9, 39.5, 28.9, 25.5, 18.0. HRMS calcd for $C_{21}H_{29}N_2O_6$ $[M+H]^+$ 405.2026, found 405.2034.

4.2.21. Cyclohexyl urea ***29***. Isolated as a light yellow solid in quantitative yield, mp 210 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.42–7.47 (m, 2H), 7.35–7.40 (m, 3H), 6.04 (d, 1H, *J*=8.1 Hz), 5.74 (d, 1H, *J*=8.4 Hz), 5.60 (s, 1H), 5.23 (d, 1H, *J*=4.8 Hz), 4.61 (d, 1H, *J*=3.3 Hz), 4.17 (dd, 1H, *J*=4.8, 9.9 Hz), 3.64–3.76 (m, 2H), 3.58 (m, 1H), 3.44–3.54 (m, 2H), 3.36 (m, 1H), 3.34 (s, 3H), 1.68–1.78 (m, 2H), 1.57–1.67 (m, 2H), 1.46–1.55 (m, 1H), 1.19–1.32 (m, 2H), 1.00–1.18 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 157.1, 137.7, 128.8, 127.9, 126.3, 100.8, 99.4, 81.9, 68.5, 68.0, 62.4, 54.6, 54.5, 47.6, 33.2, 25.2, 24.3. HRMS calcd for $C_{21}H_{31}N_2O_6$ $[M+H]^+$ 407.2182, found 407.2191.

4.2.22. 2-Chloroethyl urea ***30***. The compound was obtained as a white solid at a yield of 95%, mp 184.1 °C. ^{1}H NMR, (400 MHz, DMSO-d_6) δ (ppm) 7.40–7.47 (m, 2H), 7.33–7.39 (m, 3H), 6.34 (t, 1H, *J*=5.5 Hz), 6.07 (d, 1H, *J*=8.8 Hz), 5.58 (s, 1H), 5.20 (d, 1H, *J*=5.5 Hz), 4.61 (d, 1H, *J*=3.3 Hz), 4.15 (dd, 1H, *J*=4.8, 9.9 Hz), 3.64–3.75 (m, 2H), 3.53–3.61 (m, 3H), 3.42–3.53 (m, 2H), 3.32 (m, 2H), 3.28 (s, 3H). ^{13}C NMR, (100 MHz, DMSO-d_6) δ (ppm) 157.6, 137.7, 128.9, 128.0, 126.4, 100.8, 99.4, 81.9, 68.3, 68.0, 62.5, 54.7, 54.6, 44.7, 41.4. HRMS calcd for $C_{17}H_{24}N_2O_6Cl$ $[M+H]^+$ 387.1323, found 387.1335.

4.2.23. 2-Methyl-acrylic acid 2-ureido-ethyl ester ***31***. The compound was obtained as a white solid in quantitative yield, mp 198.8–200.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.42–7.48 (m, 2H), 7.34–7.40 (m, 3H), 6.24 (t, 1H, *J*=5.7 Hz), 6.08 (br s, 1H), 5.99 (d, 1H, *J*=8.4 Hz), 5.70 (m, 1H), 5.60 (s, 1H), 5.20 (d, 1H, *J*=5.5 Hz), 4.62 (d, 1H, *J*=3.7 Hz), 4.17 (dd, 1H, *J*=4.8, 9.9 Hz), 4.06 (m, 2H), 3.66–3.77 (m, 2H), 3.65–3.63 (m, 1H), 3.43–3.53 (m, 2H), 3.22–3.32 (m, 5H), 1.89 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 166.5, 157.7, 137.7, 135.8, 128.8, 127.9, 126.4, 125.9, 100.8, 99.4, 81.9, 68.3, 68.0, 64.2, 62.5, 54.62, 54.57, 38.1, 17.9. HRMS calcd for $C_{21}H_{29}N_2O_8$ $[M+H]^+$ 437.1924, found 437.1944.

4.2.24. (2-Hydroxy-ethyl)-urea ***32***. Isolated as a white solid in quantitative yield, mp 232.3–233.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.42–7.47 (m, 2H), 7.34–7.39 (m, 3H), 6.26 (t, 1H, *J*=5.5 Hz), 6.13 (d, 1H, *J*=8.1 Hz), 5.59 (s, 1H), 5.33 (br s, 1H), 4.78 (br s, 1H), 4.61 (d, 1H, *J*=3.3 Hz), 4.16 (dd, 1H, *J*=4.8, 9.9 Hz), 3.72 (m, 1H), 3.66 (m, 1H), 3.58 (m, 1H), 3.44–3.55 (m, 2H), 3.32–3.40 (m, 2H, overlap), 3.29 (s, 3H), 3.05 (q, 2H, *J*=5.5 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 158.2, 137.7, 128.8, 128.0, 126.4, 100.8, 99.5, 81.9, 68.3, 68.0, 62.5, 60.7, 54.7, 42.0. HRMS calcd for $C_{17}H_{25}N_2O_7$ $[M+H]^+$ 369.1662, found 369.1677.

4.2.25. Phenyl urea ***33***. Isolated as a light yellow solid in quantitative yield, mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.65 (s, 1H), 7.43–7.49 (m, 2H), 7.43–7.42 (m, 5H), 7.22 (m, 2H), 6.89 (m, 1H), 6.15 (d, 1H, *J*=8.8 Hz), 5.63 (s, 1H), 5.34 (br s, 1H), 4.71 (d, 1H, *J*=3.3 Hz), 4.20 (dd, 1H, *J*=4.8, 9.9 Hz), 3.72–3.83 (m, 2H), 3.63 (m, 1H), 3.49–3.60 (m, 2H), 3.34 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 154.8, 140.3, 137.7, 128.8, 128.6, 127.9, 126.3, 121.0, 117.3, 100.8, 99.2, 81.7, 68.3, 68.0, 62.6, 54.7, 54.2. HRMS calcd for $C_{21}H_{25}N_2O_6$ $[M+H]^+$ 401.1713, found 401.1726.

4.2.26. 4-Bromophenyl urea ***34***. The compound was obtained as a white solid at a yield of 92%, mp unstable after 265 °C. ^{1}H NMR, (400 MHz, DMSO-d_6) δ (ppm) 8.77 (br s, 1H), 7.43–7.48 (m, 2H), 7.33–7.42 (m, 7H), 6.16 (d, 1H, *J*=8.4 Hz), 5.62 (s, 1H), 5.33 (d, 1H, *J*=5.5 Hz), 4.70 (d, 1H, *J*=3.7 Hz), 4.19 (dd, 1H, *J*=4.8, 9.9 Hz), 3.72–3.82 (m, 2H), 3.49–3.66 (m, 3H), 3.33 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 154.6, 139.7, 137.7, 131.4, 128.8, 128.0, 126.4, 1119.3, 112.3, 100.8, 99.2, 81.7, 68.3, 68.0, 62.6, 54.7, 54.2. HRMS calcd for $C_{21}H_{24}N_2O_6Br$ $[M+H]^+$ 479.0818, found 479.0836.

4.2.27. Napthyl urea ***35***. Isolated as a light yellow solid in quantitative yield, mp 253.8–255.0 °C. ^{1}H NMR, (400 MHz, DMSO-d_6) δ (ppm) 8.73 (s, 1H), 8.14 (d, 1H, *J*=8.1 Hz), 8.09 (d, 1H, *J*=7.7 Hz), 7.87 (d, 1H, *J*=8.1 Hz), 7.49–7.56 (m, 3H), 7.44–7.49 (m, 2H), 7.39–7.43 (m, 1H), 7.34–7.39 (m, 3H), 6.81 (d, 1H, *J*=8.4 Hz), 5.63 (s, 1H), 5.42 (br s, 1H), 4.76 (d, 1H, *J*=3.3 Hz), 4.20 (dd, 1H, *J*=4.4, 9.9 Hz), 3.88 (m, 1H), 3.77 (t, 1H, *J*=10.1 Hz), 3.60–3.71 (m, 2H), 3.56 (m, 1H), 3.36 (s, 3H). ^{13}C NMR, (100 MHz, DMSO-d_6) δ 155.4, 137.7, 135.1, 133.7, 128.9, 128.4, 128.1, 126.4, 126.0, 125.8, 125.4, 125.0, 121.9, 121.2, 115.7, 101.0, 99.4, 81.9, 68.5, 68.1, 62.7, 54.8, 54.5. HRMS calcd for $C_{25}H_{27}N_2O_6$ $[M+H]^+$ 451.1869, found 451.1882.

Acknowledgements

We thank the financial support from National Science Foundation (grant CHE-518283). We also thank PVN Reddy, Hao Yang, and Kristopher Williams for their assistance during the preparation of the manuscript.

Supplementary data

The ^{1}H and ^{13}C NMR spectra for compounds **10**–**35** are provided in supplementary data file. The preparation of compound **4** is also provided in the Supplementary data. The photographs of gels formed by **12** and **32**, and optical micrographs of gels by compounds **19** and **24** are also shown in the Supplementary data section. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.05.071. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. Organogelators reviews (a) George, M.; Weiss, R. G. *Acc. Chem. Res.* **2006**, *39*, 489–497; (b) Terech, P.; Weiss, R. G. *Chem. Rev.* **1997**, *97*, 3133–3159; (c) Abdallah, D. J.; Weiss, R. G. *Adv. Mater.* **2000**, *12*, 1237–1247.
2. (a) Gronwald, O.; Snip, E.; Shinkai, S. *Curr. Opin. Colloid Interface Sci.* **2002**, *7*, 148–156; (b) Nonappa; Maitra, U. *Org. Biomol. Chem.* **2008**, *6*, 657–669; (c) Van Esch, J. H.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 2263–2266.
3. Estroff, L. A.; Hamilton, A. D. *Chem. Rev.* **2004**, *104*, 1201–1217.
4. (a) Yang, Z.; Liang, G.; Xu, B. *Acc. Chem. Res.* **2008**, *41*, 315–326; (b) Yang, Z.; Liang, G.; Xu, B. *Soft Matter* **2007**, *3*, 515–520; (c) Yang, Z.; Xu, B. *Adv. Mater.* **2006**, *18*, 3043–3046.

5. (a) Vintiloiu, A.; Leroux, J.-C. *J. Controlled Release* **2008**, *125*, 179–192; (b) Shaikh, I. M.; Jadhav, K. R.; Kadam, V. J.; Pisal, S. S. *Drug Deliv. Technol.* **2007**, *7*, 60–66.
6. (a) Vemula, P. K.; Li, J.; John, G. *J. Am. Chem. Soc.* **2006**, *128*, 8932–8938; (b) Vemula, P. K.; John, G. *Acc. Chem. Res.* **2008**, *41*, 769–782.
7. (a) Koshi, Y.; Nakata, E.; Yamane, H.; Hamachi, I. *J. Am. Chem. Soc.* **2006**, *128*, 10413–10422; (b) Kiyonaka, S.; Sada, K.; Yoshimura, I.; Shinkai, S.; Kato, N.; Hamachi, I. *Nat. Mater.* **2004**, *3*, 58–64.
8. Yang, Z.; Liang, G.; Ma, M.; Abbah, A. S.; Lu, W. W.; Xu, B. *Chem. Commun.* **2007**, 843–845.
9. Jung, J. H.; Amaike, M.; Nakashima, K.; Shinkai, S. *J. Chem. Soc.* **2001**, *10*, 1938–1943.
10. (a) Bhat, S.; Maitra, U. *Tetrahedron* **2007**, *63*, 7309–7320; (b) Suzuki, M.; Owa, S.; Shirai, H.; Hanabusa, K. *Tetrahedron* **2007**, *63*, 7302–7308.
11. Wang, G.; Cheuk, S.; Williams, K.; Sharma, V.; Dakessian, L.; Thorton, Z. *Carbohydr. Res.* **2006**, *341*, 705–716.
12. Nie, X.; Wang, G. *J. Org. Chem.* **2006**, *71*, 4734–4741.
13. Cheuk, S.; Stevens, E.; Wang, G. *Carbohydr. Res.* **2009**, *344*, 417–425.
14. Wang, G.; Cheuk, S.; Yang, H.; Goyal, N.; Reddy, P. V. N.; Hopkinson, B. *Langmuir* **2009**, *25*, 8696–8705.
15. Bauer, T.; Tarasiuk, J.; Pasniczek, K. *Tetrahedron: Asymmetry* **2002**, *13*, 77–82.
16. Emmerson, D. P. G.; Hems, W. P.; Davis, B. G. *Tetrahedron: Asymmetry* **2005**, *16*, 213–221.
17. Melendez, R. E.; Carr, A. J.; Linton, B. R.; Hamilton, A. D. *Struct. Bonding* **2000**, *96*, 31–61.
18. Fujita, N.; Mukhopadhyay, P.; Shinkai, S. *Ann. Rev. Nano Res.* **2006**, *1*, 385–428.
19. Si, C.; Huang, Z.; Kilic, S.; Xu, J.; Enick, R. M.; Beckman, E. J.; Carr, A. J.; Melendez, R. E.; Hamilton, A. D. *Science* **1999**, *289*, 1540–1543.
20. De Loos, M.; Van Esch, J.; Kellogg, R. M.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 613–616.
21. Brinksma, J.; Feringa, B. L.; Kellogg, R. M.; Vreeker, R.; van Esch, J. *Langmuir* **2000**, *16*, 9249–9255.
22. Estroff, L. A.; Hamilton, A. D. *Angew. Chem., Int. Ed* **2000**, *39*, 3447–3450.
23. Wang, G.; Hamilton, A. D. *Chem.—Eur. J.* **2002**, *8*, 1954–1961.
24. Wang, G.; Hamilton, A. D. *Chem. Commun.* **2003**, 310–311.
25. Adarsh, N. N.; Kumar, D. K.; Dastidar, P. *Tetrahedron* **2007**, *63*, 7386–7396.
26. Mohmeyer, N.; Schmidt, H.-W. *Chem.—Eur. J.* **2007**, *13*, 4499–4509.
27. Pierce, A. M.; Maslanka, P. J.; Carr, A. J.; McCain, K. S. *Appl. Spectrosc.* **2007**, *61*, 379–387.
28. Dautel, O. J.; Robitzer, M.; Lere-Porte, J.-P.; Serein-Spirau, F.; Moreau, J. J. E. *J. Am. Chem. Soc.* **2006**, *128*, 16213–16223.
29. George, M.; Tan, G.; John, V. T.; Weiss, R. G. *Chem.—Eur. J.* **2005**, *11*, 3243–3254.
30. De Loos, M.; Friggeri, A.; Van Esch, J.; Kellogg, R. M.; Feringa, B. L. *Org. Biomol. Chem.* **2005**, *3*, 1631–1639.
31. Moreau, J. J. E.; Vellutini, L.; Man, M. W. C.; Bied, C.; Dieudonne, P.; Bantignies, J.-L.; Sauvajol, J.-L. *Chem.—Eur. J.* **2005**, *11*, 1527–1537.
32. Tamaru, S.-I.; Uchino, S.-Y.; Takeuchi, M.; Ikeda, M.; Hatano, T.; Shinkai, S. *Tetrahedron Lett.* **2002**, *43*, 3751–3755.
33. Suzuki, M.; Nakajima, Y.; Yumoto, M.; Kimura, M.; Shirai, H.; Hanabusa, K. *Langmuir* **2003**, *19*, 8622–8624.
34. Avalos, M.; Babiano, R.; Cintas, P.; Gomez-Carretero, A.; Jimenez, J. L.; Lozano, M.; Ortiz, A. L.; Palacios, J. C.; Pinazo, A. *Chem.—Eur. J.* **2008**, *14*, 5656–5669.
35. Baddeley, C.; Yan, Z.; King, G.; Woodward, P. M.; Badjic, J. D. *J. Org. Chem.* **2007**, *72*, 7270–7278.
36. Miravet, J. F.; Escuder, B. *Org. Lett.* **2005**, *7*, 4791–4794.
37. Wurthner, F.; Hanke, B.; Lysetska, M.; Lambright, G.; Harms, G. S. *Org. Lett.* **2005**, *7*, 967–970.
38. Peng, J.; Liu, K.; Liu, X.; Xia, H.; Liu, J.; Fang, Y. *New J. Chem.* **2008**, *32*, 2218–2224.
39. Suzuki, M.; Yumoto, M.; Shirai, H.; Hanabusa, K. *Tetrahedron* **2008**, *64*, 10395–10400.
40. Pal, A.; Ghosh, Y. K.; Bhattacharya, S. *Tetrahedron* **2007**, *63*, 7334–7348.
41. Diaz, N.; Simon, F.-X.; Schmutz, M.; Mesini, P. J. *Polym. Mater. Sci. Eng. Preprints* **2005**, *93*, 589–590.
42. Lescanne, M.; Grondin, P.; d'Aleo, A.; Fages, F.; Pozzo, J.-L.; Monval, O. M.; Reinheimer, P.; Colin, A. *Langmuir* **2004**, *20*, 3032–3041.
43. (a) Madi-Puskas, M.; Laszlo, P.; Pelyvas, I. F.; Sztaricskai, F. *Org. Prep. Proceed. Int.* **1990**, *22*, 605–611; (b) Krog-Jensen, C.; Oscarson, S. *J. Org. Chem.* **1996**, *61*, 1234–1238; (c) Hough, L.; Penglis, A. A. E.; Richardson, A. C. *Can. J. Chem.* **1981**, *59*, 396–405.