12-19-2008

Glucose and Glucosamine Derivatives as Novel Low Molecular Weight Gelators

Sherwin Cheuk
University of New Orleans

Glucose and Glucosamine Derivatives as Novel Low Molecular Weight Gelators

A Dissertation

Submitted to the Graduate Faculty of the
University of New Orleans
in partial fulfillment of the
requirements for the degree of

Doctor of Philosophy

in

The Department of Chemistry

By

Sherwin Yuan Cheuk

B.S. Chemistry, Excelsior College, Albany, New York

December 2008

Dedicated to:

My mother, Phenix

My father, Shu

For and from whom,

where I’ve been and where I’ll be.

Acknowledgements:

I would like to thank first and foremost my advisor, Dr. Guijun Wang, not only for her patience, but for the sacrifices she made to guide and to support me for the past five years at the University of New Orleans. Also, I would like to thank my Ph.D. committee members (current and former) for their time: Dr. Mark Trudell, Dr. Brank Jursic, Dr. Steven Rick, and Dr. Jiye Fang. To current and former group members Dr. Xiaoping Nie, Dr. Vibha Sharma, Dr. Jean-René Ella-Menyé, Kristopher Williams, Navneet Goyal, Michael St. Martin, and Hao Yang, thank you and see you guys on the other side. Thank you to the Louisiana Board of Regents for the generous fellowship and the National Science Foundation for financial support for this project. To Dr. William Crowe, Dr. David Spivak, and the entire Department of Chemistry of Louisiana State University at Baton Rouge for helping us by providing the necessary environment and equipment to continue our research during the rough months following hurricane Katrina. Much appreciation goes to Khuong Nguyen and her family for their ever constant love and patience.

Table of Contents

List of Schemes

List of Figures

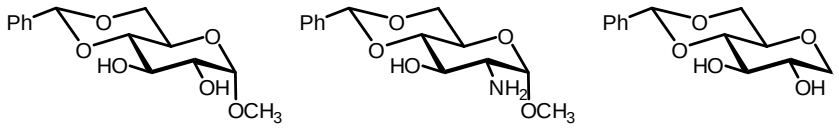
List of Tables

List of Equations

Abstract

Low molecular weight gelators (LMWGs) are small molecules that are capable of entrapping solvents to form a gel in organic solvents or aqueous solution. These compounds rely solely on noncovalent forces to form the fibrous networks necessary to entrap a variety of solvents. The organogels and hydrogels thus formed could have applications in a variety of fields from environmental to biological to medicinal.

Carbohydrates are ideal starting materials to synthesize LMWGs, because of their natural abundance, dense chirality, and biocompatibility. D-Glucose is the most common monosaccharide and D-glucosamine is isolated from natural sources, such as crab shells. Several series of compounds were synthesized using compounds **1-3** as the starting materials. These include esters, carbamates, amides, and ureas. The structure and gelation relationship was analyzed to obtain guidelines for designing new LMWGs. Compound **1** is a simple derivative of D-glucose and its terminal alkynyl esters and saturated carbamates are effective gelators. Compound **2** is a simple derivative of D-glucosamine and its amide and urea derivatives are also effective gelators. Compound **3** is formed from the deoxygenation of D-glucose.



1 **2** **3**

The design, synthesis and gelation properties of several classes of sugar based low molecular organo/hydrogelators will be discussed in this thesis in chapters 2, 3, and 4. After obtaining

highly effective organo/hydrogelators, potential applications of these novel molecular systems can be explored. Some preliminary study on using one of the gelator in enzyme assay has shown that it is possible to utilize the hydrogels to immobilize enzymes. However, future research can explore further on the applications of these gelators.

Keywords: low molecular weight gelator, carbohydrates, glucose, glucosamine, fibrillar networks, structure-gelation relationships

Chapter I. Self-Assembly of Low Molecular Weight Gelators (LMWGs)

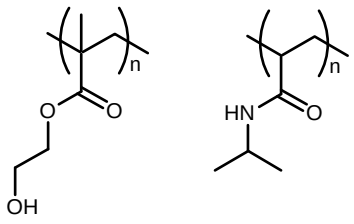
Abstract

Low molecular weight organogelators (LMOGs) have gotten attention from all areas of chemistry, because of the intricacies of the self-assembly phenomenon and their demonstrated potential uses in a variety of areas, ranging from environmental to medicinal applications. To a large degree, these molecules were discovered serendipitously, but in the recent years, more efforts have been made to specifically discover new LMOGs systmatically. The physical gelation phenomenon, as a result of the self-assembly, is not fully understood, which makes it difficult to specify a particular structure or a general class of structures for the entire spectrum of LMOGs. However, a very broad generalization is that LMOGs tend to have a polar and a nonpolar region(s). The solvent type determines how these molecules self-assemble to minimize unfavorable interactions while maximizing favorable interactions. Carbohydrates offer a great deal of options in terms of chirality and functionality. By being naturally abundant and renewable, carbohydrates contribute to the greener side of chemistry and for any potential widespread use of carbohydrate-based LMOGs, it can also reduce the cost. In addition, these LMOGs should lead to environmentally benign metabolic byproducts.

Keywords: organogelators, hydrogelators, physical gelation, carbohydrates, self-assembly, D-glucose, D-glucosamine

1.1. Introduction

Gels (from Latin *gelatus* "frozen, immobile") are semisolids, in which a relatively large amount of solvent is entrapped in a porous network of molecules, and are ever present in our everyday lives, personal and professional. They are used from food processing, shoe padding, contact lenses, as well as in biochemical and medicinal applications, such as forming the matrix for gel electrophoresis, tissue engineering, and drug delivery.[1] Despite everyday use, the exact definition of a gel state "…is easier to recognize than to define."[2] Relatively small amounts of macromolecules and supramolecules assemble in such a way that it utilizes the solvent's surface tension immobilize entire volumes of solvent. The gels that we use today are mostly made of polymers, which primarily rely on covalent bonds (noncovalent forces are secondary). Polymer hydrogels have been extensively studied for many decades. Structure of two polymer gels **1** and **2** are shown in **Figure 1.1**. The advantages of polymer hydrogels include the well-established structure gelation relationship (SGR) studies and the robustness or superb mechanical strengths. The disadvantages are that generally a relatively high concentration is required, and most often the gelation is not reversible.



1, pHEMA **2, pNIPAAM**

Figure 1.1 Two known polymeric hydrogels. **1**, Poly(2-hydroxyethyl methacrylate); **2**, poly(*N*-isopropylacrylamide)

1.2. Low molecular mass gelators

Low molecular weight gelators (LMWGs) are small molecules that can form gels in organic solvents and/or water and are divided into two categories: organogelators (LMOGs) and hydrogelators (LMHGs).[3] The role of intermolecular interactions differ when comparing the self-assembly of organogelators and hydrogelators.[4-6] Hydrogelators primarily rely on hydrophobic interactions,[7] rather than hydrogen bonding (unless the binding energies are high enough or the hydrogen bonds were protected from the solvent),[8] with the solvent and other molecules, which are also apparent in biological systems (tertiary/quartenary structure of proteins, nucleic acids). LMHGs can be used in biochemistry (enzyme entrapment,[9] bioassays,[10] etc.) and medicine (drug release,[11] nonviral drug delivery,[12-15] tissue scaffolds,[16] etc.). In contrast, in organogelation, hydrophobic forces are almost nonexistent as organic solvents have the ability to dissolve nonpolar solutes. These molecules self-assemble mainly through non-covalent dipole-dipole forces (e.g. hydrogen bonding and metal coordination) and are able to form a network entrapping organic solvents, thus forming gels. Gelation through non-covalent forces is known as physical gelation, as opposed to chemical gelation, which relies on covalent bonds (i.e. polymers). Due to the extensive and repetitive nature of these interactions by noncovalent forces, the fibrillular networks formed by LMOGs are classified as supramolecular polymers.[17] Because of the structure of LMOGs and formation of gels through self-assembly, most supramolecular gels exhibit thermoreversibility: the ability to regenerate the gel state after repeated homogenization

above the gel-sol temperature (T_{gel}). In comparison, the rheological properties of polymer gels are often altered when the gel is heated over and over again.

LMOGs have found uses in many industrial applications: hydrometallurgy, cosmetics, lubrication, etc.[1] For the extent at which LMOGs and LMHGs should be used, three concepts should be considered. LMWGs are typically made from natural materials. The abundance of the starting material should play a role in the availability of the gelator. Secondly, the simplicity, side reactions, and the amount of waste produced in the synthesis of the gelator should be taken into consideration for the environment. Lastly, the environmental and biological sustainability of these gelators will determine for what applications they may be explored.

The preparation of organogels or hydrogels using LMOGs is pretty straightforward, like making Jell-O®. In general, a certain amount of a LMOG is placed in a vial containing the testing solvent. Then it is heated above the sol-gel temperature (T_{gel}) to dissolve the compound. Gels are formed when the solution is cooled below the T_{gel}.[1] The resulting solidification or increase of the viscosity of the solvent(s) is caused by the formation of a fibrous network, which is created by the noncovalent inter and intramolecular forces. The minimum gelation concentration (MGC) is obtained through seriel dilution and heating until a stable gel is no longer formed. The MGC is analogous to the supersaturation point in the formation of crystals. The differentiation point between that of crystals and self-assembled gel networks comes at the phase separation, where the former is on a macroscopic scale and the latter is on the microscopic scale.[18]

Analysis of LMWGs in the gel-state

Understanding the rheological and thermodynamic nature of gels of LMWGs helps understand what happens on the level of macrostructures of the fibrillar networks, such as identifying the sort of interactions that make their cohesion possible.[1] Just like polymer-based gels, gels formed by small organic molecules exhibit properties of a viscoelastic (non-Newtonian) fluid, thus they are subjected to the stress and strain measurements of rheological measurements, though a constant coefficient of viscosity cannot be defined. What is typically found in the rheological measurements of these gels is the storage modulus (*G'*) of the elastic component is larger than the dissipated energy and remains constant for a period of time due to the hysteresis effects of the gel.[19] Additionally, structural-mechanical relationships of LMWGs can be related to that of thermoreversible networks of biological systems. [20-22] The purpose of analyzing the networks formed by the LMWGs is to understand how the molecules self-assemble and from this information, LMWGs can be designed efficiently and for specific purposes. One challenge of analyzing these systems is to retain the original gel structure during the sample preparation and the actual analysis.

Various spectroscopic techniques have been used to study to gels. Since NMR, IR, UV/vis, CD, and fluorescence, are temperature sensitive, they can be used to measure the temperature of which the gel forms as an alternate to DSC.[23] However, again due to hysteresis effects, the temperature at which the gel forms and melts are different no matter the method used.[1] The T1 and T2 relaxation times of NMR can be used to identify

the parts of the LMWG that have restricted conformational and translational motions,[24, 25] and in solid-state NMR for the gel-state, identify the changes in modes of self-assembly and aggregation.[26, 27] The synthesis of LMWGs with covalently linked fluorescent probes and/or UV active groups have been used in probing hydrophobic pockets, especially in aqueous environments,[28-31] and the aromatic groups of fluorescent probes also promote aggregation, both of which can be observed by small to moderate shifts in the emission spectrum. In addition to NMR, IR can be used to observe hydrogen bonding (O-H, N-H, and C=O vibrations) and it can also be used to determine whether a carboxylic acid is protonated.[32-37]

To observe the macromolecular structures of the resultant gels, analysis by electron microscopy (SEM and TEM) gives resolution up to 0.2 nm. However, because the sample preparation involves drying the sample in vacumm, the actual gel state may not be what is observed (e.g. changes in colloidial particle and fiber size, as well as fiber entanglement).[1] Cryogenic TEM (cryoTEM) and SEM (cryoSEM) provide a solution in the sense that they allowed the observation of the gel in its native state, which used liquid ethane to freeze the samples. The high viscosity of the gel makes it difficult, but very possible to form the thin film required for TEM.[38-45] CryoSEM requires more sample and the top layer of ice is etched then sputter coated so that it can be imaged.[46-48]

Small angle X-ray (SAXS) and small angle neutron scattering (SANS) are useful to observe gels on the same scale as the TEM, but the advantage lies in the minimal sample

preparation.[49] The small angle scattering techniques have become useful for looking at molecular structures on the macro scale.[50,51] X-ray powder diffraction (XRD) has been used to determine the molecular network structures formed by LMWGs, but these samples usually have to be dried. Weiss and his coworkers have been able to obtain the powder diffraction pattern of a gel in its native state by relating the XRD pattern (by subtracting the solvent) of a gel to the X-ray crystal structure.[52]

Thermodynamics of self-assembly

The phase separation that leads to the formation of fibrillular networks can be explained through a number of theoretical models,[53] one of which is spinodal decomposition. When the binary mixture moves into the area between the binodal and spinodal curves (bimodal region, **Figure 1.2**), the system becomes metastable. Further movement beyond the spinodal curve results in an unstable mixture. This causes small and random changes in density that ultimately leads to aggregation, the beginning of a fibrillular network. The formation of the fibrillular network (phase separation) continues until the binary mixture moves into a stable region.

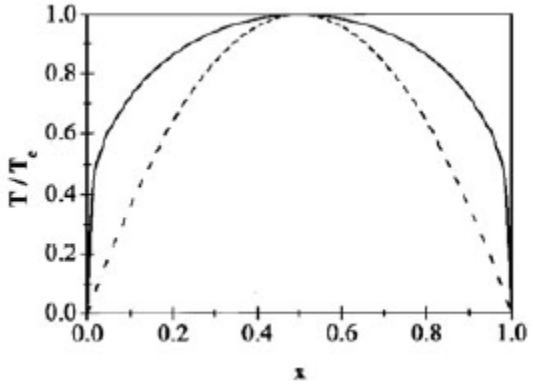


Figure 1.2. Binodal (full) and spinodal (dotted) curves of a phase diagram of a binary solution. Both curves meet at the critical point (T_c, x_c). T is the temperature of the mixture and x is the mole fraction.[53]

It's important to note that the network formed by the self-assembly of LMWGs is not thermodynamically stable.[17] For a stable gel, the sum of interactions (usually hydrogen bonding for LMOGs and hydrophobic forces for LMHGs) with other molecules and the solvent has to overcome the decrease in entropy and free rotational energy due to the ordered nature of a fibrous network as compared to free floating molecules dissolved in solution. To explain what prevents them from going back to the crystal-state, Fuhrhop and coworkers proposed the "chiral bilayer effect."[54] This theory suggested, in aqueous conditions, the transition from gel fiber to crystal is easier for racemates than enantiopure LMWGs. Since enantiopure LMWGs have the tendency to form chiral suprastructures, such as helices and ribbons, the contact between the suprastructures are minimized compared to the contact between flat sheets, which usually promote crystallization.[17] Fuhrhop also noted that while the enantiomers gave the same results, a racemic mixture of D and L-gluconamides, resulted in a decrease in solubility at high temperatures (85°C)

and the formation of plate-like crystals. The orientation of the lipid was monitored by placing a CD_2 group next to the amide nitrogen in place of the methylene. ^2H NMR can be used to monitor the intramolecular interaction of the deuterium quadrapole moment separately from the other hydrogens in the lipid. As the solution formed the gel, ^2H NMR of the methylene goes from a singlet in the sol state to a Pake doublet in the gel state. At 10°C, the singlet is not apparent, but at 40-65°C the singlet becomes apparent even when the gel state is still visible, while at 84°C the gel state completely disappears on the spectroscopic and macroscopic scales.[27] This indicated that an equilibrium between the sol and gel states exists at different temperatures and provided a reason why the sol-gel and the gel-sol temperatures are very different.

A couple of studies done by Jorgenson et al[55, 56] (**Figure 1.3**) illustrated that not only the orientation of hydrogen bond donors and acceptors greatly affect the association constant between two molecules, but secondary interactions (repulsion and attraction) play a significant role. The binding studies were done in chloroform, so these results may only be applicable to LMOGs. Studies were first done with OPLS (Optimized Potential for Liquid Simulations) computer simulations developed by Jorgensen and later verified with experimental data. OPLS is used to measure intramolecular non-bonded interactions that are three or more bonds apart.

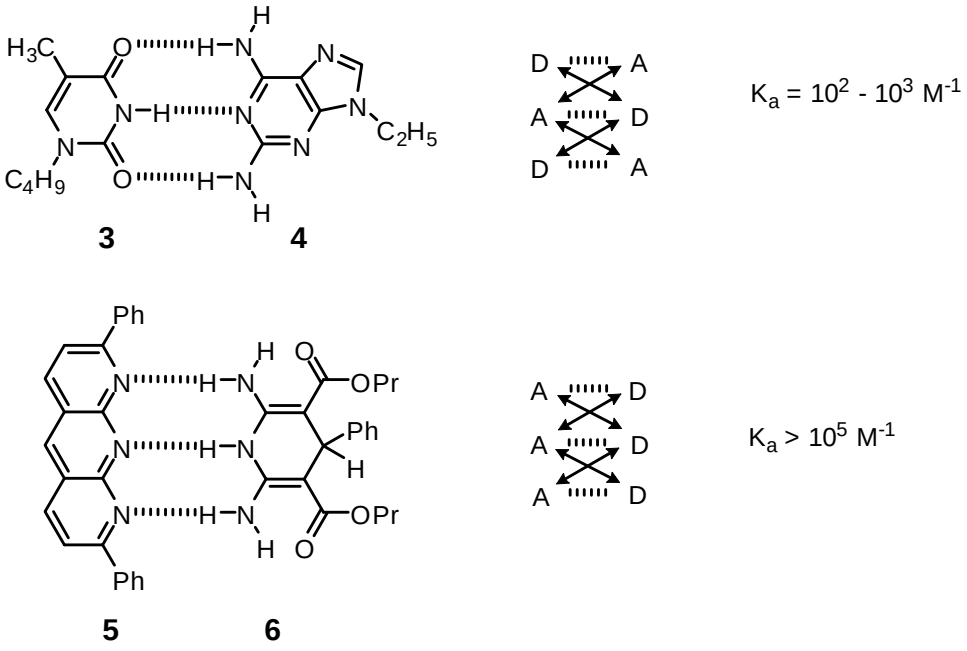


Figure 1.3. Secondary hydrogen bonding influences the association constant by several orders of magnitude. [55, 56]

1.3. Low Molecular Weight Organogelators (LMOGs)

Although, gels are typically seen as solid-like material, any non-Newtonian fluid able to increase viscosity of a solvent at appreciably low concentrations are also seen as LMOGs. In this sense, these compounds have been around for a long time, particularly in lubricants[57,58] and the cosmetics industry, where they exist as hydrocarbon or fatty acid suspensions. In the future, LMOGs may have applications in laboratories and in the environment.

As stated earlier, organogels differ from hydrogels, not only by the solvent being gelated, but also by the way the molecules self-assemble. While LMHGs self assembles according

to the hydrophobic region,[24] LMOGs focus more on hydrogen bonding, metal coordination, or dipole-dipole interactions, because of organic solvents' ability to associate with both hydrophobic and polar headgroups.[4-6] The reliance on hydrogen bonding, also provides direction in the self-assembly of LMOGs. Stucturally, LMOGs of more nonpolar solvents are characterized with large nonpolar regions and a small, but essential, polar group, which stands in contrast with typical hydrogelators. There are several LMWGs that can gel both water and nonpolar solvents, but their intermolecular interactions are suggested to be very different. Just like hydrogelators, there are no strict rules that can tell whether a molecule is going to become an LMOG, especially since there is a diverse group of organic solvents some of which are immiscible. These molecules can be categorized, but a large miscellaneous section is inevitable. The 12-hydroxyoctadecanoic acid **7** was among the first LMOGs to be studied and, like most gelators of nonpolar solvents, it is structurally distinct from the hydrogelators seen earlier. Some examples representing some known classes of LMOGs are shown below (**Figure 1.4**).

In the 1970's, fatty acid **7** and its metallic salts are among the most studied LMOG systems and have basically started the study of LMWGs in general.[1,57-59] The chirality of these molecules, and, interestingly enough, the size of the cation may determine which direction the helices turn. For example, the D and L enantiomers of LMOG **7** turn in different directions (left for D-**7** and right for L-**7**), but if a large cation (e.g., Rb^+ or Cs^+) takes the place of a smaller cation (H^+ or Li^+), the helices turn the opposite way,

representing the original state of its enantiomer.[72] Thus the chirality of the molecule may not be the sole dictator of the superstructures these molecules form.[73]

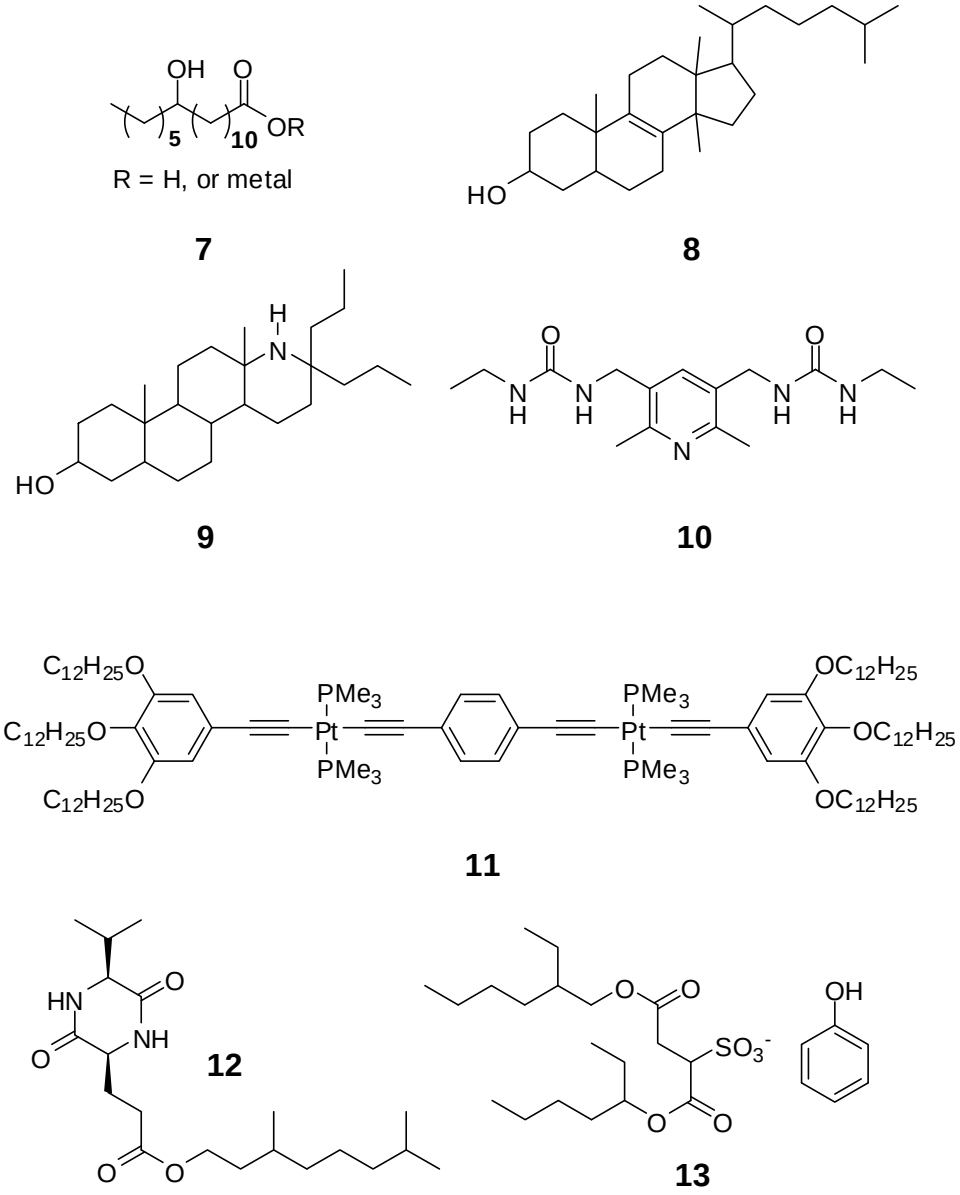


Figure 1.4. Some examples of LMOGs (**7-13**)[57,59-71]showing the wide variations in structure.

Cholesterols, like **8** and **9**, were the molecules first discovered to have liquid crystalline characteristics,[74] thus gelators of cholesterol derivatives exhibiting the liquid crystalline phenomenon should come as no surprise.[75,76] Dihydrolanosterol (DHL, **8**) and its phenyl acetate, laurate, and cinnamate ester derivatives gels oils isolated from animals in addition to silicon oils at 1-10 wt%. Like most gels before 1990, D-3α-hydroxy-17,17-dipropyl-17α-azahomoandrostanyl-17α-oxy (**STNO, 9**) was discovered by accident while oxidizing the amine.[77] Before the amine of LMOG **9** was oxidized, the resulting cholesterol was able to gel cyclohexane when exposed to a magnetic field of 4.2 T. When the magnetic field was removed, the gel collapsed, leaving behind highly birefringent fibers.[78]

Fmoc amino acid derivatives frequently gelate a wide range of solvents,[79] due to the π–π stacking of the fluorene component of the Fmoc group and the hydrogen bonding pairs associated with peptide bonds. As with hydrogels, π–π stacking plays a major role in the self-assembly of LMOGs,[80-82] which again can be monitored by UV spectroscopy, fluorescence,[83] or phosphorescence. Schanze and his group looked at a series of platinum-based acetylide gelators in regards to phosphorescence (**11**).[65] A blue shift occurs in the gel state under UV absorbance from 358 nm to 304 nm. The phosphorescence study looked at the photoluminescence spectroscopy as a function of excitation wavelength (326 to 366 nm), concentration (10^{-5} to 10^{-3} M), and temperature (23-61°C). The sol-gel state experiment in regards to concentration and temperature was monitored by an excitation wavelength of 326 nm, which clearly showed two distinct maxima at 495 nm for the gel state at 1.0 mM or <31°C, and 516 nm for the sol state at

.01 mM or >51°C. Interestingly, in the gel state, an excitation wavelength of 366 nm gives a luminescence spectrum representing the sol state (maxima at 516 nm) and an excitation at 346 nm in the gel state gives both peaks at 495 and 516 nm.[65]

In addition to the aromatic rings, LMOG **10** takes advantage of urea's ability to associate with itself in hot alcohol solvents with a primary alcohol ($HO\text{-}(CH_2)_n\text{-}CH_3$, n = 0-9).[64] Though not unheard of, LMOG **10** remained in solution in some solvents and precipitated in others after cooling and did not gel until ultrasound was applied to the solution.[108] Though not uncommon, sonogelation is a unique phenomenon in itself. Usually, ultrasound acts as a mechanical force, disrupting the noncovalent interactions by stimulating fast translational and rotational movement. Badjic and his group studied the FT-IR bands corresponding to the hydrogen bonds of the urea by monitoring the C=O vibrations at 1645 cm^{-1}(bw), 1604 cm^{-1}(s), and 1610 cm^{-1}(shoulder).[64] Starting from below the MGC, the peak at 1604 cm^{-1} intensified as the solvent evaporated and **16** started to aggregate.

Among the most well-studied bimolecular LMOGs is the phenol and p-cresol/sodium bis(2-ethylhexyl) sulfosuccinate system **(13)**,[67-71] where the hydrogen bonding occurs between the phenolic hydroxyl and the sulfate. The difference between the intermolecular forces of LMOGs and LMHGs becomes apparent as traces of water (determined through Karl Fischer titration) causes dissolution.[69] This bimolecular system forms an optically clear gel in isooctane at 0.1 M. The orientation of these molecules resembles reverse micelles with **13** surrounding and binding to the outside of a pseudo-infinite stack of phenols.[70,71]

1.4. Low Molecular Weight Hydrogelators (LMHGs)

LMHGs are formed by dissolving a small amount (0.1-10 wt%) of the gelator molecule in hot water (a polar cosolvent is sometimes added: DMSO, ethanol, etc.) and the gel is formed after cooling below the sol-gel temperature (T_{gel}). The immobilization of the solvent is obtained by the formation of a fibrous network and taking advantage of water's relatively high surface tension.[85-88] LMHGs are placed in a different category from their organogel counterparts primarily because the solvent also causes a different method of association used to assemble with other molecules. In the presence of water, hydrogen bonding, which is prevalent in organic solvents, is diminished or negated by the nature of water.[8] The main driving force for self-assembly is the same used to form the tertiary structure of proteins: hydrophobic interactions. When designing LMHGs it becomes imperative to control the hydrophobic interactions, which lack the directionality of hydrogen bonding.[7] The use of salt bridges, transition metal coordination, and carefully placed hydrogen bonding has been used to compensate for the shortcomings of and stabilize the self-assembly initiated by the hydrophobic interactions in designing LMHGs.[89]

Hydrogels formed by LMHGs are typically amphiphilic (containing polar and nonpolar regions) in structure and, at the critical micellar concentration (CMC), generally form micelles or vesicles.[90-91] Through a progression of morphologies, the micelles form ribbons, which, in turn, coalesce into the fibers observed on the micrometer to millimeter scale. Molecularly, LMHGs can be classified into what makes the polar region (usually a

naturally occurring compound) and the linkage between the polar and nonpolar regions (esters, amides, ureas, etc.).

Structurally, the biggest variation of hydrogels is the polar head group, usually naturally derived (amino acids,[31, 92-97] nucleosides,[98-100] sugars,[83, 101-106] or combinations thereof), because the nonpolar region of an amphiphilic LMHG is almost always a lipid tail or an aromatic group (**Figure 1.5**), where the former participates in hydrophobic interactions and the latter associates more through π-π stacking. To successfully gelate water, the LMHGs has to exhibit enough of hydrophobicity (including π–π stacking) to self-assemble, and also show significant secondary interactions, such as hydrogen bonding and other electrostatic interactions, to stabilize the self-assembly.

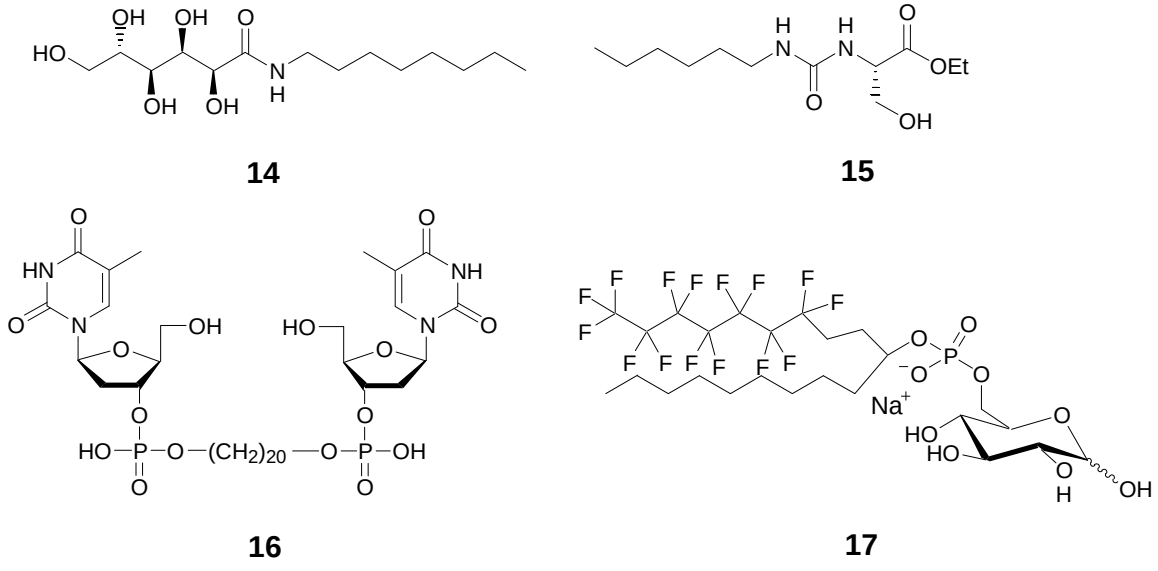


Figure 1.5. Examples of amphiphilic (**14**,[27] **15**,[93] and **17**[50]) and bolamphiphilic hydrogelators (**16**[100]).

Many studies have been directed to finding this balance between the hydrophobic and hydrophilic components of amphiphiles and bolamphiphiles (hydrophilic portions connected by a nonpolar group). Studies done by Kunitake[24] and Furhop[27,54,106,107] made great strides in regards to the design of LMHGs. Kunitake synthesized a library of over 60 compounds that varied in four parts: the length of the lipid tail, a rigid spacer, a flexible linker, and a hydrophilic head group (**Figure 1.6**).[24] Throughout the library of compounds, a number of morphologies were perceived by the Kunitake and by changing the length of the tail and/or the flexible linker. Furhop and his coworkers,[27,54] who synthesized a library of LMHGs by the addition of alkyl amines to aldonic acids, came up with the "chiral bilayer effect" discussed earlier.

Urea linkages are often placed in a separate category due to their directionality of hydrogen bonding, even being in an aqueous environment. Due to its ability to direct hydrogen bonding, urea linkages provide a greater amount of stability and predictability as compared to amides and esters, even though the hydrophobic interactions are heavily favored. A serine-urea library developed by Wang and Hamilton[93] led to the discovery of LMHG **15**. They discovered by increasing or decreasing the alkyl chain of the lipid, either meant insolubility or solubility, respectively. This example shows not only the synthesis of compound libraries to discover novel LMHGs, but also a delicate balance between hydrophobicity and hydrophilicity that is required for gelation.

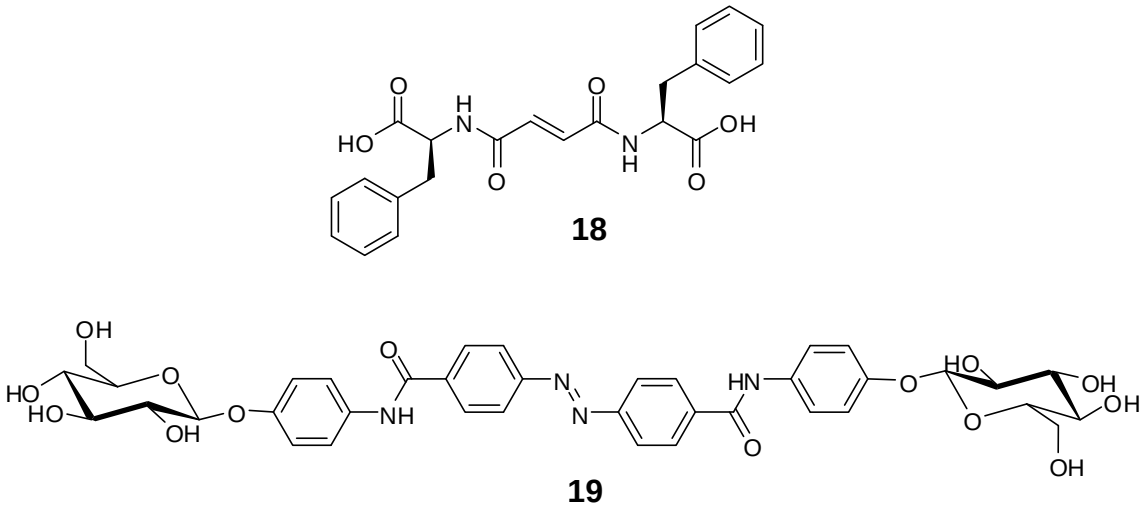


Figure 1.6. Some LMHGs with aromatic nonpolar regions (**18**[31], **19**[84]).

Some LMWGs have ionizable acids that could alter the packing modes through deprotonation. The negative or positive charges test the electrostatic repulsion and/or attraction effect on gels containing ionizable species. Compound **18** also contains an isomerizable double bond, of which only the *trans* conformer can form a gel in water. From its *cis* conformer, only through fast isomerization can the molecule gel water. Slow isomerization of **18** leads to crystallization.[25]

Compound **19** is the most efficient *pure* water gelator currently published.[83] Shinkai, et al tested the sol-gel phase transition temperatures (T_{gel}) under two conditions to determine the mode of packing. They varied the concentration from 0.02 to 0.40 wt% and increased the concentration of DMSO in water from 0-100% at a 3.0 wt% concentration. The T_{gel} increased from 32°C to 118°C with an increase in concentration of the gelator, which is observed with most gelators and is due to the increase of intermolecular interactions resulting in a higher degree of cross-linking and branching. The T_{gel} decreased from

184°C to 73°C with increasing concentration of DMSO with the gel becoming soluble between 60-80% DMSO. The decrease of the T_{gel} is indicative of weaker interactions (caused by DMSO) between the molecules, which is, with the prominent aromatic groups, is π–π stacking. This self-assembly by the azobenzene rings was verified by comparing the UV absorbance spectra in the gel and sol states.[83]

1.5. Carbohydrate-based low molecular weight gelators

In addition to the gelation of various solvents, both aqueous and organic, carbohydrates-based LMWGs (C-LMWGs) also offer the advantage of as an abundant and renewable natural resource. The prospect of multiple chiral centers can be used in the separation of enantiomers or a heterogenous catalyst used for enantioselective reactions. The multiple hydroxyls of a simple carbohydrate can be utilized as hydrogen bond donors or functionalized readily to give rise to gelators with drastically different properties. Most importantly, from a medicinal standpoint, carbohydrates, like amino acids, are natural compounds so that simply derived C-LMWGs could be used in the human body potentially without harmful side effects. The large amount of hydroxyls partakes in much of the carbohydrates solubility in water and has been used primarily to synthesize LMHGs, although there are many cases where LMOGs utilize the advantage of multiple hydrogen bonding donors and acceptors. Carbohydrates have the capability in satisfying the three criteria (from the introduction) of a usuable gelator: natural abundance, simplicity, and sustainability.

Furhop, et al have synthesized and studied the self-assembly of the first carbohydrate gelators.[27] Four aldonic acids (D-glucose, D-mannose, D-gulose, and L-mannose) and two amines (octyl and octadecyl) were condensed to give a quick library of 8 potential C-LMHGs. Compound **7** was found to produce long micellar fibers of only 4 nm in width with an CMC (or MGC) of 0.85 wt %. The D-mannonamide and D-gulonamide gave similar results at 0.93 and 0.80 wt %, respectively.

Shinkai, Hamachi, and the Shimizu groups has yielded many advancements in this area of C-LMWGs. LMHGs, such as the azobenzene derivative **12**, and LMHG **20**[108,109] were found by combinatorial synthesis using solid phase glycolipid synthesis developed by Hamachi and Shinkai.[110,111] Several alkyl and cycloalkyl ester derivatives of **20** gelled at 4 mM.[108] LMHG **20** was later used to fix lectins to identify oligiosaccharides of biological importance.[109] LMWGs **22** and **23** in addition to the glucose derivative were also found through combinatorial synthesis and can gelate various organic solvents, with many gels at concentrations below 1.0 wt %.[112-115] The β-anomer of **23** was found to be a slightly better gelator, partly due to the position of the anomeric position, but it loses the ability to gelate water. In a short synthetic sequence, the 3 position was inverted from both the glucose and mannose benzylidene derivatives and the resulting two sugar derivatives in both the α and β anomers did not gelate any of the solvents tested.[112] When the 3-position was in the axial postion, the reason for the lack of gelation was imparted to intramolecular hydrogen bonding, which is necessary to form the hydrogen bonding network.

β-Cyclodextrin **21** has been used to gel pyridine itself or in combination with toluene, chloroform, or tetrahydrofuran.[116] Exposing this system to water disrupts the hydrogen bonding and causes the molecules to crystallize, forming a ternary crystal complex of β-cyclodextrin, pyridine, and water.

Compound **25** is able to form a clear gel in pure ethylene glycol at a concentration of 1.0 mM or 3.6 wt %.[117,118] The hydrogen bonding was monitored by IR and the π–π stacking of the phenyl groups was later verified. In conjunction with what Fuhrhop noticed in his systems, the racemate of **25** did not exhibit the properties of the pure enantiomer. Extinction crosses (SAXS) were also observed suggesting a helical arrangement.

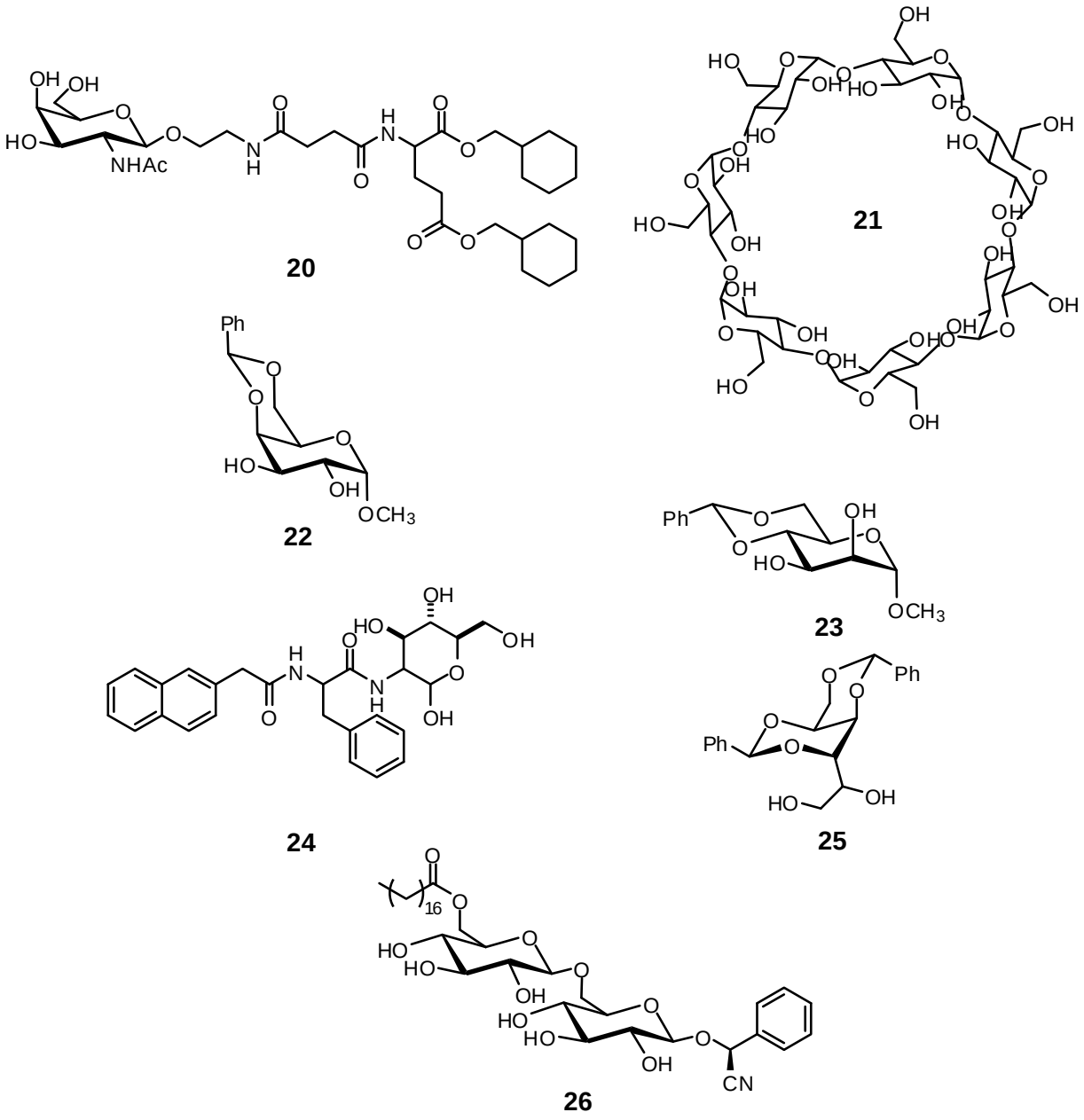


Figure 1.7. Examples of carbohydrate-based LMWGs (**20**-**26**[108-118]). Molecules **20**,[108,109] **24**,[119] and **26**[120] have applications that will be discussed.

1.6. Applications of low molecular weight gelators

Although they are less advanced than their polymer counterparts relatively new and have less mechanical strength, studies on LMOGs have indicated they can function, and in some cases, the same capacity as their polymer gels. In addition these gels have properties not seen in their polymer cousins. For instance, LMOGs exhibit the liquid crystal phenomenon (e.g. lyotropic phases, birefringence, etc.); opening up the door for possibilities of semi-solid materials with LC properties. Anisotropic gels may give way to materials with opto-electrical and photofunctional properties.[121,122] The fibrilluar network can function along distinct lines. Biologically, it can be used as a matrix for tissue regeneration[123] or drug encapsulation and release. LMWGs can be used to remove toxins and pollutants from the human body and the environment. Along with LMHGs of **20**,[108-109] **24**,[119] and **26**[120] some LMWGs with demonstrated uses are in **Figure 1.8**.

LMHG **20** was used by Hamachi and his group to immobilize various lectins, which bind to specific oligosaccharides.[109] The detection was done by utilizing fluorescein-labeled lectins and associated sugars with an attached diazobenzene quencher. The affinity of the lectin to specific sugars was measured by the fluorescence recovery by the displacement of the quencher. The activity of concavalin A, which binds selectively to mannose and glucose, did not appear to be altered while immobilized by the gel. The gels of **20** containing concavalin A or other lectins were arranged on a small array and were able to detect various oligosaccharides including glycoproteins.

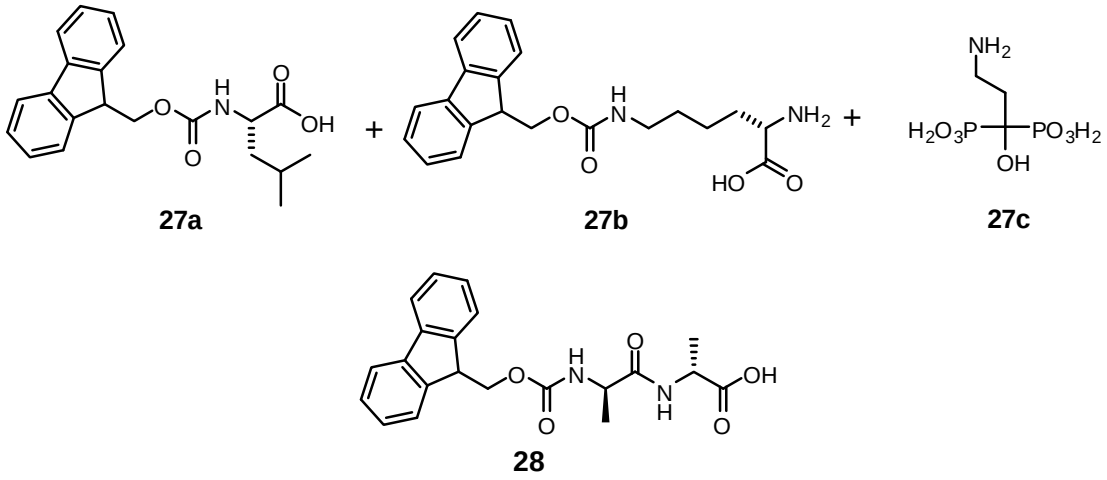


Figure 1.8. Low molecular weight hydrogelators that have published applications or demonstrated uses (**28**,[103] **27**a-c[129]).

Compound **24**, synthesized by N-hydroxysuccinimide activated coupling and both *D*- and *L*-phenylalanine derivatives, was capable of gelating water at 0.2 wt %, After rheological and biological testing, the LMHG with *D*-phenylalanine was used for testing as a wound dressing.[120] The naphthyl-*D* or *L*-Phe-*D*-glucosamine moiety of **24** demonstrated a balance between hydrophobicity and hydrophilicity, a necessity for hydrogels. The naphthyl-*D*-glucosamine and the naphthyl-*L*-Phe-*L*-Phe-*D*-glucosamine was synthesized, but failed to become LMHGs. Prior to wound treatment, compound **24′**s cytotoxicity was tested using an MTT ((3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay, which HeLa cells exhibited a 79.0% survival rate at a concentration of 100μM. A small cut was made on the mid-dorsal section of the mouse and the hydrogel (in PBS) was applied to the cut (affixed by a liquid bandage) and monitored over 18 days. By day

6, a significant difference was already noticeable and histograms showed little scar tissue compared to the control group.

Hydrophobic drugs are generally not used because of poor bioavailability, but a triggered release could open a new wave of drug targets previously unavailable. Compound **26** has been designed by George John and his coworkers specifically as a drug release system.[120] *D*-Amygdalin is naturally occurring disaccharide in almonds, and the pits of peaches and apricots. Using an enzyme, lipids were selectively added to the primary hydroxyl. One of these compounds, **26**, was able to gelate water at 0.05 wt %. Curcumin, a hydrophobic drug capable of inhibiting various HIV enzymes[124-126] and has an absorbance (free drug) at 425 nm, was immobilized in the hydrophobic region of the micelles formed by **26**, at which the drug exhibited no absorbance at 425 nm. After exposing the gel of **26** (with the encapsulated drug) to a lipase, the gel dissolved within 12 hrs at 37°C and the drug was released.

Ligand receptor interactions provide an interesting aspect in the design of LMWGs. A specific interaction could cause a gel to form or dissolve, which could have environmental impact in the cleaning up of pollutants or it could be used to release a substance (drugs, or other therapeutics). Vancomycin's antibacterial activity is well known.[127-128] Since it binds to the *D*-Ala-*D*-Ala portion of the proteoglycan wall of bacteria, synthesizing a LMWG containing a *D*-Ala-*D*-Ala portion would make sense. Xu et al[103] synthesized a variety of Fmoc protected dipeptides, including **28** and its

enantiomer Fmoc-*L*-Ala-*L*-Ala. The large π system of the Fmoc group enabled the molecules to self assemble in water into fibers with nanometer width. Exposure to vancomycin dissolves the gel of **28**, but not its enantiomer.

Chelators are useful for isolating certain aspects from a homogenous system. Compounds **27a-c** were designed to remove uranium ions from the human body.[129] Fmoc-*L*-leucine and Fmoc-*L*-lysine are not hydrogelators themselves, but form a hydrogel with a bisphosphate drug **27c** at a pH between 9.0 and 10.4. The design behind the gel was **27c**'s affinity to UO_2^{2+}. The test of the activity of the hydrogel was done by simulating a uranium wound site (scratching the back of the mice and applying uranyl nitrate) and, after 20 minutes, applying the hydrogel to the surface of the simulated wound. Compared to the control group, which either died or had significant weight loss (>35%, a symptom of uranium poisoning), the ones with the hydrogel showed no ill effects of uranium poisoning.

Conclusions

Low molecular weight gelators are a diverse group of molecules ranging from alkanes, to amino acids and sugar derivatives. In this chapter, the basic aspects of LMWGs are reviewed, and special emphases are placed on sugar based low molecular weight gelators. Despite perceived inconsistencies in structure-gelation relationships, computer modeling, as with drug design, may help with sorting the inconsistencies and lead to better (more efficient and robust) LMWGs. However, systematic approaches may be necessary to better understand and to degsin these systems. Nevertheless, one cannot underestimate the seemingly endless possibilities of serendipitous discoveries, especially with molecules this diverse. The analysis of the whole gel is necessary to observe morphologies in the natural state. Techniques, such as cryo-TEM, cryo-SEM, and XRD, will become indispensable for observing the gel morphologies. Further studies of these molecules will help understand the nature of the interactions between the molecules and how they are ordered within the aggregates. Perhaps the study of versatile gelators that are able to gelate water and organic solvents may reveal some insight into the intermolecular forces involved in gelation. LMOGs and LMHGs can have potential applications in place of where poymer gelators are used. Further studies of these relatively new systems as advanced materials replacing polymer gelators are necessary.

References

1. P. Terech, R. G. Weiss. *Chem. Rev.* **1997,** *97*, 3133-3159.

2. Jordon Lloyd, D. *Colloid Chemistry*; Alexander, J., Ed.; The Chemical Catalog Co.; New York, **1926**, *1*, 767.

3. L. Brunsveld, B. J. B. Folmer, E. W. Meijer, R. P. Sijbesma. *Chem. Rev.* **2001**, *101*, 4071-4097.

4. Eicke, H. F. *Top. Curr. Chem.* **1980**, *87*, 91-128.

5. Bourrel, M.; Schechter, R. S. *Surfactant Science Series*. Dekker, M.: New York, **1988**, *30*, 111-124.

6. Ruckenstein, E.; Nagarajan, R. *J. Phys. Chem.* **1980**, *84*, 1349-1358.

7. Israelachvili, J. N. *Intramolecular and Surface Forces*, 2nd ed.; Academic Press: New York, **1991**, 341-435.

8. Fenniri, H.; Mathivanan, P.; Vidale, K. L.; Sherman, D. M.; Hallenga, K.; Wood, K. V.; Stowell, J. G. *J. Am. Chem. Soc.* **2001**, *123*, 3854-3856.

9. Kokufuta, E.; Jinbo, E. *Macromolecules*. **1992**, *25*, 3549-3552.

10. Koshi, Y.; Nakata, E.; Yamane, H.; Hamachi, I. *J. Am. Chem. Soc.* **2006**, *128*, 10413-10422.

11. Bae, Y.H.; Kwon, I.C. *Biorelated Polymers and Gels*, Okano, T., Ed. Academic Press: San Diego, **1998**, 112-148.

12. Haider, M.; Leung, V.; Ferrari, F.; Crissman, J.; Powell, J.; Cappello, J.; Ghandehari, H. *Molecular Pharmaceutics*. **2005**, *2*, 139-150.

13. Ewert, K.; Ahmad, A.; Evans, H. M.; Schmidt, H-.W.; Safinya, C. R. *J. Med. Chem.* **2002**, *45*, 5023-5029.

14. Ilies, M. A.; Seitz, W. A.; Ghiviriga, I.; Johnson, B. H.; Miller, A.; Thompson, E. B.; Balaban, A. T. *J. Med. Chem.* **2004**, *47*, 3744-3754.

15. Goh, S. L.; Murthy, N.; Xu, M.; Fréchet, J. M. J. *Bioconjugate Chem*. **2004**, *15*, 467-474.

16. Lee, K. Y.; Mooney, D. *J. Chem. Rev.* **2001**, *101*, 1869-1880.

17. Brizard, A.; Oda, R.; Huc, I. *Top. Curr. Chem.* **2005**, *256*, 167-218.

18. Fenniri, H.; Mathivanan, P.; Vidale, K. L.; Sherman, D. M.; Hallenga, K.; Wood, K. V.; Stowell, J. G. *J. Am. Chem. Soc.* **2001**, *123*, 3854-3855.

19. Almdal, K.; Dyre, J.; Hvidt, S.; Kramer, O. *Polym. Gels Networks.* **1993**, *1*, 5-17.

20. Burchard, W.; Ross-Murphy, S. B. *Physical Networks, Polymers and Gels*; Elsevier: London, **1990**, 118-152.

21. Burchard, W.; Stadler, R.; Freitas, L. L.; Möller, M.; Omeis, J.; Mühleisen, E. *Biological and synthetic polymer networks*, Kramer, O., Ed.; Elsevier: London and New York. **1986**, 102-140.

22. Clark, A.; Ross-Murphy, S. B. *Biopolymers: Adv. Polym. Sci.* Springer-Verlag: Berlin, **1987**, *83*, 57-92.

23. Estroff, L. A.; Hamilton, A. D. *Chem. Rev.* **2004**, *104*, 1201-1218.

24. Kunitake, T.; Okahata, Y.; Shimomura, M.; Yasunami, S.; Takarabe, K. *J. Am. Chem. Soc.* **1981**, *103*, 5401-5413.

25. Frkanec, L.; Jokíc, M.; Makarevic, J.; Wolsperger, K.; Zinic, M. *J. Am. Chem. Soc.* **2002**, *124*, 9716-9717.

26. Imae, T.; Takahashi, Y.; Muramatsu, H. *J. Am. Chem. Soc.* **1992**, *114*, 3414-3419.

27. Fuhrhop, J. H.; Svenson, S.; Boettcher, C.; Rossler, E.; Vieth, H. M. *J. Am. Chem. Soc.* **1990**, *112*, 4307-4312.

28. Suzuki, M.; Yumoto, M.; Kimura, M.; Shirai, H.; Hanabusa, K. *Chem. Commun.* **2002**, 884-885.

29. Maitra, U.; Mukhopadhyay, S.; Sarkar, A.; Rao, P.; Indi, S. S. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 2281-2283.

30. Newkome, G. R.; Baker, G. R.; Arai, S.; Saunders, M. J.; Russo, P. S.; Theriot, K. J.; Moorefield, C. N.; Rogers, L. E.; Miller, J. E.; Lieux, T. R.; Murray, M. E.; Phillips, B.; Pascal, L. *J. Am. Chem. Soc.* **1990**, *112*, 8458-8465.

31. Nakashima, T.; Kimizuka, N. *Adv. Mater.* **2002**, *14*, 1113-1116.

32. Makarevic, J.; Jokic, M.; Peric, B.; Tomisic, V.; Kojic-Prodic, B.; Zinic, M. *Chem. Eur. J.* **2001**, *7*, 3328-3341.

33. Iwaura, R.; Yoshida, K.; Masuda, M.; Ohnishi-Kameyama, M.; Yoshida, M.; Shimizu, T. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 1009-1012.

34. Shimizu, T.; Masuda, M. *J. Am. Chem. Soc.* **1997**, *119*, 2812-2818.

35. Kogiso, M.; Hanada, T.; Yase, K.; Shimizu, T. *Chem. Commun.***1998**, *17*, 1791-1792.

36. Kogiso, M.; Ohnishi, S.; Yase, K.; Masuda, M.; Shimizu, T. *Langmuir.* **1998**, *14*, 4978-4986.

37. Suzuki, M.; Yumoto, M.; Kimura, M.; Shirai, H.; Hanabusa, K. *Chem. Eur. J.* **2003**, *9*, 348-53.

38. Kogiso, M.; Ohnishi, S.; Yase, K.; Masuda, M.; Shimizu, T. *Langmuir*. **1998**, *14*, 4978-4986.

39. Lambert, O.; Levy, D.; Ranck, J. L.; Leblanc, G.; Rigaud, J. L. *Biophys. J.* **1998**, *74*, 918-923.

40. Boettcher, C.; Schade, B.; Fuhrhop, J. H. *Langmuir.* **2001**, *17*, 873-877.

41. Hartgerink, J. D.; Beniash, E.; Stupp, S. I. *Science.* **2001**, *294*, 1684-1688.

42. Estroff, L. A.; Leiserowitz, L.; Addadi, L.; Weiner, S.; Hamilton, A. D. *Adv. Mater.* **2003**, *15*, 38-42.

43. Terech, P.; de Geyer, A.; Struth, B.; Talmon, Y. *Adv. Mater.* **2002**, *14*, 495-498.

44. Pochan, D. J.; Pakstis, L.; Ozbas, B.; Nowak, A. P.; Deming, T. J. *Macromolecules.* **2002**, *35*, 5358-5360.

45. von Berlepsch, H.; Bottcher, C.; Ouart, A.; Regenbrecht, M.; Akari, S.; Keiderling, U.; Schnablegger, H.; Dahne, S.; Kirstein, S. *Langmuir.* **2000**, *16*, 5908-5916.

46. Menger, F. M.; Caran, K. L. *J. Am. Chem. Soc.* **2000**, *122*, 11679-11691.

47. Menger, F. M.; Zhang, H.; Caran, K. L.; Seredyuk, V. A.; Apkarian, R. P. *J. Am. Chem. Soc.* **2002**, *124*, 1140-1141.

48. Menger, F. M.; Seredyuk, V. A.; Apkarian, R. P.; Wright, E. R. *J. Am. Chem. Soc.* **2002**, *124*, 12408-12409.

49. Terech, P. *Croat. Chem. Acta.* **1992**, *65*, 425-430.

50. Imae, T.; Funayama, K.; Krafft, M. P.; Giulieri, F.; Tada, T.; Matsumoto, T. *J. Colloid Interface Sci.* **1999**, *212*, 330-335.

51. Fukuda, H.; Goto, A.; Imae, T. *Langmuir.* **2002**, *18*, 7107-7114.

52. Ostuni, E.; Kamaras, P.; Weiss. R. G. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1324-1326.

53. Schmelzer, J. W. P. *Molecular Gels: Materials with Self-Assembled Fibrillar Networks*; Weiss, R.; Terech, P., Eds., Springer Netherlands, **2006**, 131-160.

54. Fuhrhop, J. H.; Schnieder, P.; Rosenberg, J.; Boekema, E. *J. Am. Chem. Soc.* **1987**, *109*, 3387-3390.

55. Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1990**, *112*, 2008-2010.

56. Pranata, J.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 2810-2819.

57. Boner, C. J. *Manufacture and Application of Lubricating Greases*; Reinhold Publishing Corp.: New York, **1960**, 13-66.

58. Georges, J. M. *Tribology Series*; Elsevier: Amsterdam, **1982**, *7*, 651-655.

59. Fiero, G. W. *J. Am. Pharm. Assoc.* **1940**, *29*, 502-505.

60. Technical Bulletin from Nikko Chemicals Co., Ltd., 1-4-8 Nihonbashi-Bakurocho, Japan, **1989**.

61. Bujanowski, V. J.; Katsoulis, D. E.; Ziemelis, M. J. *J. Mater. Chem.* **1994**, *4*, 1181-1183.

62. Terech, P.; Ramasseul, R.; Volino, F. *J. Colloid Interface Sci.* **1983**, *91*, 280-284.

63. Terech, P. *J. Colloid Interface Sci.* **1985**, *107*, 244-250.

64. Baddeley, C.; Yan, Z.; King, G.; Woodward, P. M.; Badjic, J.D. *J. Org. Chem*. **2007**, *72*, 7270-7278.

65. Cardolaccia, T.; Li, T.; Schanze, K. S. *J. Am. Chem. Soc.* **2008**, *130*, 2535-2545.

66. Hanabusa, K.; Matsumoto, Y.; Miki, T.; Koyama, T.; Shirai, H. *J. Chem. Soc., Chem. Commun.* **1994**, 1401-1402.

67. Mukherjee, K.; Moulik, S. P. *Langmuir.* **1993**, *9*, 1727-1730.

68. Peri, J. B. *J. Colloid Interface Sci.* **1969**, *29*, 6-9.

69. Xu, X.; Ayyagari, M.; Tata, M.; John, V. T.; McPherson, G. L. *J. Phys. Chem.* **1993**, *97*, 11350-11353.

70. Tata, M.; John, V. T.; Waguespack, Y. Y.; McPherson, C. L. *J. Am. Chem. Soc.* **1994**, *116*, 9464-9470.

71. Tata, M.; John V. T.; Waguespack Y. Y.; McPherson G. L. *J. Phys. Chem.* **1994**, *98*, 3809-3817.

72. Tachibana, T.; Kayama, S.; Takeno, H. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 415-416.

73. Terech, P.; Rodriguez, V.; Barnes, J. D.; McKenna, G. B. *Langmuir.* **1994**, *10*, 3406-3418.

74. Reinitzer, F. *Beiträge zur Kenntniss des Cholesterins, Monatshefte für Chemie (Wien)* **1888**, *9*, 421-441.

75. Hoffmann, S. *Mol. Cryst. Liq. Cryst.* **1984**, *110*, 277-282.

76. Toyne, K. J. *Critical Reports on Applied Chemistry;* Gray, G. W., Ed.; Wiley: Chichester, **1987**, *22*, 28, 131, and references cited therein.

77. Martin-Borret, O.; Ramasseul, R.; Rassat, R. *Bull. Soc. Chim. Fr.* **1979**, *7-8*, 401-404.

78. Terech, P.; Berthet, C. *J. Phys. Chem.* **1988**, *92*, 4269-4272.

79. Zhang, Y.; Gu, H.; Yang, Z.; Xu, B. *J. Am. Chem. Soc.* **2003**, *125*, 13680-13681.

80. Ajayaghosh, A; George, S. J.; Praveen, V. K. *Angew. Chem., Int. Ed.* **2003**, *42*, 332-335.

81. Van de Craats, A. M.; Mullen, K. *Adv. Mater.* **1999**, *11*, 1469-1472.

82. Nuckolls, C.; Katz, T. J.; Castellanos, L. *J. Am. Chem. Soc.* **1996**, *118*, 3767-3768.

83. Naota, T.; Koori, H. *J. Am. Chem. Soc.* **2005**, *127*, 9324-9325.

84. Kobayashi, H.; Friggeri, A.; Koumoto, K.; Amaike, M.; Shinkai, S.; Reinhoudt, D. N. *Org. Lett.* **2002**, *4*, 1423-1426.

85. Flory, P. J. *Faraday Discuss.* **1974**, *57*, 7-10.

86. Keller, A. *Faraday Discuss.* **1995**, *101*, 1-8.

87. Wang, R.; Geiger, C.; Chen, L.; Swanson, B.; Whitten, D. G. *J. Am. Chem. Soc.* **2000**, *122*, 2399-2400.

88. Sakurai, K.; Jeong, Y.; Koumoto, K.; Friggeri, A.; Gronwald, O.; Sakurai, K.; Okamoto, S.; Inoue, K.; Shinkai, S. *Langmuir*. **2003**, *19*, 8211-8217.

89. Xing, B.; Choi, M. F.; Xu, B. *Chem. Commun.* **2002**, 362-364.

90. Furhop, J. H.; Helfrich, W. *Chem. Rev.* **1993**, *93*, 1565-1582.

91. Furhop, J. H.; Koning, J. *Membranes and Molecular Assemblies: The Synkinetic Approach*; Royal Society of Cambridge, U. K., **1994**, 20-44.

92. Estroff, L. A.; Hamilton, A. D. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3447-3450.

93. Wang, G.; Hamilton, A. D. *Chem. Commun.* **2003**, *3*, 310-311.

94. Menger, F. M.; Caran, K. L. *J. Am. Chem. Soc.* **2000**, *122*, 11679-11691.

95. Suzuki, M.; Yumoto, M.; Kimura, M.; Shirai, H.; Hanabusa, K. *Chem. Commun.* **2002**, *8*, 884-885.

96. Suzuki, M.; Yumoto, M.; Kimura, M.; Shirai, H.; Hanabusa, K. *Chem. Eur. J.* **2003**, *9*, 348-354.

97. Suzuki, M.; Yumoto, M.; Kimura, M.; Shirai, H.; Hanabusa, K. *New J. Chem.* **2002**, *26*, 817-820.

98. Vinogradov, S. V.; Kohli, E.; Zeman, A. D. *Molecular Pharmaceuticals.* **2005**, *2*, 449-461.

99. Moreau, L.; Barthelemy, P.; El Maataoui, M.; Grinstaff, M. W. *J. Am. Chem. Soc.* **2004**, *126*, 7533-7539.

100. Iwaura, R.; Yoshida, K.; Masuda, M.; Yase, K.; Shimizu, T. *Chem. Mater.* **2002**, *14*, 3047-3053.

101. Koshi, Y.; Nakata, E.; Yamane, H.; Hamachi, I. *J. Am. Chem. Soc.* **2006**, *128*, 10413-10422.

102. Kimizuka, N; Nakashima, T. *Langmuir*. **2001**, *17*, 6759-6761.

103. Jung, J. H.; John G.; Masuda, M.; Yoshida, K.; Shinkai, S.; Shimizu, T. *Langmuir.* **2001**, *17*, 7229-7232.

104. Kiyonaka, S.; Shinkai, S.; Hamachi, I. *Chem. Eur. J.* **2003**, *9*, 976-983.

105. Bhattacharya, S.; Acharya, S. N. G. *Chem. Mater.* **1999**, *11*, 3504-3511.

106. Konig, J.; Boettcher, C.; Winkler, H.; Zeitler, E.; Talmon, Y.; Fuhrhop, J. *J. Am. Chem. Soc.* **1993**, *115*, 693-700.

107. Boettcher, C.; Stark, H.; van Heel, M. *Ultramicroscopy.* **1996**, *62*, 133-135.

108. Kiyonaka, S.; Sugiyasu, K.; Shinkai, S.; Hamachi, I. *J. Am. Chem. Soc*, **2002**. *124*, 10954-10955.

109. Y. Koshi, E. Nakata, H. Yamane, I. Hamachi. *J. Am. Chem. Soc.* **2006**, *128*, 10413-10422.

110. Hamachi, I; Kiyonaka, S.; Shinkai, S. *Chem. Commun.* **2000**, 1281-1282.

111. Hamachi, I; Kiyonaka, S.; Shinkai, S. *Tetrahedron Lett.* **2001**, *42*, 6141-6143.

112. O. Gronwald, K. Sakurai, R. Luboradzki, T. Kimura, S. Shinkai. *Carbohyd. Res.* **2001**, *331*, 307-318.

113. Gronwald, O.; Shinkai, S. *Chem. Eur. J.* **2001**, *7*, 4328-4334.

114. Yoza, K.; Amanokura, N.; Ono, Y.; Akao, T.; Shinmori, H.; Takeuchi, M.; Shinkai, S.; Reinhoudt, D. N. *Chem. Eur. J.* **1999**, *5*, 2722-2729.

115. Yoza, K.; Ono, Y.; Yoshihara, K.; Akao, T.; Shinmori, H.; Takeuchi, M.; Shinkai, S.; Reinhoudt, D. N. *Chem. Commun.* **1998**, 907-908.

116. De Rango, C.; Charpin, P.; Navaza, J.; Keller, N.; Nicolis, I.; Villain, F.; Coleman, A. W. *J. Am. Chem. Soc.* **1992**, *114*, 5475-5476.

117. Yamasaki, S.; Tsutsumi, H. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2053-2055.

118. Yamasaki, S.; Tsutsumi, H. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 906-908.

119. Z. Yang, G. Liang, M. Ma, A. S. Abbah, W. W. Lu, B. Xu. *Chem. Commun.* **2007**, 843-845.

120. Vemula, P. K..; Li, J.; John, G. *J. Am. Chem. Soc.* **2006**, *128*, 8932-8938.

121. Terech, P.; Gebel, G.; Ramasseul, R., *Langmuir.* **1996**, *12*, 4321-4323.

122. Rifat, A.; Hikmet, A. M. *Adv. Mater.* **1992**, *4*, 679-683.

123. Stile, R. A.; Healy, K. E. *Biomacromolecules*. **2001**, *2*, 185-192.

124. Hergenhahn, M.; Ubaldo, S.; Annette, W.; Axel, P.; Chih-Hung, H.; Ann- Lii, C.; Frank, R. *Mol. Carcinog.* **2002**, *33*, 137-145.

125. Mazumder, A.; Raghavan, K.; Weinstein, J.; Kohn, K. W.; Pommier, Y. *Biochem. Pharm.* **1995**, *49*, 1165-1170.

126. Burke, T. R., Jr.; Fesen, M.; Mazumber, A.; Yung, J.; Wang, J.; Carothers, A. M.; Grunberger, D.; Driscoll, J.; Pommier, Y.; Kohn, K. *J. Med. Chem.* **1995**, *38*, 4171-4178.

127. Kahne, D; Leimkuhler, C.; Lu, W.; Walsh, C. *Chem. Rev.* **2005**, *105*, 425-448.

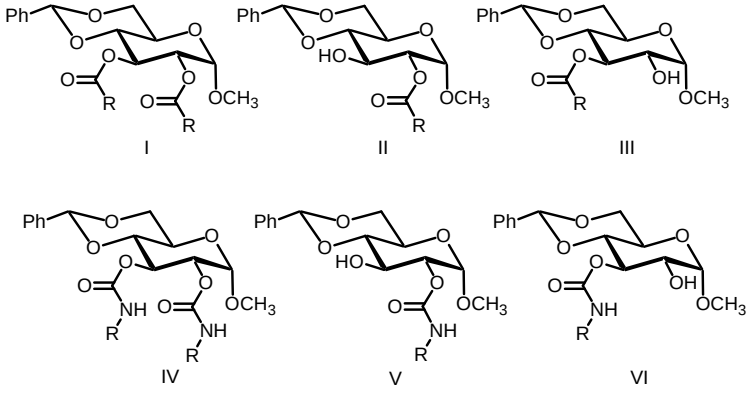
128. Peczuh, M. W.; Hamilton, A. D. *Chem. Rev.* **2000**, *100*, 2479-2494.

129. Yang, Z.; Xu, K.; Wang, L.; Gu, H.; Wei, H; Zhang, M.; Xu, B. *Chem. Commun*. **2005**, 4414-4416.

Chapter 2. D-Glucose-based low molecular weight organogelators: design, synthesis and characterizations

Abstract

Low molecular weight organogelators (LMOGs) and hydrogelators are interesting soft materials with potential applications in many areas. We synthesized and characterized a series of small glycolipids with the general structures of **I-VI** from α-D-glucopyranoside derivative. Depending on the structures of the R group and the headgroup, many of these compounds can effectively gelate organic solvents, aqueous solutions, and water. Gelators created from the library were dried and characterized under optical and scanning electron microscopy. These new materials are expected to be useful in drug delivery, tissue engineering, and purification of biomolecules. The synthesis and characterization of these novel organogelators are presented here.



Introduction

When designing a synthesis for compounds of interests such as drugs or new materials, an important thing is to consider the efficiency, cost, and availiablity of starting materials. Carbohydrates are the most abundant, renewable, and functioanl group dense natural products, and they have many of the features suitable in the design and synthesis of low molecular weight gelators. The advantage, which carbohydrates provide towards the synthesis of LMWGs, could be used to advance the chemistry of carbohydrates and advanced biocompatible materials.

Already existing in various forms in nature, soft materials formed by glycolipids are biocompatible and biodegradable could have and already have demonstrated uses in fields of biomedicine, biochemistry, industry, the environment, and material chemistry. The self-assembly phenomenon through non-covalent forces have yielded interesting soft materials (i.e., physical gels), such as hydrogels (in water) or organogels (in organic solvents).[1–4] The gelation processes by stable LMWGs thermoreversible reversible, because of the noncovalent interactions between the molecules. The different macrostructures formed by LMWGs have potential applications in forming liquid crystalline materials, templating for synthesizing other novel materials, and forming a fiberous network to function as matrices for separating peptides and amino acids, or tissue regeneration.[5-7]

Polymer based hydrogels have demonstrated uses in the fields of drug delivery, tissue engineering and regeneration, enzyme immobilization, and controlled release of other

biological agents.[8-11] Agarose (a polysaccharide isolated from kelp) gels have been widely utilized for electrophresis and DNA and protein purifications. The interlocking network of these hydrogels, which are covalently linked, give them the some of ideal properties of which they are used. Supramolecular hydrogels differ from their polymer counterpart in that they are formed by LMOGs through non-covalent forces, which give rise to the term physical (as opposed to chemical or polymeric) gels. They are an interesting new class of soft materials, which have applications in areas of biomaterials and pharmaceuticals.[12-14] Self-assembled supramolecular gels have several advantages over their polymeric analogs. 1) The monomers are easier to prepare and purify and are usually more stable. Before the preparation of polymers, the monomers are unstable and can easily (unrestrained) polymerize without the use of a catalyst. 2) The resulting materials can have tunable physical properties. The structures of LMWGs can also be readily modified to introduce functional groups that can give rise to desired physical properties. In comparison, the physical properties of polymers are almost never uniform due to side chains and molecular weight variations. 3) LMWGs are thermoreversible. Reversible physical gelation may have the advantage of entrapping or releasing biomolecules in the matrix, without affecting the properties of the entrapped agents. The noncovalent interactions between the molecules make the gels easier to dissolve or break down than polymer gels, thus allowing the entrapped substances to be separated readily. Recycling polymers causes a decrease in average molecular weight of the polymer, through breaking of covalent bonds, thus changing the physical properties of a polymer gel.

Low molecular weight gelators (LMWGs) are usually derived from naturally occurring molecules. They contain a wide range of compounds including, ureas,[15,16] saccharides,[17-21] amino acids,[22-30] nucleotides,[31] nucleosides,[32] and other structural classes.[33-37] In comparison to past LMWGs, which many of them were discovered by accident, researchers are actively pursuing novel LMWGs through rational design and/or combinatorial chemistry.[12,21] Several examples of existing hydrogelators (**1–3**) are shown in **Figure 1**. A urea derivative of serine (**1** and different variations thereof) is among the smallest of LMWGs by molecular weight (246 g/mol) and can form hydrogels in pure water at a concentration of 0.8–1 wt %.[16] The hydrogen bonds between the urea moieties allow the molecules to self-assemble into a one-dimensional array and the short alkyl group provides flexibility. The short chain galactosacetamide and glucose amino acid lipids **2** and **3** were discovered by combinatorial chemistry and were shown to be effective hydrogelators.[12,21] In addition, they can be used to immobilize enzymes and form semi-solid lectin microarrays. From an examination of various structures of LMHGs, the common features of good hydrogelators that are apparent is a hydrophilic portion that can form hydrogen-bonding interactions, a rigid region, and a flexible short alkyl chain that will allow the molecules to interact with each other through hydrophobic forces. The structures of LMOGs more diverse than LMHGs because they gelate organic solvents, which include polar solvents, such as dimethyl sulfoxide, ethanol, and acetone and nonpolar solvents, such as hexanes, ether, and toluene. Structures of LMOGs range from 12-hydroxy-octadecanoic acid or dihydrolanosterol (large hydrophobic groups with a single hydroxyl) to water soluble β-cyclodextrin.

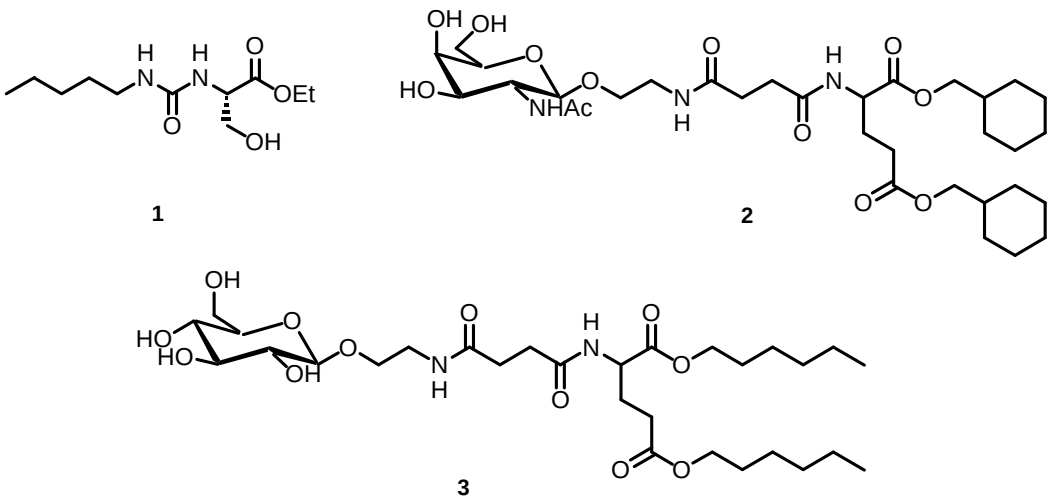
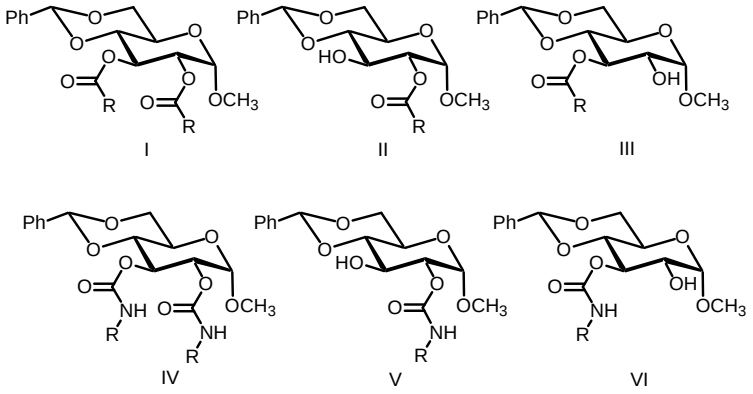


Figure 2.1. Hydrogelators formed by the simple derivatization of naturally occurring molecules

Because of the great potential of hydrogelators, the discovery of new biocompatible hydrogelators with straightforward structures, which will render large-scale synthesis more feasible, will become necessary. Carbohydrates are ideal starting materials because they are abundant natural chiral compounds with multiple sites available for functionalization. The creation of novel functional biocompatible materials from carbohydrates is important for the advancement of carbohydrate chemistry and biomaterials research. Chirality in supramolecular structures may be useful in molecular recognition with other chiral compounds. These functional materials have potential applications in drug delivery, tissue engineering, and as biocompatible materials. As part of our efforts to discover novel functional biocompatible materials, we designed and synthesized a series of D-glucose-based lipids and found that they are excellent gelators in water and other solvents. These include the diester, monoesters **I-III**, and the dicarbamate, monocarbamates **IV-VI**. Inspired by the structures of hydrogelators **1-**

3,[12,16,21] we envisioned the incorporation of short chain fatty acyl unit to the 2 or 3-hydroxyl groups via ester or carbamate linkages (**II**, **III**, **V**, **VI**) could potentially lead to small molecule hydrogelators and the diester **I** or dicarbamate **VI** could be potential organogelators. The hydroxyl groups and amide groups can provide hydrogen-bonding interactions.



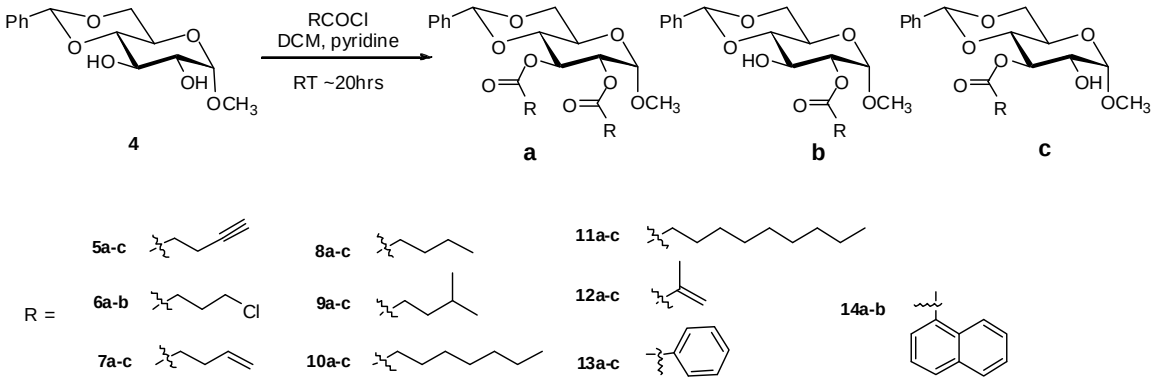
Results and Discussion

Synthesis and gelation properties of compounds I-III

Many glycolipids and other small sugar derivatives can form gels in organic solvents, but less frequently in water. Here we wish to prepare a class of simple sugar lipids and screen their gelation properties in organic solvents and water. The preparation of compounds I-III is shown in **Scheme 2.1**. Compound **4** is a simple and commercially available glucose derivative, which can form gels in organic solvents in relatively high concentrations (1-3%), but not in water.[12] Modification of the structure of compound **4** by introducing short alkyl chains could potentially lead to good gelators in water or organic solvents. To

synthesize the designed compounds efficiently, reactions were carried out in one-pot to produce the three products A, B, and C, which were then isolated by chromatography. This way, a small library of compounds was synthesized rapidly. The screening of these compounds will quickly give us information about structural influences on gelation properties.

The structure–gelation properties obtained here can be used to design other effective gelators. Compound **4** was synthesized by treating methyl a-D-glucopyranoside with dimethoxylbenzyledene acetal and a catalytic amount of p-toluenesulfonic acid (PTSA) in dimethyl formamide (DMF). Compounds **a**, **b**, and **c** were synthesized by esterification of the hydroxyl groups on the monosaccharide derivative **4** by the corresponding acid chlorides (**Scheme 2.1**). The reaction yields for each of the esters are shown in **Table 2.1**.



Scheme 2.1. Synthesis of 24 ester derivatives of compound **4**.

Table 2.1. The reaction yields (in percentage based on **4**) of ester derivatives

	Ratio of **1**:acylating reagent	**a** (diester)	**b** (2-ester)	**c** (3-ester)
5	1.0:1.0	7	36	12
6	1.0:1.3	16	62	11
7	1.0:1.3	50	35	9
8	1.0:1.3	4	44	11
9	1.0:1.3	4	42	14
10	1.0:1.3	30	43	14
11	1.0:1.3	21	59	11
12	1.0:1.3	13	45	n/a
13	1.0:1.3	3	38	22
14	1.0:1.3	13	83	4

Prior to some of the esterfication reactions, if the acyl chloride was not available, the carboxylic acid end was reacted with excess oxalyl chloride to yield the corresponding acyl chloride. By controlling the ratio of the acid and the diol, three products were obtained in this reaction. It was found that when using about 2 equiv of acid, typically two products were obtained: the diester **a** and the 2-monoester **b** although in theory only the diester **a** should be obtained. When the acid was used in 1–1.3 equiv relative to the diol, mainly the 2-monoester (compound **b**) was obtained, together with small amount of **a** and **c** as well. It is known that esterification generally favors the introduction of the acyl group at the 2-position of glucose derivative **4**. If the acyl group is not bulky, then esterification at the 3-position is also observed. The 2-monoester **b** is probably the kinetic

product and is formed first. Through random events, the 3-monoester **c** is also formed in a small amount. Either **b** or **c** can react further to give the diester. Because less than 2 equivalents of the acylating agent compared to the headgroup was used, the amount of compound **a** (diester) is reduced.

Those reactions with only fair yields may be due to the excess oxalyl chloride reacting with the hydroxyl groups on the sugar ring, thereby inhibiting the esterfication reaction with the acyl chloride. This side reaction was anticipated and excess oxalyl chloride was removed *in vacuo* with hexanes. In most cases, all three products can be obtained in one-pot. These esters can be separated by flash chromatography on silica gel using a gradient of solvent systems (hexane/acetone from 95:5 to 75:25).

Acyl group **12** was the only exception as the diester appeared as the major product. Some speculation for the reason why or why is the 2-ester **12b** significantly less, compared to the diester **12a**, may be due to the inherent reactivity and/or lack of bulk of the 4-pentenoyl group. For most of these reactions, the yields were moderate (>80%), but for some of the reactions the yields were only fair (~60%). Interestingly, the reaction with 1-naphthoyl chloride (**11**) was quantitative and the results were repeatable. The quantitative yield may be due to the reactivity of the aryl acyl chloride, which are more stable and react faster than their alkyl counterparts.

After obtaining purified compounds I-III, their gelation properties in several solvents (hexane, water, ethanol and 1:1 water: ethanol) were tested. To test the gelation

properties, 2-4 mg of each purified product and 0.2 mL of solvent was added to each testing vial. The mixture was heated and sonicated in various solvents mixtures in an attempt to solvate (homogenize) the ester derivatives. Then it was allowed to cool and stand at room temperature for about 15 minutes. Then the vial was inverted, if no liquid flows and gels stays at the bottom end of the vial upside down, we call that a stable gels. If a stable gel form, the concentration was recorded and more solvent (0.2mL) was added and the previous steps were repeated to determine the minimum gelation concentration (MGC). The gel testing results for various ester derivatives of compound **1** are shown in **Table 2.2.**

Table 2.2. Gelation testing of compounds **5-12 a-c**. Positive gelation results are listed in mg/mL. * unstable gel. I – insoluble, P – precipitate, S – soluble at 20 mg/mL

Compound	Hexane	Water	EtOH	EtOH:Water (1:1)	Clog P
5a	**5.0**	**I**	**20**	**P**	**2.24**
6a	**P**	**I**	**S**	**P**	**2.93**
7a	**P**	**I**	**S**	**10***	**3.30**
8a	**P**	**I**	**P**	**P**	**4.26**
9a	**S**	**I**	**S**	**P**	**4.00**
10a	**S**	**I**	**S**	**P**	**7.44**
11a	**S**	**I**	**S**	**I**	**9.55**
12a	**S**	**I**	**S**	**P**	**2.37**
13a	**P**	**I**	**S**	**5.0**	**4.17**
14a	**P**	**I**	**S**	**6.7**	**6.52**
5b	**10***	**4.0**	**S**	**S**	**0.82**
6b	**P**	**P**	**S**	**S**	**1.16**
7b	**P**	**12***	**S**	**S**	**1.34**
8b	**15**	**P**	**S**	**S**	**1.82**
9b	**P**	**S**	**S**	**S**	**1.69**
10b	**S**	**P**	**S**	**P**	**3.41**
11b	**P**	**P**	**S**	**P**	**4.47**
12b	**P**	**20***	**S**	**S**	**0.87**
13b	**P**	**P**	**S**	**P**	**1.72**
14b	**I**	**I**	**S**	**10**	**2.89**
5c	**3.3**	**6.7**	**S**	**S**	**0.82**
7c	**P**	**P**	**S**	**P**	**1.34**
8c	**S**	**P**	**S**	**P**	**1.83**
9c	**P**	**P**	**S**	**P**	**1.70**
10c	**P**	**P**	**S**	**P**	**3.41**
11c	**S**	**P**	**S**	**P**	**4.47**
12c	**I**	**I**	**S**	**8.8***	**0.87**
13c	**P**	**P**	**P**	**P**	**1.73**

$$\log P = \log \left(\frac{[solute]_{octanol}}{[solute]_{water}} \right)$$

Equation 2.1. Experimental calculation of the partition coefficient, *log P*. All concentration values are at equilibrium.

From the gelation results above, some trends can be observed while others require more explanation. Longer terminal alkyne derivatives like compound **5** were synthesized by coworkers of the author to study the effect of a terminal alkyne group.[38] The diesters are insoluble in water, but soluble in ethanol. Compounds **5a** and **14a** are able to gelate a 1:1 mixture of ethanol and water at 20 and 7 mg/mL, respectively. Shinkai[12, 21] reported that the hydroxyl groups were essential in the formation of gels, because they are possibly involved in the formation of the 1-dimensional hydrogen bonding network. With compounds **5a** and **14a** forming gels under aqueous conditions, that criteria may not be necessary as some LMOGs, such as **5a** and **14a**, may use other noncovalent forces to self assemble or utilize the unique property of water to form a hydrogen bonding chain. This event could be possible by observing the change in the frequency of the O-H bond by IR spectroscopy. Gels form after a supersaturation point has been reached. So while compounds **5a** and **14a** were soluble in ethanol, the introduction of water induced the molecules to self-assemble to minimize the interaction of the hydrophobic regions with water. In the process of minimizing unfavorable interactions with water, the saturated alkanes tended to precipitate out of solution, while the alkyne derivative **5a** (and others) formed stable gels. The alkyne group disrupts the packing order, thereby hindering the precipitation or crystal formation. This phenomenon is a characteristic seen in nature.

Unsaturated free fatty acids have lower melting points than their saturated counterparts and unsaturated alkyl chains are necessary for maintaining a flexible, therefore, healthy cell wall. The gelation of the naphthoyl diester (**14a**) occurs because of the presence of the large aryl groups makes π-π stacking the primary mode of self-assembly. There are no hydrogen bonding donors in these molecules, indicating hydrogen bonding is not the main driving force in the gelation of these molecules. However, the presence of water in the solvent used to gel **14a** indicated that water was necessary in the formation of the gel.

The monoester derivatives, **b** and **c**, did not fare any better than the diester derivatives in the gelation tests. The only monoesters, besides the terminal alkyne (**5b** and **5c**) and the naphthoyl (**14b)** of note are the methacryloyl (**12b** and **12c**) and the 2-pentanoyl ester (**7b**). The lack of gelation using saturated esters is most likely due to the high degree of order in the packing, causing them to precipitate out of solution. Again as seen in the diesters, the terminal alkyne and the naphthoyl derivatives, are able to gelate solvents and solvent mixtures, where the saturated compounds are not able to gelate. In addition to the reasons for the gelation of the terminal alkyne diester derivative **5a**, the molecule now has a hydrogen bond donor, which plays a significant role in the formation of a 1-dimentional hydrogen bonding network. Thus, for this reason, this molecule is able to form gels in both hexane and water. There is a small but noticeable decrease in efficiency of gelation of the naphthoyl monoesters to the diesters (6.7 mg/mL for **14a** to 10 mg/mL for **14b**). This decrease in efficiency can be attributed to the influence of π-π stacking of the naphthoyl and phenyl rings in the self-assembly of these molecules, which are destabilized by the hydrogen bonding induced by the free hydroxyl.

The methacryloyl monoester derivatives formed unstable gels, not due to the unsaturation, but the length of the carboxylate group. The length of the carboxylate chain also plays a significant role in the self-assembly of these molecules. Previous work done by the author's coworkers revealed that terminal alkynes with a length of 5 to 7 carbons were optimal for gelating various solvents.[38] Any shorter length would result in unstable gels, while longer chains would have difficulty in dissolving in aqueous solvents. X-ray crystal structures were derived from isolated crystals of compound **6b** and **10a** (**Figures 2.2** and **2.3**).

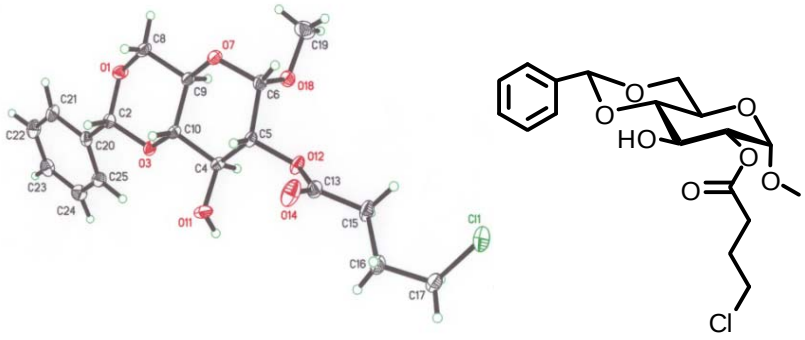


Figure 2.2. X-ray crystal structure of compound **6b**. (Provided by Dr. Ed Stevens)

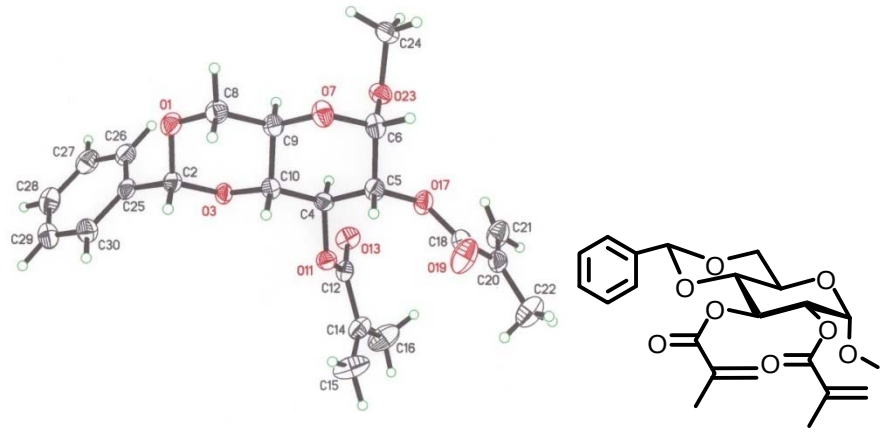


Figure 2.3. X-ray crystal structure of compound **12a**. (Provided by Dr. Ed Stevens)

Under optical microscopy, **Figure 2.4** (compound **14b**) shows a crystalline tube with localized anisotropy resulting in birefringence of the tube. **Figure 2.5** shows a tube of similar dimensions splitting into much smaller fibers. Optical microscopy (**Figures 2.7** and **2.8**) of gels of compounds **12b** and **12c** showed relatively thin fibers and indicated that the unstability was not due to a high degree of crystallinity, but rather relatively short fibers. In **Figure 2.6**, a gel of **14a** in the ethanol/water mixture revealed short and straight rods of a somewhat uniform width. The gel of **14a** destabilized within an hour of forming and was probably due to the rigidity of the molecule itself and the relatively high degree of crystallinity seen in **Figure 2.6**.

The partition coefficient defines a compound's affinity between 1-octanol to water (**Equation 2.1**) and is used in determining the compound's ability to penetrate the cell wall thus its effectiveness. For the ester derivatives, the requirement for gelation in water, hexane, but not totally inclusive, is that the *C log P* values should be near 1.0 (± 0.3) and 1.3 (± 0.5). The range of *C log P* values for water/ethanol mixtures has a much wider disparity (2.8-6.6).

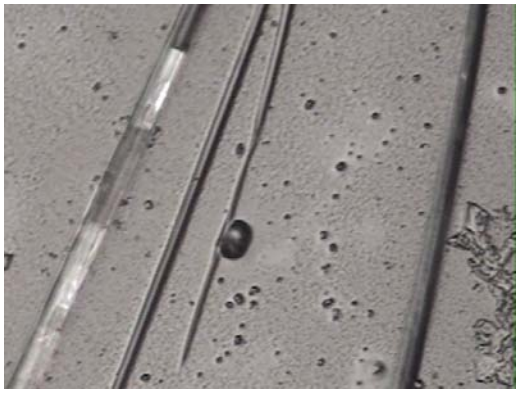


Figure 2.4. Compound **14b** at 10mg/mL in 1:1 of ethanol:water at 500x magnification.

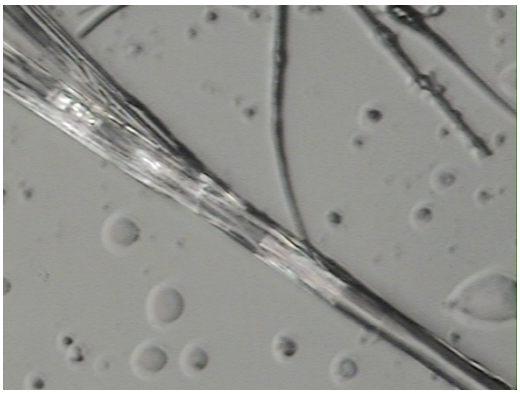


Figure 2.5. Compound **14b** at 10mg/mL in 1:1 of ethanol:water at 500x magnification.

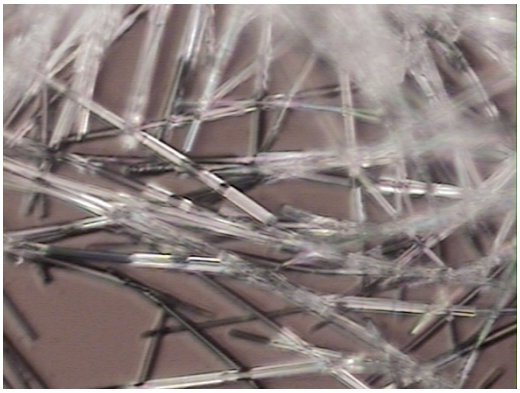


Figure 2.6. Compound **14a** at 6.7mg/mL in 1:1 of ethanol:water at 500x magnification.

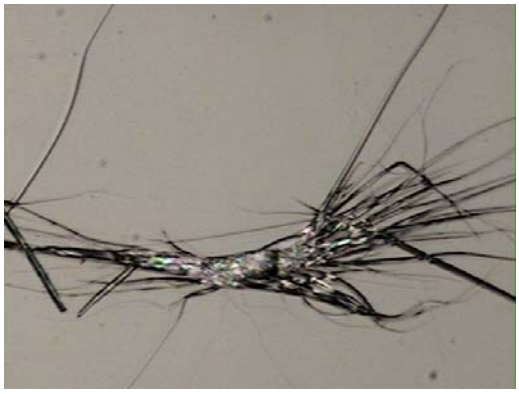


Figure 2.7. Unstable gel formed by compound **12b** at 10mg/mL in 1:1 in ethanol:water at 500x magnification.

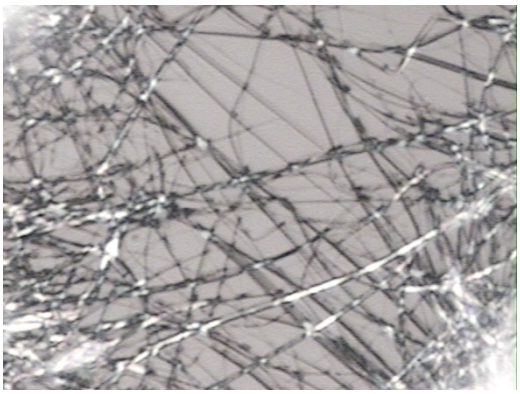
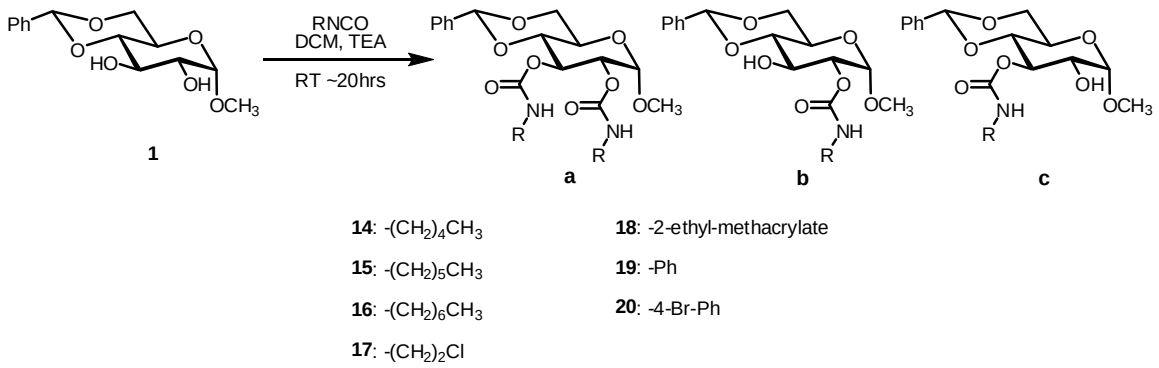


Figure 2.8. Unstable gel formed by compound **12c** at 9mg/mL in 1:1 in ethanol:water at 500x magnification.

Synthesis and gelation properties of compounds IV-VI

D-Glucose derivative **4** was used to synthesize the carbamate library. After the synthesis of the ester library, where positive gelation results were few, an improvement in the system was needed. In most cases in the ester library, the monoesters showed that the free hydroxyls were not sufficient in producing a stable hydrogen bonding network. The synthesis of a carbamate would place another hydrogen bonding donor in the structure. These reactions would place the hydrogen bond donor out of the ring, instead of inside the ring where it could potentially participate in intramolecular hydrogen bonding and therefore destabilize the intermolecular network.



Scheme 2.2. Synthesis of carbamates LMOG library from compound **4**.

Because no acid is produced from the reaction with the isocyanate, no base was thought to be required. However, after several days the reaction would not proceed, even when heated overnight. Within a few hours, after a base catalyst was added, only then did the reaction proceed smoothly. Utilizing the same concept in the synthesis of the ester library, a one-pot synthesis were done on synthesize compounds **14-20 a-c** by adding an

excess of the isocyanate (**Scheme 2.2**). These compounds were purified after workup using silica chromatography with acetone in hexanes (7.1% to 33%).

Table 2.3. Summary of yields (in percentage) of selected carbamates. Ratio of compound **1** to isocyanate is 1:1.33. The hexyl isocyanate was synthesized by Curtius rearrangement using diphenylphosphoryl azide (DPPA).

Reaction Numbers	**a**	**b**	**c**
16	11	60	28
18	5	45	23
20	7	38	0

The carbamoylation reactions proceeded slower than the esterfication reactions and the yields tended to be lower. However, when using the commercially available isocyanate, there was a noticeable increase in the functionalization at the 3-position relative to the amount functionalized at the 2-position. In the case of the isocyanate used to synthesize compounds **15 a-c**, which was synthesized by the Curtius rearrange using DPPA, the dicarbamate was not formed (excess of compound **1**), indicating that the **b** and **c** are formed first. In addition, compared to the ester library, the di-carbmates compounds are significantly less as the minor product compared to the 2-carbamates (**b**). These results suggest that functionalization at the 2-position is still favored (because of sterics), but the reaction proceeds slower than the reactions with the acyl chlorides. Several attempts to isolate the 1-naphthyl carbamate failed due to possible inherent instability of a large aryl carbamate.

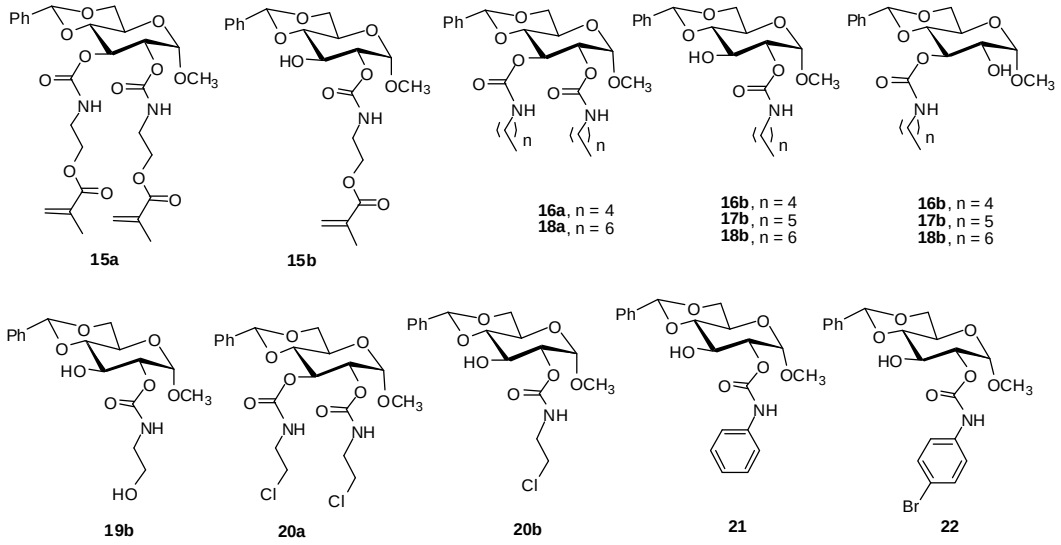


Figure 2.9. List of structures of carbamates synthesized and characterized

Gel Testing

Table 2.4 shows that the monocarbamates are more efficient gelators than their ester counterparts. However, as the dicarbamates show (no gels formed) and contrary to the suggestion that the free hydroxyl does not play a role in hydrogen bonding, at least in this system, the free hydroxyl is necessary for gelation. Also, the amide bond portion of the carbamate, acting as the additional hydrogen bond donor has been shown to play a vital role in the formation of a more stable hydrogen bonding network. Despite the rigidity of aryl rings in the ester library, compound **20b** was able to form gels efficiently in ethanol/ water mixtures (1.7 mg/mL in 2:1 H_2O:EtOH). In addition to testing aqueous ethanol, aqueous dimethyl sulfoxide (DMSO) was also tested as a cosolvent. Although no longer used in human medicine, DMSO is still widely used in veterinary medicine and is a common industrial solvent. In **Table 2.4**, DMSO proves to be a comparable cosolvent. Compound **16b** proved to be an effective gelator in both water and other aqueous mixtures, but for compound **14b**, DMSO and ethanol proved to be essential for gelation.

Table 2.4. Gelation Test results for carbamate derivatives of **1**. Concentration of DMSO and ethanol solutions were 33%. Positive gelation results are listed in mg/mL. * unstable gel. I – insoluble, P – precipitate, S – soluble at 20 mg/mL

Compound	Hexane	Water	EtOH	DMSO:Water	EtOH:Water	C log P
15a	P	I	S	P	P	2.96
15b	I	P	S	P	P	1.17
16a	P	I	S	P	P	4.98
16b	I	20	S	3.3	1.4	2.18
16c	I	I	S	10	P	2.18
17b	I	12*	S	4.0	4.0	2.71
17c	I	P	S	10	P	2.71
18a	P	I	S	P	P	7.10
18b	P	3.3	S	4.0	5.0	3.24
18c	P	P	S	10	P	3.24
19b	P	S	S	S	S	-0.50
20a	P	P	P	12*	P	1.93
20b	I	P	S	S	P	0.66
21	P	P	20	6.7	5.0	1.47
22	I	P	S	4.0	2.0	2.54

In terms of clarity, compound **14b** was the best one of all the compounds (**Figure 2.11**). Increasing the concentration of the compound resulted in an increasingly opaque, yet more robust gel. Both physical changes can be attributed to the higher degree of branching of the fibers formed by compound **14b**. Optical microscopy revealed, in addition to birefringence and other liquid crystalline characteristics of compounds **14b** and **16b**, they also exhibited similar morphologies associated with efficient gelators. In **Figures 2.13** and **2.14**, small and flexible fibers are predominant in efficient gelators. Upon further magnification with the scanning electron microscope, those small fibers observed under optical microscopy are composed of even smaller fibers of 200-400 nm in width (**Figure 2.17**). In addition to the small fibers, superstructures (helices and tubes) are also created by the self-assembly phenomenon (**Figures 2.12**, **2.13**, and **2.16**). Gels in general are often not at their lowest energy state and over a period of time the gel created by an LMOG will destabilize over time. Such was the case with compound **14b** and **16b** (**Figures 2.14** and **2.15**). Within a day or two, the gel in **Figure 2.12** appeared to 'crystallize' out of solution and, shortly after, the gel would start contracting. Examining this occurrence under optical microscopy resulted in **Figures 2.14** and **2.15**. These pictures clearly indicate the formation of plate-like crystals forming when the gel begins to destabilize.

The *C log P* values calculated *in silico* (from ChemDraw) show an interesting trend. For the most part, pure water and aqueous LMWGs had partition coefficients in the range of 1.5 to 3.3 and functionalization at the 2 position. Functionalization at the 3 position did have moderate success, but did not fare as well. There appeared to be a parabolic trend

between the MGC (positive gelation result) and the partition coefficient (**Figure 2.10**), particularly in the water/ethanol mixtures.

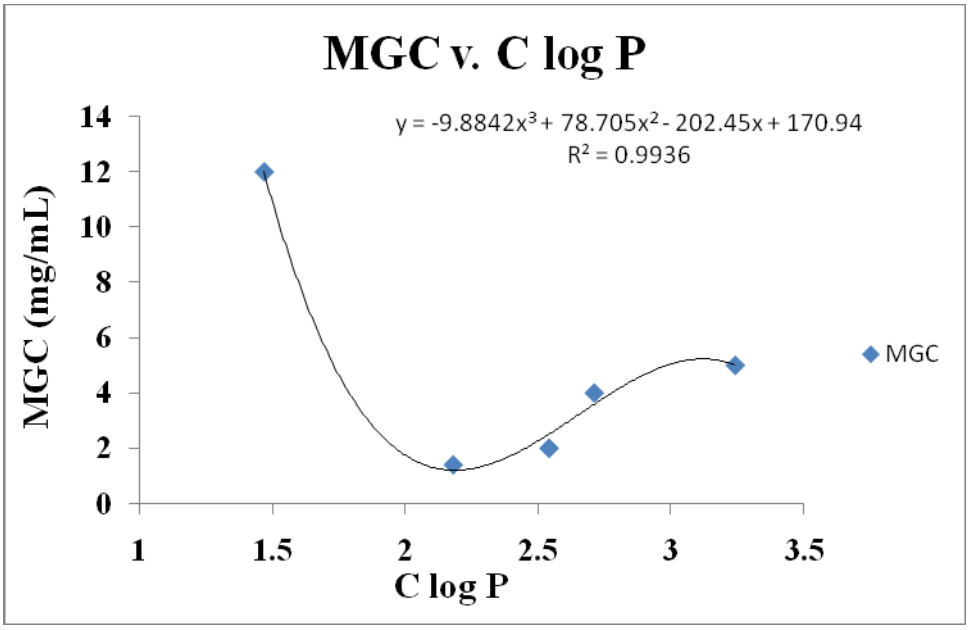


Figure 2.10. Plotting of the minimum gelation concentration (MGC in mg/mL) v. the partition coefficient (C log P) of LMWGs in ethanol/water (1:2) and functionalization at the two position.

From **Table 2.4**, functionalization at the two position made the more efficient LMWGs and, from **Figure 2.10**, a balance between hydrophobicity and hydrophilicity also makes a difference. The more efficient gelators (≤ 2.0 mg/mL) appeared to have a *C log P* values between 2.0 and 2.5, though more tests would have to confirm this finding. To confirm this data and to obtain better coorelation, more carbamates derived from compound **4** LMWGs functionalized at the 2-position with *C log P* values between 1.5 and 3.0 would have to be tested.

Figure 2.11. Compound **16b** at 1.4mg/mL in a 2:1 water:ethanol mixture

Figure 2.12. Compound **16b** at 1.4mg/mL in water:ethanol (2:1) at 1000x magnification.

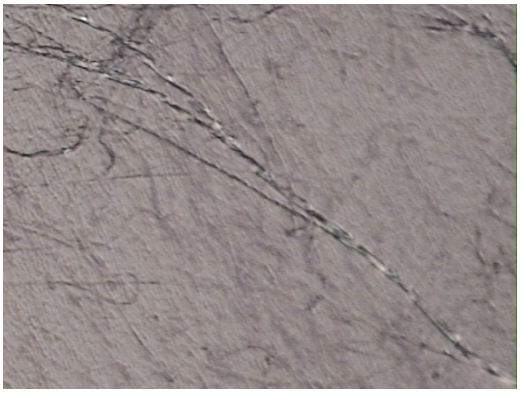


Figure 2.13. Compound **16b** at 1.4mg/mL in water:ethanol (2:1) at 1000x magnification.

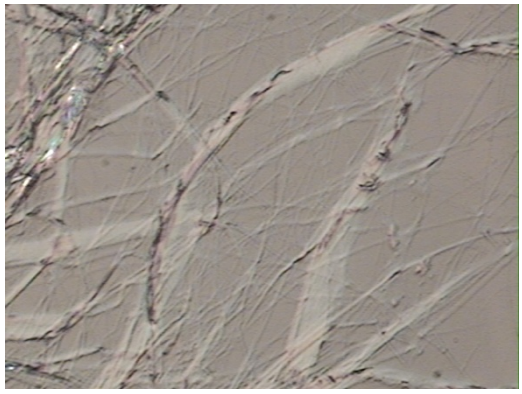


Figure 2.14. Compound **16b** at 1.4mg/mL in water:ethanol (2:1) at 1000x magnification after 10 hours.

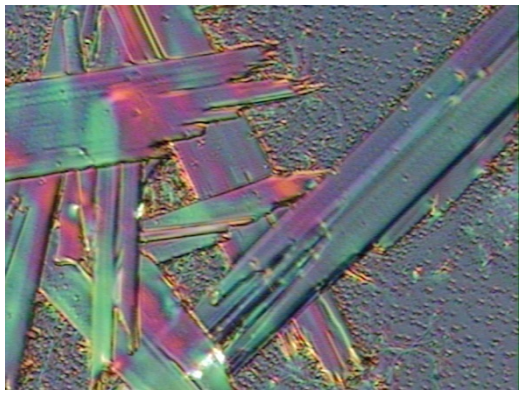


Figure 2.15. Compound **18b** at 5.0mg/mL in water:ethanol (2:1) at 1000x magnification.

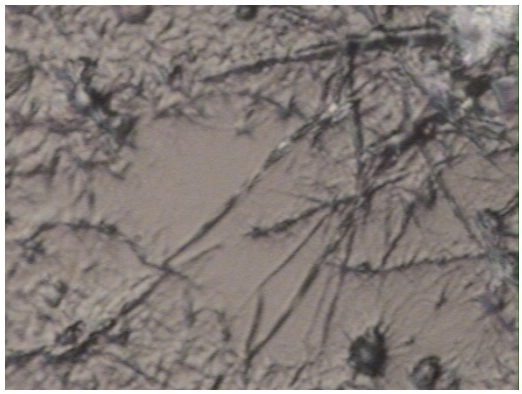


Figure 2.16. Compound **18b** at 5.0mg/mL in water:ethanol (2:1) at 1000x magnification.

Conclusion

In summary, we have synthesized and characterized two libraries of methyl α-D-glucopyranoside derivatives, the esters and the carbamates. These compounds were synthesized by a one-pot reaction and separated by chromatography. They are excellent gelators in hexane, ethanol, and water. The short chain monoesters that contain 5–7 carbon chains are versatile gelators for both water and hexane. The hydrogen bonding of the free hydroxyl groups with water and other molecules is important for their self-assembly properties. The diesters without free hydroxyl groups didnot form gels in water, but they did form gels in hexane and ethanol/water mixtures. Perhaps π–π stacking among the gelators and hydrophobic interactions of the molecules with hexane contributed to the gelation properties observed. The monocarbamates that contain 5–7 carbon chains are also excellent gelators for water and organic solvents. The additional hydrogen bond donor created by the reaction with the isocyanate was a large improvement in gelation properties over their ester counterparts. The reversible physical gelation in water or water/DMSO mixture can be useful in applications such as enzyme immobilization and drug delivery. The correlation between structures and gelation properties of these molecules may be utilized in designing other effective hydrogelators. Supramolecular hydrogels formed by small sugar derivatives can be used in enzyme purification, protein and DNA immobilization, and as scaffolding material for tissue engineering.

Experimental Section

General methods

Gelation Testing. The compounds were tested in a 1 dram vial with a rubber lined screw cap from Kimble. A starting concentration of 10-15mg/mL was used (2-3mg in 0.2mL). The suspension was heated to dissolve the compound (a homogeneous solution) and sonicated, if necessary. The solution was allowed to cool for 15-20 minutes. If a stable gel formed, 0.2-0.3 mL of the same solvent (or solvent mixture) was added and the heating/sonication and cooling was repeated. The process was repeated until the gel was no longer stable and the concentration prior to the unstable gel was recorded as the minimum gelation concentration (MGC).

Optical Microscopy. The slides were prepared after a stable gel has formed. About 20-30mm^3 of the gel was placed on a clean 3 by 1 inch glass slide and dried over night to several days. The xerogels 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.

Scanning Electron Microscopy. Samples were prepared by drying the gel (20-30 mm^3) on an aluminum pellet in a desiccator under reduced pressure for several days. A thin layer of platinum (~100-150 Ang) 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 sec. The sample was analyzed using a JEOL JSM 5410 scanning microscope with an EDAX Detecting Unit PV9757/05 ME (Model 204B+, active area = 10 mm^2).

Column Chromatography. All columns used normal phase silica gel (60Å, 40-63 mm) purchased from Sorbent Technologies®. All solvents were purchased from EMD.

General Synthesis of Compounds 5-14 a-c

In a dry round bottom flask, dry dichloromethane (DCM) (5-10 mL) dissolved compound **4** (1-4 mmol) and 3-4eq of anhydrous pyridine. If commercially available, acyl chlorides were added directly at 0°C. If the acid chloride was not commercially available, the conversion from the corresponding carboxylic acid was done using large excess (14-20x) on a millimolar scale. The carboxylic acid was dissolved in neat oxalyl chloride and reacted for 30 min or until the ^{1}H NMR showed a complete downfield shift in the α-CH_2 (from 2.5 to 3.2 ppm). Excess oxalyl chloride was removed by rotary evaporation and co-distillation with hexanes, and was immediately added to the reaction at 0°C. The temperature was allowed to warm to room temperature and react for 20 hours. The reactions were quenched by washing the reaction in water (2 x ~5 mL) and in cold and diluted $NaHCO_3$ (5%, 1 x ~3 mL). The combined aqueous phases were washed with 2 mL of DCM and the organic phased was dried over anhydrous Na_2SO_4. The crude reaction mixtures were purified using various gradients of hexanes and acetone (19-9:1).

4-Pentynoic esters

Diester **5a** was isolated as white crystals (29mg, 6.6%), mp 104.0–105.8°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.38–7.46 (m, 2H), 7.30–7.36 (m, 3H), 5.60 (pt, *J* = 9.8 Hz, 1H), 5.48 (s, 1H), 4.90–4.95 (m, 2H), 4.29 (dd, *J* = 4.9, 9.8 Hz, 1H), 3.91 (dt, *J* = 4.9, 9.8 Hz, 1H), 3.76 (t, *J* = 9.8 Hz, 1H), 3.65 (t, *J* = 9.8 Hz, 1H), 3.39 (s, 3H), 2.40–2.63

(m, 8H), 1.97 (t, J = 2.9 Hz, 1H), 1.86 (t, J = 2.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.0, 170.4, 136.8, 129.0, 128.1, 126.1, 101.4, 97.4, 82.2, 82.0, 79.0, 71.6, 69.2, 69.1, 68.7, 62.2, 55.3, 33.13, 33.07, 14.3, 14.2. HR ESIMS calcd for $C_{24}H_{27}O_8$ $[M+H]^+$ 443.1706, found 443.1710.

The 2-ester **5b** was isolated as white crystals (129mg, 36%), mp 71.8–73.5°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43–7.50 (m, 2H), 7.31–7.37 (m, 3H), 5.53 (s, 1H), 4.93 (d, J = 3.9 Hz, 1H), 4.81 (dd, J = 3.9, 9.8 Hz, 1H), 4.27 (dd, J = 4.9, 9.8, 1H), 4.18 (t, J = 9.8 Hz, 1H), 3.83 (dt, J = 4.9, 9.8 Hz, 1H), 3.74 (t, J = 9.8 Hz, 1H), 3.56 (t, J = 9.8 Hz 1H, 3.37 (s, 3H), 2.62 (t, J = 7.3 Hz, 2H), 2.51 (m, 2H), 2.30 (bs, OH), 2.00 (t, J = 2.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.3, 136.8, 129.1, 128.2, 126.2, 101.8, 97.3, 82.3, 81.1, 73.7, 69.2, 68.6, 68.2, 61.9, 55.2, 33.0, 14.2. HR ESIMS calcd for $C_{19}H_{22}O_7$ $[M+H]^+$ 363.1444, found 363.1432.

The 3-ester **5c** was isolated as white crystals (43mg, 12%), mp 174.0–175.8°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.39–7.44 (m, 2H), 7.30–7.36 (m, 3H), 5.47 (s, 1H), 5.33 (t, J = 9.8 Hz, 1H), 4.79 (d, J = 3.9 Hz, 1H), 4.29 (dd, J = 4.9, 9.8 Hz, 1H), 3.85 (dt, J = 4.9, 9.8, 1H), 3.73 (t, J = 9.8 Hz, 1H), 3.66 (dd, J = 3.9, 9.8 Hz, 1H), 3.57 (t, J = 9.8 Hz 1H), 3.45 (s, 3H), 2.62 (t, J = 7.3 Hz, 2H), 2.49 (m, 2H), 1.86 (t, 1H), 1.66 (bs, OH); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm) 171.1, 136.9, 129.0, 128.1, 126.2, 101.5, 100.0, 82.3, 78.6, 72.6, 71.7, 69.0, 68.9, 62.7, 55.6, 33.3, 14.4. HR ESIMS calcd for $C_{19}H_{22}O_7$ $[M+H]^+$ 363.1444, found 363.1445.

4-Chlorobutanoate esters (6a and 6b)

Compound **6a** was isolated in 16% yield as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43-7.39 (m, 2H), 7.37-7.32 (m, 3H), 5.59 (t, *J* = 9.8Hz, 1H), 5.49 (s, 1H), 4.91-4.88 (m, 2H), 4.29 (dd, *J* = 10.4, 4.4 Hz, 1H), 3.91 (dt, *J* = 9.8, 4.9 Hz, 1H), 3.76 (t, *J* = 10.4 Hz, 1H), 3.64 (t, *J* = 9.3 Hz, 1H), 3.57 (t, *J* = 6.8, 5.9 Hz, 2H), 3.51 (t, *J* = 6.8, 5.9 Hz, 2H), 3.40 (s, 3H), 2.51 (m, 4H), 2.03 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.4, 136.7, 128.9, 128.0, 118.9, 101.3, 97.3, 78.9, 71.4, 68.8, 68.5, 62.1, 55.2, 43.6, 30.8, 27.4, 27.2, 27.1.

Compound **6b** isolated as crystals at a 61.8% yield. m.p. 75.2-76.1°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.49-7.45 (m, 2H), 7.37-7.32 (m, 3H), 5.50 (s, 1H), 4.91 (d, *J* = 3.9 Hz, 1 H), 4.78 (d, *J* = 3.9, 9.8 Hz, 1H), 4.26 (dd, *J* = 9.8, 3.9 Hz, 1H), 4.11 (t, *J* = 9.8 Hz, 1H), 3.80 (dt, *J* = 9.8, 4.9 Hz, 1H), 3.71 (t, *J* = 10.7, 9.8 Hz, 1H), 3.57 (t, *J* = 6.8, 5.9 Hz, 2H), 3.49 (pt, *J* = 9.8, 8.8 Hz, 1H), 3.36 (s, 3H), 2.56 (t, *J* = 6.8Hz, 2H), 2.07 (p, *J* = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.3, 136.8, 129.2, 128.2, 126.2, 101.8, 97.4, 81.2, 73.4, 68.7, 68.4, 61.9, 55.3, 43.8, 31.0, 27.4. HR ESIMS calcd for $C_{18}H_{24}O_7Cl$ $[M+H]^+$ 387.1211, found 387.1205.

4-Pentenoate esters (7a-c)

The diester (**7a**) was isolated as a clear oil at a yield of 49.5%. ^{1}H NMR, (250 MHz, $CDCl_3$) δ (ppm) 7.39-7.44 (m, 2H), 7.29-7.35 (m, 3H), 5.87-5.65 (m, 2H), 5.60 (t, *J* = 9.6 Hz, 1H), 5.47 (s, 1H), 4.96-5.08 (m, 2H), 4.85-4.95 (m, 4H), 4.27 (dd, *J* = 4.7, 10.1 Hz, 1H), 3.90 (td, *J* = 4.7, 9.9 Hz, 1H), 3.74 (t, *J* = 10.1 Hz, 1H), 3.62 (t, *J* = 9.6 Hz, 1H),

3.37 (s, 3H), 2.26-2.47 (m, 8 H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) 172.2, 171.5, 136.8, 136.2, 136.1, 128.9, 128.0, 126.0, 115.4, 101.4, 97.5, 79.1, 71.4, 68.7, 62.2, 55.5, 33.3, 33.1, 28.6, 28.5. HR ESIMS calcd for $C_{24}H_{31}O_8$ $[M+H]^+$ 447.2019, found 447.1976.

The 2-ester (**7b**) was isolated as a viscous oil at a yield of 34.9%. ^{1}H NMR, (250 MHz, $CDCl_3$) δ 7.54-7.47 (m, 2H), 7.44-7.35 (m, 3H), 5.94-5.76 (m, 1H), 5.56 (s, 1H), 5.05 (bs, 1H), 5.12-4.97 (m, 1H), 4.95 (d, *J* = 3.7 Hz, 1H), 4.81 (dd, *J* = 4.7, 9.6 Hz, 1H), 4.30 (dd, *J* = 4.1, 9.6 Hz, 1H), 4.19 (pt, *J* = 9.1, 9.6 Hz, 1H), 3.81-3.91 (m, 1H), 3.67 (pt, *J* = 9.1, 10.1 Hz, 1H), 3.56 (t, *J* = 9.1 Hz, 1H), 3.40 (s, 3H), 2.50-2.58 (m, 2H), 2.36-2.46 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.7, 137.0, 136.5, 129.3, 128.3, 126.3, 115.6, 102.0, 97.6, 81.3, 73.6, 68.8, 68.6, 62.0, 55.4, 33.3, 28.8. HR ESIMS calcd for $C_{19}H_{24}O_7Na$ $[M+Na]^+$ 387.1420, found 387.1407.

The 3-ester (**7c**) was isolated as a white solid at a yield of 9%. m.p. 152-154.3°C. ^{1}H NMR, (250 MHz, $CDCl_3$) δ (ppm) 7.42-7.50 (m, 2H), 7.33-7.39 (m, 3H), 5.72-5.90 (m, 1H), 5.50 (s, 1H), 5.36 (t, *J* = 9.6 Hz, 1H), 5.03 (d, *J* = 16.9 Hz, 1H), 4.93 (d, *J* = 10.1 Hz, 1H), 4.81 (d, *J* = 3.7 Hz, 1H), 4.31 (dd, *J* = 4.1, 9.6 Hz, 1H), 3.88 (m, 1H), 3.76 (pt, 1H, *J* = 10.1, 10.5 Hz), 3.68 (dd, *J* = 3.7, 9.1 Hz, 1H), 3.60 (pt, *J* = 9.1, 9.6 Hz, 1H), 3.47 (s, 3H), 2.34-2.54 (m, 4H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.3, 137.1, 136.6, 129.1, 128.3, 126.3, 115.6, 101.6, 100.3, 78.8, 72.4, 71.9, 69.0, 62.9, 55.7, 33.7, 29.0. HR ESIMS calcd for $C_{19}H_{25}O_7$$[M+H]^+$ 365.1600, found 365.1593.

Pentanoate esters (8a-c)

Compound **8a** was isolated as an oil at a 5% yield. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.44-7.39 (m, 2H) 7.35-7.29 (m, 3H), 5.59 (t, *J* = 9.6 Hz, 1H), 5.48 (s, 1H), 4.94-4.85 (m, 2H), 4.28 (dd, *J* = 4.7, 9.9 Hz, 1H), 3.91 (td, *J* = 4.7, 9.6 Hz, 1H), 3.75 (pt, *J* = 10.1, 10.6 Hz, 1H), 3.62 (t, *J* = 9.6 Hz, 1H), 3.38 (s, 3H), 2.35-2.23 (m, 4H), 1.63-1.47 (m, 4H), 1.39-1.19 (m, 4H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.81 (t, *J* = 7.3 Hz, 3H). HR ESIMS calcd for $C_{24}H_{35}O_8$ $[M+H]^+$ 451.2332, found 451.2327.

Compound **8b** was isolated as white crystals at a 44% yield. m.p. 124.3-125.2°C. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.49-7.45 (m, 2H) 7.38-7.33 (m, 3H), 5.50 (s, 1H), 4.91 (d, *J* = 3.9 Hz, 1H), 4.78 (dd, *J* = 3.9, 9.8 Hz, 1H), 4.26 (dd, *J* = 9.8, 3.9 Hz, 1H), 4.11 (t, *J* = 9.8 Hz, 1H), 3.80 (dt, *J* = 9.8, 4.9Hz, 1H), 3.71 (pt, *J* = 10.7, 9.8 Hz, 1H), 3.49 (pt, *J* = 9.8, 8.8 Hz, 1H), 3.36 (s, 3H), 2.38 (t, *J* = 7.3 Hz, 2H), 1.87 (t, *J* = 7.3 Hz, 3H), 1.61 (p, *J* = 7.8 Hz, 2H), 1.33 (h, *J* = 7.8 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) 173.5, 136.9, 129.2, 128.3, 126.2, 101.9, 97.5, 81.3, 73.3, 68.8, 68.6, 61.9, 55.3, 33.8, 26.9, 22.0, 14.2. HR ESIMS calcd for $C_{19}H_{27}O_7$ $[M+H]^+$ 367.1757, found 367.1752.

The 3-monoester (**8c**) was isolated as white needles in 11% yield. 178.1-178.7°C. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.44-7.40 (m, 2H), 7.36-7.31 (m, 3H), 5.47 (s, 1H), 5.31 (t, *J* = 9.6 Hz, 1H), 4.78 (d, *J* = 4.1 Hz, 1H), 4.29 (dd, *J* = 9.6, 10.1 Hz, 1H), 3.85 (dt, *J* = 9.1, 10.1 Hz, 1H), 3.73 (t, *J* = 10.1 Hz, 1H), 3.64 (bs, 1H), 3.56 (pt, *J* = 9.1, 9.6 Hz, 1H), 3.45 (s, 3H), 2.36 (t, *J* = 7.8 Hz, 2H), 1.59 (p, *J* = 7.8 Hz, 2H), 1.30 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) 174.0, 137.0, 129.0,

128.2, 126.1, 101.4, 100.1, 78.7, 72.0, 71.8, 68.9, 62.7, 55.6, 34.1, 27.1, 22.0, 13.6. HR ESIMS calcd for $C_{19}H_{27}O_7$ $[M+H]^+$ 367.1757, found 367.1746.

4-Methyl butanoate esters (9 a-c)

Diester (**9a**) was isolated as a clear oil at a 3% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.41-7.45 (m, 2H), 7.32-7.36 (m, 3H), 5.64 (t, *J* = 9.9 Hz, 1H), 5.51 (s, 1H), 4.97 (d, *J* = 3.7 Hz), 4.90 (dd, *J* = 3.7, 10.3 Hz, 1H), 4.31 (dd, *J* = 4.8, 10.3 Hz), 3.94 (td, *J* = 4.8, 9.9 Hz, 1H), 3.77 (t, *J* = 10.3 Hz, 1H), 3.64 (pt, *J* = 9.5, 9.9 Hz, 1H), 3.40 (s, 3H), 2.15-2.24 (m, 4H), 2.03-2.14 (m, 2H), 0.94 (d, *J* = 6.6 Hz, 6H), 0.90 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 172.7, 171.9, 137.1, 129.2, 128.3, 126.3, 101.6, 97.8, 79.6, 71.6, 69.0, 68.6, 62.5, 55.6, 43.6, 43.3, 26.0, 25.9, 22.4. HR ESIMS calcd for $C_{24}H_{35}O_8$ $[M+H]^+$ 451.2332, found 451.2315.

The 2-ester (**9b**) was isolated as a crystalline white solid at a 41% yield. m.p. 113.1-113.8°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.47-7.51 (m, 2H), 7.35-7.49 (m, 3H), 5.53 (s, 1H), 4.95 (d, *J* = 4.0 Hz, 1H), 4.79 (pdd, *J* = 3.7, 4.0, 9.5, 9.9 Hz, 1H), 4.28 (dd, *J* = 4.4, 9.9 Hz, 1H), 4.15 (pt, *J* = 9.2, 9.5 Hz, 1H), 3.80-3.86 (m, 1H), 3.74 (t, *J* = 10.3 Hz, 1H), 3.53 (pt, *J* = 9.2, 9.5 Hz, 1H), 3.38 (s, 3H), 2.28 (d, *J* = 7.0 Hz, 2H), 2.13 (ph, *J* = 6.6, 7.0 Hz, 1H), 0.98 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 173.0, 137.1, 129.4, 128.4, 126.4, 102.1, 97.7, 81.5, 73.5, 69.0, 68.6, 62.1, 55.5, 43.3, 25.9, 22.4. HR ESIMS calcd for $C_{19}H_{27}O_7$ $[M+H]^+$ 367.1757, found 367.1742.

The 3-ester **9c** was isolated as a white solid at a 14% yield. m.p. 161.7-162.8°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.40-7.44 (m, 2H), 7.31-7.35 (m, 3H), 5.49 (s, 1H), 5.33 (pt, *J* = 9.5, 9.9 Hz, 1H), 4.79 (d, *J* = 3.7 Hz, 1H), 4.27-4.32 (m, 1H) 3.82-3.89 (m, 1H), 3.74 (t, *J* = 10.3 Hz, 1H), 3.62-3.66 (m, 1H), 3.58 (t, *J* = 9.5 Hz, 1H), 3.46 (s, 3H), 2.24 (d, *J* = 7.0 Hz, 2H), 2.09 (ph, *J* = 6.6, 7.0 Hz, 1H), 0.92 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 173.6, 137.1, 129.2, 128.3, 128.3, 101.6, 100.4, 78.9, 71.8, 69.1, 62.9, 55.8, 43.8, 29.9, 26.1, 22.4. HR ESIMS calcd for $C_{19}H_{26}O_7Na$ $[M+Na]^+$ 389.1576, found 389.1570.

Octanoate esters (10 a-c)

Compound **10a** was isolated as a white powder at 35% yield. m.p. 46.9-48.7°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.39-7.44 (m, 2H), 7.29-7.34 (m, 3H), 5.59 (t, *J* = 9.7 Hz, 1H), 5.51 – 5.46 (m, 1H), 4.95 – 4.86 (m, 2H), 4.28 (dd, *J* = 4.8 Hz, 10.2, 1H), 3.90 (td, *J* = 4.8, 9.9 Hz, 1H), 3.74 (t, *J* = 10.3 Hz, 1H), 3.62 (t, *J* = 9.6 Hz, 1H), 3.37 (s, 3H), 2.39 – 2.17 (m, 4H), 1.63 – 1.50 (m, 4H), 1.16-1.26 (m, 16H), 0.84 (dt, *J* = 6.7, 14.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.5, 172.6, 136.9, 128.9, 128.1, 126.0, 101.4, 97.6, 79.2, 68.5, 62.3, 55.3, 34.0, 31.5, 28.9, 25.0, 22.5, 14.0, 14.0. HR ESIMS calcd for $C_{30}H_{46}O_8Na$ $[M+Na]^+$ 507.3090, found 507.3066.

Compound **10b** was isolated as white crystals at 50% yield. m.p. 59.7-60.8°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.45-7.49 (m, 2H), 7.38 – 7.31 (m, 3H), 5.49 (s, 1H), 4.92 (d, *J* = 3.7 Hz, 1H), 4.75 (dd, *J* = 3.7, 9.7 Hz, 1H), 4.25 (dd, *J* = 4.5, 9.9 Hz, 1H), 4.11 (t, *J* = 9.5 Hz, 1H), 3.79 (td, *J* = 4.6, 9.8 Hz, 1H), 3.70 (t, *J* = 10.2 Hz, 1H), 3.48 (t, *J* = 9.3 Hz,

1H), 3.34 (s, 3H), 2.37 (t, *J* = 7.5 Hz, 2H), 1.60 (dd, *J* = 7.1, 14.3 Hz, 2H), 1.36 – 1.19 (m, 8H), 0.86 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.4, 136.9, 129.1, 128.2, 126.2, 101.8, 97.5, 81.3, 73.3, 68.4, 61.9, 55.2, 34.0, 31.5, 28.8, 28.8, 24.8, 22.5, 13.9. HR ESIMS calcd for $C_{22}H_{33}O_7$ $[M+H]^+$ 409.2226, found 409.2207.

Compound **10c** was isolated as a white powder at 15% yield. m.p. 117.1-118.2°C. ^{1}H NMR (400 MHz, CDCl3) δ (ppm) 7.40-7.44 (m, *J* = 2.9, 6.3 Hz, 2H), 7.29-7.35 (m, 3H), 5.47 (s, 1H), 5.32 (t, *J* = 9.7 Hz, 1H), 4.78 (d, *J* = 3.7 Hz, 1H), 4.28 (dd, *J* = 4.7 Hz, 10.1, 1H), 3.89 – 3.81 (m, 1H), 3.73 (t, *J* = 10.2 Hz, 1H), 3.67 – 3.60 (m, 1H), 3.56 (t, *J* = 9.6 Hz, 1H), 3.45 (s, 3H), 2.35 (t, *J* = 7.4 Hz, 2H), 2.24 (d, *J* = 11.3 Hz, 1H), 1.61 (dt, *J* = 7.3, 14.8 Hz, 3H), 1.16-1.25 (m, 8H), 0.82 (t, *J* = 6.8, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.0, 137.0, 129.1, 128.2, 126.2, 101.5, 100.2, 78.7, 68.9, 62.8, 55.6, 31.6, 28.9, 28.9, 25.1, 22.6, 14.1. HR ESIMS calcd for $C_{22}H_{33}O_7$ $[M+H]^+$ 409.2226, found 409.2207.

Decanoate esters (11 a-c)

Compound **11a** was isolated as a white powder at 21% yield. m.p. 46.9-48.7°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.39-7.43 (m, 2H), 7.29-7.33 (m, 3H), 5.59 (t, *J* = 9.9 Hz, 1H), 5.47 (s, 1H), 4.92 (d, *J* = 3.7 Hz, 1H), 4.88 (dd, *J* = 3.7 Hz, 9.9 Hz, 1H), 4.27 (dd, *J* = 4.8, 10.3 Hz, 1H), 3.90 (td, *J* = 4.8, 9.9 Hz, 1H), 3.74 (t, *J* = 10.3 Hz, 1H), 3.62 (t, *J* = 9.5 Hz, 1H), 3.37 (s, 3H), 2.20-2.35 (m, 4H), 1.51-1.62 (m, 4H), 1.15-1.30 (m, 24H), 3.82-3.88 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.5, 172.7, 137.2, 129.2, 128.4, 126.3, 101.7, 97.9, 79.5, 68.8, 62.6, 55.6, 32.1, 29.6, 29.3, 25.3, 22.9, 14.3. HR ESIMS calcd for $C_{34}H_{55}O_8$ $[M+H]^+$ 507.3114, found 507.3066.

Compound **11b** was isolated as a white powder at 59% yield. m.p. 59.7-60.8°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.48-7.45 (m, 2H), 7.32-7.36 (m, 3H), 5.50 (s, 1H), 4.92 (d, *J* = 3.7 Hz, 1H), 4.76 (dd, *J* = 3.7, 9.5 Hz, 1H), 4.25 (dd, *J* = 4.4, 9.5 Hz, 1H), 4.13 (t, *J* = 9.5 Hz, 1H), 3.80 (td, *J* = 4.4, 9.5 Hz, 1H), 3.71 (t, *J* = 10.3 Hz, 1H), 3.51 (t, *J* = 9.5 Hz, 1H), 3.35 (s, 3H), 2.28 and 2.37 (pt, *J* = 7.3, 7.7 Hz, 2H), 1.60 (p, *J* = 7.0 Hz, 2H), 1.22-1.32 (m, 12H), 0.86 (pt, *J* = 6.6, 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.9, 137.2, 129.5, 128.6, 16.5, 102.2, 97.8, 81.6, 73.6, 68.8, 62.3, 55.6, 32.1, 29.5, 29.2, 25.1, 22.9, 14.4. HR ESIMS calcd for $C_{24}H_{37}O_7$ $[M+H]^+$ 437.2539, found 437.2530.

Compound **11c** was isolated as a white powder at 11% yield. m.p. 117.1-118.2°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42-7.46 (m, 2H), 7.32-7.36 (m, 3H), 5.49 (s, 1H), 5.34 (t, *J* = 9.7 Hz, 1H), 4.80 (d, *J* = 3.7 Hz, 1H), 4.30 (dd, *J* = 4.7, 10.1 Hz, 1H), 3.86 (td, *J* = 4.7, 9.8 Hz, 1H), 3.74 (t, *J* = 10.2 Hz, 1H), 3.66 (dd, *J* = 3.8, 9.6 Hz, 1H), 3.58 (t, *J* = 9.6 Hz, 1H), 3.44 (s, 3H), 2.37 (t, *J* = 7.4 Hz, 2H), 1.62 (p, *J* = 7.4 Hz, 2H), 1.21 (s, 12H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.2, 137.3, 129.2, 128.4, 126.4, 101.6, 100.4, 79.0, 69.1, 62.9, 55.8, 29.6, 29.5, 29.2, 25.3, 22.9, 14.4. HR ESIMS calcd for $C_{24}H_{37}O_7$ $[M+H]^+$ 437.2539, found 437.2527.

Methacrylate esters (12 a-c)

Compound **12a** was isolated as needle-like crystals at a 21% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46-7.42 (m, 2H), 7.36-7.31 (m, 3H), 6.14 (s, 1H), 6.06 (s, 1H), 5.75 (t, *J* = 9.8 Hz, 1H), 5.60 (s, 1H), 5.53 (s, 1H), 5.03 (d, *J* = 3.9 Hz, 1H), 4.99-4.94 (dd, *J* =

3.9, 9.8 Hz, 1H), 4.35-4.29 (dd, *J* = 4.9, 9.8 Hz, 1H), 4.01-3.94 (dt, *J* = 4.9, 9.8 Hz 1H), 3.80 (pt, *J* = 9.8, 10.7 Hz, 1H), 3.75 (t, *J* = 9.8 Hz, 1H), 3.40 (s, 3H), 1.91 (s, 3H), 1.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.8, 166.1, 147.0, 135.9, 135.1, 129.0, 128.2, 127.1, 126.3, 125.8, 101.8, 97.8, 79.2, 72.1, 69.3, 69.0, 62.4, 55.2, 18.4, 18.1. HR ESIMS (*m/z*) calcd for $C_{22}H_{27}O_8$ $[M+H]^+$ 419.1706, found 419.1702.

Compound **12b** was isolated as viscous oil at a 47 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.50-7.46 (m, 2H), 7.37-7.32 (m, 3H), 6.19 (s, 1H), 5.61 (s, 1H), 5.51 (s, 1H), 4.95 (d, *J* = 3.9 Hz, 1H), 4.80 (dd, *J* = 3.9, 9.8 Hz, 1H), 4.26 (dd, *J* = 4.9, 10.7 Hz, 1H), 4.18 (pt, *J* = 8.8, 9.8 Hz, 1H), 3.82 (td, *J* = 4.9, 9.8 Hz, 1H), 3.72 (pt, *J* = 9.8, 10.7 Hz, 1H), 3.52 (t, *J* = 8.8, 9.8 Hz, 1H), 3.35 (s, 3H), 2.74 (bs, 1H), 1.94 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.0, 137.0, 135.5, 129.1, 128.1, 126.8, 126.2, 102.0, 97.5, 81.4, 73.9, 68.8, 68.6, 61.9, 55.3, 18.1. HR ESIMS (*m/z*) calcd for $C_{18}H_{23}O_7$ $[M+H]^+$ 351.1444, found 351.1436.

Compound **12c** was isolated as needle-like crystal at a 4% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44-7.40 (m, 2H), 7.35-7.30 (m, 3H), 6.13 (s, 1H), 5.58 (s, 1H), 5.49 (s, 1H), 5.48 (t, *J* = 9.8, 1H), 4.80 (d, *J* = 3.9 Hz, 1H), 4.30 (dd, *J* = 4.9, 10.7 Hz, 1H), 3.87 (m, 1H), 3.75 (pt, *J* = 9.8, 10.7 Hz, 1H), 3.69 (m, 1H), 3.63 (t, *J* = 9.8 Hz, 1H), 3.45 (s, 3H), 2.42 (d, *J* = 11.7 Hz, 1H), 1.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.6, 137.1, 135.9, 129.0, 128.3, 126.2, 101.3, 100.1, 78.9,72.9, 71.8, 69.0, 62.8, 55.6, 18.5. HR ESIMS (*m/z*) calcd for $C_{18}H_{23}O_7$ $[M+H]^+$ 351.1444, found 351.1451.

Benzoate esters (13 a-c)

Compound **13 a** was isolated as a white solid at 6% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.00-7.97 (m, 4H), 7.54-7.30 (m, 11H), 6.06 (t, *J* = 9.9 Hz, 1H), 5.57 (s, 1H), 5.24 (dd, *J* = 3.7, 9.9 Hz, 1H), 5.18 (d, *J* = 3.7 Hz, 1H), 4.38 (dd, *J* = 4.8, 10.3 Hz, 1H), 4.08 (td, *J* = 4.8, 9.9 Hz, 1H), 3.91 (t, *J* = 9.5 Hz, 1H), 3.86 (pt, *J* = 10.3, 10.6 Hz, 1H), 3.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.3, 165.9, 137.1, 133.6, 133.3, 130.2, 130.0, 129.3, 128.7, 128.5, 128.4, 126.4, 101.9, 98.1, 79.6, 72.8, 69.8, 69.2, 62.8, 55.8.

Compound **13 b** was isolated as a crystalline solid at 42% yield. m.p. 170.3-170.9°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.12-8.08 (m, 2H), 7.61-7.56 (m, 1H), 7.54-7.50 (m, 2H), 7.48-7.43 (m, 2H), 7.37-7.41 (m, 3H), 5.58 (s, 1H), 5.08 (d, *J* = 3.7 Hz, 1H), 5.04 (dd, *J* = 3.7, 9.2 Hz, 1H), 4.36 (t, *J* = 9.2 Hz, 1H), 4.34 (d, *J* = 5.1, 10.3 Hz, 1H), 3.92 (td, *J* = 4.8, 10.3 Hz, 1H), 3.80 (t, *J* = 10.3 Hz, 1H), 3.63 (pt, *J* = 9.2, 9.5 Hz, 1H), 3.40 (s, 3H), 2.74 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.5, 137.2, 133.6, 130.2, 129.7, 129.6, 128.7, 128.6, 126.6, 102.3, 98.0, 81.7, 74.3, 69.2, 69.0, 62.3, 55.7.

Compound **13 c** was isolated as white needle-like crystals at 10% yield. m.p. 204°C (dec). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.08 (d, *J* = 7.7 Hz, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.46-7.40HHHHHJHH (m, 4H), 7.33-7.29 (m, 3H), 5.60 (t, *J* = 9.5 Hz, 1H), 5.54 (s, 1H), 4.86 (d, *J* = 3.7 Hz, 1H), 4.35 (dd, *J* = 4.8, 10.3 Hz, 1H), 3.96 (td, *J* = 4.8, 9.9 Hz, 1H), 3.84 (dd, *J* = 3.7, 9.5 Hz, 1H), 3.81 (pt, *J* = 9.9, 10.3 Hz, 1H), 3.77 (t, *J* = 9.5 Hz, 1H), 3.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.9, 137.2, 133.3, 130.1, 129.2, 128.5, 128.4, 126.4, 101.7, 100.4, 79.1, 73.2, 72.2, 69.2, 63.0, 55.8.

Naphthoate esters (14 a-c)

Compound **14a** was isolated as white crystalline solid at a 13% yield. m.p. 131.6-132.1°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.00 (d, *J* = 8.4 Hz, 1H), 8.72 (d, *J* = 8.4 Hz, 1H), 8.05 (dpt, *J* = 1.1, 1.5, 7.3 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.37-7.62 (m, 11H), 6.23 (td, *J* = 1.5, 9.9 Hz, 1H), 5.67 (s, 1H), 5.51 (ddd, *J* = 1.8, 3.7, 10.3 Hz, 1H), 5.34 (d, *J* = 3.7 Hz, 1H), 4.47 (dd, J = 4.8, 10.3 Hz, 1H), 4.21 (dt, *J* = 4.8, 9.9 Hz, 1H), 4.02 (pt, *J* = 9.9, 9.5 Hz, 1H) 3.92 (t, *J* = 10.3 Hz, 1H), 3.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.7, 166.6, 136.9, 1341., 133.7, 133.5, 132.9, 131.3, 130.9, 129.2, 129.0, 128.5, 128.3, 128.2, 127.9, 127.5, 127.4, 126.1, 125.5, 125.3, 124.6, 124.4, 101.5, 98.0, 79.5, 72.2, 69.6, 68.9, 62.6, 55.5. HR ESIMS calcd for $C_{36}H_{31}O_8$ $[M+H]^+$ 591.2019, found 591.2040.

Compound **14b** was isolated as white crystals in 83% yield. m.p 174.6-175.0°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.87 (d, *J* = 8.8 Hz, 1H), 7.61 (t, *J* = 6.8, 7.8 Hz, 1H), 7.48-7.55 (m, 2H), 7.38 (m, 3H), 5.57 (s, 1H), 5.19 (d, *J* = 3.9 Hz, 1H), 5.13 (dd, *J* = 3.9, 9.8 Hz 1H), 4.39 (t, *J* = 8.8, 9.8 Hz, 1H), 4.33 (dd, *J* = 4.8, 9.8 Hz, 1H), 3.93 (dt, *J* = 3.9, 9.8 Hz, 1H), 3.80 (t, *J* = 9.8, 8.8 Hz, 1H), 3.65 (t, *J* = 8.8, 9.8 Hz, 1H), 3.43 (s, 3H), 2.61 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.0, 137.0, 135.5, 129.1, 128.1, 126.8, 126.2, 102.0, 97.5, 81.4, 73.9, 68.8, 68.6, 61.9, 55.3. HR ESIMS calcd for $C_{25}H_{25}O_7$ $[M+H]^+$ 437.1600, found 437.1589.

Synthesis of Carbamate esters

Compound **4** (1 mmol) is dissolved in 2-3 mL of anhydrous DCM. The isocyanate (1.2-1.3 mmol) and two drops of triethylamine is added into the solution. The reaction is stirred for 24 hours at room temperature. The solvent is removed under a stream of dry nitrogen and purified by column chromatography using a solvent gradient of hexanes/acetone (14-3:1). Under certain circumstances when the crude mixtures gelled onto the silica, methanol was added (up to 1%) to the column solvent. Heptanoic acid underwent a Curtius rearrangement using diphenylphosphoryl azide (DPPA) in the presence of triethylamine to form the 1-hexyl isocyanate. The yields for compounds **17A** and **17B** are calculated after the second reaction with compound **4**. Compound **19B** were isolated after hydrolysis of the methacrylate esters using a catalytic amount of sodium methoxide (10 mol%) in methanol.

Ethylmethacrylate-2-carbamates (15a and 15b)

2,3-Dicarbamate ester (**15a**) was isolated as an viscous oil at a 62% yield. ^{1}H NMR, (400 MHz, $CDCl_3$) δ (ppm) 7.30- 7.36 (m, 3H), 7.41-7.45 (m, 2H), 6.10 (s, 1H), 6.04 (s, 1H), 5.58 (s, 1H), 5.49 (d, *J* = 8.8 Hz, 1H), 5.39 (t, *J* = 9.8 Hz, 1H), 5.28 (s, 1H), 5.26 (t, *J* = 5.9 Hz, 1H), 4.98 (bm, 1H), 4.92 (d, *J* = 3.9 Hz, 1H), 4.79 (dd, *J* = 2.9, 9.8 Hz, 1H), 4.28 (dd, *J* = 4.9, 10.7 Hz, 1H), 4.14-4.24 (m, 3H), 3.90 (td, *J* = 4.9, 9.8 Hz, 1H), 3.75(pt, *J* = 9.8, 10.7 Hz, 1H), 3.60 (t, *J* = 9.8 Hz, 1H), 3.41-3.56 (m, 4H), 3.40 (s, 3H), 1.92 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.9, 155.4, 136.8, 135.8, 135.7, 127.9, 126.0, 125.7, 101.3, 98.1, 72.1, 70.0, 68.6, 67.7, 63.4, 62.2, 55.1, 39.9, 31.4, 25.4,

22.4, 19.2, 18.1, 13.9. HR ESIMS calcd for $C_{28}H_{37}N_2O_{12}$ $[M+H]^+$ 593.2347, found 593.2361.

2-Carbamate ester (**15b**) was isolated as a clear oil in a 12% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44-7.48 (m, 2H), 7.29-7.34 (m, 3H), 6.08 (s, 1H), 5.55 (s, 1H), 5.50 (s, 1H), 5.45 (bt, *J* = 5.9 Hz, 1H), 4.92 (d, *J* = 3.9 Hz, 1H), 4.68 (dd, *J* = 3.9, 9.8 Hz, 1H), 4.26 (dd, *J* = 3.9, 9.8 Hz, 1H), 4.08-4.14 (m, 2H), 3.80 (td, *J* = 4.9, 9.8 Hz, 1H), 3.72 (t, *J* = 9.8 Hz, 1H), 3.52 (pt, *J* = 8.8, 9.8 Hz, 1H), 3.37 (s, 3H), 3.32-3.36 (m, 2H), 1.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.2, 155.7, 136.9, 129.2, 128.2, 126.2, 126.0, 101.9, 98.0, 81.3, 74.1, 68.8, 68.5, 63.4, 62.0, 55.2, 40.1, 30.2,18.2. HR ESIMS calcd for $C_{21}H_{28}NO_9$ $[M+H]^+$ 438.1764, found 438.1751.

Pentyl carbamate (16 a-c)

The dicarbamate (**16a**) was isolated (54mg, 11%) as a oil. ^{1}H NMR, (400 MHz, $CDCl_3$) δ 7.40-7.44 (m, 2H), 5.27-5.31 (m, 3H), 5.47 (s, 1H), 5.36 (t, *J* = 9.8 Hz, 1H), 5.02 (bt, *J* = 4.9 Hz, 1H), 4.90 (d, *J* = 3.9 Hz, 1H), 4.77 (dd, *J* = 3.9, 9.8 Hz, 1H), 4.73 (bt, *J* = 4.9 Hz, 1H), 4.26 (dd, *J* = 4.9, 9.8 Hz, 1H), 3.88 (dt, *J* = 4.9, 9.8 Hz, 1H), 3.74 (pt, *J* = 9.8, 10.7 Hz, 1H), 3.59 (t, *J* = 9.8 Hz, 1H), 3.38 (s, 3H), 3.07-3.13 (m, 4H), 1.39-1.45 (m, 4H), 1.21-1.27 (m, 4H), 0.86 (t, *J* = 6.8Hz, 3H), 0.81 (t, *J* = 7.8Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 155.5, 137.0, 128.8, 128.0, 126.1, 101.4, 98.3, 79.4, 72.0, 69.9, 68.8, 62.3, 55.2, 41.0, 40.9, 40.4, 29.9, 29.3, 28.7, 22.3, 22.2, 13.9, 13.8. HR ESIMS calcd for $C_{26}H_{41}N_2O_8$ $[M+H]^+$ 509.2863, found 509.2850.

The 2-carbamate ester (**16b**) was isolated as white needles (237mg, 60%). ^{1}H NMR, (400 MHz, $CDCl_3$) δ 7.46-7.51 (m, 2H), 7.32-7.36 (m, 3H), 5.53 (s, 1H), 4.96 (d, 1H, *J* = 3.9 Hz), 4.92 (bs, 1H), 4.70 (dd, *J* = 3.9, 9.8 Hz, 1H), 4.28 (dd, *J* = 4.9, 9.8 Hz, 1H), 4.12 (t, *J* = 9.8 Hz, 1H), 3.82 (dt, *J* = 4.9, 9.8 Hz, 1H), 3.75 (t, *J* = 9.8 Hz, 1H), 3.55 (pt, *J* = 8.8, 9.8 Hz, 1H), 3.40 (s, 3H), 3.15 (q, *J* = 5.9, 12.7 Hz, 2H), 2.69 (bs, 1H), 1.47 (p, *J* = 6.8 Hz, 2H), 1.24-1.32 (m, 4H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 137.0, 129.2, 128.3, 126.3, 102.0, 98.2, 81.5, 75.5, 73.9, 68.9, 62.0, 55.3, 41.2, 29.4, 28.8, 22.3, 13.9. HR ESIMS calcd for $C_{20}H_{30}NO_7$ $[M+H]^+$ 396.2022, found 396.2014.

The 3-carbamate ester (**16c**) was isolated as a white solid (109mg, 28%).^{1}H NMR, (400 MHz, $CDCl_3$) δ 7.42-7.46 (m, 2H), 7.31-7.35 (m, 3H), 5.47 (s, 1H), 5.13 (t, *J* = 9.8 Hz, 1H), 4.80 (bs, 1H), 4.77 (d, *J* = 3.9 Hz, 1H), 4.28 (dd, *J* = 4.9, 9.8 Hz, 1H), 3.85 (dt, 1H, *J* = 4.9, 9.8 Hz), 3.72 (pt, *J* = 9.8, 10.7 Hz, 1H), 3.63 (dd, *J* = 2.9, 9.8 Hz, 1H), 3.53 (t, *J* = 9.8 Hz, 1H), 3.43 (s, 3H), 3.13 (q, *J* = 6.8 Hz, 2H), 2.87 (d, *J* = 9.8 Hz, 1H), 1.45 (p, *J* = 6.8 Hz, 2H), 1.25 (m, 4H), 0.84 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 137.1, 129.1, 128.1, 126.3, 101.6, 100.4, 78.9, 73.2, 72.4, 69.0, 62.7, 55.6, 41.2, 29.5, 28.8, 22.3, 14.0. HR ESIMS calcd for $C_{20}H_{30}NO_7$ $[M+H]^+$ 396.2022, found 396.2014.

Hexyl carbamates (17b and 17c)

The 2-carbamate (**17b**) was isolated as a white solid at a 45% net yield. ^{1}H NMR, (400 MHz, $CDCl_3$) δ (ppm) 7.44-7.48 (m, 2H), 7.31-7.35 (m, 3H), 5.50 (s, 1H), 5.17 (bt, *J* = 5.9 Hz, 1H), 4.94 (d, *J* = 3.9 Hz, 1H), 4.66 (dd, *J* = 3.7, 9.9 Hz, 1H), 4.25 (dd, *J* = 4.4, 9.5

Hz, 1H), 4.10 (t, *J* = 9.5 Hz, 1H), 3.79 (m, 1H), 3.72 (pt, *J* = 9.8 Hz, 1H), 3.52 (pt, *J* = 9.2, 9.5 Hz, 1H), 3.37 (s, 3H), 3.19 (bs, 1H), 3.08 (q, *J* = 5.9 Hz, 2H), 1.43 (p, *J* = 7.0 Hz, 2H), 1.19-1.28 (m, 6H), 0.85 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.8, 137.0, 129.2, 128.2, 126.3, 101.9, 98.1, 81.3, 73.9, 68.8, 68.7, 62.0, 55.2, 41.1, 31.3, 29.6, 26.3, 22.4, 13.9. HR ESIMS Calcd for $C_{21}H_{32}NO_7$ $[M+H]^+$ 410.2179, found 410.2193.

The 3-carbamate (**17c**) was isolated as a white solid at a 11% net yield. ^{1}H NMR, (400 MHz, $CDCl_3$) δ (ppm) 7.42-7.46 (m, 2H), 7.31-7.35, (m, 3H), 5.47 (s, 1H), 5.13 (t, *J* = 9.5 Hz, 1H), 4.80 (bt, *J* = 4.6 Hz, 1H), 4.77 (d, *J* = 3.7 Hz, 1H), 4.27 (dd, *J* = 4.8, 10.3 Hz, 1H), 3.85, (m, 1H) 3.74, (t, *J* = 10.3 Hz, 1H), 3.63 (m, 1H), 3.53 (t, *J* = 9.5 Hz, 1H), 3.44 (s, 3H), 3.13 (q, *J* = 7.0 Hz, 2H), 2.87 (d, *J* = 9.8 Hz, 1H), 1.44 (p, *J* = 7.0 Hz, 2H), 1.19-1.28 (m, 6H), 0.84 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.8, 137.0, 129.0, 128.2, 126.2, 101.6, 100.3, 78.8, 73.2, 72.3, 68.9, 62.7, 55.5, 31.4, 29.7, 26.3, 22.5, 14.0. HR ESIMS Calcd for $C_{21}H_{31}NO_7Na$ $[M+Na]^+$ 432.1998, found 432.1977.

Heptyl carbamates 18 a-c

The 2,3-dicarbamate ester (**18a**) was isolated as a clear oil (74mg, 13%). ^{1}H NMR, (400 MHz, $CDCl_3$) δ 7.40-7.44 (m, 2H), 7.28-7.32 (m, 3H), 5.47 (s, 1H), 5.36 (t, *J* = 9.8 Hz, 1H), 4.99 (bt, *J* = 4.9 Hz, 1H), 4.90 (d, *J* = 3.9 Hz, 1H), 4.78 (dd, *J* = 3.9, 9.8 Hz, 1H), 4.71 (bt, *J* = 4.9 Hz, 1H), 4.26 (dd, *J* = 4.9, 9.8 Hz, 1H), 3.88 (dt, *J* = 4.9, 9.8 Hz, 1H), 3.74 (pt, *J* = 9.8, 10.7 Hz, 1H), 3.53 (t, J = 9.8 Hz, 1H), 3.38 (s, 3H), 3.07-3.13 (m, 4H),

1.40-1.46 (m, 4H), 1.19-1.29 (m, 16H), 0.80-0.88 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 155.4, 137.0, 128.9, 128.1, 126.2, 101.4, 98.3, 79.4, 72.0, 69.9, 68.8, 62.3, 55.2, 45.8, 41.1, 40.9, 40.5, 31.7, 31.6, 30.3, 29.8, 29.7, 28.9, 26.8, 26.6, 22.5, 14.0. HR ESIMS calcd for $C_{30}H_{49}N_2O_8$ $[M+H]^+$ 565.3489, found 565.3494.

The 2-carbamate ester (**18b**) was isolated as white needles (220mg, 52%). ^{1}H NMR, (400 MHz, $CDCl_3$) δ 7.45-7.49 (m, 2H), 7.31-7.35 (m, 3H), 5.50 (s, 1H), 5.16 (bs, 1H), 4.95 (d, *J* = 3.9 Hz, 1H), 4.66 (dd, *J* = 3.9, 9.8 Hz, 1H), 4.28 (dd, *J* = 3.9, 9.8 Hz, 1H), 4.11 (t, *J* = 9.8 Hz, 1H), 3.82 (dt, *J* = 3.9, 9.8 Hz, 1H), 3.72 (t, *J* = 9.8 Hz, 1H), 3.51 (pt, *J* = 8.8, 9.8 Hz, 1H), 3.37 (s, 3H), 3.07 (q, *J* = 6.8 Hz, 2H), 2.69 (bs, 1H), 1.41 (p, *J* = 6.8 Hz, 2H), 1.23 (m, 8H), 0.85 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 137.0, 129.2, 128.2, 126.3, 101.9, 98.1, 81.3, 73.9, 68.7, 62.0, 55.2, 41.1, 31.6, 29.6, 28.8, 26.6, 22.5, 14.0. HR ESIMS calcd for $C_{22}H_{33}NO_7$ $[M+H]^+$ 424.2335, found 424.2331.

The 3-carbamate ester (**18c**) was isolated as a white solid (84mg, 20%). m.p. 181.5-182.5°C; IR (neat) 3558, 3446, 2925, 2859, 1726, 1516, 1372, 1180, 1096, 1071, 1057, 1000, 918, 873 cm^{-1};^{1}H NMR, (400 MHz, $CDCl_3$) δ 7.42-7.46 (m, 2H), 7.31-7.35 (m, 3H), 5.47 (s, 1H), 5.13 (t, 1H, *J* = 9.8 Hz), 4.80 (bs, 1H), 4.77 (d, 1H, *J* = 3.9 Hz), 4.28 (dd, 1H, *J* = 4.9, 9.8 Hz), 3.85 (dt, 1H, *J* = 4.9, 9.8 Hz), 3.72 (pt, 1H, *J* = 9.8, 10.7 Hz), 3.63 (dd, 1H, *J* = 2.9, 9.8 Hz), 3.53 (t, 1H, *J* = 9.8 Hz), 3.43 (s, 3H), 3.13 (q, 2H, *J* = 6.8 Hz), 2.91 (d, 1H, *J* = 9.8 Hz), 1.44 (p, 2H, *J* = 6.8 Hz), 1.19-1.27 (m, 6H), 0.84 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 137.1, 129.1, 128.1, 126.3, 101.6, 100.4,

78.9, 73.2, 72.4, 69.0, 62.7, 55.6, 41.2, 29.5, 28.8, 22.3, 14.0. HRMS ES+ Calcd for $C_{22}H_{33}NO_7$ $[M+H]^+$ 424.2335, found 424.2326

2-Hydroxy ethyl carbamates (17b)

Compound **17b** was isolated as a white powder. m.p. 154.7-156.2°C. ^{1}H NMR, (400 MHz, $CDCl_3$) δ (ppm) 7.42-7.38 (m, 2H), 7.27-7.23 (m, 3H), 5.46 (s, 1H), 4.83 (d, *J* = 3.7 Hz, 1H), 4.52 (dd, *J* = 3.7, 9.5 Hz, 1H), 4.17 (dd, *J* = 3.3, 8.8 Hz, 1H), 3.95 (t, *J* = 9.5 Hz, 1H), 3.75-3.64 (m, 2H), 3.58-3.47 (m, 2H), 3.46 (t, *J* = 9.2 Hz, 1H), 3.30 (s, 3H), 3.26-3.19 (m, 2H), 3.10-3.03 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.6, 137.0, 129.2, 128.2, 126.3, 102.0, 98.3, 81.3, 74.3, 68.8, 68.3, 62.3, 60.8, 55.2, 43.2. HR ESIMS calcd for $C_{17}H_{24}NO_8$ $[M+H]^+$ 370.1502, found 370.1493.

(2-Chloroethyl)-carbamates

Compound **18a** was isolated as crystals at a 24% yield. ^{1}H NMR, (400 MHz, $CDCl_3$) δ (ppm) 7.47-7.42 (m, 2H), 7.36-7.31 (m, 3H), 5.49 (s, 1H), 5.45-5.35 (bm, 2H), 5.17 (bt, *J* = 4.9 Hz, 1H), 4.92 (d, *J* = 3.9 Hz, 1H), 4.82 (dd, *J* = 2.9, 9.8 Hz, 1H), 4.28 (dd, *J* = 4.9, 10.7 Hz, 1H), 3.90 (td, *J* = 3.9, 9.8 Hz, 1H), 3.75 (pt, *J* = 9.8 10.7 Hz, 1H), 3.62 (pt, *J* = 8.9, 9.8 Hz, 1H), 3.59-3.42 (m, 10H), 3.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.5, 155.3, 136.9, 129.0, 128.1, 126.2, 101.5, 98.2, 79.2, 72.2, 70.3, 68.8, 62.4, 55.3, 43.8, 43.5, 42.8. HR ESIMS Calcd for $C_{20}H_{27}N_2O_8Cl_2$ $[M+H]^+$ 493.1144, found 493.1126.

Compound **18b** was isolated as a white solid at a 6% yield. ^{1}H NMR, (400 MHz, $CDCl_3$) δ (ppm) 7.46-7.50 (m, 2H) 7.33-7.38 (m, 3H) 5.53 (s, 1H) 5.42 (bt, *J* = 4.9 Hz, 1H) 4.95 (d, *J* = 3.9 Hz, 1H) 4.71 (dd, *J* = 2.9, 9.8 Hz, 1H) 4.26-4.30 (m, 1H) 4.14 (t, *J* = 9.8 Hz, 1H) 3.82 (td, *J* = 4.9, 9.8 Hz, 1H) 3.74 (t, *J* = 9.8 Hz, 1H) 3.50-3.60 (m, 2H) 3.48 (t, *J* = 5.9 Hz, 1H) 3.40 (s, 3H) 2.78 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.7, 137.0, 136.3, 129.3, 128.4, 126.3, 102.1, 98.1, 81.4, 74.2, 68.9, 68.7, 62.0, 55.4, 43.7, 42.9. HR ESIMS Calcd for $C_{17}H_{23}NO_7Cl$ $[M+H]^+$ 388.1163, found 388.1156.Hz

Phenyl Carbamate

Compound **19b** was isolated as a white solid at 42% yield. ^{1}H NMR, (400 MHz, $CDCl_3$) δ (ppm) 7.48-7.51 (m, 2H), 7.32-7.38 (m, 6H), 7.26 (pt, 2H , *J* = 7.7, 8.1 Hz), 7.04 (pt, 1H, *J* = 7.0, 7.7 Hz) 5.54 (s, 1H), 5.03 (d, 1H, *J* = 4.0 Hz), 4.79-4.83 (m, 1H), 4.30 (dd, 1H, *J* = 4.4, 9.9 Hz), 4.22 (t, 1H, *J* = 9.5 Hz), 3.86 (td, 1H, *J* = 4.4, 9.9 Hz), 3.77 (pt, 1H, *J* = 9.9, 10.3 Hz), 3.60 (pt, 1H, *J* = 9.2, 9.5 Hz), 3.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 153.0, 137.8, 137.2, 128.6, 123.9, 119.0, 102.3, 98.3, 81.6, 74.3, 68.9, 62.4, 55.6. HR ESIMS Calcd for $C_{21}H_{24}NO_7$ $[M+H]^+$ 402.1553, found 402.1538.

4-Bromophenyl carbamate

Compound **20b** was isolated as a white solid at a 20% yield. m.p. 194.1-195.7°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.47-7.52 (m, 2H), 7.32-7.40 (m, 4H), 7.17-7.25 (m, 3H), 5.55 (s, 1H), 5.02 (d, 1H, *J* = 3.8 Hz), 4.83 (dd, 1H, *J* = 3.8, 9.6 Hz), 4.31-4.33 (m, 1H), 4.24 (dd, 1H, *J* = 2.5, 9.3 Hz), 3.87 (td, 1H, *J* = 4.4, 10.2 Hz), 3.78 (pt, 1H, *J* = 9.9,

10.2 Hz), 3.59 (pt, 1H, J = 9.1, 9.3 Hz), 3.42 (s, 3H), 3.10 (bd, 1H, J = 2.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 154.0, 139.5, 139.1, 132.6, 129.7, 128.9, 127.4, 121.1, 115.6, 102.4, 99.1, 82.7, 75.2, 69.2, 63.4, 55.5. HR ESIMS Calcd for $C_{21}H_{23}NO_7Br$ $[M+H]^+$ 480.0658, found 480.0659.

References

1. Terech, P.; Weiss, R. G. *Chem. Rev.* **1997**, *97*, 3133–3159.
2. Abdallah, D. J.; Weiss, R. G. *Adv. Mater.* **2000**, *12*, 1237–1247.
3. Estroff, L. A.; Hamilton, A. D. *Chem. Rev.* **2004**, *104*, 1201–1217.
4. van Esch, J. H.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 2263–2266.
5. Abe, H.; Kikuchi, H.; Hanabusa, K. *Liq. Cryst.* **2003**, *30*, 1423–1431.
6. Jung, J. H.; Lee, S. H.; Yoo, J. S.; Yoshida, K.; Shimizu, T.; Shinkai, S. *Chem. Eur. J.* **2003**, *9*, 5307–5313.
7. Mizrahi, S.; Gun, J.; Kipervaser, Z. G.; Lev, O. *Anal. Chem.* **2004**, *76*, 5399–5404.
8. Lee, K. Y.; Mooney, D. J. *Chem. Rev.* **2001**, *101*, 1680–1869.
9. Miyata, T.; Uragami, T.; Nakamae, K. *Adv. Drug Del. Rev.* **2002**, *54*, 79–98.
10. Jen, A. C.; Wake, M. C.; Mikos, A. G. *Biotechnol. Bioeng.* **1996**, *50*, 357–364.
11. Fadnavis, N. W.; Sheelu, G.; Kumar, B. M.; Bhalerao, M. U.; Deshpande, A. A. *Biotechnol. Prog.* **2003**, *19*, 557–564.
12. Kiyonaka, S.; Sada, K.; Yoshimura, I.; Shinkai, S.; Kato, N.; Hamachi, I. *Nat. Mater.* **2004**, *3*, 58–64.
13. Tiller, J. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3072–3075.
14. Zhang, Y.; Yang, Z. M.; Yuan, F.; Gu, H. W.; Gao, P.; Xu, B. *J. Am. Chem. Soc.* **2004**, *126*, 15028–15029.
15. Estroff, L. A.; Addadi, L.; Weiner, S.; Hamilton, A. D. *Org. Biomol. Chem.* **2003**, *22*, 4124–4131.
16. Wang, G.; Hamilton, A. D. *Chem. Commun.* **2003**, *3*, 310–311.

17. Gronwald, O.; Shinkai, S. *Chem. Eur. J.* **2001**, *7*, 4328–4334.

18. Luboradzki, R.; Gronwald, O.; Ikeda, M.; Shinkai, S.; Reinhoudt, D. N. *Tetrahedron.* **2000**, *6*, 9595–9599.

19. Kobayashi, H.; Friggeri, A.; Koumoto, K.; Amaike, M.; Shinkai, S.; Reinhoudt, D. N. *Org. Lett.* **2002**, *4*, 1423–1426.

20. Gronwald, O.; Sakurai, K.; Luboradzki, R.; Kimura, T.; Shinkai, S. *Carbohydr. Res.* **2001**, *331*, 307–318.

21. Kiyonaka, S.; Shinkai, S.; Hamachi, I. *Chem. Eur. J.* **2003**, *9*, 976–983.

22. Luboradzkia, R.; Pakulski, Z. *Tetrahedron*. **2004**, *60*, 4613–4616.

23. Bhuniya, S.; Park, S. M.; Kim, B. H. *Org. Lett.* **2005**, *7*, 1741–1744.

24. Suzuki, M.; Nigawara, T.; Yumoto, M.; Kimura, M.; Shirai, H.; Hanabusa, K. *Org. Biomol. Chem.* **2003**, *22*, 4124–4131.

25. Suzuki, M.; Yumoto, M.; Kimura, M.; Shirai, H.; Hanabusa, K. A. *Chem.-Eur. J.* **2003**, *9*, 348–354.

26. Suzuki, M.; Owa, S.; Yumoto, M.; Kimura, M.; Shirai, H.; Hanabusa, K. *Tetrahedron Lett.* **2004**, *45*, 5399–5402.

27. Suzuki, M.; Sato, T.; Kurose, A.; Shirai, H.; Hanabusa, K. *Tetrahedron Lett.* **2005**, *46*, 2741–2745.

28. Menger, F. M.; Caran, K. L. *J. Am. Chem. Soc.* **2000**, *122*, 11679–11691.

29. Suzuki, M.; Yumoto, M.; Kimura, M.; Shirai, H.; Hanabusa, K. *Chem. Commun.* **2002**, *8*, 884–885.

30. Jokíc, M.; Periç, B.; Tomísíc, V.; Kojíc-Prodíc, B.; Zíníc, M. *Chem. Eur. J.* **2001**, *7*, 3328–3341.

31. Iwaura, R.; Yoshida, K.; Masuda, M.; Yase, K.; Shimizu, T. *Chem. Mater.* **2002**, *14*, 3047–3053.

32. Park, S. M.; Lee, Y. S.; Kim, B. H. *Chem. Commun.* **2003**, *23*, 2912–2913.

33. Mukhopadhyay, S.; Maitra, U.; Krishnamoorthy, I. G.; Schmidt, J.; Talmon, Y. *J. Am. Chem. Soc.* **2004**, *126*,15905–15914.

34. Heeres, A.; van der Pol, C.; Stuart, M.; Friggeri, A.; Feringa, B. L.; van Esch, J. *J. Am. Chem. Soc.* **2003**, *125*, 14252–14253.

35. van Bommel, K. J. C.; van der Pol, C.; Muizebelt, I.; Friggeri, A.; Heeres, A.; Meetsma, A.; Feringa, B. L.; van Esch, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 663–1667.

36. Zhou, S. L.; Matsumoto, S.; Tian, H. D.; Yamane, H.; Ojida, A.; Kiyonaka, S.; Hamachi, I. *Chem. Eur. J.* **2005**, *11*, 1130–1136.

37. Oda, R.; Huc, I.; Candau, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2689–2691.

38. Wang, G.; Cheuk, S.; Williams, K.; Sharma, V.; Dakessian, L.; Thorton, Z. *Carbohyd. Res.* **2006**, *341*, 705.

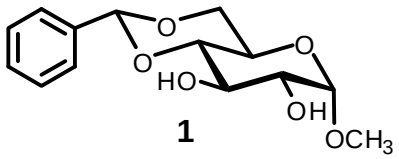
Chapter 3. D-Glucosamine derived low molecular weight organogelators: design, synthesis and characterizations

Abstract

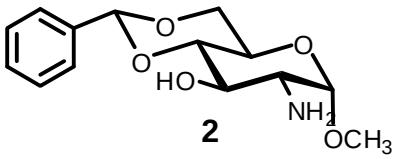
D-Glucosamine is a common carbohydrate that appears in nature. The natural abundance and unique structure of D-glucosamine make it an attractive starting material for the synthesis of functional self assembling systems. The amino group can form extra hydrogen bonding interactions with other molecules or itself, this can potentially inprove the gelation abilities. To be used in a variety of applications, LMOGs has to exhibit varying degrees of robustness in various conditions. In this chapter, we synthesized several low molecular weight organogelators (LMOGs) starting from D-glucosamine. Ureas were synthesized from the corresponding isocyanates in quantitative yields and the amides were made from activated carboxylic acids in moderate to good yields. The gelation properties of the amides and ureas in a variety of organic and aqueous solvents, and water were screened and analyzed, the structure properties correlation of the RNHCOR′ and RNHCONHR′ versus the gelators from D-glucose, ROCOR′ and ROCONHR′ are compared.

Introduction

As shown in the previous chapter and some other work from the Wang's lab,[1-3] short chain *D*-glucose derivatives exhibit good gelation properties. Compounds with a free hydroxyl groups generally show good gelation ability in more polar solvents. However, there are several drawbacks of *D*-glucose-based LMOGs. One of the drawbacks is the regioselectivity in the synthesis. When reacting with the diol derived from glucose, although the acylation reactions did show preference for the 2-position, a significant portion did react at the 3 and both positions, especially the resulting carbamates. The modest selectivity resulted in a mixture of 2 to 3 products to be purified. These works well for accessing a larger pool of products for the screening of good gelators, but to synthesize individual compound, some other strategies need to be adopted. Furthermore, the stability of esters and carbamates in the environment may be problematic since they can be hydrolyzed under basic or acidic conditions. If any LMOGs are to be used on a mass scale, these disadvantages have to be taken into consideration.



1



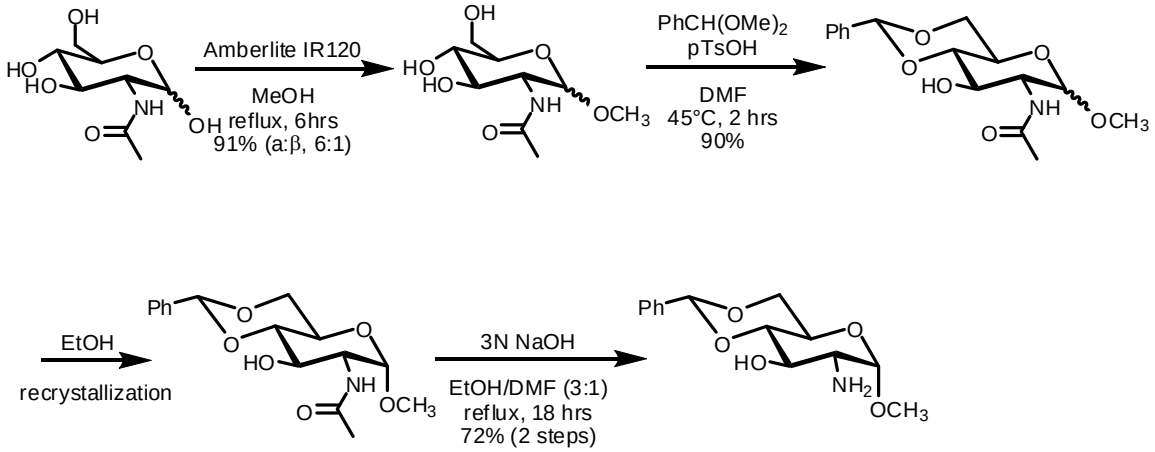
2

2-Amino-2-deoxy-*D*-glucose (*D*-glucosamine) and its acetylated derivative (N-acetyl-*D*-glucosamine) are common naturely occurring compounds. Their derivatives are also one of the main components in extracellular matrices (i.e. chitin and collagen). Also, the ionic or partial ionic character of the amine (or functionalized amine) enables the ECM to

become more "water friendly" as opposed to glucose-based polymers, such as starches and cellulose-type material, which, although are hydrophilic material, has poor water solubility and retention. A common component of ECM in loose connective tissue (e.g. synovial fluid, vitreous humour, and skin) is hyaluronic acid,[4] which contains repeating disaccharide units of α-1,4-D-glucuronic acid and β-1,3-*N*-acetyl-D-glucosamine.[5] The importance of hyaluronic acid goes beyond the necessity for sustaining human life.[6] Pure hyaluronic acid has been used as a hydrogel-based delivery system for drugs[7,8] and also as a scaffold for wound healing.[8] Another *D*-glucosamine-containing component of ECM, especially in bone, cartilage, and in the cornea is another polysaccharide called keratin sulfate.[9] Like hyaluronic acid, it contains a repeating disaccharide unit consisting of β-1,3-*D*-galactose and β-1,4-N-acetyl-*D*-glucosamine. Sulfate anions are attached to the 6 position of either sugar to varying degrees. In addition to ECM, *D*-glucosamine plays an important role in the formation of glycoproteins. Like all *D*-glucose, *D*-glucosamine's natural abundance, renewability, multiple chiral centers, and ease of isolation from natural sources make it an attractive starting material for the synthesis of LMOGs. Its omnipresence throughout the entire human body signifies its biocompatibility. To the author's best knowledge, there have been no gelation studies of using *D*-glucosamine derivative **2** to form gels as a monosaccharide unit.

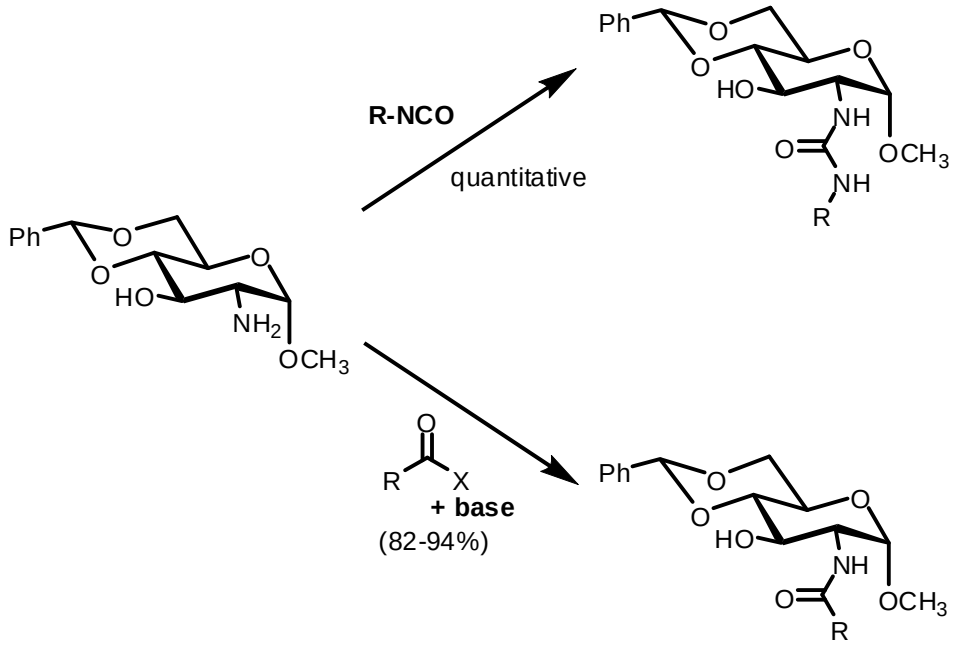
From a synthetic standpoint, the amino group being more reactive comparing to a secondary hydroxyl group. This should not only increase the selectivity of the acylation reaction, but also the rate of the reaction, thus increasing the efficiency of formation of *D*-glucosamine-based LMOGs. After acylation, whether by an activated carboxylic acid

or an isocyanate, the additional hydrogen bond should affect the hydrogen bonding array, especially in aqueous solvents where hydrogen bonding predominates, to a great extent. The stability of the resulting amides and ureas should also be noted as well. Using amides and ureas as one of the central motifs in the design of LMOGs places the emphasis of the self-assembly phenomenon on the formation of a hydrogen bonding network. Ureas are becoming a common motif in the design and synthesis of LMOGs. Urea itself is a water soluble waste (yet quite stable), usually produced from the metabolism of proteins, but as soon as more hydrophobic groups, through careful design, are added on to the nitrogens, the resulting molecule becomes an efficient gelator in water and other organic solvents.[10-18] Urea-based gelators have predictable (or assumed) self-assembly of the urea group due to the directionality of the group, this probably accounted for the extensive studies on urea derivatives. The influences of amide bonds in self-assembly are most commonly seen in the secondary structure of proteins in the formation of α-helices and β-sheets, with the amide hydrogen interacting with the carbonyl of another amino acid unit. Though they are not as stable and lack the directionality of ureas, they are being used with more frequency in the synthesis and design of LMOGs.[19-27]



Scheme 3.1. The synthesis of *D*-glucosamine derivative, **2**, from N-acetyl-*D*-glucosamine.

The synthesis above required no column purification and gram scale production of derivative **2** could be carried out in less than two days. N-Acetyl-*D*-glucosamine **3** was methylated in the presence of acidic resin. After thorough removal of methanol, the resulting white solid was dissolved in DMF (non-anhydrous) and reacted fairly quickly (within 2 hrs) with the benzyliedene acetal to yield the acetamide **6**. Clean hydrolysis of the acetamide was implemented by the use of ethanol and DMF and extracted in 10% methanol in DCM and washed with a 50% brine solution. The ^{1}H NMR ($CDCl_3$, 400 MHz) of **2** taken after workup is in **Figure 3.3**.



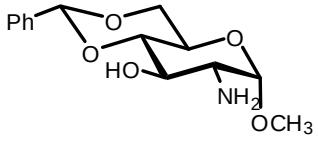
Scheme 3.2. Synthesis of amides and ureas from compound **2**.

D-Glucosamine amide LMOGs

The free amine was easily functionalized with activated carboxylic acids and isocyanates as shown in **Scheme 3.2**. The amide library was synthesized by using activated carboxylic acids (i.e. chlorides, anhydrides, and EDCI coupling). A small amount of the free amine (60-100mg) was dissolved in anhydrous THF or DMF and 3 equivalents of diisopropylethylamine. The resulting solution was cooled and equilibrated to 0°C, in which the activated carboxylic acid was added dropwise if liquid or one aliquot of solid. After 2 hrs, the reaction was worked up using a 5% $NaHCO_3$ solution (2x1mL) and a 5% MeOH solution in DCM (2mL). After a brief wash with brine, the solution was dried over Na_2SO_4 and purified using 10-20% of the 5-10% MeOH solution in DCM in hexanes.

Light sensitivity was taken as an extra precaution for compound **15**. All gelation tests were done by the inversion method.

Table 3.1. Library of amides derivatives of **2** and corresponding minimum gelation concentrations (MGCs) in mg/mL.



R = Me- **7**; $H_3C(CH_2)_4$- **8**; $HCC(CH_2)_8$- **9**; Ph- **10**;  **11**; N-Boc-Gly- **12**; $H_3C(CH_2)_5$- **13**; $H_3C(CH_2)_6$- **14**; $H_3C(CH_2)_4CCCC(CH_2)_8$- **15**

Compound	Water	Hexane	EtOH	Water:DMSO (2:1)	Water:EtOH (2:1)	C Log P
7	C	I	S	S	S	-0.39
8	C	C	S	1.3	1.3*	1.73
9	I	C	S	1.7	2.0	2.49
10	2.0*	I	Cr	2.0	5.0*	1.10
11	10	P	S	5.0	5.0	-3.61
12	Cr	C	S	S	Cr	0.91
13	I	1.7	S	1.0	2.0	2.26
14	I	2.0*	S	1.2	1.6	2.79
15	I	P	S	10	2.9	5.73

* unstable gel; G, gel at room temperature; I, insoluble; C, coaservate at 10 mg/mL; Cr, crystallization; S, soluble at ~10 mg/ml

Nearly none of the amides were able to gelate water at or below 10 mg/mL (~1.0 wt%) with the exception of the pyridinium acetamide (compound **11**). Since the acetamide (compound **7**) was not able to gelate pure water, the pyridinium ion must have interacted

with the water while the rest of the molecule associated in more hydrophobic regions. The effect of ions will be studied later. However, most of the amides studied were capable of forming stable gels in aqueous mixtures at fairly low concentrations (≤5.0mg/mL). Aqueous mixtures of ethanol or dimethylsulfoxide (DMSO) were tested also. Ethanol is of considerable interest of late because of its uses as biofuels and that it can be obtained from renewable resources. DMSO has long been used (though no longer for human uses) for the delivery of hydrophobic drugs through the skin. A 33% solution of DMSO in water was used because of its ability to gelate a wide range of these libraries compounds. Most of these compounds did not form gels in pure water, but in the presence of ethanol or DMSO. The effective gelation ability increased dramatically with the latter being the greatest. Therefore, ethanol and DMSO must have induced self-assembly by affecting the hydrophobic regions of the LMOGs and/or by disrupting the crystalline state.

Many literatures suggest π -π stacking may influence the self-assembly of fibers of which may cause a shift in the UV absorption of the aromatic regions.[28-31] These shifts in absorption may enable us to observe self-assembly or disassembly in real time. However, when we incorporated the phenyl amide (**10**), the gels that formed tend to destabilize over a short period time, turning into a coaservate (gelatinous particulates). It may be possible that adding an aryl group may decrease gelation ability, by destabilizing the hydrogen bonding network.[19] Interesting to note that compound **10**'s most stable gel was that in the aqueous DMSO.

N-Boc Glycine (**12**) was prepared for two purposes. 1) The bulkiness of the t-butyl group should prevent the compound from crystallizing out and the additional NH may assist as an additional H-bonding donor. 2) The glycine unit may be deprotected and funtionalized with an additional amide or urea linkage. However, the gelation tests were not favorable and the deprotection of the N-Boc group also resulted in the deprotection of the benzyliedene acetal. N-Fmoc protected glycine may be of some use, not only because its removal in piperidine should not affect any other functional group, but also to influence gelation as cited in several papers dealing with the gelation N-Fmoc amino acids.

The straight chain amides turned out to be quite versatile and efficient LMOGs as they were able to efficiently gelate a range of solvents from hexane to aqueous mixtures of ethanol and DMSO, but not pure water. The concept of self-assembly in hexane is a lot easier to grasp than in binary mixtures, such as that of DMSO and water. The nonpolar hexanes are able to interact with the lipid portion of the molecules while the heteroatoms of the sugar derivative congregate in such a way that it minimizes unfavorable interactions. This change upon mixing of solvents, as well as its increase in stability, provides a great deal of information, but not yet complete, about the self-assembly of these molecules. The reason why DMSO and ethanol are able to dissolve these compounds, as well as many others, is because of hydrophobic and hydrophilic regions coexist in the same compounds. For example, ethanol's hydroxyl functions in a similar fashion to water, hydrogen bonding with other heteroatoms, but the ethyl region enables

it to associate with more hydrophobic regions. However, in the previous chapter we have found that the longer chain ester was able to gel pure ethanol. DMSO, although somewhat different (much higher polarity), functions in approximately the same fashion, but may convert into its 'ionic' form enabling it to dissolve salts. The inability of most of these compounds to self-assemble into stable gels in pure water may be due to the instability of certain portions of the compound in pure water, which the addition of ethanol or DMSO possibly stabilizes.

Amides are most associated with peptide bonds of proteins, which are the most extensively studied in terms of hydrogen bonding. The amide C-N bond can exist either in the s-*cis* or s-*trans* conformations with the latter being the most predominant form (>98.5%). For a s-*cis* bond to be stable, it will need two intramolecular hydrogen bonds (5 kcal/mol) to overcome about 8 kcal/mol[28] in favor of the s-*trans* conformer. Since the LMOGs synthesized are stable for long periods of time in aqueous solvents and it is conformationally impossible to stabilize a s-*cis* conformer with two hydrogen bonds, the s-*trans* conformer is most likely predominant within the self-assembled network containing these compounds. As it turns out, a calculated minimized energy model (**Figure 3.1**) gives a s-*trans* conformer, which appears to be stabilized by two intramolecular hydrogen bonds: 1) The amide hydrogen and the lone pair of electrons of the methoxy oxygen, 2) The secondary hydroxy of the sugar and the carbonyl oxygen. The stabilization of a s-*cis* conformer can only take place only if the substituents of the sugar are at axial positions (**Figure 3.2**), which is a highly unstable conformer.

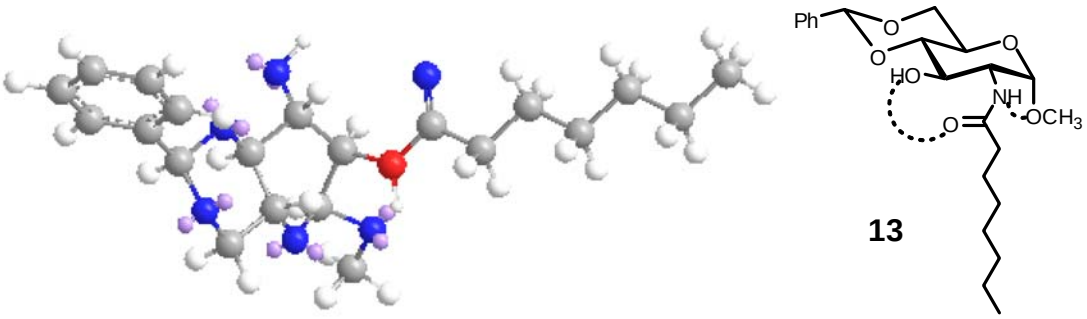


Figure 3.1. *Trans* conformation of compound **13**.

The diacetylene LMOGs are also of interest because of its ability to display different colors as a result of a formation of an extensive conjugated system between individual molecules upon exposure to UV radiation and heat. Derivative (**15**) was also synthesized to further explore the diacetylene moiety in this system. The resulting polymer is pink and upon heating, the polymer is yellow, but when cooled, the gel turns back to pink, thus giving a thermosensitive gel.

D-Glucosamine urea LMOGs

The urea library was synthesized by combining compound **2** (30-50mg) and the corresponding isocyanate in stoichiometric quantities in anhydrous THF (0.8-1.0mL). The solution was sonicated and later heated by a heat gun to dissolve any gel that may have formed. The solution was then dried and ^{1}H and ^{13}C NMR were all done in d_6-DMSO and showed that the yields were pure enough (≥ 90%) without purification

(**Figure 3.2**). The synthesis of the ureas marked a significant step for this library from a synthetic standpoint as none of the compounds had to be purified and most of them provided to be good to excellent gelators, especially in the aqueous mixtures. The presence of a secondary hydroxyl did not appear to affect the reactivity or selectivity of the primary amine, as all reaction appeared to give quantitative yields (from crude ^{1}H NMR, d_6-DMSO, 400 MHz). As compared to reactivity versus the D-glucose derivative where it took several hours to overnight to react sufficiently with the isocyanate to yield a mixture of compounds with about a 2:1 ratio with 2 and 3 positions, the isocyanate reacted within minutes with compound **2** exclusively at the amine (**Figure 3.2**). In addition, to form the carbamate, a catalytic amount of base (a tertiary amine) had to be used, while the formation of the urea compounds required no base. This reaction occurred much faster than the formation of the amides.

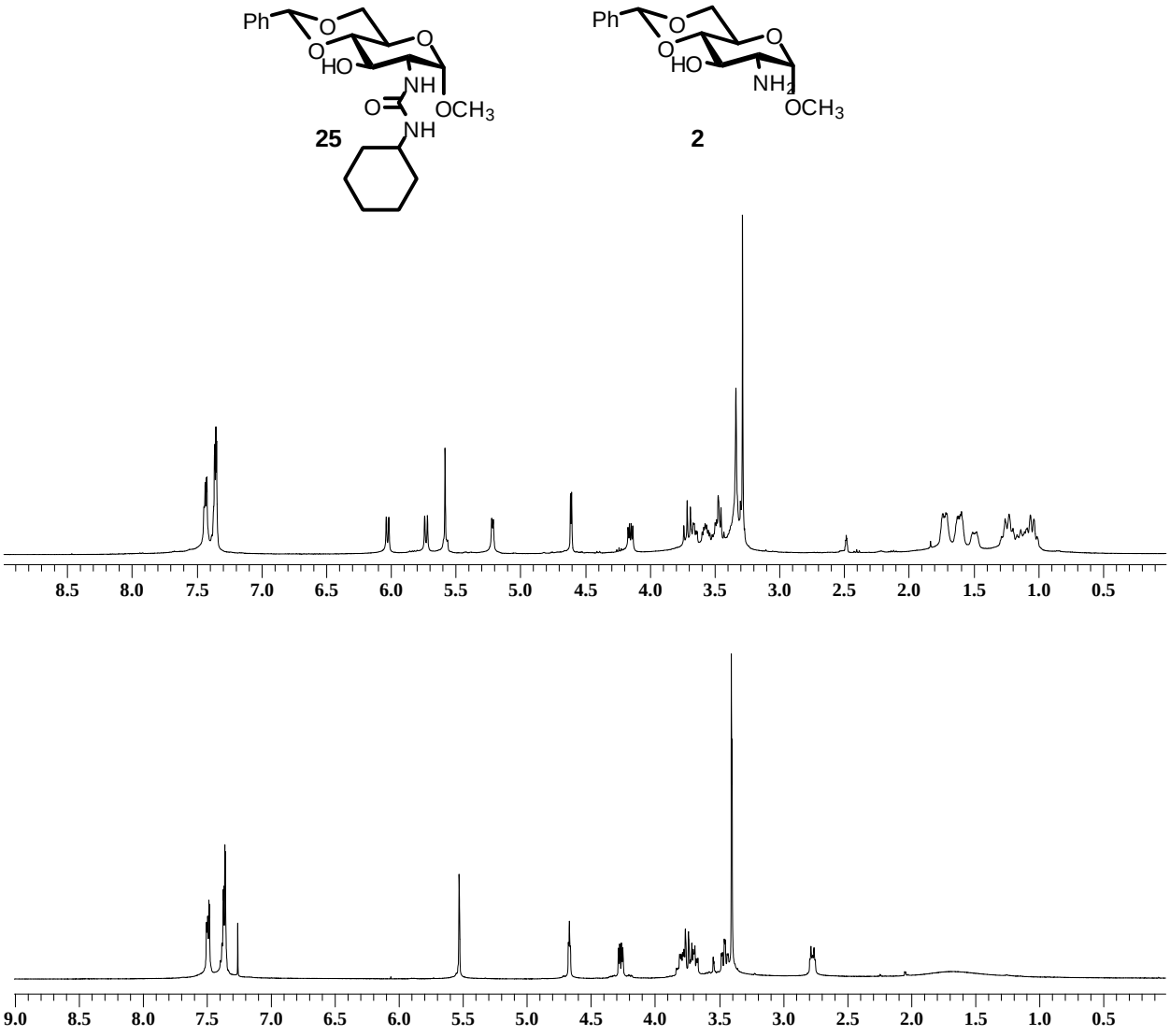
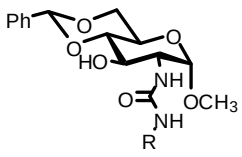


Figure 3.2. ^{1}H NMRs of urea **25** (d_6-DMSO, 400 MHz, above) and starting material compound **2** ($CDCl_3$, 400 MHz, below).

Table 3.2. Library of urea derivatives of **2** and corresponding MGCs (mg/mL).



$H_3C(CH_2)_6$-	$H_3C(CH_2)_4$-	$H_3C(CH_2)_5$-	4-Br-Phenyl-	1-Naphthyl-
16	**17**	**18**	**19**	**20**
Phenyl-	2-Cl-Ethyl-	2-Ethyl methacrylate-	2-Hydroxyethyl-	Cyclohexyl-
21	**22**	**23**	**24**	**25**

Compound	Water	THF	EtOH	Water:DMSO (2:1)	Water:EtOH (2:1)	C log P
16	P	S	10	1.0	1.7*	3.05
17	1.0*	S	S	1.0	1.3*	1.99
18	P	S	S	1.0	1.5	2.52
19	I	S	I	C	2.0	2.38
20	I	C	C	2.0	Cr	2.39
21	I	P	10	P	Cr	1.22
22	C	S	P	S	C	-1.32
23	P	S	C	P	C	1.08
24	2.5	P	P	C	3.3	0.59
25	C	Cr	10	C	1.3	1.91

* unstable gel; G, gel at room temperature; I, insoluble; C, coaservate at 10 mg/mL; Cr, crystallization; S, soluble at ~10 mg/mL.

Ureas differ from amides and carbamates because of the additional –NH group. When comparing the amides and carbamates with esters, the extra hydrogen bond donor for the amides and carbamates greatly increased the efficacy of gelation. Thus the need for a second hydrogen bond donor was apparent because of its role in the self-assembly. The ureas should determine whether a third hydrogen bond donor is necessary. The increase in intermolecular interactions was especially noted in the sharp increase in the melting

point ranges from other compounds. Compound **21** had a melting point well over 300°C, exceeding that of most organic compounds.

The alkyl ureas **16**, **17**, and **18**, just as the alkyl amides, proved to be the more versatile LMOGs than the aromatic ureas **19**, **20**, and **21**. Aromatic side chains are more rigid than their alkyl counterparts and the larger the aromatic side chains contribute, along with the urea moiety, are the driving forces of self-assembly. The methacrylate ester (**23**) was synthesized for the possibility of cross-linking the gels through polymerization. Another LMOG (**24**) was synthesized after cleaving the ester to yield the alcohol, this resulted in a stable a stable hydrogelator, which did not form a gel sitting at room temperature (after several hours as a cloudy suspension), until a brief sonication. Sonication increases the vibrational energy of on the molecular level, which would be conceivably harder or, in this case, easier for molecules to self assemble. Trying to sonicate for more than 5-10 seconds results in a gelatinous precipitate indicating excess sheer mechanical forces has been applied to the gel.

Just as with the esters and carbamate derivatives, optical microscopy (OM) and scanning electron microscopy (SEM) were done to analyze the gels on a macromolecular scale. Although both gels of the alkyl amide (**13**) and aromatic urea (**19**) (**Figure 3.3**) appear as translucent, they exhibit a difference in their morphology as well as their stability. Compound **13** (as well as the other alkyl derivatives **8** and **14**) gelled in an aqueous solution of DMSO and exhibited more robustness than most gels for an extended period

of time at a low concentration (1.3mg/mL). On the other hand, compound **19** formed a stable gel, but it falls apart upon standing within 20-30 minutes.

These solvents were chosen because they most accurately display the effect of the addition of a hydrogen bonding donor. The most stable gels were the alkyl straight chains. The optical microscopy of the xerogels (dried gels) revealed that the a flexible fibers lead to more effective gelators and the straight alkyl chains (as opposed to aromatic groups) tend to form these morphologies, especially in aqueous solvents.

Optical microscopy reveals a stark difference in the morphology of these gels. In **Figures 3.4** and **3.5** (compound **13**), the gel has two distinct parts: a highly branched region and a noodle-like region. These morphologies are not existent in **Figures 3.6** and **3.7**. (compound **19**), in which more rigid fibers and a higher degree of crystallinity is observed. SEMs of compound **24** shows that the large fibers (3μm in width) observed under OM are composed of a bundle of much smaller fibers (~300nm in width). When compound **13** is observed under SEM, the gel appears to take a wrinkled appearance, upon closer inspection, the xerogel of **13** is composed of a dense network of fibers.

Figure 3.3. Pictures of compound **13** at 1.0 mg/mL (~0.1 wt%) in 2:1 H_2O:DMSO (left) and 2.0 mg/mL (~0.2 wt%) in 4:1 H_2O:DMSO (right).

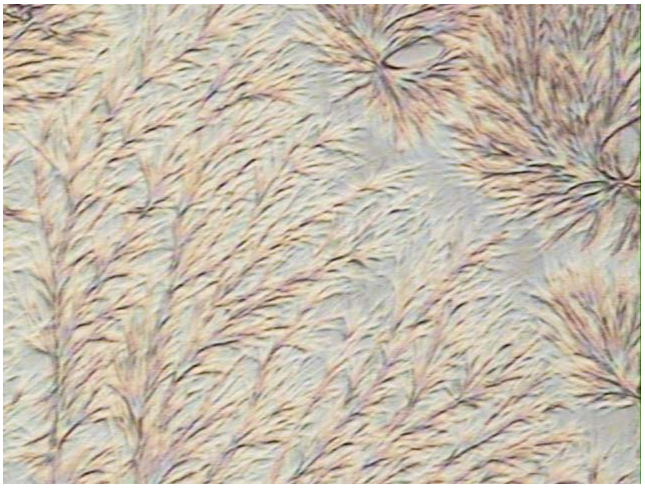


Figure 3.4 Compound **13** at 500x magnification (1.2 wt% in 3:1 H_2O:DMSO)

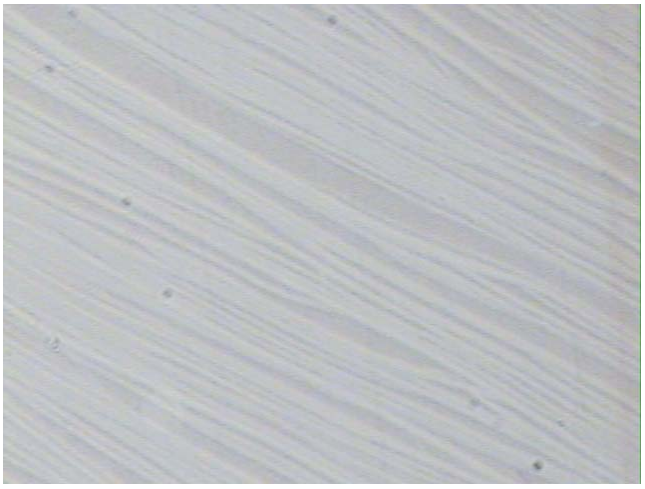


Figure 3.5. Compound **13** at 1000x magnification (1.2 wt% in 3:1 H_2O:DMSO)

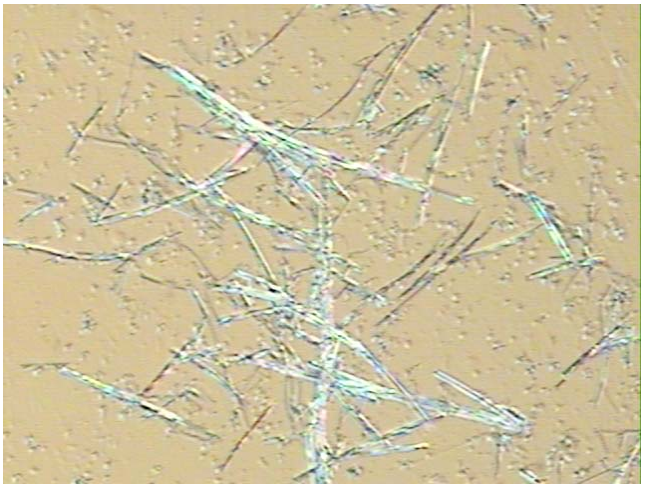


Figure 3.6. Compound **19** at 200x magnification (2.0 wt% in 3:1 H_2O:EtOH)

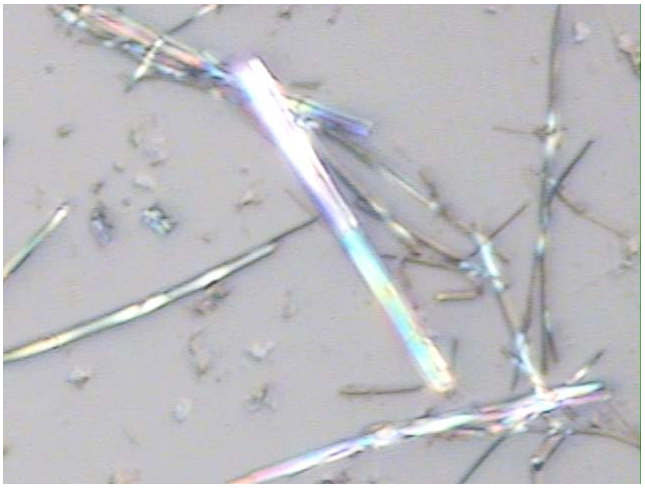


Figure 3.7. Compound **19** at 1000x magnification (2.0 wt% in 3:1 H_2O:EtOH)

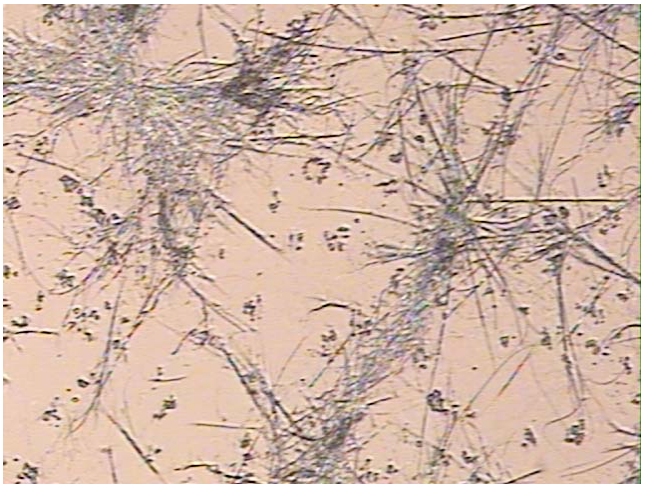


Figure 3.8. Compound **24** at 100x at 2.5 mg/mL in H_2O.

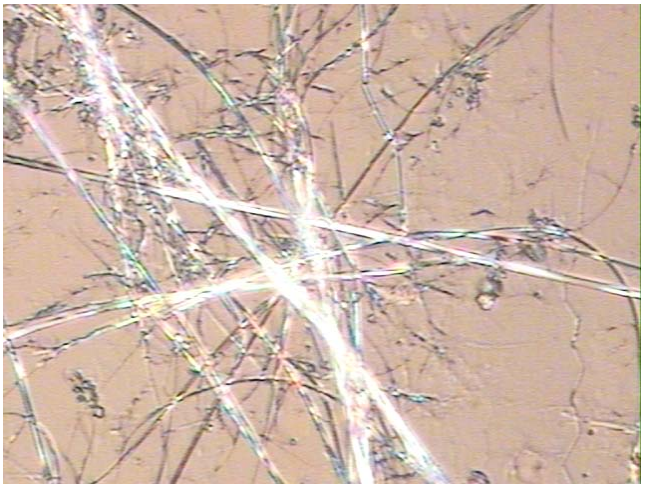


Figure 3.9. Compound **24** at 500x at 2.5 mg/mL in H_2O.

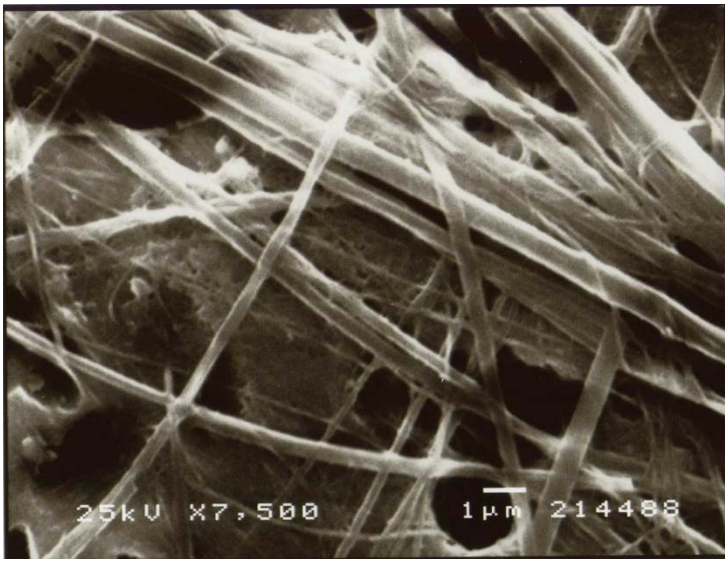


Figure 3.10. SEM image of **24** (2.5 mg/mL in H_2O)

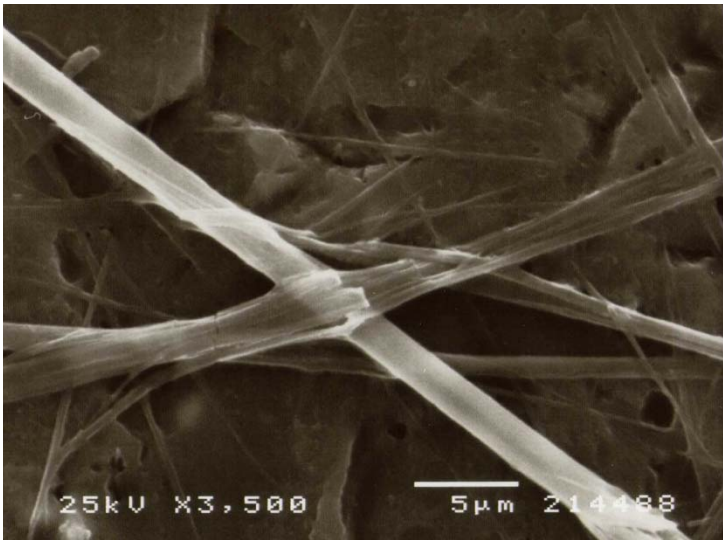


Figure 3.11. SEM image of **24** (2.5 mg/mL in H_2O)

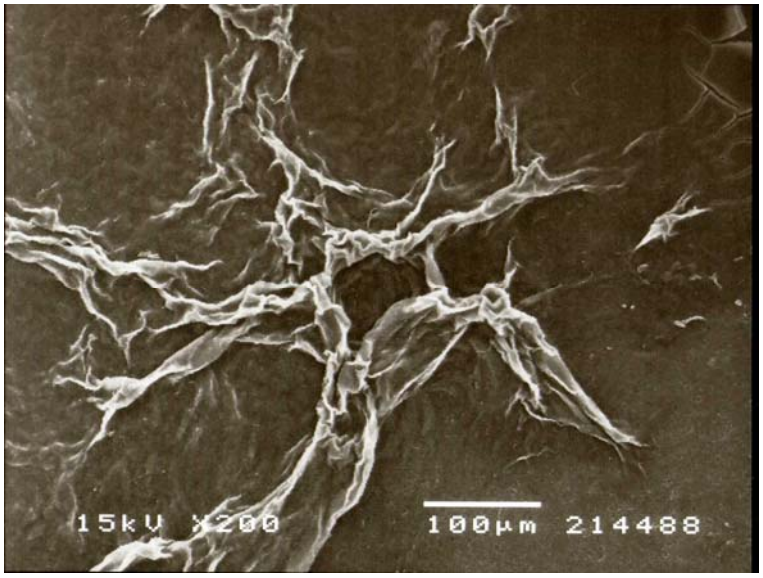


Figure 3.12. SEM image of **13** (1.2mg/mL in 2:1 H_2O:DMSO)

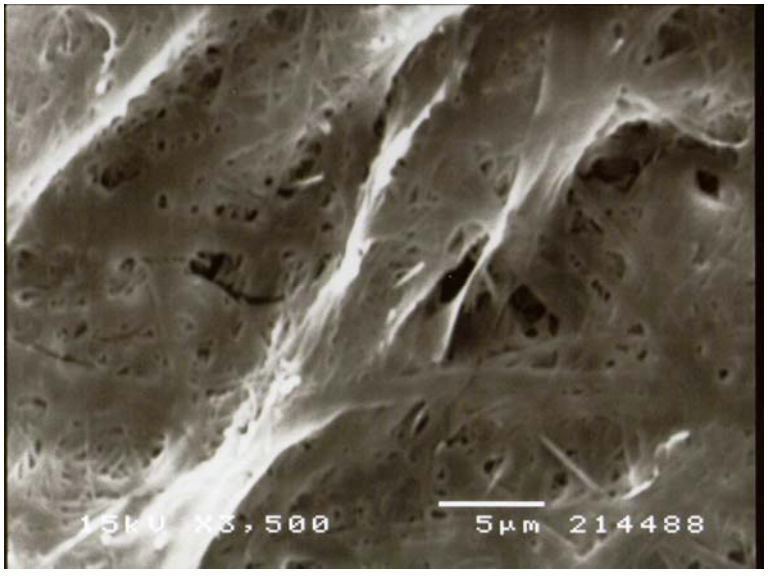
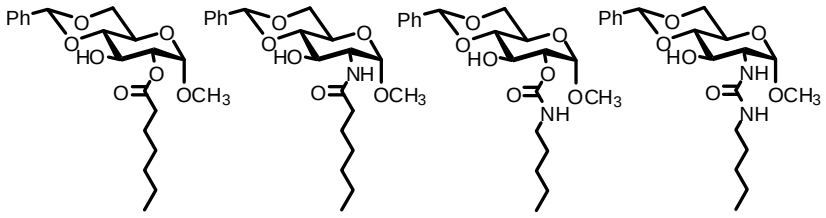


Figure 3.13. SEM image of **13** (1.2mg/mL in 2:1 H_2O:DMSO)

The amides derivatives were compared to the urea derivatives of compound **2**. This corroborated with the ester and carbamates comparison from the previous chapter which showed similar characteristics when an additional hydrogen bond donor is added. **Table 3.3** shows four analogous compounds (an ester, amide, carbamate, and urea) with similar alkyl chain lengths and differing only in the number (0-2) and position of the hydrogen bond donors. The trends in gelation ability became apparent in that the addition of a hydrogen bond donor significantly increases the gelation properties, especially comparing to the ester. The solvents also appear to have some sort of effect. Hydrophobic forces are dominant in hydrogels, whereas hydrogen bonding is the primary force in organogels. Though aqueous solutions of dimethylsulfoxide and ethanol may sometimes be classified as hydrogels, the addition of water miscible organic solvents places more emphasis on hydrogen bonding and less on hydrophobic forces, which possibly explains why there is a large increase in gelation efficiency when a hydrogen bond donor (-NH) is added to the LMOG. Since there is a notable difference in the gelation ability between the ester and carbamate derivatives of compound **1** (and notably efficient), indicates the –NH, a hydrogen bond donor, is essential to the formation of the one-dimensional network and is most likely not intramolecularly hydrogen bonded. When the hydrogen bond donor (–NH group) is shifted closer to the pyranoside ring as in compounds **13** and **17**, there is a significant decrease of MGC in the 33% DMSO aqueous solution, but little to no change in the 33% ethanol aqueous solution. This change shows that the position of the hydrogen bond donor affects the gelation ability to a certain degree. Compound **13** is an amide, and amides, like **13**, should favor the *trans* conformer (by about 8 kcal/mol over *cis*),[32] which places the amide hydrogen in close proximity (~2.7 Å) to the lone pair of the methoxy

group. Intramolecular hydrogen bonding should act as hinderance to gelation. However, due to the fact that compound is an efficient gelator, indicates that the amide hydrogen is not involved in intramolecular hydrogen bonding, but rather it is much involved in the self-assembly of a one-dimensional array. In the previous chapter, few of the 2 or 3 monoesters of *O*-4,6-Benzylidene-α-methyl-D-glucopyranoside (**1**) form gels in water or in aqueous solution. The dramatic change in gelation indicates that a hydrogen bond donor at the 2-position is essential for this system to form gels in aqueous solvents. Whether the 3-hydroxy plays a secondary role in hydrogen bonding in the amide system is in question. Perhaps capping it with a small group (methyl) might affect the self-assembly. The role of the carbonyl oxygen, especially in amide and urea systems, might play a significant role in this system, because, as seen in nature, the NH's of the amides and ureas are known to hydrogen bond with carbonyl groups. The urea added an additional hydrogen bond donor and an interesting trend in the solvent effects became apparent. From the urea, there was a small decrease in the MGC from the amide in the 33% DMSO solution and from the carbamate in the 33 % ethanol solution, but a more significant decrease in the MGC from the amide in the 33% ethanol solution and the carbamate in the 33% DMSO solution was also noted.

Table 3.3. Comparing LMOGs with similar alkyl chain lengths. Positive gelation results are noted in mg/mL. C, coaservate; P, precipitate; I, insoluble



26 **13** **27** **17**

Solvent(s)	26	13	27	17
H_2O	I	C	20	2.0
H_2O:DMSO 2:1	P	1.3	3.0	1.0
H_2O:EtOH 2:1	P	1.8	1.4	1.3

Conclusions

A straight forward synthesis was done towards the synthesis of a D-glucosamine derivative **2**. The amine was easily functionalized with both activated carboxylic acids and isocyanates to yield stable amide and urea derivatives. For both libraries, the alkyl derivatives proved to be the most stable and efficient LMOGs. The amino group at the 2 position made a significant difference in gelation ability and supports the theory that a hydrogen bond donor is necessary for gelation of this system. The ureas and amides derived from D-glucosamine showed excellent gelation properties. They are also characterized with optical microscopy and scanning electron microscopy to discern between stable and unstable gels. These small molecules can be useful for entrapping large biomoelcules such as enzymes and provide a good media for enzymatic reactions.

Experimental Section

General Methods

Gelation Testing. The compounds were tested in a 1 dram vial with a rubber lined screw cap from Kimble. A starting concentration of 10-15mg/mL was used (2-3mg in 0.2mL). The suspension was heated to dissolve the compound (a homogeneous solution) and sonicated, if necessary. The solution was allowed to cool for 15-20 minutes. If a stable gel formed, 0.2-0.3 mL of the same solvent (or solvent mixture) was added and the heating/sonication and cooling was repeated. The process was repeated until the gel was no longer stable and the concentration prior to the unstable gel was recorded as the minimum gelation concentration (MGC).

Optical Microscopy. The slides were prepared after a stable gel has formed. About 20-30mm^3 of the gel was placed on a clean 3 by 1 inch glass slide and dried over night to several days. The xerogels 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.

Scanning Electron Microscopy. Samples were prepared by drying the gel (20-30 mm^3) on an aluminum pellet in a desiccator under reduced pressure for several days. A thin layer of platinum (~100-150 Ang) 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 sec. The sample was analyzed using a JEOL JSM 5410 scanning microscope with an EDAX Detecting Unit PV9757/05 ME (Model 204B+, active area = 10 mm^2).

Compounds 2. *N*-Acetyl-D-glucosamine (3.00g) was dissolved in refluxing methanol (50ml) with suspended Amberlite IR-120 acidic resin (5.00g) for 24 hrs. Resin was filtered and rinsed with methanol, which was removed *in vacuo* to yield 2.85g (89%) of a mixture of α and β anomers (~7:1). Without purification, the α/β methyl mixture was dissolved in 40ml of DMF, 9.0ml of dimethyl bezylidene acetal, and 0.3g of p-toluenesulfonic acid at 40°C for 2hrs. DMF and excess acetal was removed in vacuo to yield a 3.57g (91%) white solid (mixture of α and β anomers). The α anomer was recrystallized in EtOH, which was then dissolved in 160ml of refluxing 3N NaOH ethanol/DMF (3:1) for 16 hours. Reaction was diluted with a 10% MeOH in DCM (~150ml) and 50% brine solution (2x100ml). After drying the DCM layer over anhydrous Na_2SO_4, the NMR indicated the product (light orange solid) could be used without further purification (2.23g, 72%). A small amount of the β anomer (~50mg) was isolated via chromatography from a previous reaction in which there was no recrystallization prior to the deacetylation. Reaction was purified using silica column chromatography in 5% methanol in chloroform.

Compound **2** was isolated as a slightly yellow solid in 72% yield. 164.5-165.2 m.p. °C. ^{1}H NMR, (400 MHz, $CDCl_3$) δ (ppm) 7.47-7.51 (m, 2 H), 7.34-7.38 (m, 3H), 5.51 (s, 1H), 4.64 (d, *J* = 3.7 Hz, 1H), 4.25 (dd, *J* = 4.0, 9.2 Hz, 1H), 3.74-3.81 (m, 1H), 3.71 (pt, *J* = 9.2, 10.3 Hz, 1H), 3.65 (pt, *J* = 9.2, 9.5 Hz, 1H), 3.42 (t, *J* = 9.2 Hz, 1H), 3.38 (s, 3H), 2.74 (dd, *J* = 3.7, 9.5 Hz, 1H), 2.40 (bs, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.2, 129.1, 128.2, 126.3, 101.8, 101.0, 82.0, 71.5, 69.0, 62.5, 56.5, 55.3.

General methods for the synthesis of amides

Method A

O-4,6-Benzylidene-2-amino-2-deoxy-α-methyl-D-glucopyranoside (50-80mg) and the corresponding carboxylic acid (1.1 eq) were mixed in anhydrous 1ml of THF. 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI-HCl, 1.2 eq) and diisopropylethyl amine (DIEA, 3.0 eq) are added. Reaction is stirred for 6-8hrs before being diluted with 3ml of dichloromethane and washed with 2ml of H_2O and 2x2ml of dilute HCl (~0.1N). Solution was dried with anhydrous Na_2SO_4. Purification was carried out using 6-30% acetone in hexane.

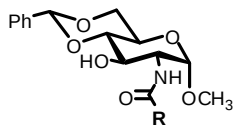
Method B

O-4,6-Benzylidene-2-amino-2-deoxy-α-methyl-D-glucopyranoside (50-80mg) and DIEA (3 eq) are mixed in anhydrous THF at 0°C. The corresponding acyl halide (1.1 eq) was added dropwise. After 2 hrs the reaction was diluted with 3ml of DCM and washed with 2ml of H_2O and 2x2ml of dilute HCl (~0.1N). The organic layer was dried with anhydrous Na_2SO_4. Purification was carried out using 6-30% acetone in hexane.

Method C

O-4,6-Benzylidene-2-amino-2-deoxy-α-methyl-D-glucopyranoside (100-200mg) and DIEA (3eq) are mixed in anhydrous THF at 0°C. The corresponding acid anhydride (1.1 eq) was added and stirred for 2hrs at 0°C. The reaction was slowly warmed to room temperature for another 2hrs. The reaction was diluted with 2-3ml of DCM and washed

with 2x2ml of H2O and 2ml of brine. The DCM layer was dried with anhydrous Na_2SO_4. Purification was carried out using 10-50% acetone in hexane.



R = Me- (7), $H_3C(CH_2)_4$- (8), $HCC(CH_2)_8$- (9), Ph- (10), $Br\text{-}CH_2$- (11), N-Boc-Gly- (12), $H_3C(CH_2)_5$- (13), $H_3C(CH_2)_6$- (14), $H_3C(CH_2)_4CCCC(CH_2)_8$- (15)

Compound 8. Method B. The product was obtained as a white solid at a yield of 86%. ^{1}H NMR, (400 MHz, $CDCl_3$) δ (ppm) 7.49-7.52 (m, 2H), 7.34-7.40 (m, 3H), 5.86 (d, *J* = 8.4 Hz, 1H), 5.58 (s, 1H), 4.21-4.31 (m, 2H), 3.91 (pt, *J* = 9.5, 9.9 Hz, 1H), 3.77-3.81 (m, 2H), 3.73 (d, *J* = 3.7 Hz, 1H), 3.60 (m, 1H), 3.42 (s, 3H), 2.26 (pt, *J* = 7.3, 7.7 Hz, 2H), 1.66 (p, *J* = 7.3 Hz, 2H), 1.30-1.36 (m, 4H), 0.90 (pt, *J* = 7.0, 7.3 Hz, 3H). ^{13}C NMR, (100 MHz, $CDCl_3$) δ (ppm) 175.1, 137.2, 129.3, 128.4, 126.4, 102.0, 99.1, 82..2, 69.9, 68.9, 62.4, 55.4, 54.1, 54.0, 36.4, 31.2, 25.2, 22.2, 13.8. HR ESIMS calcd for $C_{20}H_{30}NO_6$ $[M+H]^+$ 380.2073, found 380.2071.

Compound 9. Method A. The product was obtained as a white solid at a yield of 84%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.49 (dd, *J* = 2.8, 6.4 Hz, 2H), 7.39 – 7.32 (m, 3H), 5.89 (d, *J* = 8.6 Hz, 1H), 5.55 (s, 1H), 4.71 (d, *J* = 3.8 Hz, 1H), 4.27 (dd, *J* = 2.7, 7.8 Hz, 1H), 4.25 – 4.18 (m, 1H), 3.88 (t, *J* = 9.6 Hz, 1H), 3.80 – 3.74 (m, 1H), 3.58 (t, *J* = 8.9 Hz, 1H), 3.39 (s, 3H), 2.26 – 2.20 (m, 2H), 2.16 (t, *J* = 7.0 Hz, 2H), 1.93 (t, *J* = 2.4 Hz, 1H), 1.62 (dd, *J* = 6.2, 13.0 Hz, 2H), 1.49 (dd, *J* = 7.1, 14.5 Hz, 2H), 1.29 (s, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.9, 137.3, 129.4, 128.5, 126.5, 102.1, 99.0, 82.3, 71.0, 69.1, 68.4, 62.6, 55.5, 54.2, 36.8, 29.4, 29.3, 29.1, 28.9, 28.6, 25.8, 18.6. HR ESIMS calcd for $C_{25}H_{36}NO_6$ $[M+H]^+$ 446.2543, found 446.2524.

Compound 10. Benzylamide. **Method B.** The product was obtained as a white crystalline solid at a yield of 92%. ^{1}H NMR ($CDCl_3$, 400MHz) δ (ppm) (rotamers) 7.71-7.66 (m, 3H), 7.40-7.35 (m, 3H), 7.34-7.28 (m, 2H), 7.25-7.20 (m, 2H), 7.11 and 7.02 (d, *J* = 7.7 Hz, 1H), 5.46 (s, 1H), 4.73 and 4.69 (d, *J* = 3.7 Hz, 1H), 4.24-4.14 (m, 1H), 4.07-4.01 (m, 1H), 3.87 (t, *J* = 9.9 Hz, 1H), 3.72 (td, *J* = 3.7, 10.6 Hz, 1H), 3.62 (dd, *J* = 8.8, 10.6, Hz, 1H), 3.51 (t, *J* = 9.2 Hz, 1H), 3.49-3.43 (m, 1H), 3.39 (t, *J* = 9.2 Hz, 1H),3.25 (s, 3H), 3.23-3.20 (m, 1H). ^{13}C NMR ($CDCl_3$, 100MHz) δ (ppm) (rotamers) 168.8, 136.9, 133.6, 131.6, 128.9, 128.3, 128.0, 127.0, 126.9, 126.0, 101.7, 98.8, 98.1, 81.8, 71.8, 71.6, 70.6, 68.7, 68.6, 55.154.8, 54.6, 54.1. HR ESIMS calcd for $C_{21}H_{24}NO_6$ $[M+H]^+$ 386.1604, found 386.1595.

Compound 11. Pyridinium acetamide. **Method C.** This product was isolated from reaction with bromoacetamide following displacement by pyridine. The product was obtained as a yellow solid at a yield of 88%. ^{1}H NMR ($CDCl_3$, 400MHz) δ (ppm) 8.88 (dd, *J* = 1.5, 5.5 Hz, 2H), 8.58 (tt, *J* = 1.5, 8.1 Hz, 1H), 8.07 (dd, *J* = 6.6, 7.7 Hz, 2H), 7.48-7.44 (m, 2H), 7.34-7.29 (m, 3H), 5.58 (s, 1H), 4.74 (m, 1H), 4.25-4.20 (m, 1H), 4.12 (dd, *J* = 3.7, 10.3 Hz, 1H), 3.98 (pt, *J* = 9.5, 9.9 Hz, 1H), 3.86-3.75 (m, 2H), 3.62 (t, *J* = 9.2 Hz, 1H), 3.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 100MHz) δ (ppm) 166.1, 147.2, 147.1, 138.5, 130.0, 129.0, 129.0, 128.7, 128.5, 127.4, 103.0, 100.1, 82.7, 70.1, 69.7, 63.8, 55.9. LR ESIMS calcd for $C_{21}H_{25}N_2O_6^+$ 401.2, found 401.2.

Compound 12. Method A. Isolated as a wet solid in 62% yield. ^{1}H NMR ($CDCl_3$, 400MHz) δ (ppm) 7.51-7.47 (m, 2H), 7.37-7.33 (m, 3H), 6.56 (d, *J* = 8.6 Hz, 1H), 5.54 (s, 1H), 4.70 (d, *J* = 3.7 Hz, 1H), 4.26 (td, *J* = 4.0, 9.2 Hz, 1H), 4.20 (dd, *J* = 3.7, 9.5 Hz, 1H), 3.90 (pt, *J* = 9.5, 9.9 Hz, 1H), 3.84-3.69 (m, 3H), 3.60 (t, *J* = 9.2 Hz, 1H), 3.47 (d, *J* = 1.1 Hz, 2H), 3.38 (s, 3H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$, 100MHz) δ (ppm) 171.2, 156.6, 137.3, 129.3, 128.4, 126.5, 102.0, 99.2, 81.8, 80.3, 69.8, 69.0, 62.8, 55.5, 54.1, 44.3, 28.4. HR ESIMS calcd for $C_{21}H_{31}N_2O_6$ $[M+H]^+$ 439.2080, found 439.2067.

Compound 13. Method B. The product was obtained as a white crystalline solid at a yield of 87%. m.p. 197.8-198.1°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.45-7.49 (m, 2 H), 7.32-7.37 (m, 3 H) 6.08 (d, J = 8.7 Hz, 1 H), 5.54 (s, 1 H), 4.69 (d, J = 3.8 Hz, 1 H), 4.25 (d, J = 5.3 Hz, 1 H), 4.15 (dd, J = 3.7, 10.2 Hz, 1 H), 3.87 – 3.79 (m, 1 H), 3.79 – 3.72 (m, 2 H), 3.55 (t, J = 9.0 Hz, 1 H), 3.37 (s, 3 H), 2.30 – 2.10 (m, 5 H), 1.60 (dt, J = 7.3, 14.9 Hz, 3 H), 1.27 (s, 7 H), 0.85 (t, J = 6.7 Hz, 3 H). ^{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, 53.9, 53.8, 36.6, 36.5, 31.4, 28.7, 25.5, 22.4, 14.0. HR ESIMS calcd for $C_{21}H_{32}NO_6$ $[M+H]^+$ 394.2230, found 394.2237.

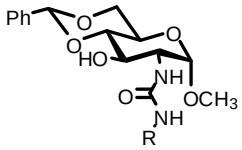
Compound 14. Method B. The product was obtained as a white crystalline solid at a yield of 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.53 – 7.49 (m, 2H), 7.42 – 7.33 (m, 3H), 5.86 (d, *J* = 8.6 Hz, 1H), 5.58 (s, 1H), 4.73 (d, *J* = 3.9 Hz, 1H), 4.29 (dd, *J* = 2.5, 7.8 Hz, 1H), 4.27 – 4.20 (m, 1H), 3.91 (t, *J* = 9.6 Hz, 1H), 3.79 (dd, *J* = 3.1, 8.5 Hz, 2H), 3.63 – 3.57 (m, 1H), 3.42 (s, 3H), 3.16 (s, 1H), 2.29 – 2.23 (m, 2H), 1.71 – 1.60 (m, 3H),

1.30 (dd, J = 4.9, 10.5 Hz, 10H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.75, 137.06, 129.17, 128.26, 126.30, 101.91, 98.77, 82.07, 70.95, 68.81, 62.27, 55.28, 53.99, 36.65, 31.66, 29.10, 28.97, 25.59, 22.59, 14.06. HR ESIMS calcd for $C_{22}H_{34}NO_6$ $[M+H]^+$ 408.2386, found 408.2395.

Compound 15. Method A. The product was obtained as a white crystal at a yield of 84%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46-7.49 (m, 2H), 7.36-7.32 (m, 3H), 5.82 (d, J = 8.8 Hz, 1H), 5.55 (s, 1H), 4.70 (d, J = 3.7 Hz, 1H), 4.28 – 4.25 (m, 1H), 4.21 (td, J = 3.9, 9.8 Hz, 1H) 3.88 (pt, J = 9.5, 9.9 Hz, 1H), 3.78 – 3.75 (m, 2H), 3.57 (pt, J = 8.8, 9.2 Hz, 1H), 3.39 (s, 3H), 3.11 (bs, 1H), 2.25 – 2.19 (m, 6H), 1.67 – 1.55 (m, 2H), 1.54 – 1.44 (m, 4H), 1.39 – 1.22 (m, 12H), 0.87 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100MHz) δ (ppm) 174.8, 137.0, 129.1, 128.2, 126.2, 101.8, 98.9, 82.0, 69.7, 68.7, 65.2, 65.1, 62.5, 55.2, 55.0, 53.9, 53.8, 36.4, 31.4, 30.9, 29.0, 28.8, 28.6, 28.2, 27.9, 25.5, 22.0, 19.0, 18.2, 14.0, 13.8. HR ESIMS calcd for C32H46NO6 [M+H]+ 540.3325, found 540.3308.

Formation of Ureas

The corresponding isocyanate and 50 mg of the O-4,6-benzylidene-2-amino-2-deoxy-α-methyl-D-glucopyranoside (**2**) were mixed at stochiometric amounts in 0.8-1.0ml THF in a 1 dram vial with a screw cap. After the reaction has gelled, the vial was heated with a heat gun until all material has dissolved. ^{1}H NMR was done in d_6-DMSO. Yields for all compounds synthesized in this library are quantitative. A portion of the β-anomer of compound **2** was reacted with the 4-bromophenyl isocyanate to yield **19β**.



$H_3C(CH_2)_6$-	$H_3C(CH_2)_4$-	$H_3C(CH_2)_5$-	4-Br-Phenyl-	1-Naphthyl-
16	**17**	**18**	**19**	**20**
Phenyl-	2-Cl-Ethyl-	2-Ethyl methacrylate-	2-Hydroxyethyl-	Cyclohexyl-
21	**22**	**23**	**24**	**25**

Compound 16. Isolated as a light yellow solid. ^{1}H NMR (400 MHz, DMSO) δ (ppm) 7.47–7.40 (m, 2H), 7.39–7.32 (m, 3H), 6.04 (t, *J* = 5.4 Hz, 1H), 5.78 (d, *J* = 8.4 Hz, 1H), 5.61–5.57 (m, 1H), 5.21 (d, *J* = 5.0 Hz, 1H), 4.60 (d, *J* = 3.2 Hz, 1H), 4.15 (dd, *J* = 4.6, 9.8 Hz, 1H), 3.76–3.67 (m, 2H), 3.65 (dd, *J* = 3.1, 8.8 Hz, 1H), 3.61–3.53 (m, 2H), 3.53–3.41 (m, 2H), 3.28 (s, 3H), 2.96 (dd, *J* = 6.3, 12.5 Hz, 2H), 1.52–1.06 (m, 10H), 0.84 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 157.93, 137.78, 128.87, 128.02, 126.42, 100.88, 99.53, 82.02, 68.53, 68.07, 62.53, 54.74, 54.63, 40.14, 39.93, 39.72, 39.51, 39.30, 39.20, 39.09, 38.89, 31.31, 29.98, 28.49, 26.41, 22.08, 13.97. HR ESIMS calcd for $C_{22}H_{35}N_2O_6$ $[M+H]^+$ 423.2495, found 423.2500.

Compound 17. Isolated as a light yellow solid. ^{1}H NMR, (400 MHz, d_6-DMSO) δ (ppm) 7.47-7.43 (m, 2H), 7.39-7.35 (m, 3H), 6.08 (t, *J* = 5.1 Hz, 1H), 5.82 (d, *J* = 8.4 Hz, 1H), 5.60 (s, 1H), 5.23 (d, *J* = 4.8 Hz, 1H), 4.62 (d, *J* = 3.7 Hz, 1H), 4.17 (dd, *J* = 4.8, 9.9 Hz, 1H), 3.73 (pt, *J* = 9.9, 10.3 Hz, 1H), 3.70 (td, *J* = 3.7, 9.2 Hz, 1H), 3.59 (td, *J* = 4.8, 9.2 Hz, 1H), 3.56- 3.50 (m, 1H), 3.48 (pt, *J* = 8.4, 9.2 Hz, 1H), 3.30 (s, 3H), 2.98 (q, *J* = 6.6 Hz, 2H), 1.32-1.40 (p, *J* = 6.6 Hz, 2H), 1.32 -1.20 (m, 4H), 0.86 (pt, *J* = 6.6, 7.0 Hz, 3H). ^{13}C NMR, (100 MHz, d_6-DMSO) δ (ppm) 157.6, 137.4, 128.5, 127.7, 126.1, 100.5, 99.2, 81.7, 68.2, 67.7, 62.2, 54.4, 54.3, 38.8, 29.3, 28.3, 21.6, 13.6. HR ESIMS calcd for $C_{20}H_{31}N_2O_6$ $[M+H]^+$ 395.2182, found 395.2196.

Compound 18. Isolated as a light yellow solid. m.p. 183.7-184.1°C. ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 7.47-7.43 (m, 2H), 7.39-7.35 (m, 3H), 6.07 (t, *J* = 5.5 Hz, 1H), 5.80 (d, *J* = 8.4 Hz, 1H), 5.60 (s, 1H), 5.22 (bs, 1H), 4.62 (d, *J* = 3.7 Hz, 1H), 3.73 (t, *J* = 10.3 Hz, 1H), 4.17 (dd, *J* = 4.8, 9.9 Hz, 1H), 3.72-3.66 (m, 1H), 3.55-3.62 (m, 1H), 3.49 (pt, *J* = 8.8, 9.9 Hz, 1H), 3.30 (s, 3H), 2.98 (q, *J* = 6.2 Hz, 2H), 1.35 (p, *J* = 6.6 Hz, 2H), 1.25 (bs, 6H), 0.86 (pt, *J* = 6.6, 7.0 Hz, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) 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, 39.1, 31.0, 29.8, 26.0, 22.0, 13.8. HR ESIMS calcd for $C_{21}H_{33}N_2O_6$ $[M+H]^+$ 409.2339, found 409.2355.

Compound 19β. Isolated as a light orange solid. ^{1}H NMR, (400 MHz, d_6-DMSO) δ (ppm) 8.12 (d, *J* = 7.7 Hz, 1H), 7.81 (s, 1H), 7.54 (dd, *J* = 1.5, 8.1 Hz, 1H), 7.43-7.47 (m, 2H), 7.35-7.39 (m, 3H), 7.21-7.29 (m, 2H), 6.87 (td, *J* = 1.5, 7.7 Hz, 1H), 5.61 (s, 1H), 5.42 (bs, 1H), 4.44 (d, *J* = 8.4 Hz, 1H), 4.22 (dd, *J* = 4.0, 9.9 Hz, 1H), 3.71-3.77 (m, 1H), 3.56-3.62 (m, 1H), 3.40-3.47 (m, 3H), 3.67 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 154.8, 137.9, 137.8, 132.4, 128.9, 18.0, 126.4, 123.0, 121.0, 111.6, 102.8, 100.7, 81.4, 70.8, 67.9, 65.8, 56.1. HR ESIMS calcd for $C_{21}H_{24}N_2O_6Br$ $[M+H]^+$ 479.0818, found 479.0836.

Compound 19α. Isolated as a light orange solid. ^{1}H NMR, (400 MHz, d_6-DMSO) δ (ppm) 8.12 (d, *J* = 7.7 Hz, 1H), 7.81 (s, 1H), 7.54 (dd, *J* = 1.5, 8.1 Hz, 1H), 7.43-7.47 (m, 2H), 7.35-7.39 (m, 3H), 7.21-7.29 (m, 2H), 6.87 (td, *J* = 1.5, 7.7 Hz, 1H), 5.61 (s, 1H), 5.42 (bs, 1H), 4.44 (d, *J* = 8.4 Hz, 1H), 4.22 (dd, *J* = 4.0, 9.9 Hz, 1H), 3.71-3.77 (m, 1H),

3.56-3.62 (m, 1H), 3.40-3.47 (m, 3H), 3.67 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 154.8, 137.9, 137.8, 132.4, 128.9, 18.0, 126.4, 123.0, 121.0, 111.6, 102.8, 100.7, 81.4, 70.8, 67.9, 65.8, 56.1. HR ESIMS calcd for $C_{21}H_{24}N_2O_6Br$ $[M+H]^+$ 479.0818, found 479.0836.

Compound 20. Isolated as a light yellow solid. ^{1}H NMR, (400 MHz, d_6-DMSO) δ (ppm) 8.10 (dd, J = 1.5, 8.1 Hz, 1H), 8.05 (s, 1H), 7.43-7.47 (m, 2H), 7.53 (dd, J = 1.5, 7.7 Hz, 1H), 7.35-7.49 (m, 3H), 7.23-7.30 (m, 2H), 6.88 (td, J = 1.5, 7.7 Hz, 1H), 5.63 (s, 1H), 5.33 (d, J = 5.9 Hz, 1H), 4.72 (d, J = 3.7 Hz, 1H), 4.20 (dd, J = 4.8, 9.9 Hz, 1H), 3.80 (m, 1H), 3.76 (t, J = 10.3 Hz, 1H), 3.62 (m, 3H), 3.52 (m, 2H), 3.37 (m, 1H), 3.35 (s, 3H). ^{13}C NMR, (100 MHz, d_6-DMSO) 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. HR ESIMS calcd for $C_{21}H_{24}N_2O_6Br$ $[M+H]^+$ 479.0818, found 479.0808.

Compound 21. Isolated as a light yellow solid. m.p. >300°C. ^{1}H NMR, (400 MHz, d_6-DMSO) δ (ppm) 8.63 (s, 1H), 7.47-7.43 (m, 2H), 7.40-7.34 (m, 5H), 7.20 (pt, J = 7.7, 8.1 Hz, 2H), 6.87 (pt, J = 7.0, 7.3 Hz, 1H), 6.14 (d, J = 8.8 Hz, 1H), 5.61 (s, 1H), 5.32 (bs, 1H), 4.69 (d, J = 3.3 Hz, 1H), 4.18 (dd, J = 4.8, 9.9 Hz, 1H), 3.81-3.72 (m, 2H), 3.62 (td, J = 4.4, 9.2 Hz, 1H), 3.51 (t, J = 8.8 Hz, 1H), 3.32 (s, 1H),. ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 154.6, 140.0, 137.4, 128.5, 128.4, 127.7, 126.1, 120.7, 117.0, 100.5, 99.0, 81.5, 68.1, 67.7, 62.3, 54.4, 53.9. HR ESIMS Calcd for $C_{21}H_{25}N_2O_6$ $[M+H]^+$ 401.1713, found 401.1726.

Compound 22. Isolated as a light yellow solid. m.p. 184.1°C (dec). ^{1}H NMR, (400 MHz, d_6-DMSO) δ (ppm) 7.46-7.42 (m, 2H), 7.39-7.34 (m, 3H), 6.36 (t, *J* = 5.9 Hz, 1H), 6.08 (d, *J* = 8.4 Hz, 1H), 5.58 (s, 1H), 5.20 (bs, 1H), 4.61 (d, *J* = 3.7 Hz, 1H), 4.16 (dd, *J* = 4.8, 9.9 Hz, 1H), 3.65-3.75 (m, 2H), 3.61-3.48 (m, 6H), 3.46 (pt, *J* = 8.8, 9.2 Hz, 1H), 3.31 (m, 3H), 3.28 (s, 3H). ^{13}C NMR, (100 MHz, d_6-DMSO) δ (ppm) 157.3, 137.4, 128.5, 127.7, 126.1, 100.6, 99.1, 81.7, 68.0, 67.7, 62.2, 54.4, 54.3, 44.4, 41.1. HR ESIMS calcd for $C_{17}H_{24}N_2O_6Cl$ $[M+H]^+$ 387.1323, found 387.1335.

Compound 23. Isolated as a light yellow solid. m.p. 198.8-200.1°C. ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 7.47 – 7.43 (m, 2H), 7.40 – 7.36 (m, 3H), 6.25 (t, *J* = 5.5 Hz, 1H), 6.08 (s, 1H), 6.01 (d, *J* = 8.8 Hz, 1H), 5.70 (pt, *J* = 1.83, 1.47, 1H), 5.60 (s, 1H), 5.22 (d, *J* = 5.1 Hz, 1H), 4.62 (d, *J* = 3.7 Hz, 1H), 4.17 (dd, *J* = 4.8, 9.9 Hz, 1H), 4.08 – 4.04 (m, 2H), 3.76 – 3.66 (m, 2H), 3.62 – 3.54 (m, 2H), 3.54 – 3.45 (m, 2H), 3.30 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 166.4, 157.7, 137.7, 135.7, 128.8, 127.9, 126.3, 125.8, 100.8, 99.4, 81.9, 68.2, 68.0, 64.2, 62.4, 54.6, 54.6, 38.1, 17.9. HR ESIMS calcd for $C_{21}H_{29}N_2O_8$ $[M+H]^+$ 437.1924, found 437.1944.

Compound 24. Isolated as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 7.46 – 7.42 (m, 2H), 7.39 – 7.35 (m, 3H), 6.26 (t, *J* = 5.5 Hz, 1H), 6.13 (d, *J* = 8.1 Hz, 1H), 5.59 (s, 1H), 5.33 (bs, 1H), 4.61 (d, *J* = 3.3 Hz, 1H), 4.16 (dd, *J* = 4.4, 9.9 Hz, 1H), 3.75 – 3.63 (m, 2H), 3.61 -3.55 (m, 2H), 3.54 – 3.42 (m, 2H), 3.40-3.32 (m, 2H), 3.29 (s, 3H), 3.05 (q, *J* = 5.5 Hz, 2H) HR ESIMS calcd for $C_{17}H_{25}N_2O_7$ $[M+H]^+$ 369.1662, found 369.1677.

Compound 25. Isolated as a light yellow solid. m.p. 210°C (dec). ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 7.45-7.41 (m, 2H), 7.38-7.34 (m, 3H), 6.03 (d, J = 7.8 Hz, 1H), 5.73 (d, J = 8.4 Hz, 1H), 5.58 (s, 1H), 5.21 (d, J = 4.8 Hz, 1H), 4.61 (d, J = 3.5 Hz, 1H), 4.15 (dd, J = 4.7, 9.9 Hz, 1H), 3.74 – 3.67 (m, 1H), 3.75 – 3.63 (m, 2H), 3.61 – 3.53 (m, 1H), 3.48 – 3.41 (m, 1H), 3.34 (s, 3H), 1.72 (dd, J = 4.0, 8.1 Hz, 2H), 1.61 (dd, J = 4.0, 8.8 Hz, 2H), 1.49 (dd, J = 3.7, 8.3 Hz, 1H), 1.30 – 0.97 (m, 4H). ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 157.3, 137.8, 128.9, 128.0, 126.4, 100.9, 99.5, 82.0, 68.6, 68.1, 62.5, 54.7, 54.6, 47.7, 33.3, 25.3, 24.4. HR ESIMS calcd for $C_{21}H_{31}N_2O_6$ $[M+H]^+$ 407.2182, found 407.2191.

References

1. Wang, G.; Cheuk, S.; Williams, K.; Sharma, V.; Dakessian, L.; Thorton, Z. *Carbohyd. Res.* **2006**, *341*, 705-716.

2. Cheuk, S.; Stevens, E.; Wang, G. *Carbohyd. Res*. **2008**. *Submitted*.

3. Nie, X.; Wang, G. *J. Org. Chem.* **2006**. *71*, 4734-4741.

4. Fraser, J. R.; Laurent, T. C.; Laurent, U. B. *J. Intern. Med.* **1997**, *242*, 27-33.

5. Knudson, C. B.; Knudson, W. *Semin. Cell Dev. Biol.* **2001**, *12*, 69-78.

6. Shu, X. Z.; Liu, Y.; Luo, Y.; Roberts, M. C.; Prestwich, G. D. *Biomacro.* **2002,** *3*, 1304-1311.

7. Luo, Y.; Prestwich, G. D. *Bioconjugate Chem.* **1999**, *10*, 755-763.

8. Lee, H.; Lee, K.; Park, T. G. *Bioconjugate Chem.* **2008**, ASAP Article.

9. Information obtained from http://en.wikipedia.org/wiki/Keratan_sulfate on May 16, **2008**.

10. de Loos, M.; van Esch, J.; Stokroos, I.; Kellogg, R. M.; Feringa, B. L. *J. Am. Chem. Soc.* **1997**, *119*, 12675-12676.

11. Wurthner, F.; Hanke, B.; Lysetska, M.; Lambright, G.; Harms, G. S. *Org. Lett.* **2005**, *7*, 967-970.

12. Wang, C.; Zhang, D.; Zhu, D. *J. Am. Chem. Soc.* **2005**, *127*, 16372-16373.

13. Barboiu, M.; Cerneaux, S.; van der Lee, A.; Vaughan, G. *J. Am. Chem. Soc*. **2004**, *126*, 3545-3550.

14. Dautel, O. J.; Robitzer, M.; Lere-Porte, J.-P.; Serein-Spirau, F.; Moreau, J. J. E. *J. Am. Chem. Soc.* **2006**, *128*, 16213-16223.

15. Vince, J.; Orel, B.; Vilcnik, A.; Fir, M.; Surca Vuk, A.; Jovanovski, V.; Simoncic, B. *Langmuir*. **2006**, *22*, 6489-6497.

16. Zhou, Y.; Yi, T.; Li, T.; Zhou, Z.; Li, F.; Huang, W.; Huang, C. *Chem. Mater.* **2006**, *18*, 2974-2981.

17. Wang, G.; Hamilton, A. D. *Chem. Eur J.* **2002**, *8*, 1954-1961.

18. Suzuki, M.; Nakajima, Y.; Yumoto, M.; Kimura, M.; Shirai, H.; Hanabusa, K. *Org. Biomol. Chem*. **2004**, *2*, 1155-1159.

19. Willemen, H. M.; Vermonden, T.; Marcelis, A. T. M.; Sudhölter, E. J. R. *Langmuir.* **2002,** *18,* 7102-7106.

20. Kim, C.; Kim, K. T.; Chang, Y.; Song, H. H.; Cho, T.-Y.; Jeon, H.-J. *J. Am. Chem. Soc.* **2001**, *123*, 5586-5587.

21. Jung, J. H.; John, G.; Yoshida, K.; Shimizu, T. *J. Am. Chem. Soc.* **2002**, *124*, 10674-10675.

22. Frkanec, L.; Jokic, M.; Makarevic, J.; Wolsperger, K.; Zinic, M. *J. Am. Chem. Soc.* **2002**, *124*, 9716-9717.

23. Yabuuchi, K.; Rowan, A. E.; Nolte, R. J. M.; Kato, T. *Chem. Mater.* **2000**, *12*, 440-443.

24. Bhuniya, S.; Park, S. M.; Kim, B. H. *Org. Lett.* **2005**, 7, 1741-1744.

25. Imae, T.; Gagel, L.; Tunich, C.; Platz, G.; Iwamoto, T.; Funayama, K. *Langmuir*. **1998**, *14*, 2197-2200.

26. Lampkins, A. J.; Abdul-Rahim, O.; Li, H.; Castellano, R. K. *Org. Lett.* **2005**, *7*, 4471-4474.

27. Tomioka, K.; Sumiyoshi, T.; Narui, S.; Nagaoka, Y.; Iida, A.; Miwa, Y.; Taga, T.; Nakano, M.; Handa, T. *J. Am. Chem. Soc.* **2001**, *123*, 11817-11818.

28. Suzuki, M.; Yumoto, M.; Kimura, M.; Shirai, H.; Hanabusa, K. *Chem. Commun.* **2002**, 884-885.

29. Maitra, U.; Mukhopadhyay, S.; Sarkar, A.; Rao, P.; Indi, S. S. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 2281-2283.

30. Newkome, G. R.; Baker, G. R.; Arai, S.; Saunders, M. J.; Russo, P. S.; Theriot, K. J.; Moorefield, C. N.; Rogers, L. E.; Miller, J. E.; Lieux, T. R.; Murray, M. E.; Phillips, B.; Pascal, L. *J. Am. Chem. Soc.* **1990**, *112*, 8458-8465.

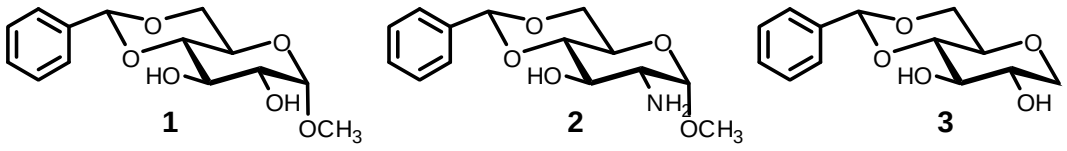
31. Nakashima, T.; Kimizuka, N. *Adv. Mater.* **2002**, *14*, 1113-1116.

32. Voet, D.; Voet, J.; Pratt, C. *Fundamentals of Biochemistry (Upgrade Edition)*. Ed. David Harris, John Wiley & Sons, Inc. **2002**, 126.

Chapter 4. 1-Deoxy-D-Glucopyranoside-based low molecular weight organogelators and potential applications of organogelators derived from glucose and glucosamine

Abstract

Depending on the targeted use of gels, the discovery aspect in the field of low molecular weight gelators, relies heavily on the availability (or natural abundance) of the starting material. Previously, new gelators were discovered from D-glucose derivative **1** and D-glucosamine derivative **2**. To further explore the role of the oxygens within the sugar ring in formation of the hydrogen bond network, the 1-methoxy group was replaced with a hydrogen (3).



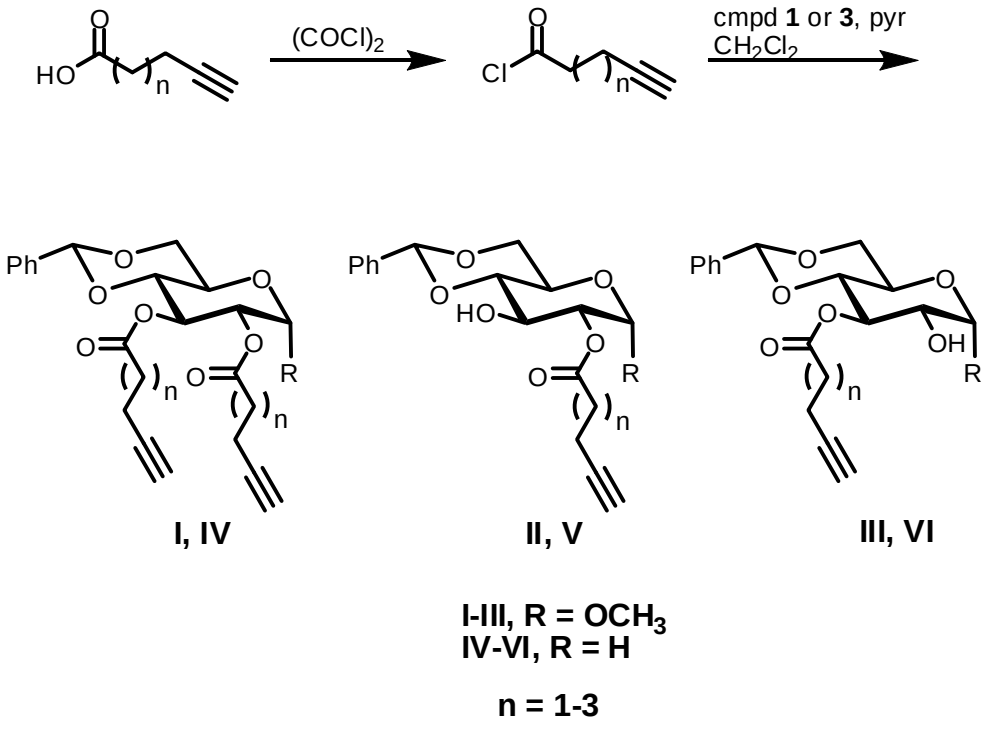
Terminal alkynyl ester (TAE) derivatives of compound **3** were synthesized and characterized. Compared to the TAE derivatives of compound **1**, derivatives of compound **3** were not efficient gelators. The 1-methoxy group may be necessary in the formation of a hydrogen bonding network necessary to form a gel. A fluorescence study was conducted to test for the presence of hydrophobic pockets. These gels will be applied to enzymatic assays, where enzymes will be entrapped in a matrix formed by carbamate gelators.

Introduction

The structure-gelation relationships of the various methyl-O-4,6-benzylidene-D-hexopyranosides were extensively studied by Shinkai and coworkers.[1-5] The study was to determine what roles the positions of the hydroxyls or functionalized hydroxyls would in the gelation of various organic solvents and water. All of the α anomer and some of the β anomer derivatives were tested for gelation abilities. The studies concluded with the mannose and galactose derivatives being the more effective gelators. In addition, the sugar derivatives with the 3-position (allose, altose, gulose, and idose) at the axial position did not produce any organo or hydrogelators. Presumably, the axial 3-hydroxyl is involved in intramolecular hydrogen bonding and took away a hydrogen bond donor necessary for forming a hydrogen bonding array, an essential characteristic of LMOGs. One of the focuses of the intramolecular hydrogen bonding was the 1-methoxy position. By flipping the anomeric position of the mannose derivative to the β anomer, Shinkai, et al observed a large increase (from the α anomer) in gelation ability.[3] This observation poses a question in regards to the structure gelation relationship of the 1-methoxy group: Did the methoxy group move to a more favorable position or was the methoxy group an obstruction at the α position? The objective of this study will determine the latter part of this question.

Of the α-methoxy derivatives, the terminal alkynyl esters with 5-7 carbons were the most efficient and versatile gelators, gelating both hexane and water. By replacing the α-methoxy group with a hydrogen, hydrogen bonding will not be available at that position. Compound **3** was synthesized from a 4-5 step reaction sequence carried out by members

of Dr. Wang's research group from D-glucose.[6] The terminal alkynyl acid chlorides of 5-7 carbons long were chosen to complement the α-methoxy analogs.



Scheme 4.1. Synthesis of terminal alkynyl esters of compounds **1** and **3**.

The second part of this chapter deals with the applications of all gelators studies in this thesis. Molecules from previous chapters were used in the formation of aqueous gels. Compound **9** from the carbamate library was chosen because of the relative clarity of the gel compared to the others, which allowed light to pass through to be read by the detector in the spectrometer.

Results and Discussion

The synthesis of compounds **4-6** (**a-c**) were synthesized using the same reaction conditions used to synthesize the ester derivatives of compound **1**, except that compound **3** was used. The best gelators from the library terminal acetylene esters (TAEs) of compound **1** from Dr. Wang's group previously were 5-7 carbons long.[6] Any longer or shorter results generally in precipitation or increased solubility. Any analogs of the TAE's (branched, heteroatoms, or saturated), usually resulted in no gelation.[7] By giving a direct comparison, the structure gelation relationship in regard to the TAE gelator library can be elucidated.

The synthetic yields reported in **Table 4.1** are isolated yields for pure products. In contrast to the reaction yields of compound **1**, where the 2-ester was the major product, the isolated yields of the 2 and 3-esters of compound **3** does not give a discernable major product. Instead, the 2 and 3-esters come out in similar quantities and, in some cases, the 3-ester is the major product. In the synthesis of the α-methoxy esters, the 2-ester was the major product, possibly because of the configurations of C-1 and C-2 positions. The positioning allows intramolecular hydrogen bonding to take place, which can make the 2-hydroxyl relatively more nucleophilic than the 3 position. In compound **3**, without the α-methoxy to hydrogen bond to the 2-hydroxyl, the 2 and 3-hydroxyls were more or less equally nucleophilic. The amount of diester was significantly less than the amounts of the 2 and 3 esters. This observation of diester formation mirrors the synthesis of the esters of compound **1**.

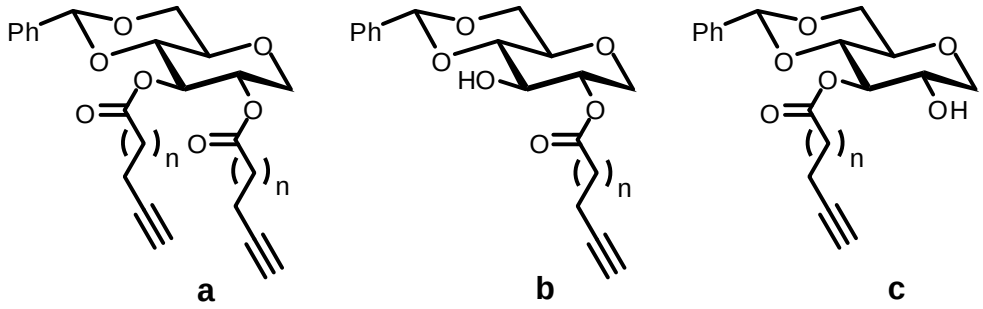


Table 4.1. Percent yields of acylation of compound **3** (unoptimized, pure isolated yields). The values of n for compound 4-6 are 1-3, respectively.

	a	**b**	**c**
4	9.1	14.6	23.0
5	4.5	16.3	19.5
6	3.3	21.5	20.1

Like the ester derivatives of compound **1**, these compounds were separated readily using hexanes and acetone (19:1 to 9:1). From the crude mixture on TLC (hexanes:acetone, 5:1), three spots can be seen, although the difference in the r.f. value for the 2 and 3-esters was less than .05. The diesters, with no free hydroxyl was the most nonpolar with the highest r.f. values. By NMR, the 2 and 3-esters were discerned by the position of the certain ^{1}H NMR (400 MHz, $CDCl_3$) signals (**Figure 4.2**). ^{1}H NMR signals for the methine group next to the unfunctionalized alcohols appear between 3.5 and 4.0 ppm. When these hydroxyls are esterfied, these protons shift ~0.5 ppm downfield from their respective positions to 4.0-4.5 ppm. The proton at the 2-position is coupling with the three neighboring protons, 2 axial (similar environments) and 1 equatorial, resulting in a ^{1}H NMR signal of a triplet of doublets. In contrast, the proton at the 3-position has two

neighboring axial protons in similar environments resulting in a triplet or a pseudo triplet (doublet of doublets). The ^{1}H NMR signals at 5.1 and 5.4 ppm of the diester bearing identical characteristics (coupling constants and integration values) to their monoester counterparts further justifies the use of these signals to discern the 2 and 3-esters.

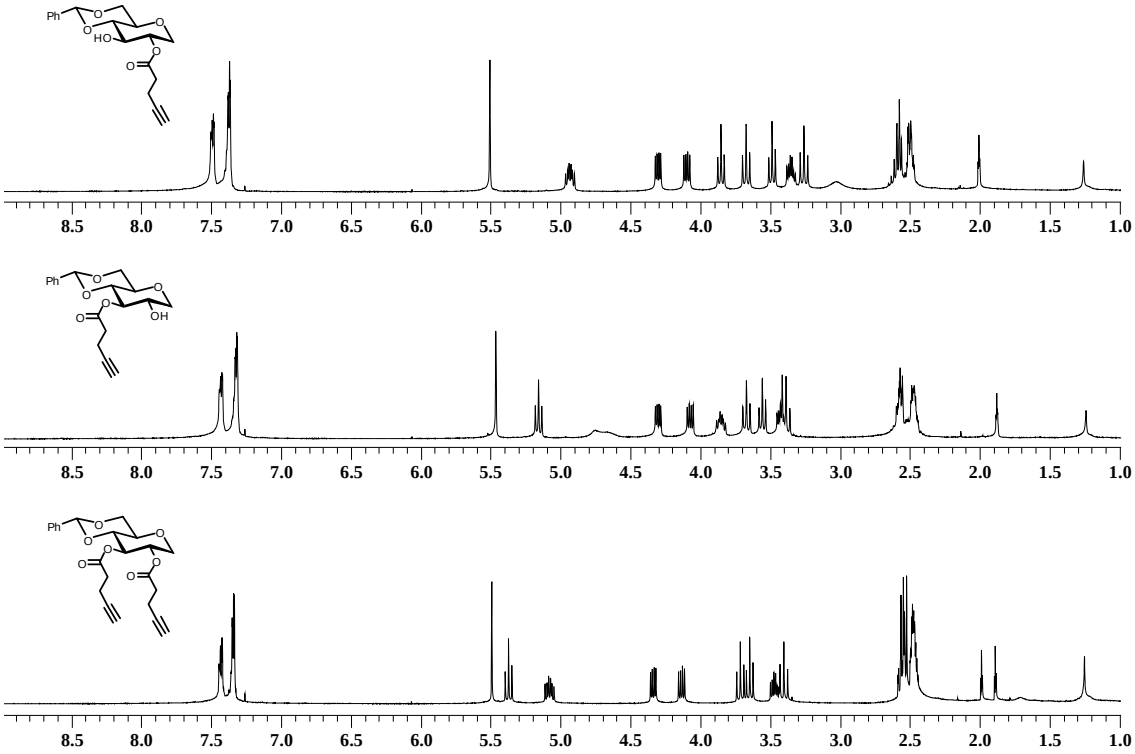


Figure 4.1. ^{1}H NMRs (400 MHz, $CDCl_3$) of the 4-pentynoate esters of compound **3.**

The gelation results for the TAE's of compound **3** are listed in **Table 4.2**. The diesters (**a**), 2-esters (**b**), and the 3-esters (**c**) gelated some solvents or mixtures. The diesters of 5-6 carbon derivatives (**4a** and **5a**) were able to gelate hexanes at about 1.0 wt%. Of the 2-esters, the 5 and 7 carbon esters (**4b** and **6b**) were able to form gels in a water:DMSO mixture (2:1). Only the 3-ester of the 5 carbon TAE (**4c**) was able to gelate pure water (20 mg/mL). As expected, the diesters, with no free hydroxyl, were insoluble in water.

The importance of a free hydroxyl, as pointed out earlier, proved to be essential as the 2 and 3-esters were able to gelate aqueous mixtures and pure water, respectively.

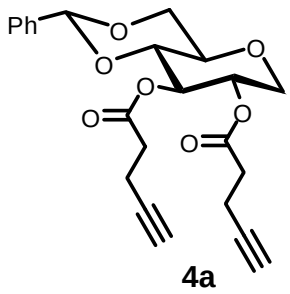
Table 4.2. Gelation results for terminal alkynyl esters of compound **3.** MGC is in mg/mL.

Compound	Hexane	Water	EtOH	DMSO:Water	EtOH:Water	C log P
4a	10	I	P	P	P	2.42
5a	10	I	S	P	P	3.08
6a	P	I	S	P	P	3.84
4b	P	I	S	6.7	S	0.99
5b	P	P	S	P	P	1.32
6b	P	P	S	6.7	P	1.70
4c	I	5.0	S	S	S	0.99
5c	P	I	S	P	P	1.32
6c	P	P	S	S	P	1.70

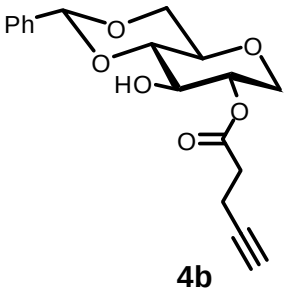
All concentrations in mg/mL;G, gel at room temperature; Gp, unstable gel; P, precipitation; S, soluble at ~20 mg/mL; ratio of solvents in ( ).

Compared to the gelation results of the terminal alkynyl esters of compound **1**,[6] under the same conditions, there was a some degree of decrease in gelation efficiency and ability. Take the example of the 4-pentynyl derivatives of compound **3** compared to its compound **1** analogs in **Table 4.3** (The 6 and 7 carbon analogs were synthesized by other members of Dr. Wang's group). The α-methoxy diester (**8a**) was able to gelate ethanol in

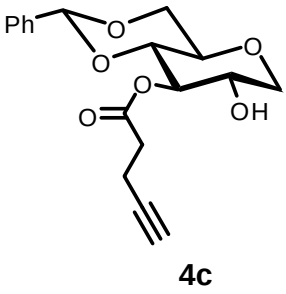
addition to hexane. For a more striking comparison, compound **4b** was insoluble in water, but its analog **8b** gelated at 4.0 mg/mL (0.40 wt%). Another significant difference is compound **8c**'s ability at less than 4 mg/mL to gelate both pure water and hexane.



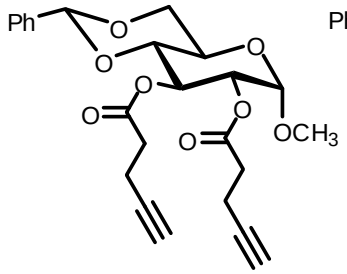
4a



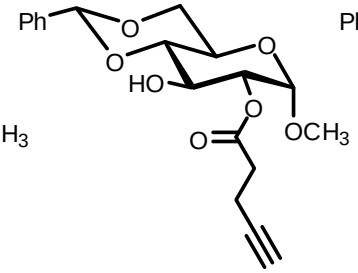
4b



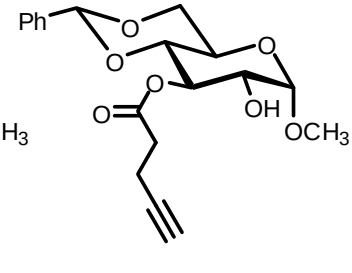
4c



8a



8b



8c

Table 4.3. Comparing 4-pentynyl derivatives of compounds **1(8a-c)** and **3(4a-c)**.

Compound	**Hexane**	**Water**	**EtOH**
4a	10	I	P
8a	5.0	I	20
4b	P	I	S
8b	10**	4.0	S
4c	I	5.0	S
8c	3.3	3.3	S

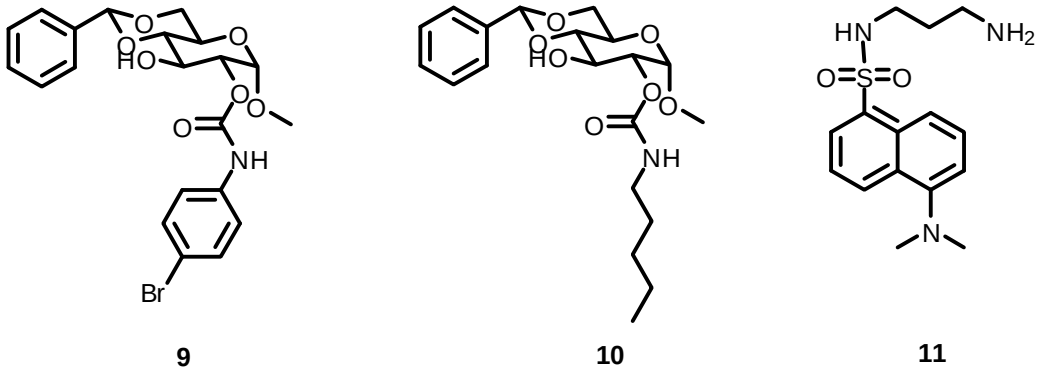
Further Characterization and applications of LMWGs

Fluorescence studies

The self-assembly of LMWGs in aqueous solvents is driven by the minimization of hydrophobic interaction with the solvent, which may result in the formation of hydrophobic pockets. These pockets, in turn, may have a variety of uses, such as a delivery system for drugs with poor bioavailability due to a high degree of hydrophobicity.[8] Conceptually, a gel could be formed to encapsulate a drug and upon exposure to biological or chemical triggers, the gel collapse and release the drug at or near the target area. Controlled release makes treatments more effective by lowering the overall, but increasing the effective concentration of the drug, leading to less potential side effects.

Fluorescence spectroscopy can be used to test the hydrophobic pockets. [8-19] Fluorophores are typically extensive aromatic or extensively conjugated compounds with several heteroatoms attached. As a result, most of these compounds are more soluble in organic solvents and only partially soluble in water. Hypothetically, the incorporation of the fluorophores into the hydrophobic regions should cause a change in the fluorescence properties of the fluorophore. Several LMWGs contain covalently linked fluorophores as a driving force in self-assembly through π-π stacking, which can be monitored by a shift in the fluorescence emission.

Compounds **9** and **10** were described in chapter 2, found to be excellent gelators in aqueous solvents, and had a lesser degree of opacity than the other gels formed. These compounds were used to form gels in ethanol and water (2:1) at 3 and 2 mg/mL, respectively (**Figures 4.3** and **4.4**). The fluorophore used is N-(3-aminopropyl)-5-(dimethyl-amino)-naphthalene-1-sulfonamide (3-aminopropyl-dansylamide, **11**). The excitation and emission were monitored separately for each compound during the sol-gel transition. The excitation wavelength remained constant at 360 nm (lit. 362 nm) in gels of compounds **9** and **10** across the sol-gel transition. However, in the sol-gel transition of compound **9** the emission wavelength (λ_{max} = 528 nm) and intensity varied.



9 **10** **11**

Figure 4.2. The gels of compounds **9** and **10** were used to study the effects on the fluorescence spectra of DANS derivative **11**.

Compound **9** had an additional excitation (325 nm) and emission peaks (712 nm) due to the 4-bromophenyl substituent as these peaks are not present in the fluorescence spectra of compound **10**. The emission spectra of the DANS derivative **11** in the gel of

compound **9** not only showed an expected decrease in the intensity of the fluorescence (599 to 515, 14%), but λ_{max} of **11** had a red shift of 8 nm. The decrease in intensity could be due to the fluorescence being scattered in the gel as the gel becomes occluded when it forms and less signal reaches the detector. However, the wavelength shift may be caused by the assimilation of the fluorophore into the matrix of compound **9**. The red shift is most likely due to the partial absorption of the energy by the surrounding matrix or the π-π stacking of the self-assembly of **9**.

On the other hand, the gel of compound **10** does not have an additional phenyl ring and the fluorophore (**11**) did not show any shift in the emission spectra. However, a secondary peak at 692 nm does show an interesting trend. The intensity of the peak at 692 nm decreases as much as 75% upon cooling, but when the gel is fully formed, the intensity at 692 nm goes back up. The secondary peak is most likely caused by fluorescence resonance energy transfer (FRET). The decrease of the secondary fluorescence intensity and the subsequent increase is most likely due to the process of self-assembly of compound **10**.

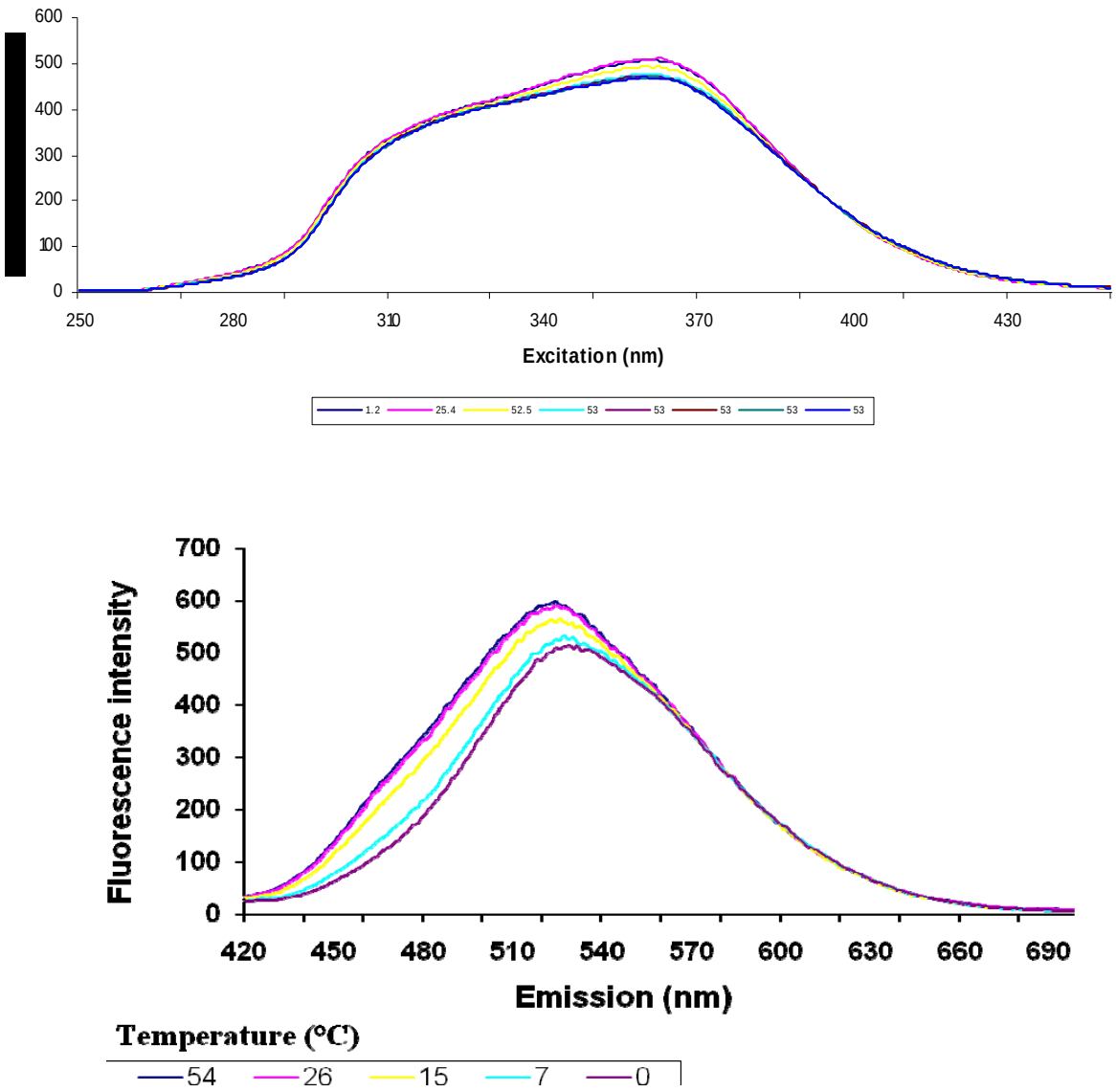


Figure 4.3. Exictation (above) and emission (below) spectra of compound **11** during the sol-gel transition of compound **9**.

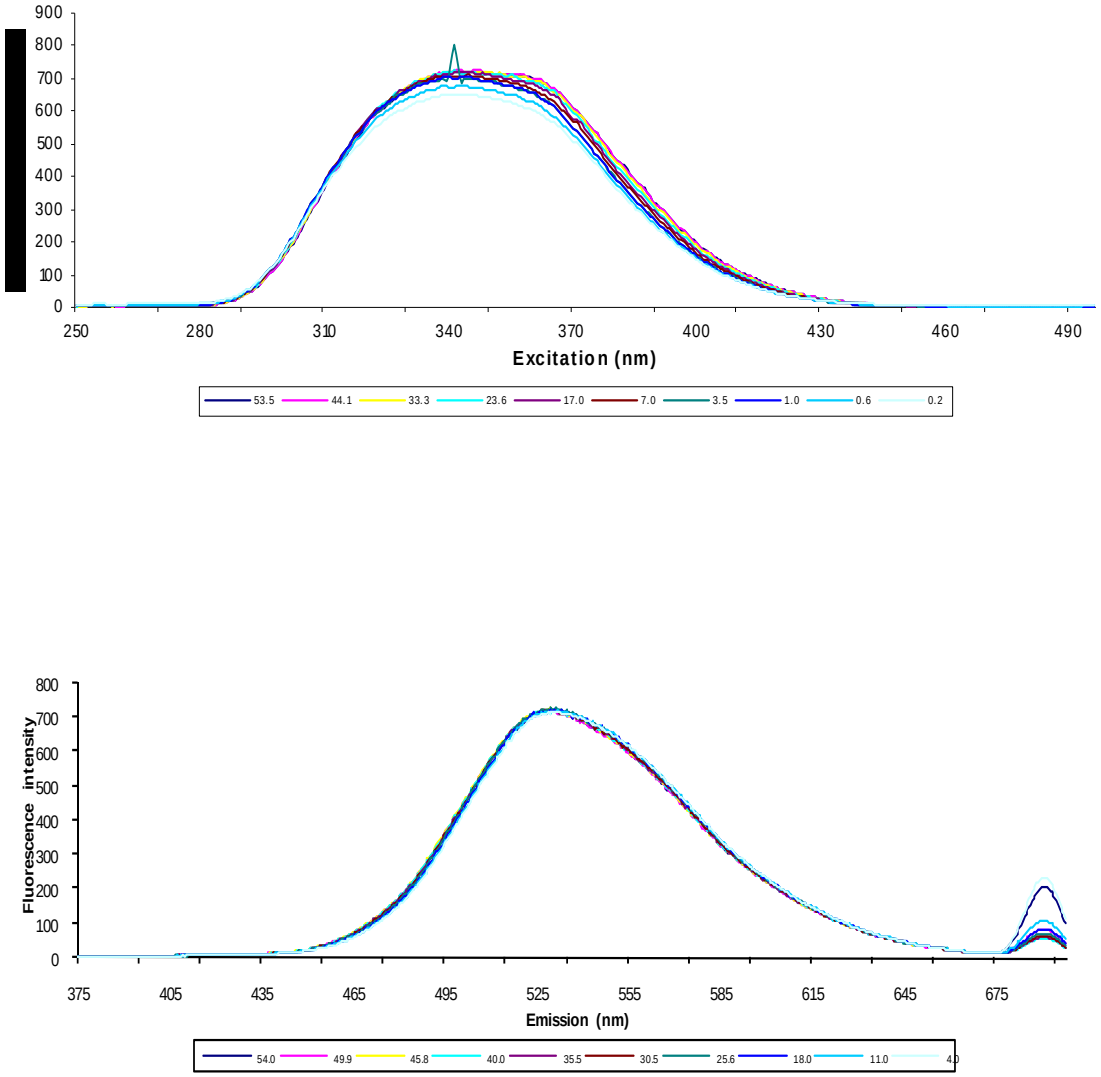


Figure 4.4. Excitation (above) and emission (below) spectra of compound **11** during the sol-gel transition of compound **10**.

Trypsin Inhibition Assay

The immobilization of enzymes in both polymer and low-molecular weight gels has been reported to both decrease and increase enzymatic activity.[20-24] If an enzyme were to retain its activity in a LMWG matrix, a semi-solid enzymatic assay could be used to analyze a variety of enzymes.[21] Instead of running a battery of blood tests or water samples, a small chip containing pertinent enzymes could be soaked in a sample and on site results would be available instead of sending and waiting for lab results allowing for onsite diagnostics.

In this experiment, a serine protease, trypsin, was used in an enzymatic fluorescence assay. A p-nitroanilide containing amino acid was used as the substrate. The release of the p-nitroaniline (λ_{abs} = 405 nm) as a result of cleavage by trypsin is monitored by a spectrophotometer. The inhibitor used was a high molecular weight protein isolated from egg white. Compound **10** was used because of the relative optical clarity and its unique morphological characteristics seen under optical microscopy. From **Figure 4.5**, the maximum and minimum absorbance at 405 nm were added and divided in half to obtain the IC_{50}. The experimental IC_{50}'s for the liquid and gel assays were 4.22 and 13.2 mg/mL, respectively. The differences in the gel assay results are possibly due to the clarity of the gel and the slow diffusion rate of the inhibitor (due to its size). There are still many questions and experiments to do such as varying the types of inhibitor and the different gels present in our gelator library.

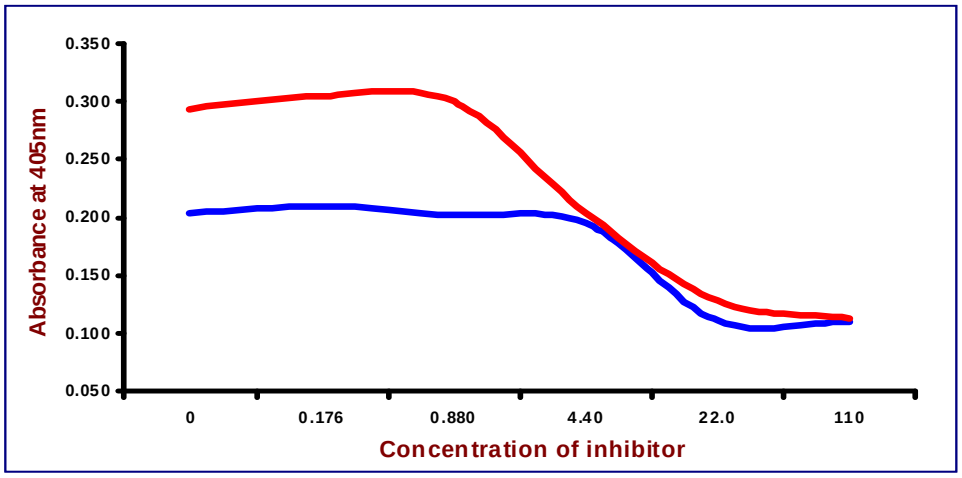


Figure 4.5. Comparative analysis of the inhibition of trypsin in liquid (red) and gel (blue) phases. Gel created from compound **10** in aqueous DMSO. IC_{50}'s, based on absorbance, are 4.22 mg/mL and 13.2 mg/mL, respectively.

Conclusion

The results show that the oxygen at the 1 position of D-glucose, plays an important role in the formation of a hydrogen bond network by ester derivatives of compound **1**. In this case, the TAE gelators need the 1-methoxy group. Whether this plays a different role in the 1-deoxy carbamates remain to be seen. One hurdle in the synthesis of these compounds is the purification. Methods are currently being worked out to figure the purification out.

The preliminary applications, fluorescence spectrometry and enzyme assay, already showed some promising results. The fluorescence spectrometry showed that there is some sort of hydrophobic domain within the gel matrix and domain could be used to store hydrophobic compounds of an important nature. The gel-based enzymatic assay did not show any significant difference in the IC_{50}, but much more experiments are needed to observe to utility of these gel systems, these are essential prior to use in the formation of an enzymatic array.

Experimental Section

Fluorescence spectroscopy. A Perkin Elmer LS 55 Luminescence Spectrometer coupled with a VWR Scientific Model 1160A water heater was used to monitor fluorescence during sol-gel and gel-sol transition. Dansyl amide **11** was dissolved in DMSO at a concentration of 1 mg/mL before being serially diluted to a concentration of 0.1 mg/mL. Gels of compounds **9** and **10** were formed directly in the cuvette in DMSO containing compound **11** at 3 and 2 mg/mL, respectively (final concentration of compound **11** is 0.033 mg/mL).

Trypsin Assay. The following materials were purchased from Sigma and used without further purification: trypsin, Nα-benzoyl-DL-arginine-4-nitroanilide HCl, polyethylene glycol 6000, Hepes buffer, Tris base, tween 20, trypsin inhibitor (T9253). The fluorescence assay was conducted on a FL_x800 Microplate Fluorescence Reader from Bio-tek Instruments, Inc. KC junior in conjunction with Microsoft Excel XP was used to process the data from the reader.

Synthesis of Ester derivatives of compound **1**

Compounds **4-6 a-c** were synthesized by converting the corresponding terminal alkynyl carboxylic acid to the acyl chloride using excess of oxalyl chloride. After confirming complete conversion to the acyl chloride, hexane was used to codistill the excess oxalyl chloride. The acyl chloride was then mixed with compound **1** in 5 mL of DCM and 4 equivalents of pyridine were used. The reaction stirred for 20 hours. After washing with distilled water (2 x 2 mL) and brine and drying over anhydrous sodium sulfate, the crude

product was purified using hexanes and acetone (19-7:1). All yields reported are pure isolated yields.

4-Pentynyl esters (4 a-c)

Compound 4a. This product was isolated as a white crystalline solid at a yield of 9.1%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43-7.39 (m, 2H), 7.35-7.31 (m, 3H), 5.47 (s, 1H), 5.35 (t, *J* = 9.5 Hz, 1H), 5.09-5.02 (m, 1H), 4.32 (dd, *J* = 4.8, 10.3 Hz, 1H), 4.11 (dd, *J* = 5.9, 11.0 Hz, 1H), 3.69 (t, *J* = 10.3 Hz, 1H), 3.63 (t, *J* = 9.5 Hz, 1H), 3.45 (td, *J* = 4.8, 9.5 Hz, 1H), 3.38 (t, *J* = 11.0 Hz, 1H), 2.57-2.42 (m, 8H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.87 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.7, 172.6, 137.1, 129.3, 128.4, 126.3, 101.7, 84.0, 79.1, 72.4, 71.7, 69.7, 69.0, 68.8, 67.7, 33.9, 33.7, 29.9, 27.9, 27.7, 24.2, 24.0, 18.3, 18.2. HRMS ESI calcd for $C_{23}H_{24}O_7Na$ [M + Na^+] 435.1420, found 435.1406.

Compound 4b. This product was isolated as a white crystalline solid at a yield of 14.6%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.49-7.45 (m, 2H), 7.37-7.33 (m, 3H), 5.49 (s, 1H), 4.91 (td, *J* = 5.5, 10.3 Hz, 1H), 4.28 (dd, *J* = 4.8, 10.6 Hz, 1H), 4.07 (dd, *J* = 5.9, 11.0 Hz, 1H), 3.83 (t, *J* = 9.2 Hz, 1H), 3.65 (t, *J* = 10.3 Hz, 1H), 3.47 (t, *J* = 9.2 Hz, 1H), 3.33 (td, *J* = 5.1, 9.9 Hz, 1H), 3.24 (pt, *J* = 10.6, 11.0 Hz, 1H), 2.62-2.53 (m, 2H), 2.51-2.44 (m, 2H), 1.99 (t, *J* = 2.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.1, 137.0, 129.4, 128.4, 126.4, 101.9, 84.0, 81.2, 71.6, 71.1, 68.8, 68.7, 67.3, 33.5, 29.7 27.7, 23.8, 18.1. HRMS ESI calcd for $C_{18}H_{21}O_7Na$ [M + Na^+] 355.1158, found 355.1166.

Compound 4c. This product was isolated as a white crystalline solid at a yield of 23.0%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43-7.39 (m, 2H), 7.32-7.28 (m, 3H), 5.44 (s, 1H), 5.14 (pt, *J* = 9.2, 9.5 Hz, 1H), 4.28 (dd, *J* = 5.1, 10.6 Hz, 1H), 4.05 (dd, *J* = 5.9, 11.4 Hz, 1H), 3.83 (td, *J* = 5.9, 9.9 Hz, 1H), 3.65 (pt, *J* = 9.9, 10.3 Hz, 1H), 3.54 (pt, *J* = 9.2, 9.5 Hz, 1H), 3.43-3.33 (m, 2H), 2.58-2.53 (m, 2H), 2.47-2.42 (m, 2H), 1.87-1.84 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.8, 137.1, 129.2, 128.4, 126.2, 101.5, 84.1, 78.7, 76.8, 71.4, 70.7, 69.8, 68.9, 68.8, 33.9, 29.8, 24.1, 18.1. HRMS ESI calcd for $C_{18}H_{20}O_7Na$ [M + Na^+] 355.1158, found 355.1147.

5-Hexynyl esters (5 a-c)

Compound 5a. This product was isolated as a white crystalline solid at a yield of 4.5%. ^{1}H NMR (400 MHz, CDCl3) δ (ppm) 7.45 – 7.41 (m, 2H), 7.38 – 7.32 (m, 3H), 5.50 (s, 1H), 5.35 (t, *J* = 9.5 Hz, 1H), 5.09 – 5.01 (m, 1H), 4.34 (dd, *J* = 4.9, 10.5 Hz, 1H), 4.13 (dd, *J* = 5.8, 11.1 Hz, 1H), 3.71 (t, *J* = 10.3 Hz, 1H), 3.64 (t, *J* = 9.5 Hz, 1H), 3.47 (td, *J* = 4.9, 9.7 Hz, 1H), 3.39 (t, *J* = 10.8 Hz, 1H), 2.50 – 2.41 (m, 4H), 2.22 (dtd, *J* = 2.6, 6.9, 9.6 Hz, 4H), 1.98 (t, *J* = 2.6, 1H), 1.94 (t, *J* = 2.6, 1H), 1.86 – 1.76 (m, 4H). ^{13}C NMR (101 MHz, CDCl3) δ (ppm) 172.4, 172.4, 137.1, 129.3, 128.5, 126.3, 101.7, 83.3, 83.1, 79.0, 72.6, 71.7, 69. 8, 69.6, 69.4, 68.8, 67.7, 33.0, 32.8, 31.1, 29.9, 23.8, 23.6, 17.9, 17.8. HRMS ESI calcd for $C_{25}H_{28}O_7Na$ [M + Na^+] 463.1733, found 463.1743.

Compound 5b. This product was isolated as a white crystalline solid at a yield of 16.3%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.53 – 7.47 (m, 2H), 7.42 – 7.35 (m, 3H), 5.55 (s, 1H), 4.96 (ddd, *J* = 5.8, 9.2, 10.4 Hz, 1H), 4.34 (dd, *J* = 5.0, 10.5 Hz, 1H), 4.12 (dd, *J* =

5.8, 11.1 Hz, 1H), 3.90 (t, *J* = 9.2 Hz, 1H), 3.71 (t, *J* = 10.3 Hz, 1H), 3.54 (t, *J* = 9.3 Hz, 1H), 3.39 (td, *J* = 5.0, 9.7 Hz, 1H), 3.30 (t, *J* = 10.8 Hz, 1H), 2.60 – 2.44 (m, 2H), 2.28 (td, *J* = 2.6, 6.9 Hz, 2H), 1.99 (t, *J* = 2.6 Hz, 1H), 1.87 (p, *J* = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.8, 137.1, 129.5, 128.6, 126.5, 102.1, 81.3, 72.9, 71.8, 71.2, 69.5, 68.8, 67.4, 32.9, 29.9, 23.6, 17.9. $C_{19}H_{22}O_7Na$ [M + Na^+] 369.1314, found 369.1319.

Compound 5c. This product was isolated as a white crystalline solid at a yield of 19.5%. ^{1}H NMR (400 MHz, CDCl3) δ (ppm) 7.43 – 7.38 (m, 2H), 7.35 – 7.28 (m, 3H), 5.45 (s, 1H), 5.07 (t, *J* = 9.2 Hz, 1H), 4.28 (dd, *J* = 4.9, 10.4 Hz, 1H), 4.01 (dd, *J* = 5.3, 11.3 Hz, 1H), 3.76 (dd, *J* = 9.6, 14.9 Hz, 1H), 3.64 (t, *J* = 10.2 Hz, 1H), 3.52 (t, *J* = 9.4 Hz, 1H), 3.40 (td, *J* = 4.9, 9.7 Hz, 1H), 3.32 (t, *J* = 10.9 Hz, 1H), 2.50 (t, *J* = 7.3 Hz, 1H), 2.19 (td, *J* = 2.5, 7.0 Hz, 1H), 1.93 (t, *J* = 2.5 Hz, 1H), 1.71 (p, *J* = 7.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.0, 137.1, 129.1, 128.3, 126.2, 101.4, 83.3, 78.8, 76.4, 71.3, 70.6, 69. 5, 69.3, 68.8, 33.0, 31.0, 23.7, 17.6. HRMS ESI calcd for $C_{19}H_{22}O_7Na$ [M + Na^+] 369.1314, found 369.1308.

6-Heptynyl Esters (6 a-c)

Compound 6a. This product was isolated as an oil at a yield of 3.3%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44 – 7.40 (m, 2H), 7.38 – 7.30 (m, 3H), 5.50 (s, 1H), 5.35 (t, *J* = 9.5 Hz, 1H), 5.05 (td, *J* = 5.8, 10.0 Hz, 1H), 4.34 (dd, *J* = 4.9, 10.5 Hz, 1H), 4.12 (dd, *J* = 5.8, 11.1 Hz, 1H), 3.71 (t, *J* = 10.3 Hz, 1H), 3.63 (t, *J* = 9.5 Hz, 1H), 3.47 (td, *J* = 4.9, 9.7 Hz, 1H), 3.39 (t, *J* = 10.8 Hz, 1H), 2.34 (ddd, *J* = 7.7, 12.0, 14.5 Hz, 4H), 2.20 (td, *J* = 2.5, 7.0 Hz, 2H), 2.11 (td, *J* = 2.6, 7.0 Hz, 2H), 1.96 (t, *J* = 2.5 Hz, 1H), 1.92 (t, *J* = 2.5 Hz, 1H), 1.70 (ddd, *J* = 4.5, 9.0, 11.1 Hz, 4H), 1.51 (dq, *J* = 7.1, 21.2 Hz, 4H). ^{13}C NMR

(100 MHz, $CDCl_3$) δ (ppm) 172.7, 172.6, 137.1, 129.3, 128.4, 126.3, 101.7, 84.0, 79.1, 72.4, 71.7, 69.7, 69.0, 68.8, 67.7, 33.9, 33.7, 29.9, 27.9, 27.7, 24.2, 24.0, 18.3, 18.2. HRMS ESI calcd for $C_{27}H_{33}O_7$ [M + H^+] 469.2226, found 469.2219.

Compound 6b. This product was isolated as a white crystalline solid at a yield of 21.5%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (400 MHz, CDCl3) δ 7.48-7.44 (m, 2H), 7.38 – 7.30 (m, 3H), 5.48 (s, 1H), 4.87 (td, *J* = 5.8, 10.3 Hz, 1H), 4.27 (dd, *J* = 4.9, 10.4 Hz, 1H), 4.05 (dd, *J* = 5.8, 11.0 Hz, 1H), 3.79 (t, *J* = 9.2 Hz, 1H), 3.64 (t, *J* = 10.3 Hz, 1H), 3.46 (t, *J* = 9.3 Hz, 1H), 3.32 (td, *J* = 4.9, 9.7 Hz, 1H), 3.22 (t, *J* = 10.8 Hz, 1H), 2.39-2.25 (m, 2H), 2.17 (td, *J* = 2.6, 7.0 Hz, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.71 (p, *J* = 7.4 Hz, 2H), 1.52 (p, *J* = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.1, 137.0, 129.4, 128.4, 126.4, 101.9, 84.0, 81.2, 71.6, 71.1, 68.8, 68.7, 67.3, 33.5, 29.7, 27.7, 23.8, 18.1. HRMS ESI calcd for $C_{20}H_{24}O_7$ Na [M + Na^+] 383.1471, found 383.1480.

Compound 6c. This product was isolated as a white crystalline solid at a yield of 20.1%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (400 MHz, CDCl3) δ 7.47 – 7.43 (m, 2H), 7.39 – 7.32 (m, 3H), 5.49 (s, 1H), 5.08 (t, *J* = 9.3 Hz, 1H), 4.31 (dd, *J* = 4.9, 10.4 Hz, 1H), 4.05 (dd, *J* = 5.7, 11.4 Hz, 1H), 3.79 (td, *J* = 5.8, 9.8 Hz, 1H), 3.68 (t, *J* = 10.2 Hz, 1H), 3.57 (t, *J* = 9.4 Hz, 1H), 3.43 (td, *J* = 4.9, 9.7 Hz, 1H), 3.34 (t, *J* = 11.0 Hz, 1H), 2.43 (t, *J* = 7.3 Hz, 2H), 2.12 (td, *J* = 2.6, 6.9 Hz, 2H), 1.94 (t, *J* = 2.5 Hz, 1H), 1.75 (p, *J* = 7.1 Hz, 2H), 1.53 (dt, *J* = 7.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 137.1, 129.2, 128.4, 126.2, 101.5, 84.1, 78.7, 76.8, 71.4, 70.7, 69.8, 68.9, 68.8, 33.9, 29.8, 24.1, 18.1. HRMS ESI calcd for $C_{20}H_{24}O_7$Na [M + Na^+] 383.1471, found 383.1487.

References

1. Gronwald, O.; Shinkai, S. *Chem. Eur. J.* **2001**, *7*, 4328–4334.
2. Luboradzki, R.; Gronwald, O.; Ikeda, M.; Shinkai, S.; Reinhoudt, D. N. *Tetrahedron.* **2000**, *6*, 9595–9599.
3. Gronwald, O.; Sakurai, K.; Luboradzki, R.; Kimura, T.; Shinkai, S. *Carbohydr. Res.* **2001**, *331*, 307–318.
4. Kiyonaka, S.; Shinkai, S.; Hamachi, I. *Chem. Eur. J.* **2003**, *9*, 976–983.
5. Yoza, K.; Amanokura, N.; Ono, Y.; Akao, T.; Shinmori, H.; Takeuchi, M.; Shinkai, S.; Reinhoudt, D. N. *Chem. Eur. J.* **1999**, 5, 2722–2729.
6. Wang, G.; Cheuk, S.; Williams, K.; Sharma, V.; Dakessian, L.; Thorton, Z. *Carbohyd. Res.* **2006**, *341*, 705-714.
7. Nie, X.; Wang, G. *J. Org. Chem.* **2006**, *71*, 4734-4741.
8. Vemula, P. K.; Li, J.; John, G. *J. Am. Chem. Soc*. **2006**, *128*, 8932-8938.
9. Kim, T. H.; Seo, J.; Lee, S. J.; Lee, S. S.; Kim, J.; Jung, J. H. *Chem. Mater.* **2007**, *19,* 5815–5817
10. Heeres, A.; van der Pol, C.; Stuart, M.; Friggeri, A.; Feringa, B. L.; van Esch, J. *J. Am. Chem. Soc.* **2003**, *125*, 14252-14253.
11. Geiger, C.; Stanescu, M.; Chen, L.; Whitten, D. G. *Langmuir.* **1999**, *15*, 2241-2245.
12. Tong, X.; Zhao, Y. *J. Am. Chem. Soc.* **2007**, *129*, 6372-6373.
13. An, B.-K.; Lee, D.-S.; Lee, J.-S.; Park, Y.-S.; Song, H.-S.; Park, S. *J. Am. Chem. Soc.* **2004**, *126*, 10232-10233.

14. Montalti, M.; Dolci, L. S.; Prodi, L.; Zaccheroni, N.; Stuart, M. C. A.; van Bommel, K. J. C.; Friggeri, A. *Langmuir*. **2006**, *22*, 2299-2303.

15. Kamikawa, Y.; Kato, T. *Langmuir*. **2007**, *23*, 274-278.

16. Coates, I. A.; Hirst, A. R.; Smith, D. K. *J. Org. Chem*. **2007**, *72*, 3937-3940.

17. Palui, G.; Banerjee, A. *J. Phys. Chem. B.* **2008**, *112*, 10107-10115.

18. Wang, R.; Geiger, C.; Chen, L.; Swanson, B.; Whitten, D. G. *J. Am. Chem. Soc.* **2000**, *122*, 2399-2400.

19. Tsou, C.-C.; Sun, S.-S. *Org. Lett*. **2006**, *8*, 387-390.

20. Mitra, R. N.; Das, D.; Roy, S.; Das, P. K. J. *Phys. Chem. B.* **2007**, *111*, 14107-14113.

21. Koshi, Y.; Nakata, E.; Yamane, H.; Hamachi, I. *J. Am. Chem. Soc.* **2006**, *128*, 10413-10422.

22. Shome, A.; Debnath, S.; Das, P. K. *Langmuir*. **2008**, *24*, 4280-4288.

23. Mahajan, S. S.; Paranji, R.; Mehta, R.; Lyon, R. P.; Atkins, W. M. *Bioconjugate Chem*. **2005**, *16*, 1019-1026.

24. Yang, Z.; Liang, G.; Xu, B. *Acc. Chem. Res.* **2008**, *41*, 315-326.

Chapter 5: Concluding remarks

To summarize the research results in Chapters 2, 3, and 4, we can draw some conclusions regarding the design, synthesis, and properties of several series of sugar based gelators. Figure 5.1 shows the several sugar headgroups (**1-3**) used in this study. A series of esters, carbmates were prepared using compound **1**. The esters of compound **2** have been compared to those of compound **1** to determine the role of the 1-methoxy group in the self assembly of the terminal alkynyl esters. A series of amides and urea derivatives were prepared using compounds **3**. The following are detailed summary for each of these systems.

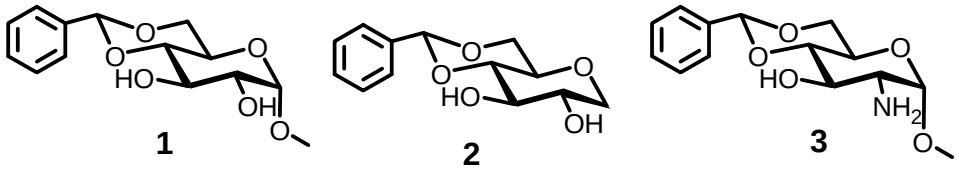


Figure 5.1. Core structures of LMWG library synthesized by the author.

5.1. Esters derivatives of compound 1

Among the ester derivatives of compound **1** that were synthesized, several of them showed positive gelation results in either hexane, ethanol, water or water and ethanol mixture. The structures of these compounds are shown in **Figure 5.2**. The terminal alkynyl derivatives and the aryl derivatives were the more efficient gelators.[1-2] For the short chain alkynyl esters, we found that 5-7 carbon chain monoesters gave the best gelation results.[1] Diesters **4**, **7**, and **9** don't have available hydrogen bonds donors, but

monoesters **5**, **6** and **8** have one free hydroxyl group that can be used to form hydrogen bonds. These results indicated that besides hydrogen bonding, many other non covalent forces are important in the self-assembly of these compounds. These include π–π stacking, van der Waals interactions. The essential requirement is that that the molecules can self-assemble into entangled network therefore entrapping the solvent. The 2,3-dinapthoyl (**7**) and the 2,3-dibenzoyl (**8**) esters were able to gelate water/ethanol, indicating the use of π–π stacking as the driving force for self-assembly. The 2,3-(4-pentynoyl) (**4**) esters also formed gels in both hexane and ethanol by using Van der Waals interactions in self-assembly. From **Table 2.2** (in Chapter 2), the 3-(4-pentynoyl) ester (**6**) gelated both water and hexane. In order to do so, the molecule must be able to form both micelles and reverse micelles in water and hexane, respectively. Another interesting note is the *C Log P* values calculated *in silico* by ChemDraw. Monoesters having a partition coefficient close to 1.0 gave positive gelation results (stable and unstable).

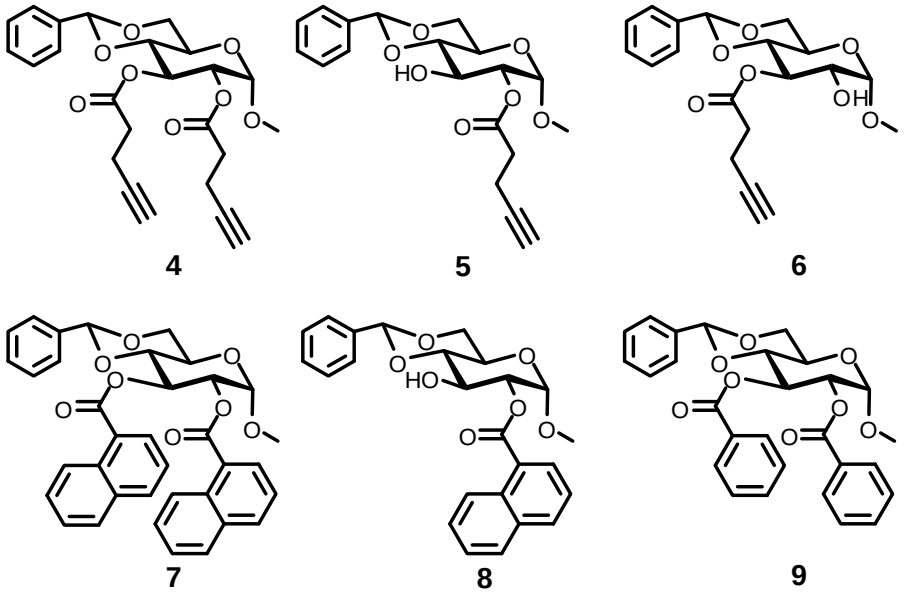


Figure 5.2. Ester derivatives of compound **1** which had positive gelation results.

5.2. Ester derivatives of compound 2

These compounds were synthesized to determine the role of the α-methoxy group. The terminal alkynyl esters were among the most efficient gelators from the ester library derived from compound **1**.[1] The removal of the methoxy group resulted in a sharp reduction in gelation, but these compounds did exhibit some gelation ability. This observation indicated that the α-methoxy group is useful in the formation of a fibrillar network and may or may not be involved in the hydrogen bonding array. Some similarities to the gelation of compounds in the di-ester derivatives of compound **1** have been observed. Compounds **10** and **13** were able to gelate pure hexane and form relatively unstable gels. Although, the monoesters **11**, **12** and **14** also exhibited similar

gelation properties to the corresponding analogs containing α-methoxyl group, the MGCs were relatively lower.

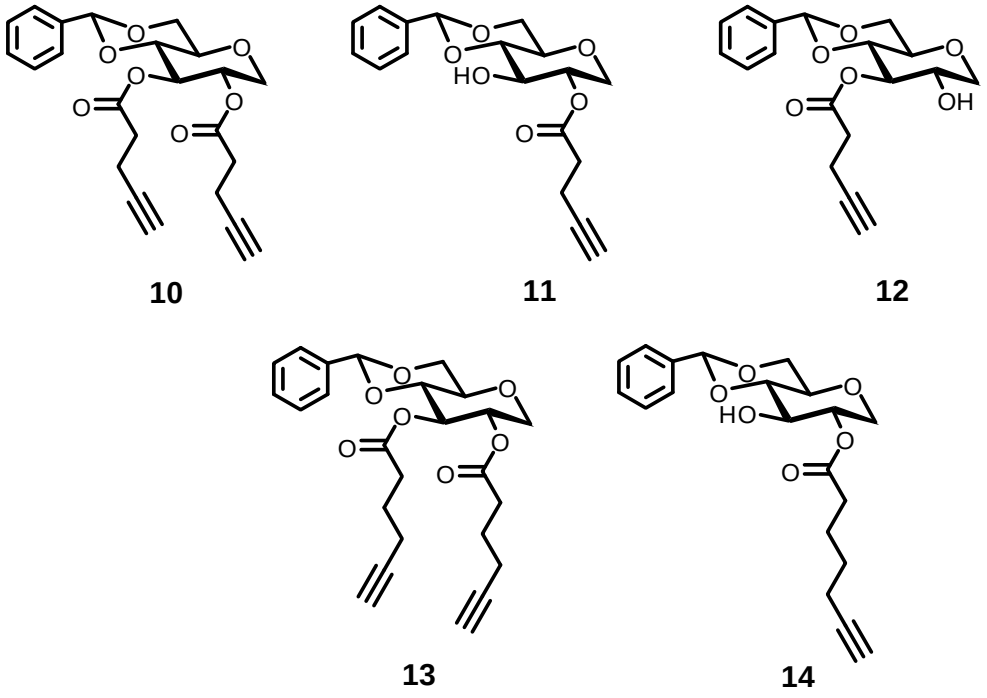


Figure 5.3. Ester derivatives of compound **3** exhibiting positive gelation.

5.3. Carbamate derivatives of compound 1

Among the carbamate derivatives studied here, the 2-mono carbmate derivatives showed the best gelation results. Several of these compounds are shown in Figure 5.4, the saturated alkyl derivatives of 5-7 carbons (**9-11**) and the aryl monocarbamate (**12** and **13**) derivatives performed well in aqueous mixtures of ethanol or DMSO. The short chain alkyl derivatives formed the most stable gels at lower concentrations. Further studies using IR, NMR, and small angle x-ray scattering or x-ray powder diffraction will be needed to help understanding the packing modes of these molecules. In comparison to the

esters, the NH plays an essential role in the self assembly process. However, when the compound was functionalized at both positions, the compound failed to gelate any of the solvents tested. This result indicates that either the 2 or 3 position needs to remain a hydroxyl, with the latter being the better of the two. Therefore, it seems that both the hydroxyl group and the NH group are important in the self-assembling processes. The NH most likely associates with the carbonyl of a neighboring molecule and forms the main backbones of the fibrillar network. The hydrogen bonding through the free hydroxyl is probably involved in creating branches. The free hydroxyl group also participates in the association perhaps through hydrogen bonding with ring oxygen or solvent, thus creating branching points. Branch formation occurs by crystallographic mismatches and is essential in the formation of mechanically stable gels. The *C Log P* values from ChemDraw have shown that the gelators in the ethanol/water mixtures have values in the range of 1.5-3.3 with the better gelators having values between 2.0 and 2.8.

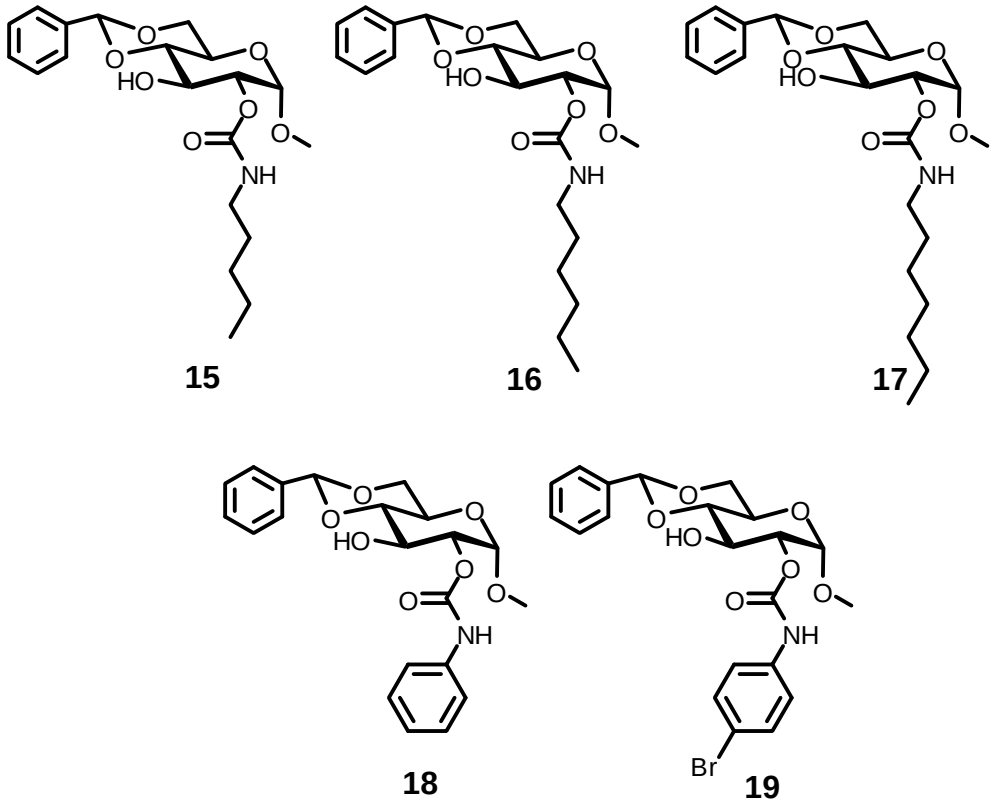


Figure 5.4. Carbamate derivatives of compound **1**, which formed stable gels.

5.4. Amide derivatives of compound 2

The amide derivatives of compound **2** showed great promise and formed better gelators than the ester analogs, thus showing the same trend as the carbamates: an NH is important in the formation of self-assembled networks. The main difference here is the position of the NH. With the NH in closer proximity to the ring, the NH could participate in intramolecular hydrogen bonding. Several amides that were able to form stable gels are shown in Figure 5.5. From the positive gelation results in **Table 3.2**, there is no doubt that the NH has a strong positive influence in the formation of gel networks. Also, the lengths of the alkyl chains make a difference. Just as with the esters and carbamates,

alkyl chains with lengths of 6-8 provides remarkably stable gels at lower concentrations (≤1.5 mg/mL) than their respective carbamates. With just the acetamide derivative of **2**, the compound forms unstable gels at high concentrations. In contrast, longer alkyl lengths only result in a modest drop in gelation efficiency. This is perhaps due to the additional stability provided by van der Waals interaction of the longer alkyl chains. The octanoyl amide, **22** was also able to gelate both aqueous solutions of DMSO and ethanol in addition to pure hexane. Like compound **6**, the molecular conformation of **22** allows the formation of both micelles and reverse micelles enabling the molecule to gelate both aqueous solutions and hexane, respectively. The *tert*-butoxy group of the glycine amide provided too much steric bulk which interfered with the self-assembly given that the molecule could not gelate any of the solvents tested.

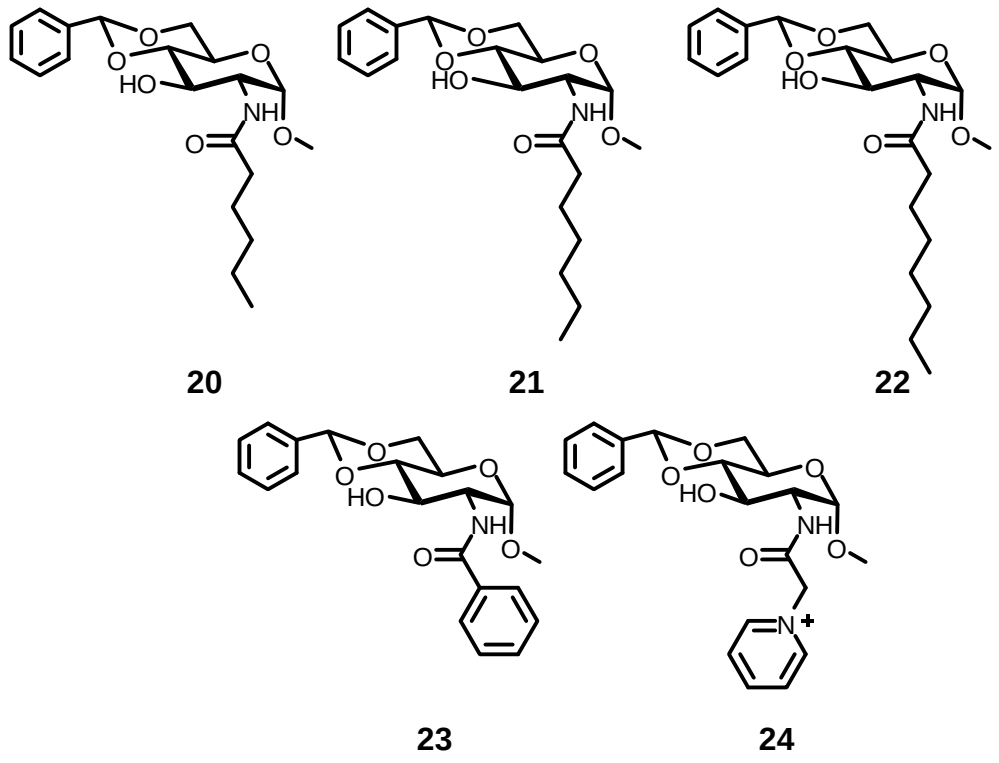


Figure 5.5. Amide derivatives of compound **2** that formed stable gels.

The aryl derivatives of the carbamates and the amide can provide some insight on how these molecules were interacting with each other. The phenyl carbamates **18** formed stable gels at 5.0 mg/mL in a water/ethanol mixture, while the phenyl amide **23** formed an unstable gel at the same concentration in the same solvent mixture. The lack of flexibility or degrees of freedom of the amide bond created a molecule that was too rigid. If an additional CH_2 or more was inserted between the phenyl ring and the carbonyl, then the molecule will become more flexible and perhaps a better gelator. On the other hand, the pyridinium acetamide, **24** was able to gelate pure water efficiently while carbamate **18** was not able to. The presence of the pyridinium ion increases solubility and gelation efficiency in water. For the most part, the *C log P* values of the amide gelators ranged from 1.7 to 2.8. An increase in the alkyl chain (and a resulting higher partition coefficient) also formed gels, but there was a significant decrease in gelation efficiency, notably in aqueous DMSO.

5.5 Urea derivatives of compound 2

The one-dimension hydrogen bonding of the urea moiety drives self-assembly and because the synthesis is usually facile and quantitative, many urea derivatives have been synthesized as LMWGs. The carbamates and amides have demonstrated a large increase in gelation efficiency from the ester analogs because of the addition of an additional NH. However, according to **Table 3.3**, the substitution of a second hydrogen bonding NH for the hydrogen acceptor oxygen seemed to have a marginal effect on the MGC, but it did

have a notable increase in mechanical strength (less likely to destabilize). Several urea derivatives that can form stable gels are shown in **Figure 5.6**. The alkyl ureas **25-28** were able to form stable gels in aqueous DMSO at 1.0 mg/mL. The cyclohexyl derivative **29** also performed just as well as the alkyl derivatives. The 2-chloroethyl urea failed to produce a gel as did the carbamate and ester analogs. The presence of a chloro substituent at the end disrupts the gelation process. From the gelation results from the esters, carbamates, and ureas, the chloro group promoted precipitation. Without the chloro group the compound is allowed to associate via hydrogen bonding by the urea and van der Waals interaction along the alkyl chain. The *CLog P* values of the ureido gelators ranged from 2-3, except the hydroxyl ethyl urea which had a partition coefficient of 0.6.

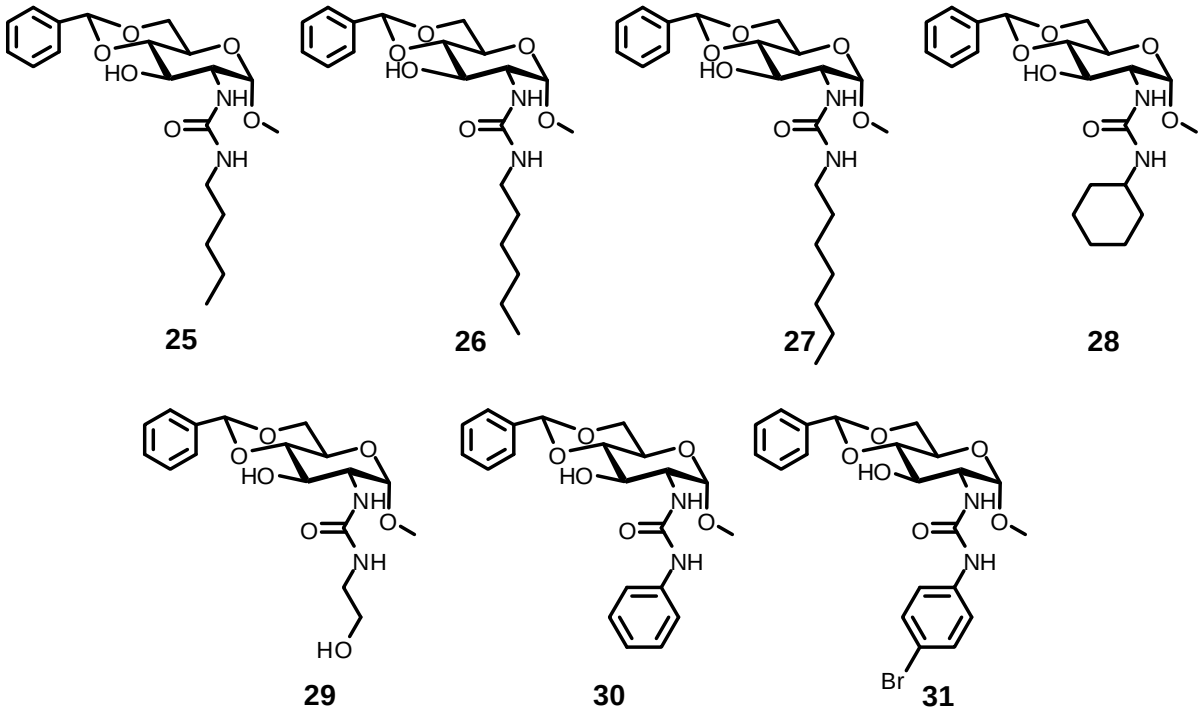


Figure 5.6. Urea derivatives of compound **2** which can form stable gels.

Final Conclusions and Future Research

Among the four classes of monosaccharide derivatives synthesized: esters, carbamates, amides, and ureas, we found that in general the later three classes of compounds are better organogelators, with 5-7 carbon chain lengths being optimal for hydrogelation. Hydrogen bonding plays an important role in the self-assembling process. The long nonpolar alkyl chain serves to interact with one another via van der Waals interactions. Substitutions along these alkyl chains usually disrupt the gelation process, either by increasing the packing order, leading to precipitation or crystallization, or decreasing it to the point of solubility. The sugar headgroup containing an amino group such as compound **2** is suitable for further derivatization and forming good gelators. For example, amides and ureas typically gelate more efficiently than esters, shorter (butyl and pentyl) and longer chain amides can be synthesized to determine the optimal length for the amide system. The pyridinium acetamide contains cationic functional group, it may be worthwhile to synthesize other derivatives containing the same pyridinium functional group. Ureas or thioureas can also be synthesized, these compounds are easy to prepare and typically leading to good gelators. These good hydrogelators found in the current research can be explored for further applications in several systems: exploration their effectiveness in enzyme immobilization, designing analytical tools to understanding molecular interactions, and as matrix for delivery of biological agents, etc.

References

1. Wang, G.; Cheuk, S.; Williams, K.; Sharma, V.; Dakessian, L.; Thorton, Z. *Carbohyd. Res.* **2006**, *341*, 705-716.

2. Gronwald, O.; Shinkai, S. *Chem. Eur. J.* **2001**, *7*, 4328–4334.

Vita

The author was born in Metairie, Louisiana on February 6, 1980. He graduated from Benjamin Franklin High School in New Orleans. He attended the U.S. Military Academy at West Point, New York from June 1998 to August 2002. Credits were transferred to Excelsior College at Albany, New York upon which he received his Bachelors of Science in Chemistry. He then joined the Department of Chemistry at the University of New Orleans in August 2003 and started his Ph.D. research work in Dr. Guijun Wang's group in October 2003.