

University of New Orleans

ScholarWorks@UNO

University of New Orleans Theses and
Dissertations

Dissertations and Theses

5-20-2011

Synthesis and Characterization of Monosaccharide-derived Low Molecular Weight Gelators

Kristopher Aaron Williams
University of New Orleans

Follow this and additional works at: <https://scholarworks.uno.edu/td>

Recommended Citation

Williams, Kristopher Aaron, "Synthesis and Characterization of Monosaccharide-derived Low Molecular Weight Gelators" (2011). *University of New Orleans Theses and Dissertations*. 135.
<https://scholarworks.uno.edu/td/135>

This Dissertation-Restricted is protected by copyright and/or related rights. It has been brought to you by ScholarWorks@UNO with permission from the rights-holder(s). You are free to use this Dissertation-Restricted in any way that is permitted by the copyright and related rights legislation that applies to your use. For other uses you need to obtain permission from the rights-holder(s) directly, unless additional rights are indicated by a Creative Commons license in the record and/or on the work itself.

This Dissertation-Restricted has been accepted for inclusion in University of New Orleans Theses and Dissertations by an authorized administrator of ScholarWorks@UNO. For more information, please contact scholarworks@uno.edu.

Synthesis and Characterization of Monosaccharide-derived 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
Chemistry

by

Kristopher Aaron Williams

B.S., University of New Orleans, 2005

May, 2011

For my wife Melissa, my children, Lundin and Sarah,
my mother, Debbie, and Joe and Mary,
whose support made this possible

Table of Contents

List of Abbreviations.....	iv
Abstract	v
Chapter 1	1
Introduction.....	2
Discussion.....	8
Conclusion	66
Chapter 2	73
Introduction.....	74
Results & Discussions	80
Conclusion	91
Chapter 3	105
Introduction.....	106
Results & Discussion.....	109
Conclusion	115
Chapter 4	128
Introduction.....	129
Results & Discussion.....	134
Conclusion	149
Vita.....	167

List of terms and abbreviations

Bolamphiphile: a molecule which contains two hydrophilic groups tethered together by a hydrophobic region

LMWG: low molecular weight gelator; small molecule compounds which self-assemble through non-covalent interactions to form supramolecular gels

LMHG: low molecular weight hydrogelator; LMWGs which form gels in water

LMOG: low molecular weight organogelator; LMWGs which form gels in organic solvents

Abstract

Low molecular weight gelators (LMWGs) are interesting materials whose applications are as diverse and wide ranging as their molecular structures. These materials self-assemble through the formation of non-covalent intermolecular forces and interactions to form supramolecular assemblies that trap solvent within their matrices. Because of the non-covalent nature of the forces of self-assembly, the gelation process is typically thermally reversible. In addition, low molecular weight gelators can also be modified to respond to various stimuli, such as change in pH, presence of enzymes or metal cations, or exposure to light. The design of low molecular weight gelators is often difficult, and most new classes of low molecular weight gelators are discovered by serendipity. As such, it is often useful to use structural templates in the design of LMWGs. Biomolecules, such as steroids, amino acids and peptides, and carbohydrates make excellent templates due to their inherent propensity to self assemble. A review of the current literature regarding the use of biomolecules as templates for the design and synthesis of LMWGs will be presented in chapter 1. Our research group has been active in the research of carbohydrate-based LMWGs for several years, and these results are also briefly reviewed in the related chapters. The synthesis and characterization of ester derivatives of D-galactose, D-glucose, and amide derivatives of D-glucosamine will be discussed in chapters 2-4, along with their evaluation for gelation in aqueous and organic solvents, such as hexane, ethanol, water, and aqueous DMSO or ethanol mixtures.

Keywords: low molecular weight gelators, supramolecular gelators, amino acid, steroid, carbohydrate

Chapter I. Review of low molecular weight gelators derived from biomolecule templates

Abstract: Low molecular weight gelators are important soft materials with wide-ranging applications. Gelation of these compounds occurs due to one-dimensional self-assembly of the individual molecules into higher order aggregates, which trap solvent molecules by surface tension and capillary forces. Since self-assembly is the driving force for gelation, templates which are prone to self-assembly are useful starting points for the design of low molecular weight gelators. Biomolecules, such as amino acids, steroids, and carbohydrates, are not only prone to self-assembly, but are also naturally abundant and can be functionalized with relative ease, making them ideal templates for the design of supramolecular gelators. This review of the recent literature will discuss a variety of different low molecular weight gelators which have been synthesized from amino acids, steroids, and carbohydrates.

Introduction

Gels are semisolid materials which can serve a variety of purposes and are found ubiquitously in our everyday lives; gels are prevalent in nature, within the cells and tissues of the body, and are also present in variety of synthetic, man-made materials. While the exact definition of a gel was often an early point of contention among scientists, the word “gel” is derived from the latin word “gelāre” meaning “to freeze”.¹ The current definition of a gel, according to the Merriam-Webster dictionary, is “a colloid in a more solid form than a sol”.¹ While this definition is quite broad, it gives us two critical pieces of information about gels: 1) gels are colloids, and as such, contain microscopic particles of a solid that are homogeneously dispersed throughout a liquid medium; and, 2) a gel is more solid than liquid. A more succinct definition given by the esteemed Nobel laureate P. J. Flory defined a gel as “a colloidal dispersion with a continuous structure over macroscopic dimensions, which is permanent on the analytical time scale, and which is solidlike in its rheological behavior”.² The colloidal dispersion causes an increase in the viscosity in the liquid medium by forming a matrix which entraps the liquid. In doing so, the system attains a semisolid consistency, lying somewhere between the liquid and solid state.

A common qualitative test for gelation is the inversion test. Upon homogeneously dispersing the gelator in the solvent, usually through heating, the sample is allowed to rest undisturbed until it has cooled back down to room temperature and ample time has been given for gelation to occur (the time required for gelation can vary greatly, from a few minutes to several hours, or even days, and depends on the gelator type, structure, solvent, etc.). The sample is then inverted to determine whether or not flow takes place; if the sample does not flow, and is found to be both self-supporting, it is deemed to be a gel. A more quantitative assessment

for gelation, which has been utilized more frequently in the literature over the past few years, is oscillating rheometry measurements. Rheometry is able to measure relative viscosity and elasticity of complex liquids, such as gels. Since a gel is defined to be a semisolid which is more solid than liquid, rheometry can be used to quantitate how solid or liquid the system is, based on its response to mechanical stress or strain.

As mentioned previously, gels are comprised of matrices of self-assembled gelator molecules, which entrap the solvent. The manner in which this matrix is formed is often used to classify the type of gel. If this matrix is formed through covalent bonding, as is the case with polymeric compounds which form gels, the resulting gel is called a polymer gel, chemical gel, or covalent gel. The majority of the gels which occur in nature and those that are created synthetically for commercial or industrial use are polymer gels. Notable examples include gelatin (for which gels are named), agarose (used as a growth medium in microbiology), hyaluronin (present in the extracellular matrix of animals), and polyacrylamides (used in contact lenses). Polymer gels have been studied for several decades, and are fairly well understood. Chemical gels are typically formed through a cross-linking process which creates additional covalent bonds, leading to a higher degree of branching in the polymer chains. This cross-linking creates a porous matrix in which the solvent molecules can be trapped. Because of the covalent nature of the polymer gel matrix, these gels are typically very strong, and possess a high degree of elasticity.

The other class of gels is that in which the matrix of the gel is formed by noncovalent interactions; these gels are referred to as low molecular weight gels (LMWGs), physical gels, or supramolecular gels. Low molecular weight gelators typically anisotropically self-assemble in solution to form one-dimensional, fibrous assemblies on the nanoscale, which typically undergo

further self-assembly to form microscale fibers, tubules, etc.^{3,4} These higher order microfibers become entangled, and effectively trap solvent within their matrix.^{3,4} It is thought that in most cases, the solvent molecules do not help to comprise the gel matrix, but rather, simply become entrapped via capillary forces²⁶; there have been a few reports in which the experimental evidence indicates that the solvent molecules are helping to comprise the nanofibrous matrix.³⁰

The self assembly process is guided by a variety of different forces, depending on the solvent or solvents being used. For aprotic, organic solvents, hydrogen bonding is often the most important force for guiding the self assembly process, though π -stacking interactions of aromatic rings, metal coordination, and electrostatic interactions can also play a significant role.³ For water, and to a lesser extent, polar protic organic solvents, hydrogen bonding and electrostatic interactions are not as significant, due to the ability of the solvent to participate in these types of interactions; hydrophobic forces (and other Van der Waals forces) and π stacking are the major contributors to self assembly of LMWGs in water.^{3b} Regardless of the nature of the solvent, a delicate balance between hydrophobicity and hydrophilicity of the gelator molecules must be maintained for gelation to occur; if the gelator molecule is too soluble, complete solvation will occur instead of self-assembly, while extreme solvophobicity can lead to exclusion of the solvent, causing precipitation or recrystallization.

Low molecular weight gelators possess several, distinct advantages in relation to polymer-based gelators. Due to the noncovalent forces which make up the gel matrix, low molecular weight gelators are thermoreversible, a property which many polymer gels do not possess (some polymer gels are thermoreversible, while some simply exhibit volumetric changes in response to changes in temperature, but many exhibit no thermoreversibility).¹⁷ Supramolecular gels possess better bioavailability, are generally less toxic, and are more easily

metabolized than polymer gels, due to the fact that they are comprised of small molecules rather than large polymers, and are often be designed to be biocompatible.¹⁴ This provides an explicit advantage for the use of supramolecular gels in biomedical applications, especially those for use *in vivo*. The formation (or degradation) of the gel matrix is typically fast in supramolecular gels, with most gelators able to undergo the sol-to-gel transition in a matter of seconds to minutes.

Historically, due to the complex nature of non-covalent gelation, gelators were often found serendipitously, rather than through any type of rational design. Early studies focused on a “structure-gelation relationship”, trying to elucidate what structural features would invoke self-assembly and subsequent gelation. After a great deal of research in the past few decades, it is now possible to predict whether a molecule will be able to undergo supramolecular gelation with a reasonable degree of accuracy. Through rigorous study, the complex nature of physical gelation has become fairly well understood, though there are still some gaps in our knowledge. In addition to the simple desire to solve the puzzle of why low molecular weight gelators form gels, there were other motives regarding the tenacity with which LMWGs were studied: supramolecular gelators offer many advantages that polymer gelators do not.

Because the interactions which form the gel network are noncovalent, they can typically be broken up by supplying kinetic energy (raising the temperature) to the system; hence, supramolecular gels are typically thermally reversible (unlike most chemical gels).¹⁷ In addition, depending on the types of functional groups present in the gelator molecules, other triggers for gel-to-sol and/or sol-to-gel transitions may be available, including change in pH⁶⁻¹², treatment with enzymes^{13,14}, or treatment with reducing or oxidizing agents^{15,16}. Because of this, low molecular weight gelators have become the subject of great interest over the last few decades. While they are not as well studied as polymer gels, significant interest in the research of low

molecular weight gelators began in the 1990s (Figure 1).⁵ A recent surge in LMWG publications has taken place over the last decade, owing to a change in the focus of the papers. Earlier publications focused on thoroughly characterizing the gels in order to understand gelation and how structure and design of the gelators correlated with their gelation ability. More recent papers have shifted their focus to the potential applications of the gelators as smart materials, though comprehensive characterization of these gels is still important. As such, the techniques for characterization of supramolecular gelators and their potential applications warrant some further discussion.

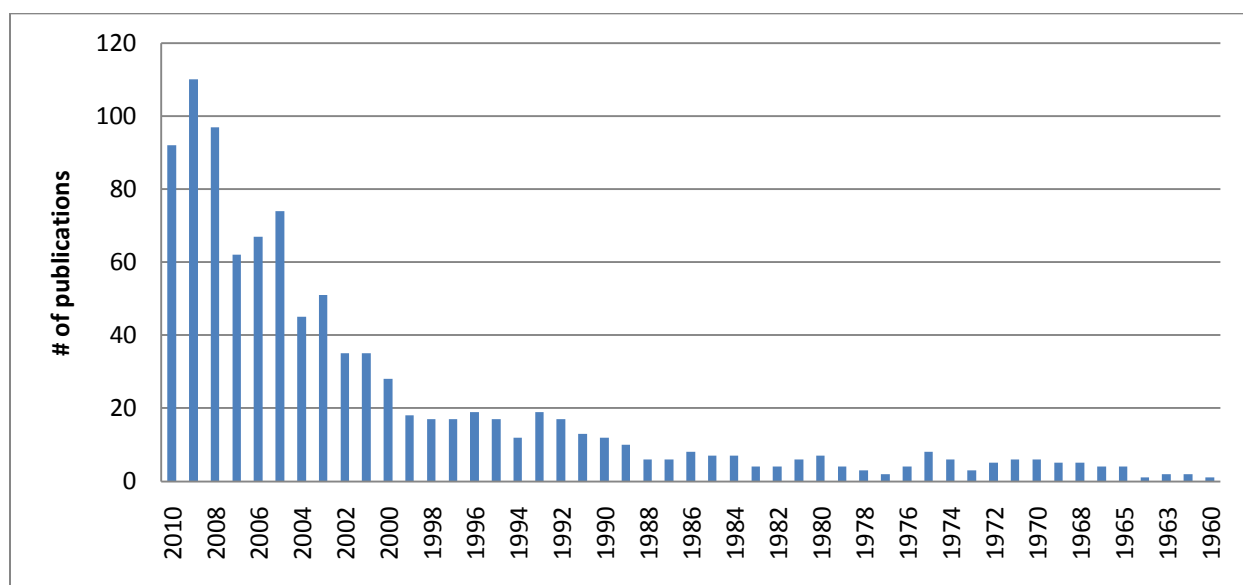


Figure 1. Histogram of Scientific Publications of Low Molecular Weight (Mass) Gelators / Supramolecular Gelators.⁵

As unique smart materials, supramolecular gelators lend themselves to a variety of specialized applications, due in part to their reversible nature, which can often be triggered by a variety of stimuli. The majority of applications for low molecular weight gelators, especially low molecular weight hydrogelators, seem to be in the area of biomedical applications¹⁷, especially as triggered-release carrier systems for drug delivery¹⁸. Other important applications include the use of physical gels as chemical sensors¹⁹, organocatalysts²⁰, photoelectronic and nanoelectronic devices²¹, templates for growing nanomaterials²², environmental cleaning agents²³, and even as bacteriostatic²⁴ and cytotoxic agents²⁵.

One application of particular interest is the use of hydrogels as a media for cell growth. The use of hydrogels as a matrix for cell growth is fairly common in polymer hydrogels^{26,27}, owing in part to the fact that the adhesion and proliferation of different cell lines has been found to be dependent on the mechanical strength of the gel (polymer gels typically exhibit greater mechanical strength, due to the fact that the cross-linking is covalent rather than supramolecular in nature)²⁷. However, there are a few examples where supramolecular hydrogels have been used as a matrix for the growth of cell cultures.^{28,29} One of the most ground-breaking examples of the use of a low molecular weight hydrogelator as a medium for cell culture was that reported by Stupp et al., in which an oligopeptide, IKVAVEAAAAGGG, functionalized with a C₁₆ alkyl tail, was able to form a hydrogel.²⁹ The hydrogel not only served as a medium for cell growth, but was able to direct cell differentiation of murine neural progenitor cells.

As the understanding of supramolecular gelator systems increases, gelators can be designed with specific applications in mind. This often allows for research groups to implement functional groups into the structure which not only promote the supramolecular interactions necessary for gelation, but impart the properties responsible for carrying out the desired

application of the material as well. Due to the diversity of their applications, and the intriguing nature of their self-assembly, low molecular weight gelators have become an intensely-researched, interdisciplinary field, spanning the areas of synthetic organic and organometallic chemistry, physical chemistry, molecular biology, analytical chemistry, and materials science.

II. Discussion: Biomolecules as templates for low molecular weight gelators

In addition to the classification of gels by their mode of aggregation (chemical vs. supramolecular), there are a variety of criteria by which gels can, and frequently are, classified. For instance, low molecular weight gels are frequently classified as organogels or hydrogels, depending on whether the gelation medium is organic solvent or water. This can often be convenient since the forces which lead to self-aggregation often differ depending on the solvent medium. In addition, one can also classify physical gels by the functional groups present in the molecule, as different functional groups have been found to facilitate gelation, due to their propensity for self-assembly. The types of forces which promote gelation are dependent on the nature of the functional group, so different functional groups promote different, specific forces for self-assembly. For instance, esters, amides, ureas, alcohols, and amines can promote hydrogen bonding, aromatic rings can undergo aggregation via π -stacking interactions, and aliphatic rings and chains interact by hydrophobic Van der Waals forces. As such, many gels contain one or more of the following types of functional groups: amino acids/peptides, carbohydrates, cholesterols, amides/ureas, aromatic rings, and long hydrocarbon chains. Classification of supramolecular gelators according to the type (or types) of functional groups that they possess is frequently employed in the literature, and will be utilized herein.

A. Amino-Acid Based Low Molecular Weight Gelators

By far, the most widely represented structural motif found within physical gels is that of the amino acid. This is not surprising, as the self-assembly of peptides into their secondary structures, and their subsequent folding into their native conformations has been intensely studied. As the individual building blocks of proteins, the chemical structure of amino acids gives rise to a variety of different noncovalent interactions which can be harnessed for self-assembly, including hydrophobic packing, π -stacking, electrostatic interactions, and hydrogen bonding. Hydrogen bonding between the amino group and carbonyl group has been found to be an important interaction for self-assembly, even in water. By mimicry of nature's careful selection of side chains in a particular sequence, scientists can produce synthetic materials which harness these intermolecular interactions to propagate anisotropic growth into nanofibers, leading to gelation. Many prominent research groups have relied on amino acids to serve as the template for their design of supramolecular gelators.

One of the most active research groups in the field of amino acid based supramolecular gelators is Bing Xu's group. Since 2004, the Xu group has published several papers in the field, with a focus on the applications of the gels that is common in the current literature. Xu et al. have published examples of amino acid based gelators which are triggered by enzymatic activity,³¹⁻³³ and they even report cases in which the compounds undergo such enzyme-triggered gelation *in vivo*, resulting in intracellular hydrogelation³⁴⁻³⁶. All of these papers were summarized in a nice review.³³ The Xu group has also published several papers in which amino acid-based supramolecular gelators are used in drug delivery³⁷⁻³⁹. In addition, Bing Xu has also written an

informative perspective on the potential applications of low molecular weight hydrogelators in biology and medicine.⁴⁰

One of the Xu group's first forays into the field of enzymatic hydrogelation was reported in 2006, with the design and synthesis of a novel pentapeptide hydrogelator, Nap-FFGEY **1** (Figure 2).³¹ This pentapeptide, which was acylated at the N-terminus with a 2-(naphthalen-1-yl)acetyl group, was found to gel water at 0.6 wt%. The design was based on the fact that the Nap-FF moiety (which is common to nearly all of the enzymatic hydrogelators studied by the Xu group³¹⁻³⁶) is known to self-assemble, and the EY sequence is known to accept phosphorylation by tyrosine kinases. Glycine, the simplest amino acid, was used as the linker because it was unlikely that it would significantly affect either the self-assembly or the enzymatic activity. Treatment of the hydrogel of **1** with a kinase, in the presence of ATP, was found to bring about a gel-to-sol transition within 24 hours; treatment of the resulting aqueous solution with phosphatase was found to render the hydrogel again within one hour. Interestingly, cryo-TEM showed that the morphology of the initial gel and the gel obtained upon treatment with the phosphorylase were different. The initial gel formed nanofibers of varying size while the dephosphorylated gel formed more uniform nanotubules. This effect is thought to be due to an equilibrium process bringing about a slower sol-to-gel transition to form more stable assemblies. Finally, Xu et al. showed that a subcutaneous injection of the phosphorylated precursor led to *in vivo* gelation within one hour, and that the gel was biocompatible, as exhibited by the comparable weight loss of the mice to those in the control group.

The Xu group used the same Nap-FF moiety to display how β -lactamases could also be used to promote supramolecular hydrogelation.³² The Nap-FF moiety was functionalized at the C-terminus with a 2-aminothiol linker, to which a cephem subunit was attached to give

compound **2** (Figure 2). Within thirty minutes of treatment with various β -lactamases, the cephem subunit of **2** undergoes hydrolysis and cleaves from the Nap-FF moiety to give the free thiol compound **3** (Figure 2), which spontaneously gels water. An assay was conducted using the cell lysates of several strains of *E. coli*, and it was found that the hydrogel of **3** was formed in the presence of both broad-spectrum and extended-spectrum β -lactamases, but not in the presence of β -lactamase negative strains. This indicates that a gel-based β -lactamase assay could serve as a more accurate assay in comparison to the existing nitrocefin assays, which give a false positive for some β -lactamase negative strains. This could prove useful for the future study of β -lactam antibiotics, their mechanism of inactivation in bacteria which produce β -lactamase, and potential inhibitors of β -lactamase.

Intracellular hydrogelation was explored by the Xu group using the hydrogelator Nap-FF-NHCH₂CH₂OH **4** (Figure 2), which forms hydrogels at concentrations as low as 0.08 wt%.³⁴ Esterification of the terminal hydroxyl group with succinic acid yielded compound **5** (Figure 2) which did not form hydrogels. It was found that treatment of an aqueous solution of **5** with esterase triggered hydrolysis of the ester to once again afford compound **4**, which spontaneously gels at 37°C. The ester precursor **5** was placed in a culture solution of HeLa cells at a concentration of 0.08 wt%, and was found to be taken up by the cells. After three days, the majority of the cells had died, and TEM analysis of the dead cells showed the presence of nanofibers which are morphologically similar to those present in the hydrogel of Nap-FF-NHCH₂CH₂OH **4**. Live cells showed no evidence of these nanofibers. In the presence of the same concentration of **5** (0.08 wt%), mammalian fibroblast cells (NIH3T3) were found to proliferate, showing no signs of cell death. Treatment of both cell cultures (HeLa and NIH3T3) with a fluorescent esterase indicator, carboxyfluorescein diacetate, showed a much greater

expression of esterase in the HeLa cells, which explains why cell death was observed in the HeLa cells but not in the mammalian fibroblast cells.

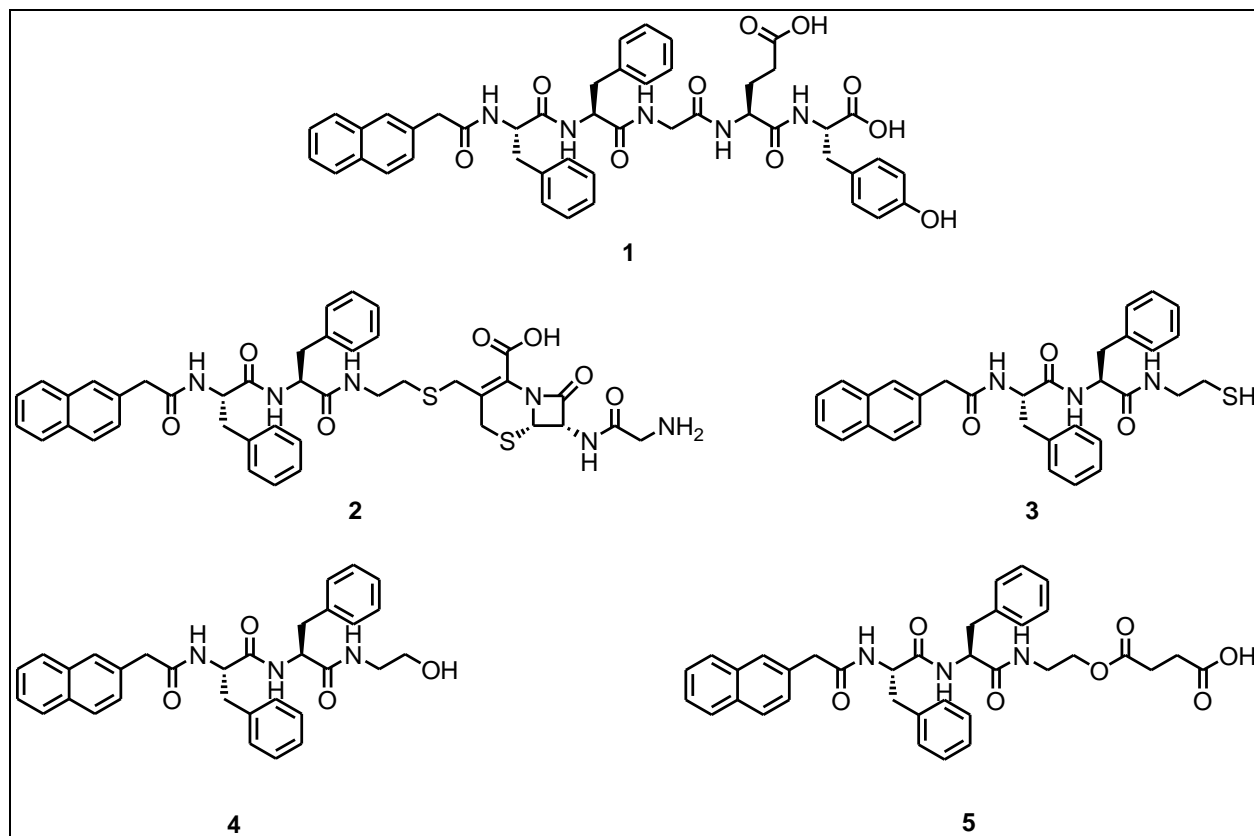


Figure 2. Enzymatically-triggered Nap-FF hydrogelators (**1**, **3**, and **4**) and precursors (**2** and **5**).

In another report regarding intracellular hydrogelation by amino acid based hydrogelators, Bing Xu et al. present yet another hydrogelator based on the Nap-FF motif, Nap-FFY **6** (Figure 3), which has a minimum gelation concentration of 0.4 wt%.³⁵ Phosphorylation of the tyrosine hydroxyl group gives compound **7** (Figure 3), which is soluble in water; treatment of **7** with a tyrosine phosphatase cleaves the phosphate group to again give Nap-FFY **6**, which spontaneously gels in aqueous solution. According to *in vitro* rheometry experiments, the

dephosphorylation of **7** was relatively rapid at ambient temperature, with nearly 50% conversion occurring almost instantly (the minimum gelation concentration was found to be 125 $\mu\text{g/mL}$). To explore intracellular gelation, overexpression of phosphatase in a strain of *E. coli* (BL21) was induced by treatment with isopropyl- β -D-thiogalactopyranoside (IPTG) and plasmids. Introduction of a 10.4 μM solution of phosphorylated precursor **7** to the culture medium induced intracellular gelation within twenty four hours, as exhibited by the gelation of the lysed collected cells and their subsequent HPLC analysis. Control experiments showed that in the absence of the IPTG or the phosphorylated Nap-FFY **7**, no gelation occurred. In addition, staining with Congo Red only stained the cells which were both induced to overexpress phosphatase and exposed to **7** (staining with Congo Red is indicative of intracellular gelation, as Congo Red binds to nanofibers comprised of B-sheet like structures, and has been shown to bind to the nanofibers formed by the hydrogels of **4** and **6**³⁶). Two other tyrosine containing peptides, Nap-DFDFY **8** and Nap- β^3 -HPhg- β^3 -HPhgY **9** (β^3 -HPhg is β^3 -homophenylglycine; both structures are shown in Figure 3), showed identical results, which suggests that the intracellular formation of nanofibers is responsible for the bacteriostatic effect rather than a specific enzymatic interaction of **6** or **7**.

Drug delivery is a common application for supramolecular gelators, and the Xu group has reported several amino acid-based, low molecular weight hydrogelators which have been utilized for the delivery of therapeutic agents.³⁷⁻³⁹ N-Fmoc-protected L-leucine **10** (also known as NPC 15199) and N ^{α} -Fmoc-protected L-lysine **11** are known anti-inflammatory agents (Figure 3).⁴¹ These compounds have limited solubility in water at neutral pH, but were found to be soluble upon addition of one equivalent of sodium carbonate; Xu reports that adding either of the solutions to the other, while heated, led to hydrogelation upon cooling.³⁷ The hydrogel of **10** and **11** was translucent, but could be made transparent if two equivalents of sodium carbonate were

used, indicating that use of more base allowed more of the gelator molecules to be incorporated into the gel matrix. The hydrogel was stable to acidic and neutral media, and was shown to be able to incorporate 5-fluoro-2'-deoxyuridine **12** (Figure 3), an antineoplastic agent, into the hydrogel, exhibiting its potential as a vehicle for drug delivery. A model for aggregation was proposed in which the carbonate anions take part in the hydrogen bonding array, and neighboring fluorenyl groups π -stack in an antiparallel fashion.

Xu et al. also report that instead of using sodium carbonate, a biphosphonate drug, Pamidronate, can be used to promote gelation of the two Fmoc-protected amino acids.³⁸ This drug is used clinically to chelate uranyl ions and reduce uranium poisoning, and was chosen because of ability to hydrogen bond in a manner analogous to the carbonate ion. It was found that the use of four equivalents of Pamidronate **13** (Figure 3) gave a transparent gel that was stronger, and whose nanofibers were more dense, than the opaque gels obtained from the use of only one or two equivalents of the chelating agent. The hydrogel formed by **10**, **11**, and **13** was applied to the wounds of mice twenty minutes after they had been exposed to nonradioactive uranyl nitrate, and a therapeutic effect was observed, as compared to a control group. The mice exhibited no changes in their daily behavior which would indicate toxicity, showed very little weight loss, and all remained alive; the mice of the control group, which were not treated with the hydrogel of **10**, **11**, and **13**, exhibited up to 35% weight loss and expired within three to eight days.

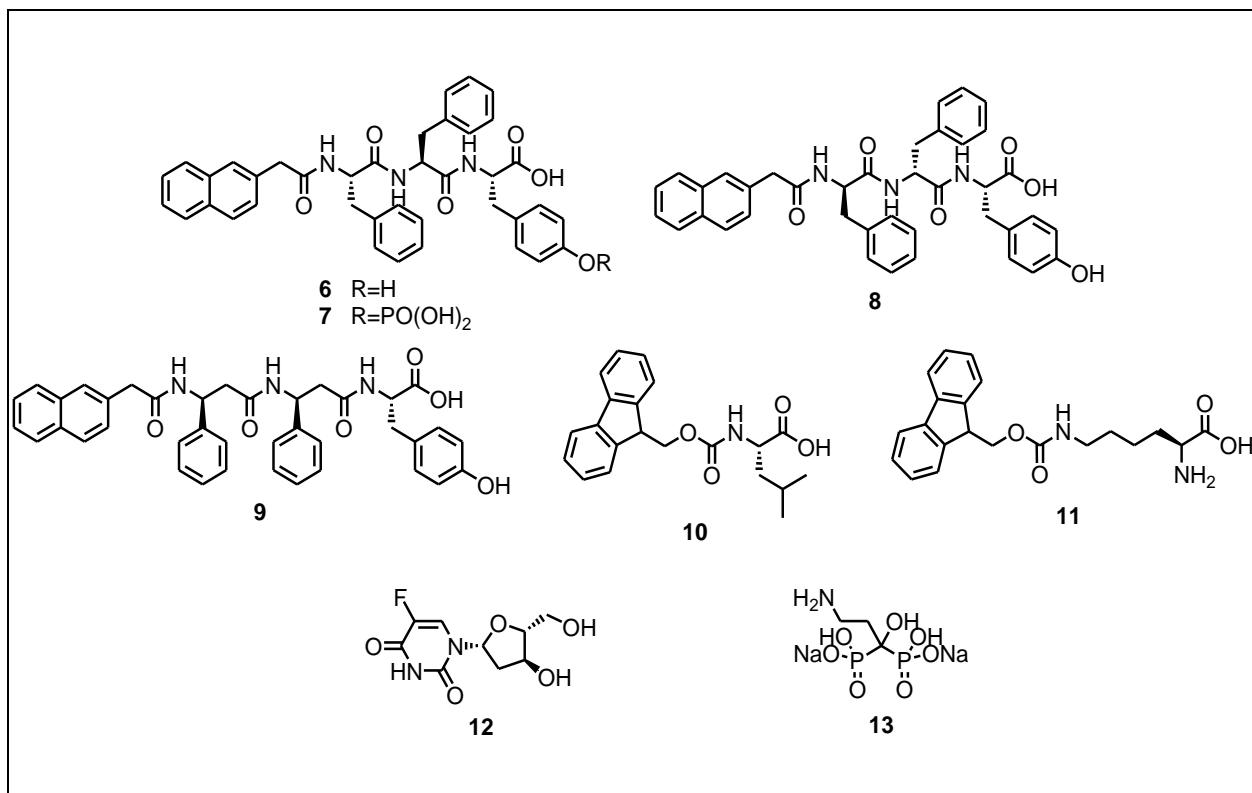


Figure 3. Structures of peptide hydrogelators **6**, **8**, **9** and hydrogel components **10-13**.

In 2009, Bing Xu and coworkers reported the use of another series of Nap-FF-like hydrogelators **14-17** (Figure 4), in which the L-phenylalanine groups were replaced with unnatural variants: D-phenylalanine (**15**), *s*-β³-H-phenylglycine (**16**), and L-4-fluorophenylalanine (**17**).³⁹ These unnatural amino acids were utilized because it was believed that they would be resistant to enzymatic digestion while remaining biocompatible, providing long term stability in the body without any acute toxicity. While all four compounds were able to form hydrogels, the D-phenylalanine and *s*-β³-H-phenylglycine compounds **15** and **16** were found to be resistant to hydrolysis by proteinase K, indicating that they would be suitable vectors for drug delivery requiring long term stability. The hydrogel of **15** was found to be

biocompatible through in vitro assays on HeLa cells and in vivo testing on mice, in which no toxicity, subsequent infection, or inflammation was observed. A radio tracer ($^{125}\text{I-NaI}$) was then incorporated into the hydrogel of the D-phenylalanine compound **15**, which was then injected in the subcutaneous layer of mice. The release of the radio tracer was found to be constant over a twelve hour period following the injection, and was found to be about twice as slow as an analogous saline injection of the tracer. Radio-labeled Epidepride **18** (Figure 4), an iodine-containing drug widely used as a dopamine D2 receptor imaging agent, was also embedded in the gel, and its controlled release was found to be similar to that of the $^{125}\text{I-NaI}$ tracer.

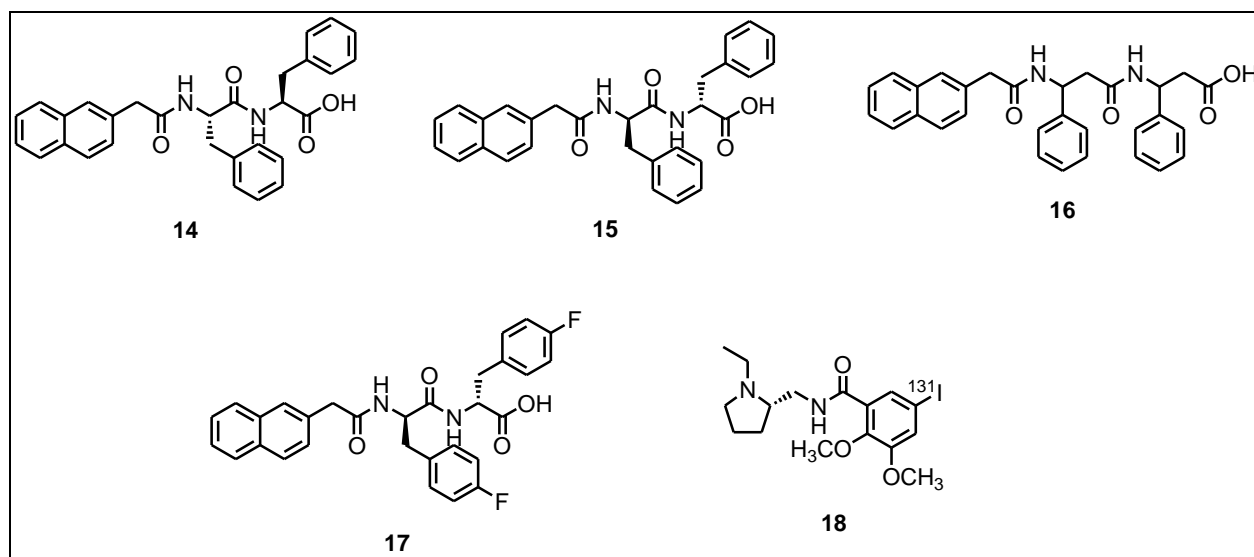


Figure 4. Structure of hydrogelators **14-17** and radio-labeled Epidepride **18**.

Shinshu University in Nagano, Japan hosts two other prominent research groups in the area of amino acid low molecular weight gelators: the research groups of Kenji Hanabusa and Masahiro Suzuki. Suzuki is the former student of Hanabusa, and has continued to collaborate with his former advisor in his research since becoming a professor at Shinshu University. Over

the past five years, they have published several papers together regarding amino acid based supramolecular gelators, the majority of which feature a rather simplistic design; various amino acids, usually L-lysine, are functionalized with long chain alkyl groups.⁴⁴⁻⁴⁹ Most of their papers focus on analysis of the gels, rather than on potential applications.

In 2005, Suzuki and Hanabusa et al. reported that analogues of L-valine **19a-c** and L-isoleucine **20a-c** (Figure 5), which had been functionalized with an octadecylamine group at the C-terminus and an octanedioic acid group at the N-terminus, were able to gelate a variety of organic solvents and oils.⁴⁴ The octanedioic acid moiety was installed as a methyl ester to give compounds **19a** and **20a**, which were deprotected to afford the free acids **19** and **20b**. Subsequent deprotonation of the carboxylic acid groups of **19** and **20b** provided the sodium salts **19c** and **20c**. All six of the compounds were screened for gelation in various organic solvents, oils, and water. The esters (**19a** and **20a**) and free acids (**19b** and **20b**) were insoluble in water, but gelled many of the organic solvents and oils at concentrations as low as 0.7 g/L. The sodium salts (**19c** and **20c**) were insoluble in many of the organic solvents and oils, though they were able to gelate some organic solvents at higher concentrations. In addition, while the sodium salts **19c** and **20c** did not gel pure water, it was found that hydrogels could be formed in the presence of the cationic surfactants n-dodecyltrimethylammonium chloride or n-hexadecyltrimethylammonium chloride (no gelation occurred in the presence of anionic or nonionic surfactants). Comparison of FT-IR data of the organogel of **20b**, the hydrogel of **20c** and dodecyltrimethylammonium chloride in D₂O, and the chloroform solutions of **20a** and **20b** showed that intermolecular amide hydrogen bonding interactions that are typical of amino acid gelators were taking place in both the organogel and the hydrogel. Shifts in the alkyl region for the hydrogel to lower wavenumbers indicated that there were also strong hydrophobic

interactions taking place between the alkyl chains. Electrostatic interactions between the ammonium cation and the carboxylate anion may also contribute to the self-assembly of the gel, though no evidence was offered by the authors to support this claim.

As stated previously, most of Suzuki and Hanabusa's supramolecular gelators are derived from functionalization of L-lysine.^{45-47,49} In 2005, they reported a series of versatile, dimeric, L-lysine monosodium salt gelators **21-27**, in which two L-lysine units are linked by a diacid of varying length (4-12 carbons) at their N^α-termini, and the amino groups of the side chains are acylated with lauric (dodecanoic) acid groups (Figure 5). It was found that when the carboxylic acid groups of both lysine units were deprotonated, no gelation occurred, but the monosodium salts were able to gelate water, a variety of organic solvents, and some aqueous solutions. When the diacid linker was less than eight carbons (compounds **21-25**), an even-odd effect was observed, in which the even-numbered chains (**21**, **23**, and **25**) exhibited stronger aggregation than the odd numbered chains (**22** and **24**), as observed by ¹H NMR, variable temperature FT-IR and a higher gel-sol transition temperature. The results suggested that there were alternate hydrogen bonding modes for the odd and even-numbered chain compounds, due to the parallel or antiparallel arrangement of the carbonyl groups of the linker.

Suzuki and Hanabusa reported organogelation by a series of N^ε-lauroyl-L-lysine derivatives **28-33** which were functionalized at the N^α-terminus with a variety of branched and unbranched alkanoyl groups (Figure 5).⁴⁶ Six different alkanoyl groups were used in the study: hexanoyl **28**, dodecanoyl (lauroyl) **29**, cyclohexylcarbanoyl **30**, 2-ethylhexanoyl **31**, 3,5,5-trimethylhexanoyl **32**, and 2-heptylundecanoyl **33**. The branched alkanoyl groups (**31-33**) performed the best, with the 2-heptylundecanoyl analogue **33** exhibiting organogelation in 24 of the 26 organic solvents and oils tested. IR and NMR were again used to analyze the differences

between the gel and sol states, showing that the hydrogen bonding which is typical of the amide groups was primarily responsible for the self-assembly (though there were some weak interactions between the carboxylic acid groups); interestingly, the IR also showed that Van der Waal's interactions of the alkanoyl side chains were also helping to promote self-assembly in the unbranched analogues, due to their ability to pack more efficiently.

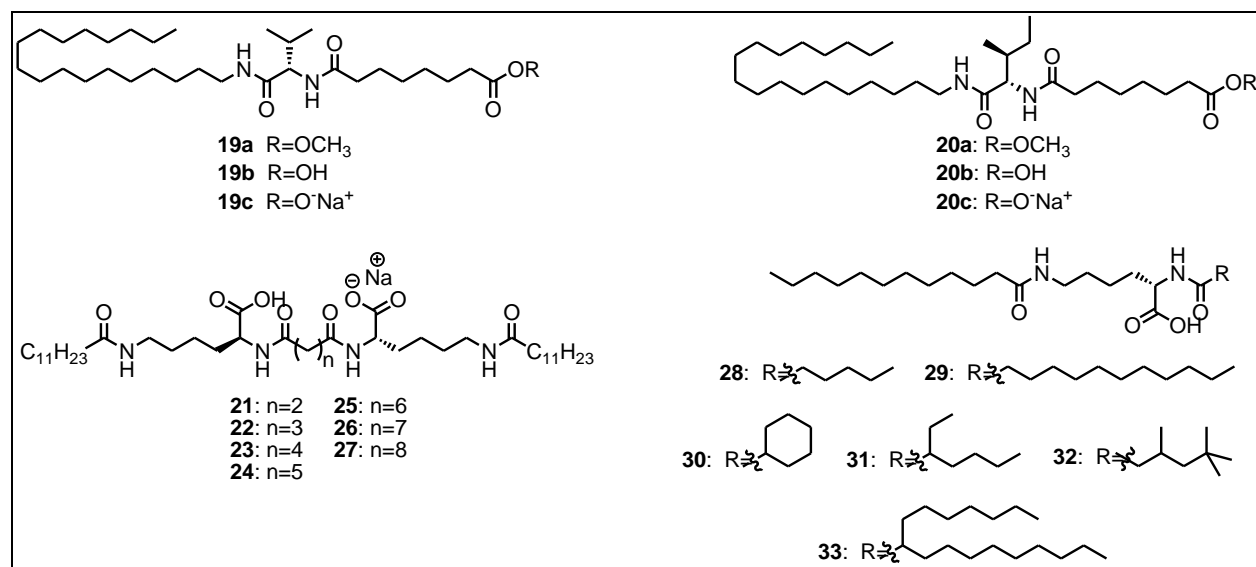


Figure 5. Structures of L-lysine-based low molecular weight gelators synthesized by Suzuki & Hanabusa et al.⁴⁴⁻⁴⁹

Suzuki and Hanabusa also explored two-component amino acid gelator systems, with the ethyl **34** or dodecyl ester **35** of N^ε-dodecyl-L-lysine serving as one component, and one of five N-dodecanoyl L-amino acids (valine **36**, phenylalanine **37**, alanine **38**, glycine **39** were used, along with the N^α,N^ε-didodecanoyl lysine **29** that was previously reported) as the other component (Figure 6).⁴⁷ Individually, the amino acids were poor gelators for the organic solvents tested, often recrystallizing or forming precipitates; in one case, a metastable gel was

formed that collapsed into a precipitate within 24 hours. When mixed together however, most of the combinations (the ethyl ester lysine component **34** with the glycine component **39** gave poor results) yielded stable gels in a variety of organic solvents and oils; if the individual solutions containing the components were mixed together at higher temperature, it took about two hours after cooling to room temperature for gelation to occur, while mixing the solutions together after they had cooled to room temperature separately gave a gel within five minutes. The improved gelation of the two-component system compared to the gelation of the individual components is attributed to the formation of an ion pair between the basic amino group of the lysine component (**34** or **35**) and the free carboxylic acid group of the other amino acid component (**29** and **36-39**).

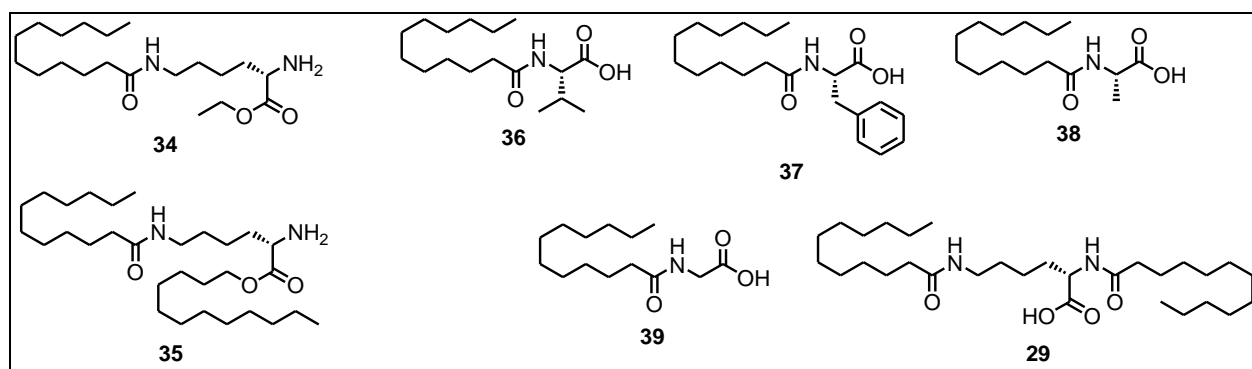


Figure 6. Structures of two-component supramolecular gelators derived from L-amino acids.

In 2009, Suzuki and Hanabusa published a comprehensive review on L-lysine based supramolecular gelators, discussing many of the types of L-lysine gelators that are described above, in addition to many other systems published by other groups.⁴⁹ The review discusses both organogelators and hydrogelators based on L-lysine (Figure 7). Some of the organogelators include: simple analogues, in which the C-termini are esterified with various alkyl groups and the α and ϵ amino groups are acylated to form amides and ureas (**40-42**); dumbbell shaped

gelator **43**, which is similar in structure to the monosodium salt hydrogelators **21-27** shown above; various two component systems, similar to the ones shown in Figure 6, which utilize functionalized lysine units as one or both of the components of a salt pair; photoactive metalloorganogelator **44**, which is comprised of ruthenium and bipyridinyl ligands that are functionalized with lysine groups; and dendritic systems, such as compound **45**, in which several exhaustively Boc-protected lysine units are linked together in various combinations to form dendritic branches, which are connected via an alkylene or an alkylsulfide linker. Various hydrogelators of L-lysine are also discussed, and include: positively charged imidazolium- and pyridinium-containing species; negatively charged species, which have a negatively charged carboxylate at the C-terminus; and non-ionic lysine derivatives, which contain polar, water soluble sugar groups or shorter alkyl chains.

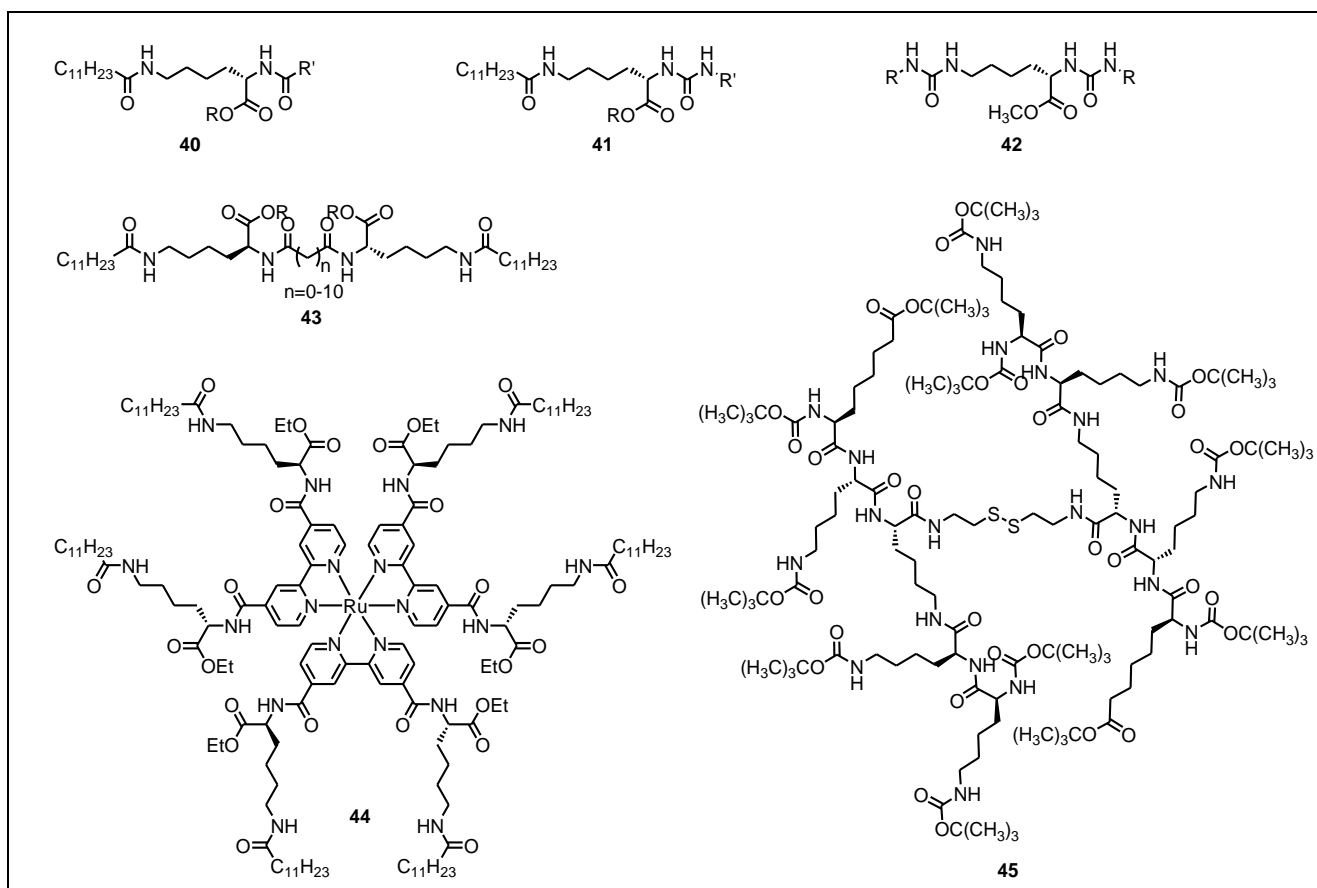


Figure 7. Examples of simple, dumbbell, metal-ligand, and dendrimer L-lysine-based supramolecular organogelators.

Yang's group, in collaboration with Hanabusa, published an interesting example of the use of an amino acid hydrogelator as a chiral template for the synthesis of silica nanostructures from achiral precursors.⁴⁸ Bolaamphiphilic L- or D-valine derivatives **46** and **47**, which were linked at the C-termini by a diaminoalkane tether and acylated at the N-termini with 6-pyridiniumhexanoyl groups (Figure 8), were found to gel water. Furthermore, when 1,4-bis(triethoxysilyl)benzene was treated with acid or base in the hydrogel medium, 1,4-phenylene-silica nanofibers which possessed helicity were formed. The helicity was dependent upon whether the L-valine gelator **46** or the D-valine gelator **47** was used, with the L-valine derivative

giving left-handed silica nanofibers and the D-valine derivative giving right-handed fibers. The pH, concentration of the gelator, and magnitude of the mechanical stirring were all found to have a bearing on the silica nanofiber formation (>5.0 wt% of the gelator and vigorous stirring promoted homogeneity). FESEM, TEM, and WAXRD were used to analyze the silica nanofibers, and it was found that the fibers formed under basic conditions possessed a higher degree of order in their packing than the fibers formed using acidic conditions. Silica nanofibers such as these, which possess chirality, may find use as chiral catalysts for organic synthesis.

The research group of Prasanta Kumar Das has been actively researching the use of amino acids as low molecular weight gelators for the last several years. Most of their supramolecular gelators are derived from functionalization of L-tryptophan or L-phenylalanine.⁵⁰⁻⁵³ In 2007, Das et al. reported a series of trimethylamino-L-tryptophan-based hydrogelators **48-52** (Figure 8), which were acylated at the C-terminal with a series of alkylamines (C₁₀-C₁₈).⁵⁰ The authors found that the minimum gelation concentration was inversely proportional to the alkyl chain length of the C-terminal side chain, with the longer chains giving more efficient gelation. It was also found that the trimethylammonium group (Me₃N-) was necessary for gelation; when the trimethylammonium group of compound **52** was replaced with an ammonium group (H₃N-), the resulting compound was unable to gel water. The gels formed by compounds **49-52** were transparent, and were stable for several months and across a pH range of 2-10. The gel-sol transition temperature increased with concentration, in accordance with typical supramolecular gel behavior. SEM and AFM were used to study the morphology of the gels, which showed the normal, nanofibrous assemblies, and CD, NMR (1D and 2D NOESY), FTIR, luminescence (using the fluorescent probe ANS), and XRD were used to probe the molecular packing. Hydrophobic packing of the alkyl side chains, hydrogen

bonding of adjacent, parallel amide groups, and π -cation type interactions between the trimethylammonium group and the indole ring all contributed to the supramolecular packing. Similar cation- π interactions were not observed for the ammonium analogue, again showing the necessity for the methyl groups at the cationic center.

Another series of gelators (**53-62**, shown in Figure 8) was synthesized and studied to probe the effects of changing the aromatic side chain (phenylalanine, tyrosine, O-methyl tyrosine, sodium salt of tyrosine), as well as the effect of changing the substitution at the N-terminus (trimethylammonium chloride, ammonium chloride, free amino group).⁵¹ The C-terminus was acylated with a hexadecylamino group for all of the analogues in this study. It was found that the trimethylammonium group (**53-56**) was necessary for hydrogelation, as the phenylalanine, tyrosine, and O-methyl tyrosine derivatives which had either a free amino group (**57-59**), or an ammonium group (**60-62**) at the N-terminus failed to form gels. For the trimethylammonium derivatives (**53-56**), the phenylalanine derivative **53**, tyrosine methyl ether **55**, and tyrosine sodium salt **56** were able to form hydrogels; however, the tyrosine analogue **54** failed to gel water. The supramolecular interactions of the gels were studied by NMR (¹H and 2D NOESY), luminescence (again using ANS as a fluorescent probe), and CD spectroscopy. Because the sodium salt **56** could form gels while its protonated analogue **54** could not, the authors were able to use change in pH to trigger a gel-sol or sol-gel transition; below physiological pH of 7.4, the salt became protonated, and precipitation occurred, while addition of sodium hydroxide to the free tyrosine compound **54** reforms the hydrogel. Controlled release studies at different pH values (7.4, 5.5, 2.0) were conducted with vitamin B12 and cytochrome c for all three hydrogels. As they contain no basic groups, no significant variation in release occurred for phenylalanine derivative **53** and O-methyl tyrosine compound **55** over the pH range

tested. However, since the tyrosine sodium salt **56** showed pH reversible gelation, it came as no surprise that it also exhibited pH responsive controlled release, exhibiting more rapid release at pH lower than 7.4.

Das et al. studied a series of amphiphilic L,L-dipeptides (**63**) which were acylated at the N-terminus with a hexadecanoyl group (Figure 8).⁵² The amino acid residues were varied, and included phenylalanine, tryptophan, alanine, valine, isoleucine, and leucine; either phenylalanine or tryptophan was present in each analogue. Both the free acids and the sodium salts were screened for gelation in various aromatic organic solvents, carbon tetrachloride, and water. It was found that subtle shifts in the hydrophathy index (balance between hydrophilicity and hydrophobicity) and the order of the residues affected the gelation significantly. Generally, conversion of the compounds into the corresponding sodium salts improved gelation, and afforded gelation in water (free acids typically did not gel water). SEM and AFM were used to study the morphology of the gels, and CD, FTIR, luminescence, and XRD were used to understand the supramolecular interactions. Hydrogen bonding between adjacent, antiparallel carboxylic acid groups, and between adjacent, parallel stacked amide groups, along with hydrophobic interactions between the alkyl chains, gives rise to the supramolecular matrix. The gelators, due to their pH responsive nature, were found to act as phase-selective carriers for the dye crystal violet **64** (Figure 8). The dye and one of the sodium salt gelators could be added to a mixture of toluene and water, and phase selective gelation of the aqueous phase occurs, trapping the dye in the hydrogel. Treatment with HCl causes the gel to break up, and the resulting dispersion can be heated to give a gel of the toluene layer, with the dye trapped in the organogel.

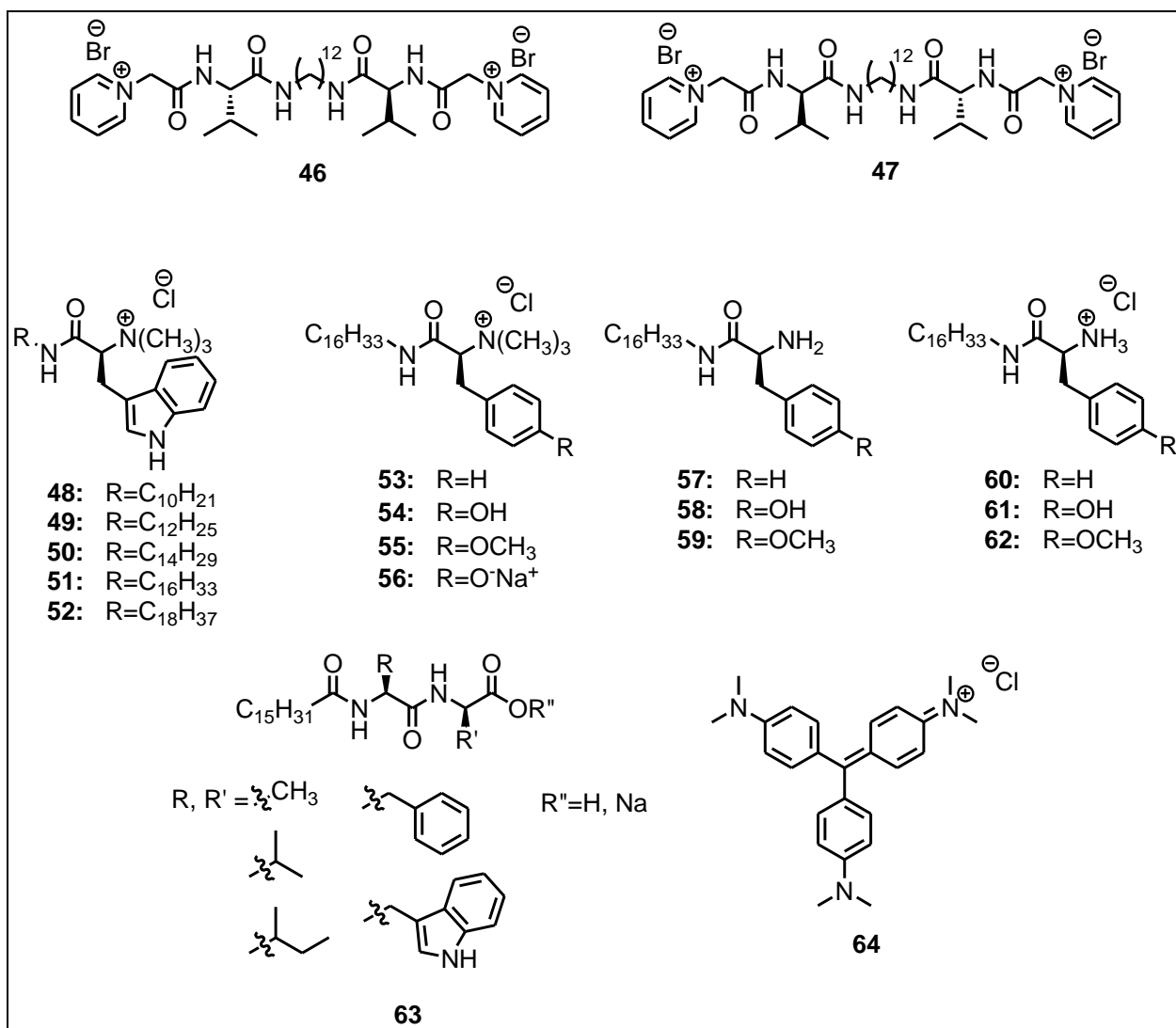


Figure 8. Amphiphilic valine dipeptide gelators **46** and **47**, aromatic L-amino acid gelators **48-63**, and organic dye crystal violet **64**.

A recent publication by the Das group reports a series of amino acid-based, low molecular weight gelators **65** that can gel various ionic liquids **67-69** (Figure 9).⁵³ The resulting "ionogels" were thoroughly characterized by SEM, DSC, ¹H NMR, FTIR, and luminescence (fluorescence). Nineteen different compounds were synthesized in the study by varying the

amino acid (tryptophan, phenylalanine, isoleucine, valine, and alanine were used), the acyl group at the N-terminus (hexadecanoyl, benzoyl, and cyclohexanoyl were used), or the amino group which was coupled to the C-terminus (hexadecanamine or cyclohexylamine were used). A structure-gelation relationship was established, and it was found that a delicate balance of the hydrophobicity and hydrophilicity was important for gelation. The presence of an aromatic moiety tended to increase the gelation efficacy, as did the C-terminal hexadecyl amine group, and the cyclohexanoyl group at the C-terminus; the best compound **66** was the N-cyclohexanoyl tryptophan analogue with the C-terminal hexadecanamine group. Seven different pyridinium and imidazolium ionic liquids (**67-69**) were screened for gelation (some of the ionic liquids were solids at room temperature, and were therefore made into 9:1 IL:water mixtures and tested). The ionogels were used as a template for the synthesis of titanium oxide nanoparticles, and were found to produce nanoparticles with a uniform shape and size (25-30 nm) according to SEM, AFM, and XRD. In the absence of the ionogel template (no gelator or below the MGC), aggregation of the TiO₂ particles occurred. The ionogels were also used in a dye-absorption experiment, and were found to absorb the cationic dye crystal violet **64** and the anionic dye naphthol blue black **70** (Figure 9). The ionogel which was formed by the ionogelator **66** and the hydrophobic ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate **67** was able to absorb both of the dyes more quickly than the corresponding organogel in toluene or the ionic liquid in the absence of the gelator, as observed by the UV-vis absorbance spectra of the aqueous phase.

Miravet and Escuder have also published several papers regarding amino acid-based LMWGs in the past few years.⁵⁴⁻⁵⁶ In 2006, Escuder and Miravet reported an organogelator derived from the tetrapeptide, GAGA, which is a recurring sequence in the β -sheet secondary

structures of *Bombix mora* silk proteins, by functionalization of both termini with long alkyl chains.⁵⁴ The resulting compound **71** was able to gelate tetrahydrofuran, chloroform, toluene, and cyclohexane at 5 mg/mL, and also formed an opaque gel in acetonitrile at 10 mg/mL.

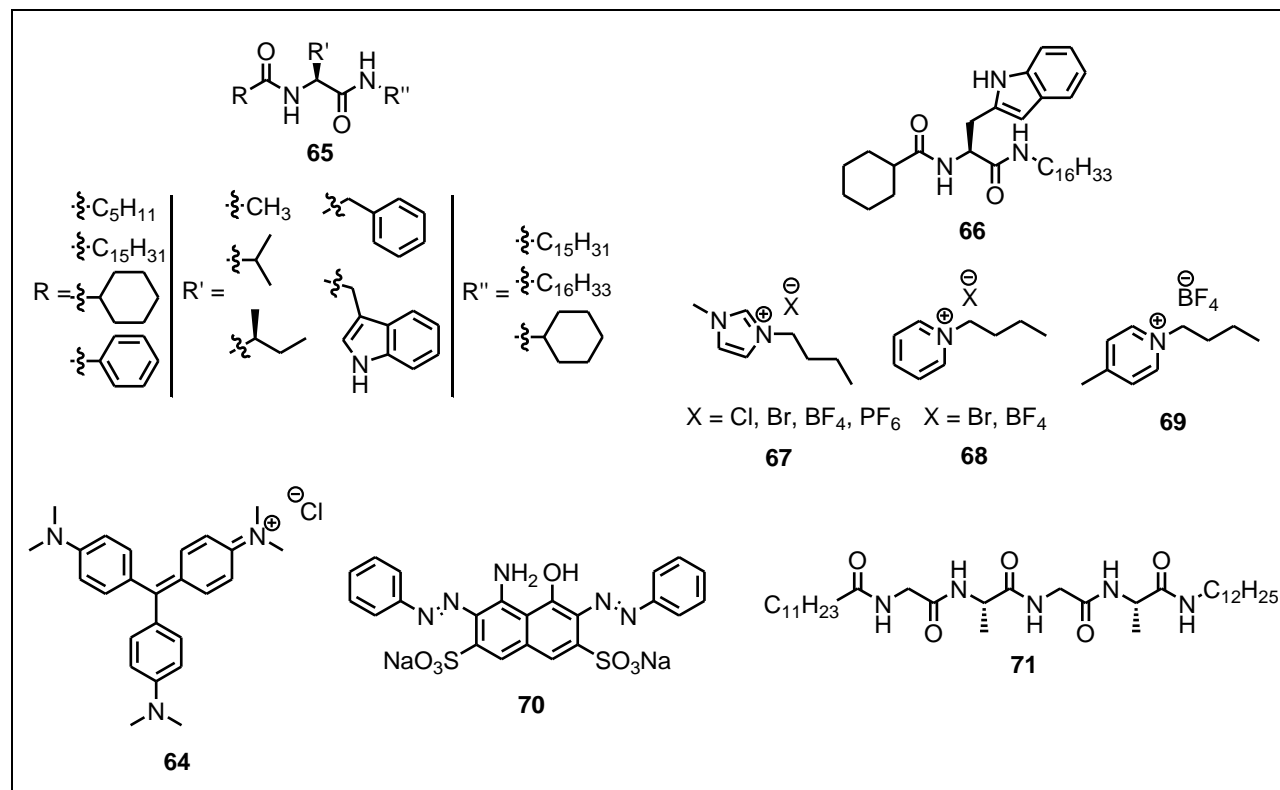


Figure 9. Structures of ionogelators **65**, **66**, ionic liquids **67-69**, dyes **64** and **70**, and silk-inspired organogelator **71**.

XRD, FTIR, and CD spectroscopy confirmed that antiparallel β -sheet motifs were present in the gels, and that the alkyl chains were undergoing hydrophobic packing. The TEM images of the gels formed by **71** all showed the typical, entangled, fibrous morphologies associated with

low molecular weight gelators. Cryo-SEM imaging showed slightly different morphologies, which the authors describe as “fibrillar domains surrounded by micrometer sized pools filled with solvent”; the authors did note, however, that the fibers possessed similar dimensions as those in the TEM images.

The research group of D. K. Smith and I. Hamley, in a collaboration with Miravet and Escuder, reported a series of bolaamphiphilic lysine dimers (**72-75**) which were able to gel toluene and other organic solvents (Figure 10).⁵⁵ The compounds were linked at their C-termini by a 1,9-diaminononane linker, and the α and ϵ amino groups were functionalized with Boc or Cbz groups. The affect that the variations in the amino functionalizations had on the solubility of the gelator were studied using ^1H NMR, and the data was used to calculate several thermodynamic parameters. The calculated enthalpy and entropy of solvation were found to be in good agreement with the gel-sol transition temperatures and other experimental observations.

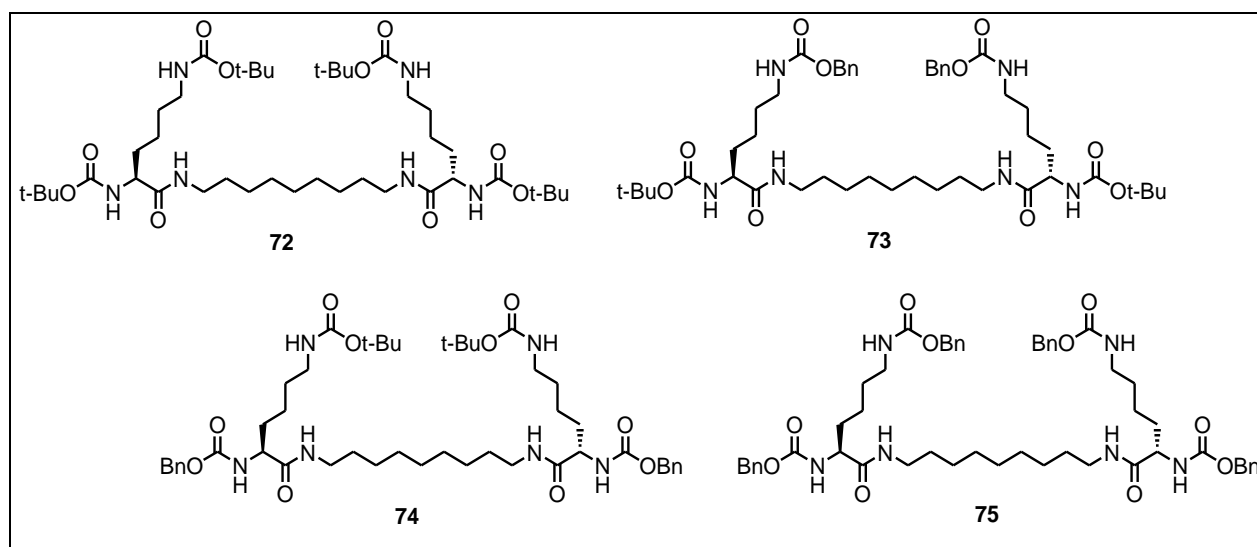


Figure 10. Structure of bolaamphiphile lysine organogelators **72-75**.

In 2009, Escuder and Miravet reported a bolaamphiphilic organogelator **76** (Figure 11) which was created by linking two L-proline-L-valine dipeptides at the C-termini of the valine residues with 1,8-diaminooctane.⁵⁶ The compound was able to gelate nitromethane and nitroethane, and furthermore, the organogel was found to catalyze the nitroaldol Henry reaction between nitromethane or nitroethane and various p-substituted benzoic acids (Figure 11). The organogel of **76** showed increased activity as compared to the solution (at higher temperature) or a non-gelling analogue (at the same temperature and concentration), and gave less of the undesired elimination or double addition side products. The increased activity of the gel is attributed to greater basicity of the proline residues due to the self-assembly.

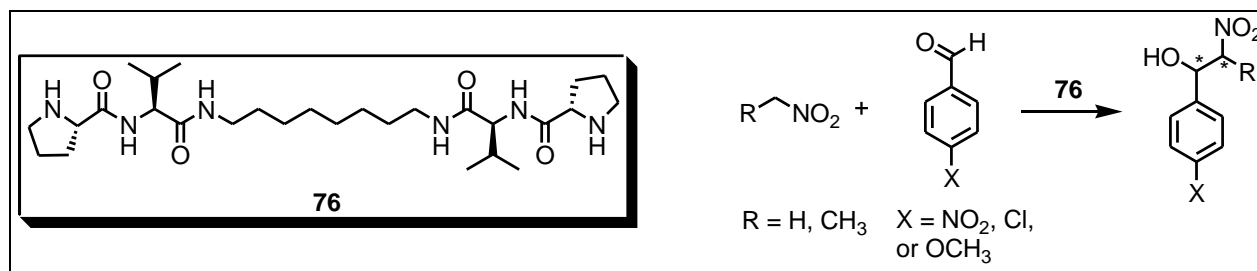


Figure 11. Structure of bolaamphiphile organogelator **76** and its role as a catalyst for the nitroaldol Henry reaction.

Shinkai's group, who works with a variety of structurally varied low molecular weight gelators and polymeric gelators, has published two recent papers regarding the use of amino acids functionalized with gallic acid (linked by a 1,2-diaminoethane linker) which form binary organogels with 2-anthracenecarboxylic acid (2-Ac) in a variety of organic solvents (Figure

12).^{57,58} This binary organogelator systems **77-79** self-assemble through hydrogen bonding and electrostatic interactions. Because of the interactions between the chiral amino acid and the achiral 2-anthracenecarboxylic acid, photodimerization of the 2-anthracenecarboxylic acid occurs stereoselectively via chirality transfer. In the first paper regarding this system, D-alanine was used as the amino acid, and was linked to the tridodecyl ether of gallic acid with a 1,2-diaminoethane linker.⁵⁷ Mixing the alanine moiety and 2-anthracenecarboxylic acid in cyclohexane (or other organic solvents) yielded a thermoreversible organogel **77**. The gel concentration was kept at about four times the minimum gelation concentration to impart greater rigidity to the matrix, and photodimerization was carried out by exposure to 366 nm light.

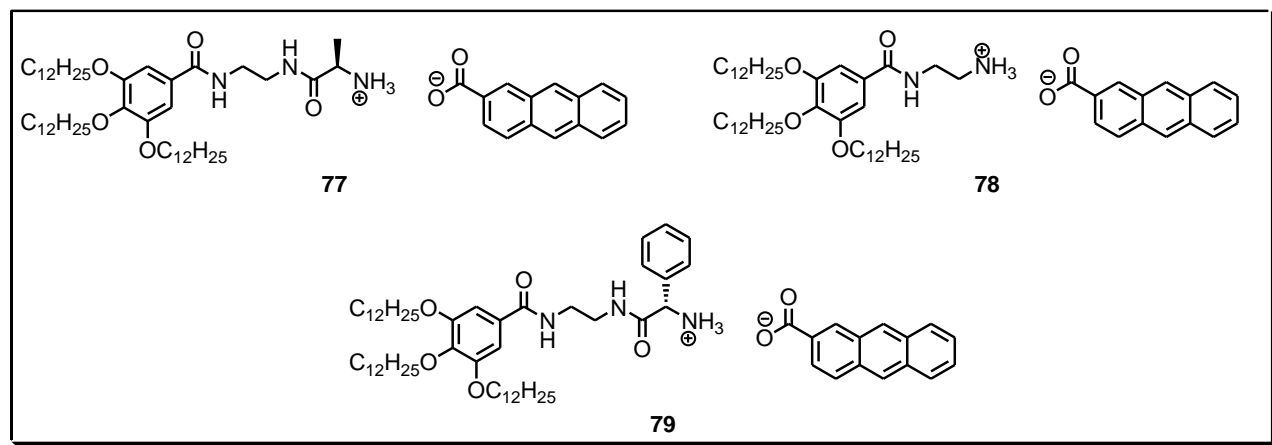


Figure 12. Binary organogelators **77-79** and their role as a chiral template for anthracenecarboxylic acid photodimerization.

In an attempt to better understand this binary system, Shinkai and coworkers designed two additional gelators (**78** and **79**) where the D-alanine unit was replaced with L-2-phenylglycine or nothing (just the gallic acid with the diaminoethane linker) and screened other organic solvents, including the chiral solvent, glycidyl methyl ether (as a racemic mixture; only the compound without the amino acid was tested in enantiomerically pure R and S glycidyl methyl ether).⁵⁸ In the racemic solvent, the achiral gelator **78** gave the same head-to-head stereoselectivity as the previously reported D-alanine system in cyclohexane, but the selectivity was less pronounced; when the enantiomerically pure solvent was used, or when the gels were heated to the sol state, the head-to-tail isomers were the major product. The phenylglycine derivative **79** gave predominantly the head-to-tail isomers, regardless of whether the reaction took place in the gel or sol state. In addition, unlike the initially studied D-alanine/2-Ac/cyclohexane system, the gels remained intact after the photocyclization reaction, and in all of the cases, the gels were found to have higher gel-sol transition temperatures after the reaction. Based on the study, the authors found that the head-to-head stereoselectivity is imparted by the rigidity of the gel, which is increased in nonpolar solvents, where the π -stacking and hydrogen bonding interactions are stronger. The head-to-tail selectivity is favored for more solvated systems (weaker gels), bulkier amino acid substituents, and more polar solvents, which weaken the supramolecular matrix by disrupting the interactions between the gelator molecules. While the stereoselectivity of this system isn't ideal, these initial studies provide preliminary data for further optimization of the system.

Van Esch and coworkers have done some interesting work on a tripodal amino acid hydrogelator systems, in which a central *cis,cis*-1,3,5-cyclohexanetricarbonyl moiety **80** is trifunctionalized with a variety of acidic, basic, or neutral amino acids (Figure 13).^{12,59} The

initial paper focused on the effect that changing the amino acid residues had on gelation, and attempting to use pH as a trigger for hydrogelation.¹² Six different analogues were screened, either mono or dipeptides, which were acidic (**81, 82**), neutral (**83, 84**), or basic (**85, 86**), in an effort to induce pH triggered gel-sol transitions (two additional analogues, **87** and **88**, were also synthesized and screened, but failed to form gels).

With the preliminary data obtained and analyzed, the van Esch group then explored how the use of some of their neutral gelators (**89-92**) in the presence of different surfactants could produce some novel nanostructures.⁵⁹ Depending on the surfactant used, “worm-like” micelles or vesicles could be entrapped or embedded in the gel, with the gel fibers being comprised of only gelator molecules, and the micelles or vesicles containing only surfactant molecules. One of the basic analogues, **89**, which contained a terminal quinoline unit, was able to reversibly gelate in response to changes in pH. Upon exposure to acidic media, the gel was broken down, leaving the vesicles intact. The gelator molecules were then able to diffuse into the vesicles, and subsequent neutralization again led to gelation, forming gel fibers inside the vesicles. Similar experiments controlled release experiments were conducted by Raghavan et al., who showed that fatty acid vesicles could be embedded in a gelatin hydrogel, and then induced to undergo a phase transition to micelles in response to a change in pH.⁶⁰ Some controlled release experiments were also performed, in which the vesicles were loaded with calcein dye, which they released upon the transition to micelles.

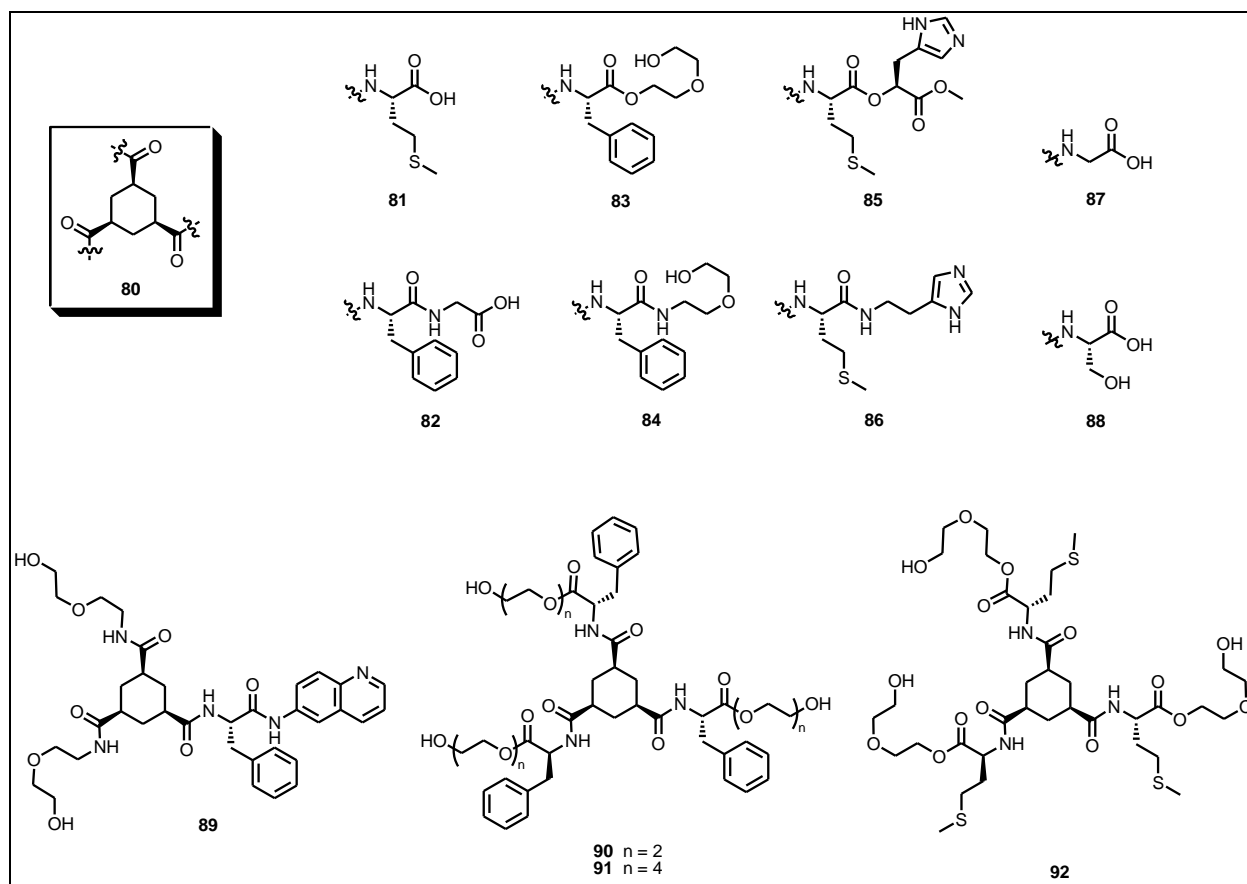


Figure 13. *cis,cis*-tricyclohexylcarbonyl scaffold **80**, amino acid substituents **81-88**, and hydrogelators **89-92**.

B. Carbohydrate-based Low Molecular Weight Gelators

As mentioned previously, another popular motif found in low molecular weight gelators is that of carbohydrates. While not as heavily explored as their amino acid based counterparts,

carbohydrate-based, supramolecular gelators share many of the same advantages: natural abundance, biocompatibility, relative ease of functionalization, inherent chirality, and presence of functional groups which can participate in the intermolecular interactions necessary for self-assembly. Many of the hydrogels found in nature contain sugars, though they are often polymeric; as such, much of the research on carbohydrate-based gelators deals with chemical gels rather than low molecular weight gels.^{26,27,61-66} In addition, the self-assembly of sugar systems is not as well understood as that of amino acids. Still, many researchers set out to design or discover low molecular weight carbohydrate gelators, in order to capitalize on the advantages of their inherent reversibility, flexibility, etc., which result from their noncovalent nature. The carbohydrate moieties in these supramolecular systems can range from simply substituted monosaccharides⁶⁷⁻⁷⁴, to more complex systems containing oligomeric saccharide units⁷⁵⁻⁷⁸.

One of the simpler systems reported in recent years is 1,2-O-(1-ethylpropylidene- α -D-glucofuranose **93**, which was found by the Luboradzki group to gel a variety of organic solvents at concentrations as low as 0.05 wt% (Figure 18).⁶⁷ The gel formed by monosaccharide **93** in toluene was studied by FTIR, Raman, and ¹H NMR spectroscopy, and hydrogen bonding via the free hydroxyl groups was found to be the predominate force for self-assembly. The gel-sol transition temperature was found to increase with concentration, as is customary of supramolecular gelators; this data was used to calculate the enthalpy of dissolution for gelator **93**, which was 72 kJ/mol (highest value for a monosaccharide gelator at the time of publication). The gel-sol transition temperature range was fairly broad, suggesting that the H-bonding networks form aggregates of varying size.

Sakurai and Shinkai reported another simple monosaccharide low molecular weight hydrogelator in 2005.⁶⁸ The monosaccharide, methyl 4,6-O-(p-nitrobenzylidene)- α -D-

glucopyranoside **94**, was able to gel water very efficiently, forming translucent gels at concentrations as low as 0.5 wt% (Figure 18). The authors found that the addition of DNA caused the hydrogel of **94** to become opaque, and caused gelation to occur at lower concentrations, though the resulting gels were less stable, partial gels. The inclusion of DNA caused an increase in the crystallinity of the system, as observed by optical microscopy and x-ray powder diffraction patterns. Fluorescence microscopy and energy-dispersive x-ray spectroscopy indicated that the DNA was incorporated into the gel fibers. It was also found that addition of methyl β -cyclodextrin to the DNA-incorporated hydrogel of **94** caused a gel-to-sol transition, indicating that the gel could have potential as a delivery vehicle (especially for gene therapy) with controlled release by the cyclodextrin. The gel-to-sol transition was quantified by a fluorescence assay measuring the expression of green fluorescence protein. The DNA caused an increase in expression of the protein (as observed by the fluorescence intensity of the control solution, which contained only DNA), but in the presence of the monosaccharide-DNA gel, the expression was decreased; addition of 3 and 10 mM methyl β -cyclodextrin increased the expression (10 mM increased expression of the protein to the same level as the control).

Bing Xu's group has reported the use of a D-glucosamine-based hydrogel in the treatment of wounds.⁶⁹ The gelators **95** and **96** are comprised of D-glucosamine which is N-functionalized with either L- or D-phenylalanine to form an amide bond; the amino acid is N-functionalized with a 2-naphthylacetyl group (Figure 14). The L-Phe analogue **95** gelled water at 2.0 mg/mL, and the rheology studies indicated that its hydrogel was stronger and more viscoelastic than the corresponding D-Phe analogue **96**. TEM imaging showed that the hydrogel of **95** was comprised of densely packed nanofibers of varied size, while the hydrogel of D-Phe analogue **96** was made up of nanoribbons which were more uniform in size; the greater degree of

cross-linking and density of the nanofibers of the L-Phe gel supports the data from the rheology study. Circular dichroism showed that the gelators self-assembled in β -sheet type assemblies. A cytotoxicity assay showed that the hydrogel formed by the D-Phe analogue **96** was slightly more biocompatible, and it was explored as a wound healing agent; mice were cut on their middorsal skin, and the hydrogel was applied ~30 seconds after the cut was made, and was covered by a liquid bandage. After six days, the wounds of the mice which were treated with the hydrogel healed much faster and exhibited less scar tissue than those of the control group, which received only the liquid bandage. No toxicity was observed in the mice treated with the hydrogel over 18 days, and histological cross-sections of the wound areas of the mice showed that the hydrogel-treated wounds were at later stages of the wound healing process, validating the visual observations of the wounds.

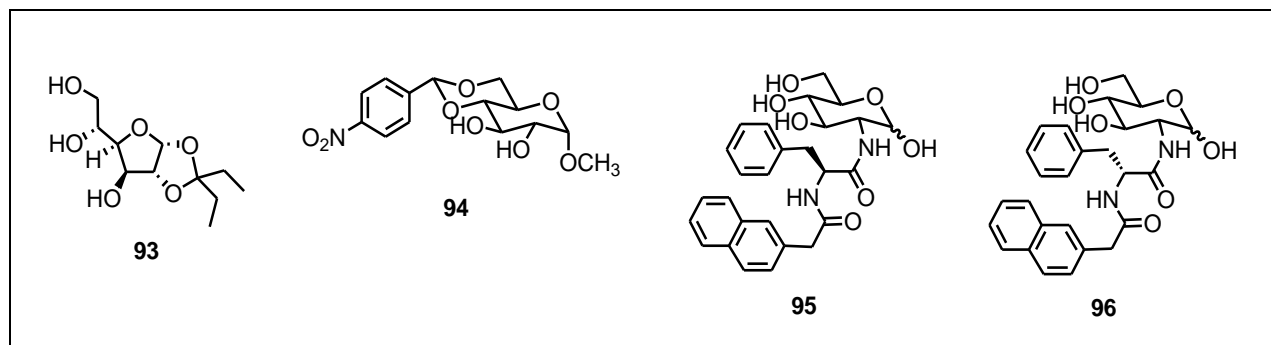


Figure 14. Monosaccharide low molecular weight gelators **93-96**.

A collaborative effort by the research groups of John and Shimizu in 2004 gave some insight into how the degree of unsaturation in the hydrocarbon tail of simple, glucose-based glycolipids **97-100** could affect their organogelation ability (Figure 15).⁷⁰ The compounds which were studied were β -phenoxy-D-glucopyranosides which contain pentadecyl chains with varying

degrees of unsaturation (all *cis*), which were attached to the phenyl ring meta to the phenolic oxygen. Four different compounds were studied: a completely saturated analogue **97**, the pentadec-8-enyl analogue **98**, the pentadec-8,11-dienyl derivative **99**, and the pentadec-8,11,14-trienyl compound **100**. A mixture of all four compounds (~1:10:3:6) was also screened for gelation. The saturated compound **97** was found to gelate a variety of organic solvents, including various nonpolar solvents and several 1:1 organic-aqueous or aqueous alcohol mixtures. Increasing the degree of unsaturation decreased the gelation efficacy, due to disruption of the stacking of the hydrophobic alkyl chains. The monounsaturated compound **98** was only able to form unstable gels in nonpolar solvents, but it was found that it was able to form some of the same gels as the saturated analogue **97** at lower temperature (10°C), though they were significantly less stable; the diene **99** and triene **100** analogues failed to form any gels (even at -6°C), and were soluble in most of the solvents tested. The mixture, which was 50% monoalkene **98**, exhibited similar gelation to the gels formed by the pure monoalkene, though some of the gels were found to be slightly more stable. XRD indicated different packing modes for the aqueous and organic gels, and showed some differences between the saturated and unsaturated aqueous gels, likely due to the kinking of the tail by the double bond. Variable temperature NMR showed that π -stacking of the phenyl ring was playing a part in the aggregation, due to the shifting and changes of the multiplicity of the aromatic signals at higher temperatures. SEM images of the gels showed that the saturated **97** and monounsaturated **98** compounds formed the typical fibrous assemblies in most of the solvents screened, although the cyclohexane gel of the monounsaturated compound **98** exhibited some sheet like assemblies. It was found that these sheets were the result of the xerogel drying process, as optical microscopy of the gel indicated the normal fibrous assemblies.

Another monosaccharide-based low molecular weight gelator was recently reported by the Wan group.⁷¹ The gelator, 4-(4'-ethoxyphenyl)phenyl- β -O-D-glucopyranoside **101**, was able to form gels in acetone, butanol, and 1,2-dichloroethane at concentrations at or above 5 mg/mL (Figure 15). The focus of the paper, however, is the study of the transition of the gel into a crystalline system, which takes place in dioxane/water mixture. The xerogel of **101** in dioxane/water 1:4 was studied by TEM, XRD, and FT-IR, the gel was studied by CD and UV-Vis (as compared to the compound in solution), and an x-ray crystal structure of compound **101** from acetonitrile was obtained, in order to compare and contrast the results with those obtained from the other techniques. The gel-to-crystal transition of **101** was found to be similar to the zipping up of a zipper, and as the transition takes place, the molecules shift, causing different intermolecular interactions to predominate in the crystal form as compared to the gel form. In the gel phase, the molecules were found to self-assemble into helical ribbons, with the molecules aligning in a bilayer motif such that the ethoxy tails of both layers overlapped with one another.

The predominant force for this self-assembly was the π -stacking of the phenyl rings of the individual layers, which were stacked at a slight angle, inducing helicity. As the surface tension forces which guide supramolecular gelation were overcome (which is thought to occur because the shortness of the ethoxy tails do not allow for significant hydrophobic interactions), the individual layers slide toward one another, such that greater overlap of the tails of the individual layers occurs, and the ethoxy groups overlap with the phenyl rings of the opposite layer. The π -stacking forces are interrupted by this shift, due to the intercalation of the ethoxy tails, but the shift also causes the monosaccharide groups of adjacent molecules of a layer to move close enough to one another to undergo hydrogen bonding. In addition, as the molecules are “zipped up” the ethoxy groups get close enough to the monosaccharide groups of the other

layer, that hydrogen bonding between the ethoxyl oxygen and the primary hydroxyl hydrogen of the monosaccharide group takes place. Thus, the intermolecular interactions shift from a surface tension-mediated fibril formation where π -stacking is predominant to an array in which hydrogen bonding is the primary intermolecular force.

Fang's group has reported a series of gelators with general structure **102**, in which a naphthalenesulfonyl group is tethered by different diamino linkers to a gluconic acid moiety (Figure 15).⁷² The length of the linker of **102** was changed to determine the effect on gelation, and the authors chose hydrazine ($n=0$), ethylenediamine ($n=2$), propylenediamine ($n=3$), butylenediamine ($n=4$), and 1,6-diaminohexane ($n=6$). The compounds were screened for gelation at a standard concentration of 2.5 % w/v in a variety of organic solvents and water. The compound with the shortest linker, the hydrazine derivative ($n=0$), was found to be a hydrogelator, but was insoluble in all of the organic solvents tested. The ethylenediamine analogue ($n=2$) was found to be an ambidextrous gelator, not only gelling water more efficiently than the hydrazine derivative, but gelling most of the organic solvents screened. The longer chain linker compounds ($n\geq 3$) showed similar efficacy for gelling organic solvents, but could not gel water. The derivatives with the shorter linkers exhibited ribbon-like structures while the longer chain derivatives exhibited what the authors deemed to be "cauliflower or cotton-like structures", as observed by SEM. The authors also found that the xerogels of the ethylenediamine analogue ($n=2$) from different solvents exhibited different contact angles. Absorbance, fluorescence, CD, FTIR, ¹H NMR, and XRD were used to probe the intermolecular interactions which lead to self-assembly and propose a model for intermolecular packing. The molecules pack due to π -stacking (J-aggregation) of the naphthalene moieties and hydrogen bonding between the hydroxyl groups of the sugar and the amino groups of the linker to give one

dimensional fibrils, which stack helically. The fibrils orient themselves with either the sugar groups or the naphthalene groups pointing outward, depending on the solvent (the CD spectra of the hydrogel gives positive signals, while that of the organogel gives negative signals). The fibrils further aggregate to form larger fibers which make up the gel matrix.

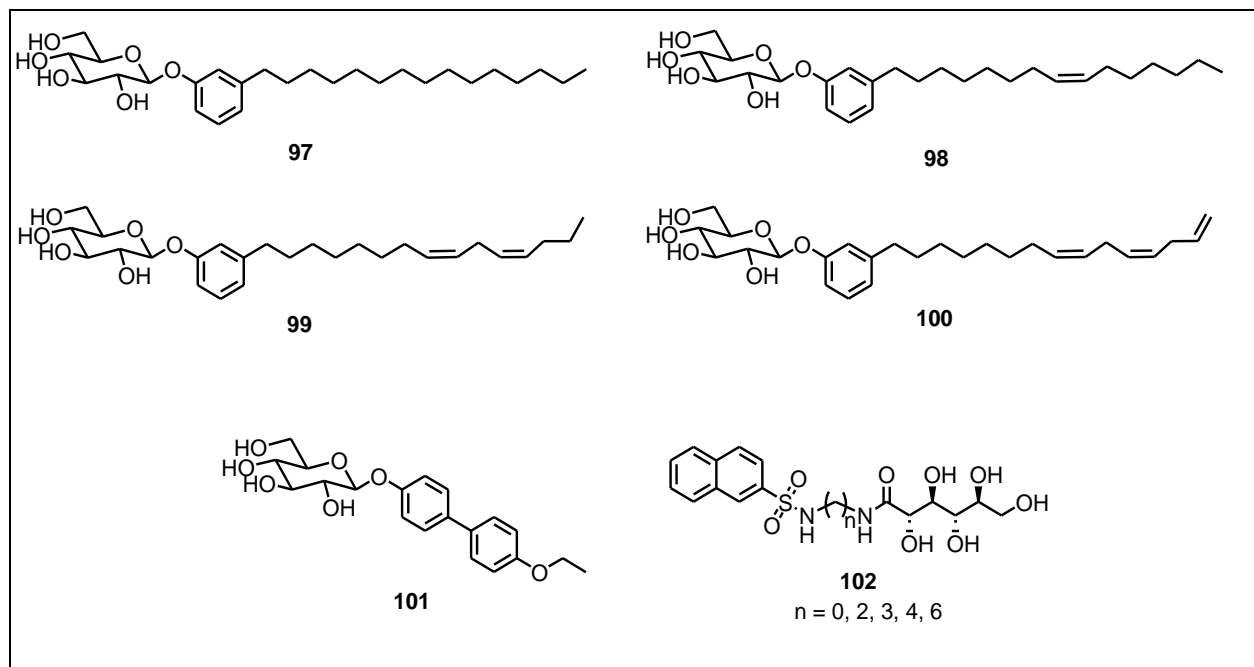


Figure 15. Aryl glycoside gelators **97-101** and glucuronic acid gelator **102**.

Kimizuka and Nakashima have shown that carbohydrates can act as low molecular weight gelators for properly functionalized ionic liquids (Figure 16).⁷³ The ionic liquids used in the study, 1-methyl-4-methoxymethylimidazolium bromide **107** and 1-methyl-4-methoxyethylimidazolium bromide **108**, were able to dissolve a variety of sugars, including glucose, cyclodextrin, amylase, and agarose, at concentrations of at least 10 mg/mL. It was observed that agarose was able to gelate the methoxyethyl ionic liquid **108** at 30 mg/mL, so

gluconic acid derivatives **103-105**, which had been functionalized with glutamic acid diesters (or diamides) containing long chain alkyl groups, were screened for their ability to gelate the ether-containing ionic liquids. The dodecyl ester **103** and the hexadecyl ester **104**, which are insoluble in water, as well as the N,N'-di(3-dodecyloxy)propyl amide **105**, which is water soluble, were all found to gelate the ionic liquids, forming opaque "ionogels" which were stable over three months. The carbohydrate moiety was found to be necessary for gelation, as the similarly structured compound **106**, in which the gluconic acid group was replaced with a trimethylundecanoylammonium bromide group, was unable to gelate, or even be homogeneously dispersed, in the ionic liquids. DSC of the gels indicated that the glycolipids **103-105** were arranged in bilayer membranes, which further assemble into the typical fibrous assemblies associated with low molecular weight gelators, as observed by SEM. Interestingly, for the diamide analogue **105**, the fibers were found to undergo a thermoreversible phase transition into vesicles at higher temperatures; no vesicle formation was observed for the esters **103** and **104**.

Zhang and coworkers have shown that methyl 4,6-O-(4'-aldehydephenylidene)- α -D-glucopyranoside **109** can form thermoreversible, opaque hydrogels at 8 mg/mL (Figure 17).⁷⁴ In addition, the hydrogelator was found to be deactivated by treatment with cysteine **110** (eight other amino acids were tested, but none of them deactivated the gelator) or aqueous acid; treatment with L-cysteine led to the formation of thioaminal **111** (confirmed by ¹H NMR and MS), which was soluble in water, while aqueous acid (pH < 3) hydrolyzed the acetal. The controlled release of the 4,6-O-pyrene acetal of methyl- α -D-glucopyranoside **112** (10 μ M) and the disodium salt of fluorescein **113** (50 μ M) from the hydrogel upon treatment with 0.5 M cysteine solution (serine was used as a control) were studied using fluorescence spectroscopy.

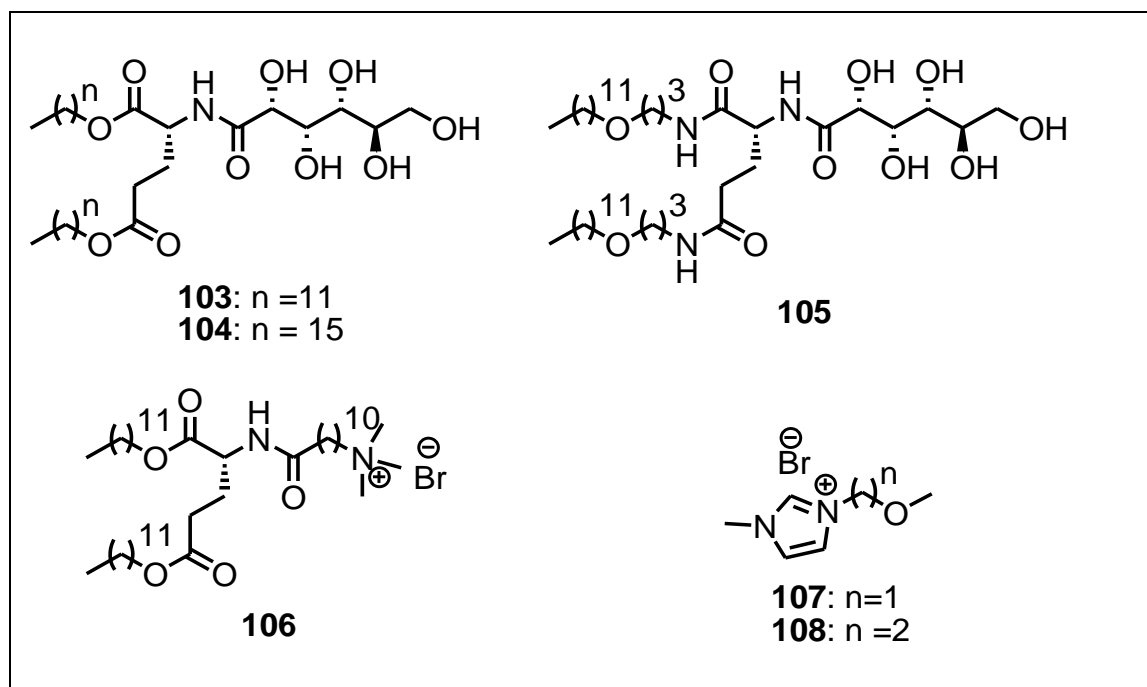


Figure 16. Glycopeptide LMWGs **103-105**, quaternary ammonium derivative **106**, and ionic liquids **107-108**.

While the fluorescein derivative **113** was found to diffuse out of the gel rapidly, regardless of whether the gel was disrupted by cysteine, the pyrene-appended glucopyranoside **112** exhibited good controlled release characteristics in the presence of cysteine, which were dependent on the elapsed time and the hydrogel concentration. The discrepancy between the release of the fluorescein and the pyrene monosaccharide are believed to have occurred because of a greater propensity of the monosaccharide fluorophore to undergo similar intermolecular interactions to those of the gelator molecules.

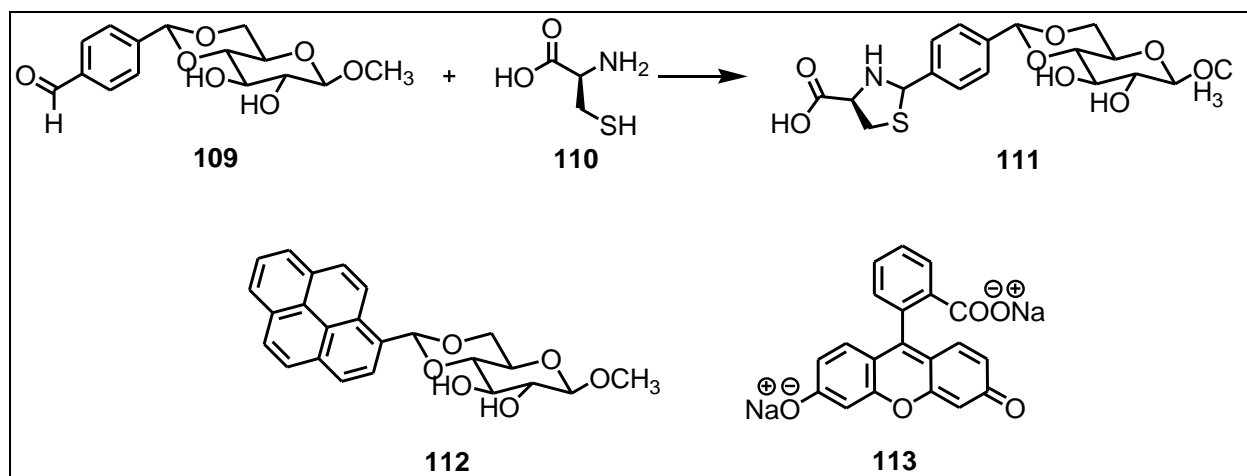


Figure 17. D-Glucose-based hydrogelator **109**, its reaction with cysteine **110** to form nongelator **111**, and fluorescent probes **112** and **113** used to study controlled release.

Oligosaccharide systems have also been utilized as low molecular weight gelators.⁷⁵⁻⁷⁸ John et al. report a series of hydrogelators derived from amygdalin **114** by enzymatic esterification of the primary hydroxyl group (Figure 18).⁷⁵ These glycolipids **115-117** were synthesized in a single step, in >90% yield, without the need for cumbersome protection/deprotection steps. The compounds were able to gel water and a variety of organic solvents at concentrations as low as 0.05 wt% or 0.2 wt%, respectively (the longer chain derivatives proved to be more versatile and efficient). The SEM of the gels showed that the organic gels had a grasslike morphology, while the hydrogel was comprised of helical ribbons; an x-ray crystal structure of the shortest chain compound in water was obtained, along with XRD data for a variety of the gels, which allowed the authors to propose distinct packing modes for the organogels and hydrogels. A hydrophobic drug, curcumin, was used to study enzyme-triggered controlled release from the gel, as promoted by a hydrolase (Lipolase 100L, type EX). The release was measured by absorbance, since curcumin is UV active. When the drug was

entrapped in the hydrogel, no UV signal was seen; as the hydrolase degraded the gel, the curcumin was freed, and a UV signal at 425 nm was detected. Temperature dependent studies showed that the rate of gel degradation was temperature dependant, increasing with increasing temperature (no degradation occurred at 25°C, even after two days). Gel degradation was found to be dependent on the concentration of the hydrolase as well, degrading faster when exposed to higher enzyme concentrations.

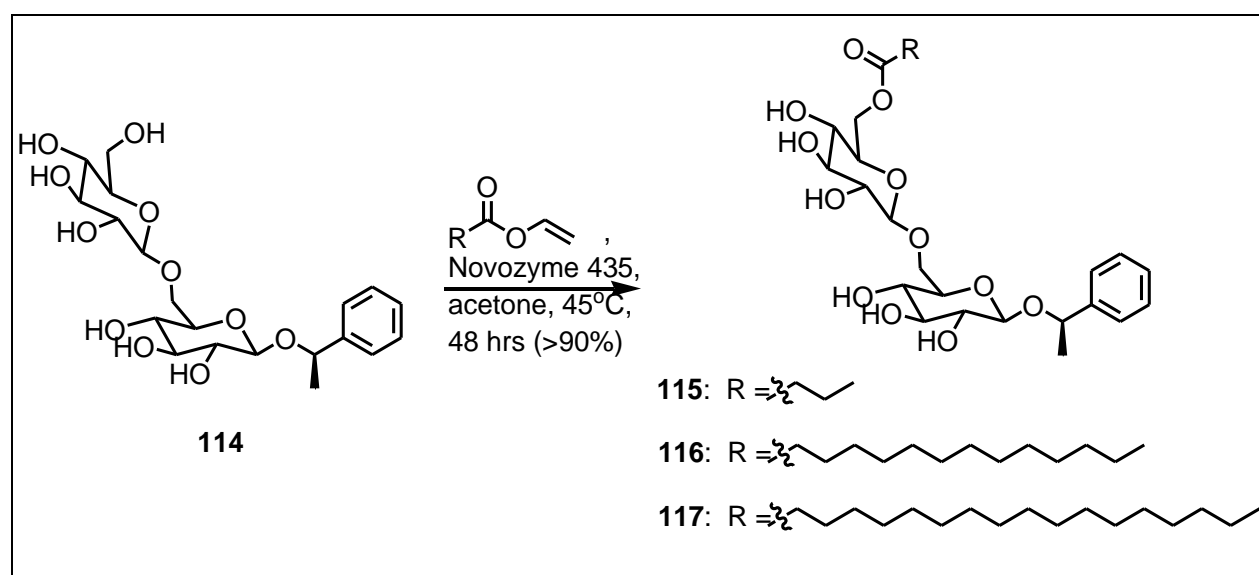


Figure 18. Structure of amygdalin **114** and amygdalin ester LMWGs **115-117**.

Bhattacharya and co-workers reported an interesting hydrogelator **118** (X=OH) comprised of an azobenzene core which was tetrasubstituted with D-xylose monosaccharide units (Figure 19).⁷⁶ The authors originally synthesized a series of compounds, using an azobenzene **118** or bis-terephthalamide core **119** and **120** which was tetrasubstituted with a variety of different functionalized furanosides. The synthesis of the azobenzene tetrasaccharides **118** was quite a bit more elaborate than most supramolecular gelators, involving a dimerization

of nitrobenzene containing two diacetal-protected D-glucofuranoside units to form the azobenzene core, followed by selective acetal deprotection for the primary hydroxyl containing alcohol, oxidative cleavage to give the D-xylofuranosiduronic acid, and an optional functionalization of this newly installed carboxylic acid group with butanol, benzylamine, glycine, or glycine ethyl ester. The bis-terephthalamide derivatives **119** and **120** were constructed in a similar fashion, through dimerization of terephthaloyl chloride with two furanoside-disubstituted aminobenzene units, followed by the same selective deprotection and oxidative cleavage steps. Unfortunately, it was found that only the unfunctionalized D-xylofuranosiduronic acid containing azobenzene **118** (X=OH) was able to gel water, demonstrating the importance of both the azobenzene group and the free carboxylic acid group for gelation (the glycine-functionalized, where X=NHCH₂COOH, derivative did not gel either). The compound was able to gel water (pH 7) at a minimum gelation concentration of 0.1 wt% (it had to be dissolved in 10 μ L of DMSO or methanol first), and the effect of adding DMSO, various salts, or changing the pH were analyzed according to their effect on the gel-sol transition temperature and the minimum gelation concentration (MGC). Addition of DMSO caused a decrease in the thermal stability of the gel, as exhibited by a decrease in the gel-to-sol transition temperature. A pH range of 4-10 was utilized for the pH study, and both the gel-to-sol transition temperature and the MGC showed that the gelator was more efficient at lower pH; as the pH decreases, more of the carboxylic acid groups are protonated and available for hydrogen bonding. The addition of various salts slightly decreased the stability of the gels (MGC increased from 1 to 2 mg/mL, while T_{gel} dropped \sim 8-10 $^{\circ}$ C), but interestingly, the salts affected the kinetics of gelation and afforded gels with different morphologies, as observed by SEM. Finally, the authors studied the effects of photoirradiation, since the azobenzene group can be

isomerized using UV light (~350 nm). In DMSO solution, the trans-to-cis isomerization was completed within fifteen minutes; the hydrogel did not photoisomerize after twenty minutes of UV exposure, indicating that the self-assembly hinders photoisomerization of the double bond.

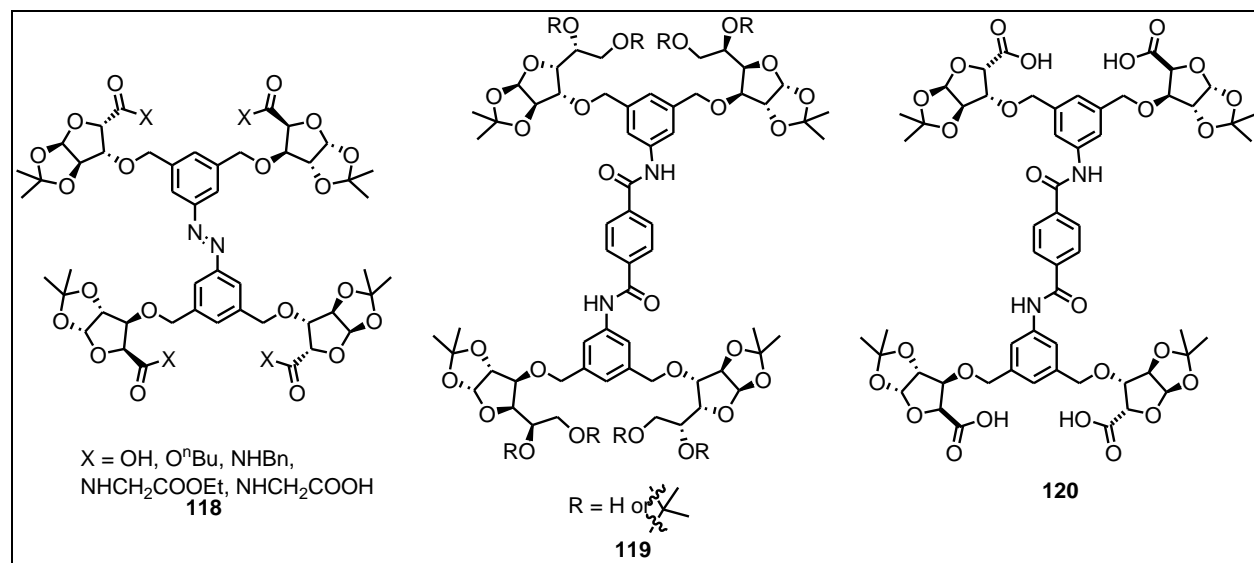


Figure 19. Azobenzene tetrasaccharides **118** and bis-terphthalamide tetrasaccharides **119** and **120**.

Stoddart and Zhao report a light-responsive hydrogel based on a supramolecular complex formed by a cholesterol-appended cyclodextrin **121** and a poly(acrylic) acid **122** which was functionalized with azobenzene side chains at ~8% of its acid groups (Figure 20).⁷⁸ The system takes advantage of the well-studied host-guest chemistry of oligosaccharides like cyclodextrins in order to promote hydrogelation. The cyclodextrin **121** was functionalized with a single deoxycholate unit via a triethylenetetramine linker. The linker provides enough flexibility so that the deoxycholate unit can reside within the hydrophobic pocket of the cyclodextrin ring. The poly(acrylic) acid copolymer **122** was acylated at ~8% of its carboxylic acid groups with 4-(2'-hydroxyethyl)azobenzene units (azobenzenes with ethylene glycol units attached at the para

position of the benzene ring). When the two compounds were mixed (~3:2 ratio of deoxycholate to azobenzene units) at pH 9, formation of a red, transparent hydrogel took place. The hydrogelation was determined (by ^1H ROESY NMR) to occur due to inclusion of the azobenzene unit inside the hydrophobic cavity of the β -cyclodextrin ring; this forces the deoxycholate moiety out into the aqueous environment, where it undergoes hydrophobic Van der Waals interactions with other deoxycholate groups to promote self-assembly. In the absence of the azobenzene copolymer, the deoxycholate groups reside in the hydrophobic pocket of the cyclodextrin ring, and are not available to aggregate with one another.

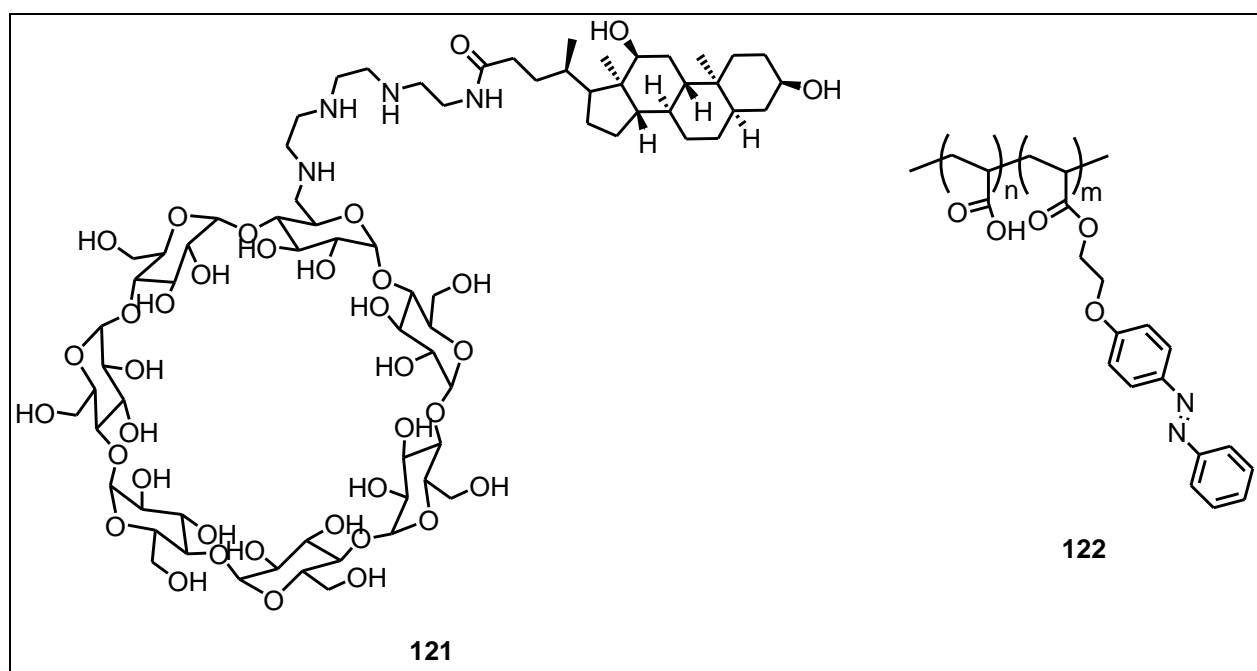


Figure 20. Structures of binary hydrogelator components β -cyclodextrin **121** and azobenzene poly(acrylic acid) **122**.

Induced circular dichroism spectroscopy and UV-vis spectroscopy were used to study the supramolecular interactions which occur during photoirradiation, which causes azobenzene to

undergo a trans-to-cis isomerization (~350 nm). Upon exposure to UV light, a gel-to-sol transition took place, and it was found that the azobenzene was no longer residing in the cyclodextrin hydrophobic pocket. The photoisomerization was reversible if the resulting solution was treated with visible light of ~450 nm, returning the system to the hydrogel state.

C. Steroid-Based Low Molecular Weight Gelators

Another prominent functional group found within the structures of low molecular weight gelators is the steroid ring system. The self-assembly of cholesterol and other steroids is fairly well studied; this hydrophobic ring system can self-assemble via hydrophobic Van der Waal's interactions, leading to the formation of anisotropic assemblies required for gelation. In addition, like carbohydrates and peptides, steroids can act as signaling agents for a variety of biological processes. This can lend extra utility to many cholesterol-based supramolecular gelator systems. Some of the pioneers in the field of low molecular weight gelators have worked on steroid-based systems, including the research groups of Seiji Shinkai⁸¹⁻⁸⁵ and Richard Weiss⁸⁶⁻⁸⁸.

In 2004, Shinkai's group reported a cholesterol-based supramolecular organogelator coordination complex.⁸¹ The complex was comprised of Cu(I) ions which were ligated by two, symmetric bipyridinyl ligands **123**; the bipyridinyl ligand was functionalized at both ends with carbamate-linked cholesteryl groups (Figure 21). The tetrahedral coordination complex was able to form gels in benzonitrile, butyronitrile, and THF:acetonitrile 1:1 (v/v), and the butyronitrile gel exhibited an interesting thermochromic transition from reddish brown to greenish blue upon cooling and subsequent gel formation. The thermochromism was found to be reversible over many cycles. The cholesterol groups were found to be necessary for gelation and the

thermochromic behavior, as the analogous complex formed by the Cu(I) ions with a similar bipyridinyl ligand **124**, in which the cholesterol groups were replaced by 2-ethylhexanol groups, did not gelate butyronitrile or undergo the color change upon heating and cooling. UV-Vis and CD spectroscopy, and TEM were used to characterize the butyronitrile gel formed by Cu(I) and **123**, which was found to be comprised of left-handed helical fibers. The authors also showed that the gel-sol and sol-gel transitions could be triggered by redox reactions; oxidation of the Cu(I) ions to Cu(II) by NOBF₄ induced a gel-sol transition, while reduction of the resulting Cu(II) complex using ascorbic acid once again afforded the gel upon cooling. UV, CD, and TEM analysis of the gel obtained from reducing the Cu(II) complex to Cu(I) were found to be nearly identical to the initial Cu(I) gel.

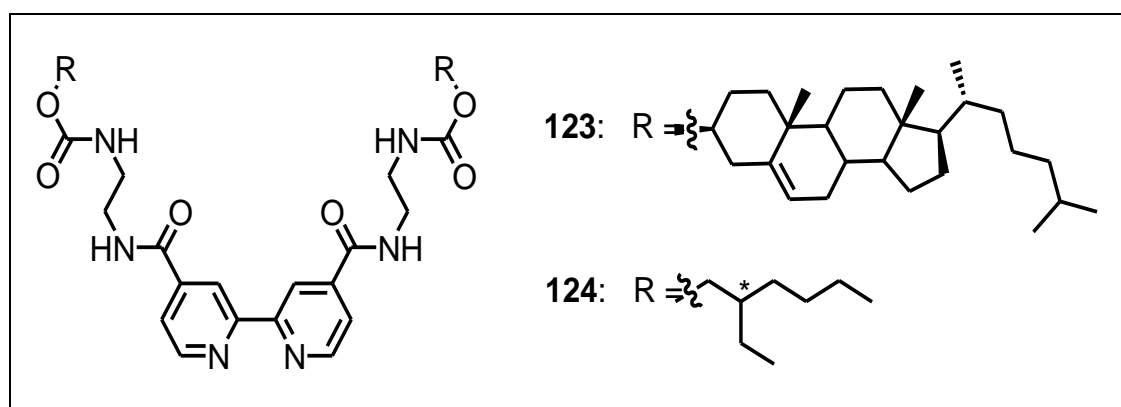


Figure 21. Structure of bis-pyridinyl cholesteryl organogelator **123** and non-gelator **124**.

Shinkai and co-workers reported a similar cholesterol-based organogelator **125** in which two cholesterol groups were appended to a perylene core via carbamate linkages (Figure 22).⁸² A series of compounds **125-128** was synthesized by varying the functionalization of the bay positions of the perylene core, but only the unfunctionalized derivative **125** was able to form

gels. Since the gelator was only able to form partial gels in p-xylene, benzene, and toluene but was insoluble in most alcohols, different mixtures of p-xylene with various alcohols were screened for gelation; many of these mixtures afforded stable, transparent gels of **125** at concentrations above 0.5 wt%. The optimal solvent system was found to be p-xylene:1-propanol 3:1 (MGC of ~0.2 wt%), in which the gel exhibited a fairly high gel-sol transition temperature which was found to increase with concentration, as is typical for low molecular weight gelators.

Optical microscopy and TEM images of the gel of **125** showed the fibrous assemblies which are typically formed by low molecular weight gelators, and the CD spectrum indicated that the perylene moieties twist in an anticlockwise fashion, giving S-chirality, which is not observed in solution. Although the bay-functionalized derivatives **126-128** did not form gels, mixed gels could be formed if the concentration of the unfunctionalized derivative **125** was 50 mol% or greater. This proved to be beneficial, as all of the compounds had different (but overlapping) excitation and emission maxima which were determined by UV absorption and fluorescence spectroscopy. The bay-unfunctionalized derivative **125** was found to have a fluorescence quantum yield of 93%, while the other derivatives exhibited lower efficiency (49-0.1%).

The fluorescence of several mixed gel systems were analyzed, indicating that efficient energy transfer was taking place between the different analogues. Interestingly, the fluorescence intensity of the bay-substituted analogues **126-128** seemed to increase in the gel phase (as opposed to the solution phase) of the mixed gels, despite their lower quantum yields, indicating that gelation improves the efficiency of the energy transfer. Energy transfer from the bay-unfunctionalized derivative **125** to the t-butylphenoxy derivative **126** and the phenyl derivative **127**, and subsequent energy transfer from the two phenyl compounds to the morpholine analogue

128 was found to take place, according to a comparison of the fluorescence spectra of the different mixed gels. The morpholine derivative, which had the lowest fluorescence quantum yield (0.1%) was found to act as an energy sink, as exhibited by its weak fluorescence in the mixed gel system. Since the mixed gel system absorbs light in the visible light region, and the energy can be efficiently transferred to the morpholine analogue **128**, which acts as an energy sink, this organogel system could potentially serve as a means to harvest energy from sunlight.

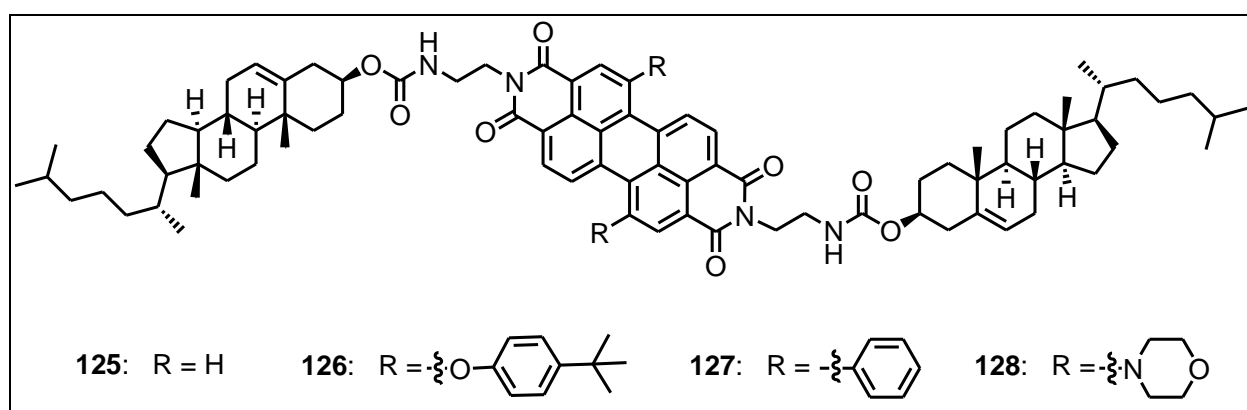


Figure 22. Structure of cholesterol appended perylene organogelators **125-128**.

Sugiyasu, Fujita, and Shinkai reported another pair of fluorescent organogelators **129** and **130**, which contained a phenanthroline core which was symmetrically functionalized with two pendant cholesterol groups (Figure 23).⁸³ The cholesterol groups were attached via either a carbamate linkage (**129**) or an ester linkage (**130**), and analogues **131** & **132**, where the cholesterol groups were replaced with 2-ethylhexanol groups were also prepared. The carbamate-linked cholesterol analogue **129** was able to gelate a variety of different organic solvents, while the ester-linked derivative **130** was only able to form gels in organic solvents in the presence of acid. The UV-Vis and fluorescence excitation and emission bands of all of the

compounds were red shifted upon protonation by TFA, and the gels exhibited similar behavior upon protonation. The CD spectra of the gels of carbamate-linked **129** (with and without TFA) and the gel formed by the protonated ester-linked compound **130** were similar in the 250-300 nm range, indicating that packing of the chiral cholesterol units induce helicity in the packing of the phenanthroline moieties. The signals at higher wavelength (>300 nm) were quite different for the carbamate and ester derivatives, indicating differences in their aggregation, likely due to stronger hydrogen bonding by the carbamate groups. TEM and AFM showed the normal fibrous assemblies found in supramolecular gels.

The TFA treated gels were also able to induce polycondensation of tetraethylorthosilicate by adsorption of the anionic silica particles onto the cationic phenanthroline moieties. Since the organogel fibers were shown to undergo one-dimensional energy transfer and were helically twisted, the polycondensation of the silica created insulated nanowires. The helicity of the organic fibers are transcribed onto the polymeric silica coating, imparting chirality onto the normally achiral polymer; in turn, the polycondensation of the silica onto the organic fibers serves to “lock down” the assembly, converting it from a metastable system to a more permanent, stable one. The gel-sol transition temperature of the gel of ester-linked **130** increased dramatically after the transcription of silica (to over 100°C), indicating that the “inorganic backbone” of the silica serves to reinforce the fibers created by the gelation of the organic molecules. Heating of the composites to higher temperatures (>300°C) removed the organic nanofibers via calcination, demonstrating that it is feasible to remove the organic gelator template, though the silica nanofibers were enlarged by about threefold in the course of the process, according to the TEM images.

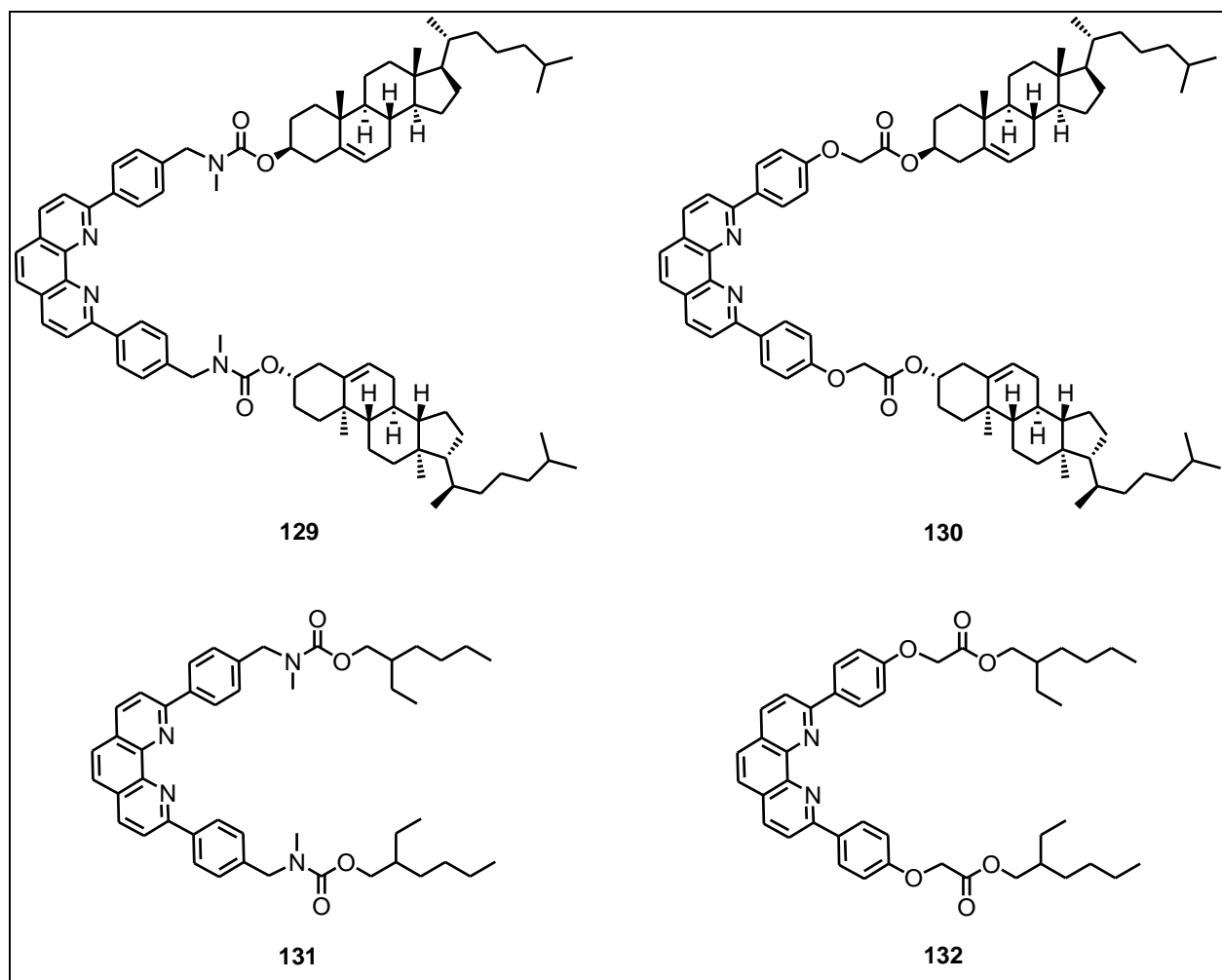


Figure 23. Cholesteryl phenanthroline organogelators **129-130**, and nongelator analogues **131-132**.

Shinkai and co-workers developed a series of oligothiophene gelators (Figure 24) with the general structure **133** which were functionalized at both ends with cholesterol groups via ethylene diamide linkers (thiophene was amide linked, cholesterol was carbamate linked).⁸⁴ The series was comprised of the tetra-, penta-, and hexathiophene derivatives which formed transparent gels in several nonpolar organic solvents at concentrations as low as 1.5 mM. The Van der Waals interactions which lead to aggregation of the cholesterol moieties helped the polythiophene rings, which normally rapidly rotate between syn and anti conformations in

solution, to selectively adopt the anti configuration, in order to maximize π -stacking interactions (the predominance of the anti configuration was confirmed by CD and Raman spectroscopy). In this way, the cholesterol and thiophene groups exhibit cooperative modes of aggregation. The gels were also found to be thermochromic, exhibiting a color change from red to yellow upon heating. In addition, it was also found that the gel-sol transition could be stimulated by redox conditions; addition of FeCl_3 as an oxidizing agent facilitated a transition from the red gel to a reddish-brown solution, and subsequent treatment of the solution with ascorbic acid gave the red gel again. The entire redox cycle was done at room temperature, showing that the transition can be done without heat and providing an alternative triggering mechanism for the phase transition of the system.

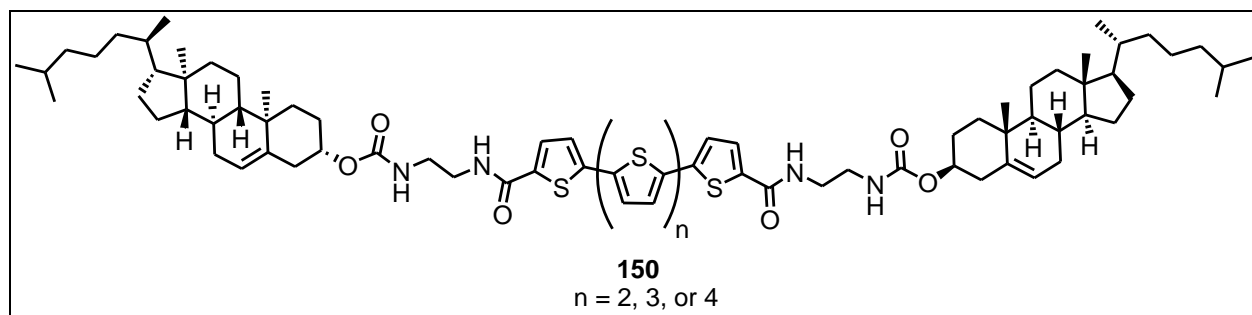


Figure 24. Cholesterol-containing oligothiophene organogelators **133**.

Shinkai et al. reported a simpler series of organogelators **134-137** (Figure 25) derived from cholesterol, which may have been inspired by the previously reported phenanthroline system. In this streamlined system, the cholesterol is still functionalized with a carbamate group, which is directly functionalized with 4-aminopyridine, 3-aminopyridine, or 2-aminopyridine, to give compounds **134**, **135**, and **136**, respectively.⁸⁵ A diverse range of polar and nonpolar

organic solvents and water were screened for gelation, and it was found that the 3-aminopyridinyl derivative **135** performed poorly, only gelling anisole and partially gelling toluene, while the 2-aminopyridinyl analogue **136** formed partial gels in many of the polar solvents and nonpolar aliphatic solvents. The 4-aminopyridinyl analogue **134** was found to be both a versatile and efficient gelator, gelating most of the organic solvents tested, at concentrations as low as 0.5 wt%. The morphologies of the gels were found to be heavily dependent on the nature of the gelating solvent and preparation of the xerogels.

The properties of the gels, including their morphology, were also found to change in response to the addition of various transition metal ions, with Ag(I) ions eliciting the most favorable response. The solution formed by the 3-pyridinyl derivative **135** in benzene was found to gelate in the presence of silver triflate, and the resulting gel exhibits a fibrillar structure (the solution contained rod-like assemblies). Finally, the authors demonstrated that the organogel could be used as a template for the growth of polymeric porphyrin nanotubes. A solution of zinc-chelated porphyrins **137**, which were tetrasubstituted with methacrylate ester groups, was allowed to diffuse into the gel, causing the gel to turn a bright violet color. Shifts in the UV absorption spectra indicated that the porphyrins were interacting with the pyridinyl groups of the organogelator molecules via interactions with the zinc ions. Polymerization of the methacrylate groups was then photoinduced, and the organogelator molecules were partially removed by washing the reaction mixture with chloroform, in which the compound is soluble. Upon partial isolation, it was found that the organogelators formed porphyrin nanotubes, as observed by TEM.

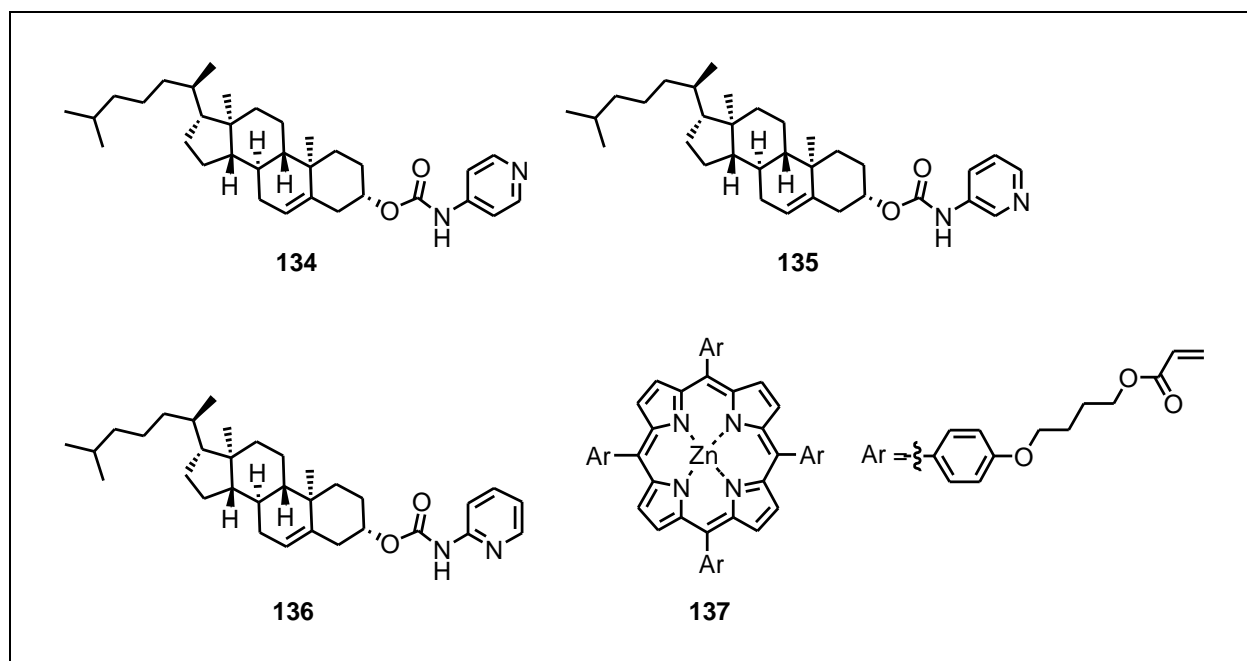


Figure 25. Cholesteryl-aminopyridinyl carbamate organogelators **134-136** and porphyrin **137**.

Richard Weiss has published several papers, including a detailed review⁸⁷, regarding steroid-based organogelators.⁸⁶⁻⁸⁸ Several of the systems that the Weiss group has studied belong to the so-called ALS family of compounds.^{86,87} ALS stands for aromatic-linker-steroid, and all of the compounds in this family contain an aromatic moiety tethered to a steroid by a spacer, or linker, as the name suggests. The aromatic moieties, linkers, and steroid components can vary widely in structure and functionalization, giving rise to a potentially large chemical space in which these compounds reside. Weiss has also worked on steroid-based organogelators which do not belong to the ALS family, including a recent paper that discusses another series of organogelators derived from esters of the naturally-occurring Arjunolic acid.⁸⁸

In a collaboration with Pierre Terech (co-author for the heavily cited, fundamental review regarding organogelators³), Weiss and co-workers have reported an organogelator from the ALS family, 5 α -cholestan-3 β -yl N-(2-naphthyl)-carbamate **138**, or CNC, which can gel n-nonane and

n-dodecane (Figure 26).⁸⁶ The main focus of the paper is to understand the kinetics of gelation, which the authors do by applying the results obtained from time-dependent circular dichroism spectroscopy, fluorescence spectroscopy, small angle neutron scattering, and rheology to the Avrami model for crystallization and microscopic phase separation. Different concentrations and incubation temperatures were utilized in the study as well, in order to determine their effect on the kinetics; optical microscopy images show that the morphology of the aggregates evolves with increasing incubation temperature for the 1.0 wt% gel of **138** in n-octane. As each technique gives a different type of information, a fairly conclusive picture of the gelation kinetics can be obtained. The results from all four analyses suggest that one-dimensional, interface-controlled growth results from an instantaneous (zero-order) nucleation mechanism.

The rheology experiments indicated that there were two types of nucleation kinetics which occur: early on, independent nucleation to form independent fibrils takes place, which then transitions into a period where supramolecular cross-linking occurs to form the extended network. This difference in kinetics is only seen in the rheology measurements, and the authors attribute the discrepancy to the inability of the other techniques to differentiate between the two types of fibers (individual fibrils and “cross-linked” fibers). The kinetics model indicated that a sharp dependence on temperature occurs at around 30°C and above (at which point, gelation slows down significantly), which correlates well with the observed morphological changes in the optical microscopy images taken at various temperatures. In this temperature range (>30°C), a concentration dependence also exists, where the gelation rate falls off rapidly below 1.0 wt%, as one would expect.

A review by Weiss and Matthew George, another prominent researcher in the supramolecular gelator field, focuses on ALS supramolecular gelators, though a brief discussion

of simpler systems is included as well.⁸⁷ Using cholesteryl-4-(2-anthryloxy)butanoate **139** as a reference point, the review discusses the effects that structural variations on the aromatic, linker, or steroid portion of the molecules have on gelation (Figure 26). According to the report, it is believed that structural variations which force the molecules to deviate from a “rod-like” shape have a detrimental effect on gelation. For the variation at the aromatic portion of the molecule, the authors conclude that larger, more “rod-like” aromatic moieties promote gelation better than shorter ones. The ideal linker portion of the molecules is four carbons in length, and usually contains a carbamate, amide, urea, or ester functionality at one or both of the ends, to help promote hydrogen bonding and increase intermolecular aggregation. Deviations in the length of the linker can alter gelation by changing the shape of the molecules to a less rod-like form. In addition, the addition of hydrogen bonding groups must be done carefully, as hydrogen bonding can promote aggregation that is not anisotropic, hindering gelation.

Variations in the steroidal unit are less explored, and at the time of the publication, the authors report that no comprehensive studies involving systematic alteration of the steroid moiety had been reported. However, Weiss and George do point out that long hydrocarbon tail groups are preferred over shorter chains, and polar ester groups are also not well tolerated. In addition, the presence of the double bond at C5 seems to affect the overall solubility of the compounds, and may also affect gelation due to conformational changes in the steroidal rings, which would affect their aggregation.

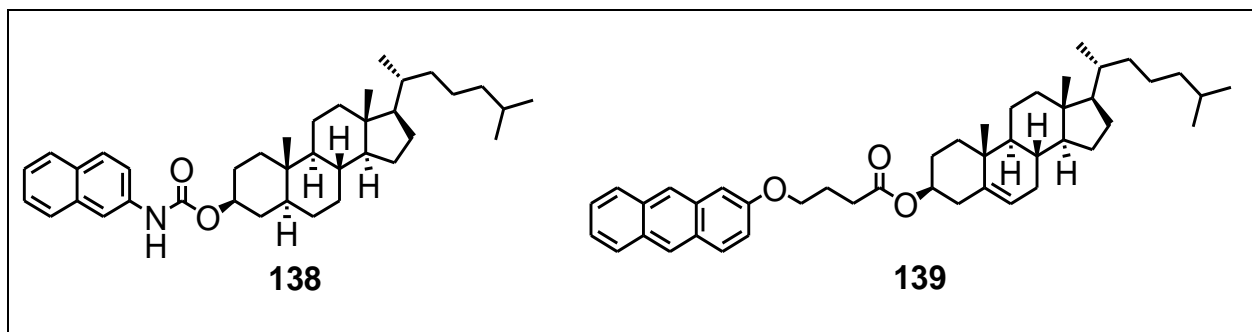


Figure 26. Structure of 5 α -cholestan-3 β -yl N-(2-naphthyl)-carbamate **138** and cholesteryl-4-(2-anthryloxy)butanoate **139**.

Weiss and co-workers reported a series of organogelators derived from esterification of Arjunolic acid **140**, a naturally occurring plant metabolite obtained from *Terminalia arjuna* (Figure 27).⁸⁸ The molecule contains no aromatic group, and as such, is not a member of the ALS family of gelators. The authors hoped that the absence of the aromatic moiety would help them to better understand the directing effect of the steroidal group on self-assembly. Although Arjunolic acid **140** is technically not a steroid, its structure is quite similar (it is a triterpenoid), and it should self-assemble in the same fashion. Arjunolic acid was esterified with a variety of different n-alkyl halides (or tosylates) to give the corresponding esters; the methyl **141**, ethyl **142**, butyl **143**, octyl **144**, decyl **145**, dodecyl **146**, hexadecyl **147**, and octadecyl **148** esters were synthesized, along with the p-nitrobenzyl ester **149**.

Gel testing showed that the esterification improved solubility in nonpolar aliphatic and aromatic organic solvents, and promoted gelation. The ethyl ester **142** was able to gel most of the aromatic solvents at 3 wt%, while many of the aliphatic solvents were gelled at 0.2 wt%. The butyl arjunoate **143** was able to gel a few more of the solvents, but at higher concentrations. The longer chain esters (**144-148**) were only able to gel the aliphatic solvents, and the

nitrobenzyl ester **149** could gel aromatic and aliphatic solvents, many at concentrations of 1 wt%. Right-handed helical ribbons or fibers were observed by SEM and TEM, which were found to be ~10 times larger than the molecular length, suggesting that the molecules pack into individual fibrils, which then entangle into bundles to form the larger fibers. DSC and XRD analysis showed that the gels were disordered, and not very crystalline in character, as one would expect from an entangled fibrous network. Time-dependent CD analysis of the gel formation of the nitrobenzyl ester **149** in chloroform:cyclohexane 1:1 as it cooled from ~80°C was used to analyze the kinetics of gelation, and showed that one-dimensional nucleation and growth were occurring.

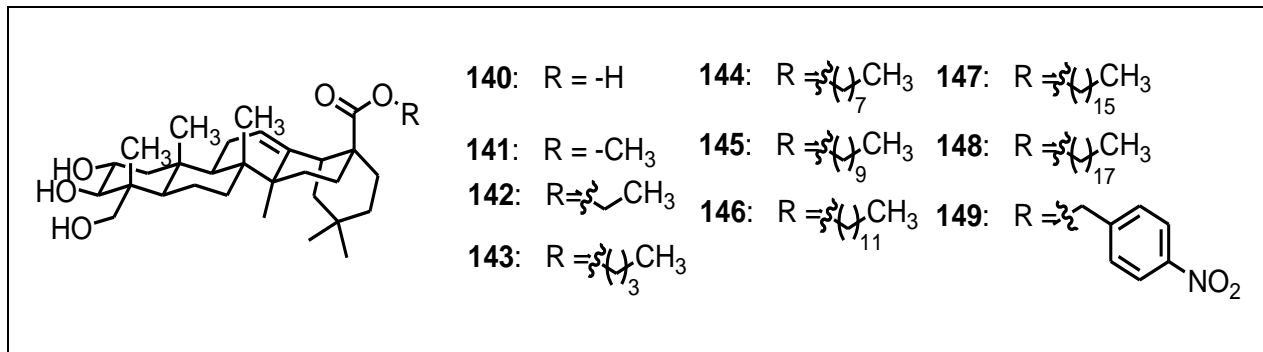


Figure 27. General structure of arjunolic acid **140** and its esters **141-149**.

Zhang and co-workers have reported a cholesterol-based gelator **150** which contains an N-phenolic maleimide unit attached via a carbonate linkage (Figure 28).⁸⁹ The maleimide unit was found to readily react with thiols via a conjugate addition reaction to give compounds **151** and **152**, which also formed gels in various organic solvents. SEM and AFM images of the gels showed that the xerogels were comprised of spongy, nanofibrous networks with fibers ~50 nm in diameter (~200 nm for the n-dodecylthiol derivative), though globular, worm-like assemblies

were also observed for both thiol derivatives by AFM. CD for the compounds showed no signals in solution, while strong signals were observed for the cyclohexane gels of maleimide **150** and n-dodecylthiol derivative **152**. The gel of the n-hexylthiol compound **151** exhibited weaker signals which were opposite to those exhibited by the n-dodecylthiol derivative **152**, indicating that the fibers which make up the gels have the opposite helicity. Based on the d-spacing values obtained from XRD, the authors propose a parallel, head-to-tail arrangement of the molecules.

The authors showed that the conjugate addition reaction could be used as a chemoresponsive trigger for gelation by adding a solution of n-hexylthiol and triethylamine (as a catalyst) to the gel formed by the unfunctionalized maleimide **150** compound in cyclohexane. After two hours, a gel-to-sol transition was observed, since the n-hexylthiol compound **151** had a higher minimum gelation concentration value than the unfunctionalized maleimide analogue **150**. In principle, similar sol-to-gel transitions should also be possible, since the thiol functionalized compounds were able to gelate additional solvents that the unfunctionalized maleimide compound could not; however, the authors did not report any such chemically-triggered sol-to-gel transitions.

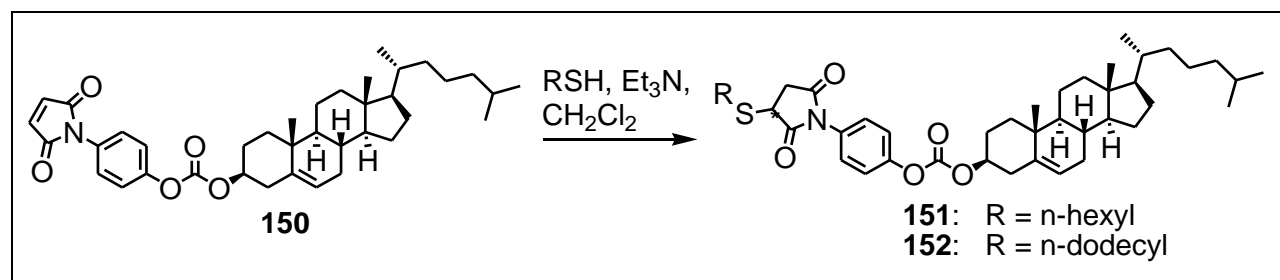


Figure 28. Cholesterol-containing maleimide gelator **150** and its conjugate addition products **151-152**.

Lu et al. have reported an organogelator **153** which is able to gelate benzene, toluene, cyclohexane, and several mixtures of these solvents, at concentrations as low as 0.4 wt% (Figure 29).⁹⁰ The gelator contains a salen moiety which is appended on both ends with cholesterol units, and was found to exhibit some interesting thermochromic and photochromic behavior. SEM imaging of the xerogel showed that the cyclohexane gel of **153** was comprised of the typical entangled fibrous networks, with fibers ranging from 25-100 nm. The conformation of the molecule was determined using semi-empirical quantum modeling, XRD was used to determine the d-spacing, and UV-Vis analysis showed a red shift, indicating J-aggregation. All of this information was used to propose a packing structure for the gel, in which the V-shaped molecules are packed in a parallel fashion, at an angle; these individual fibrils then entwine and entangle to form the larger fibers observed by SEM.

The sol-to-gel transition was accompanied by a thermochromic transition from a nearly colorless solution to a bright yellow gel. This transition was found to be reversible, and was exhibited over many heating-cooling cycles. The UV-Vis and fluorescence spectra showed a temperature dependency as well, as one would expect, and the thermochromic behavior was found to arise from tautomerization between the lower energy E-OH state and the higher energy Z-NH state. When ethanol was added to the cyclohexane gel of **153**, the gel underwent a gel-to-sol transition, presumably due to disruption of the hydrogen bonding network. The gel, which had strong green emission, had a quantum yield ~600 times greater than the solution, which weakly emits blue light.

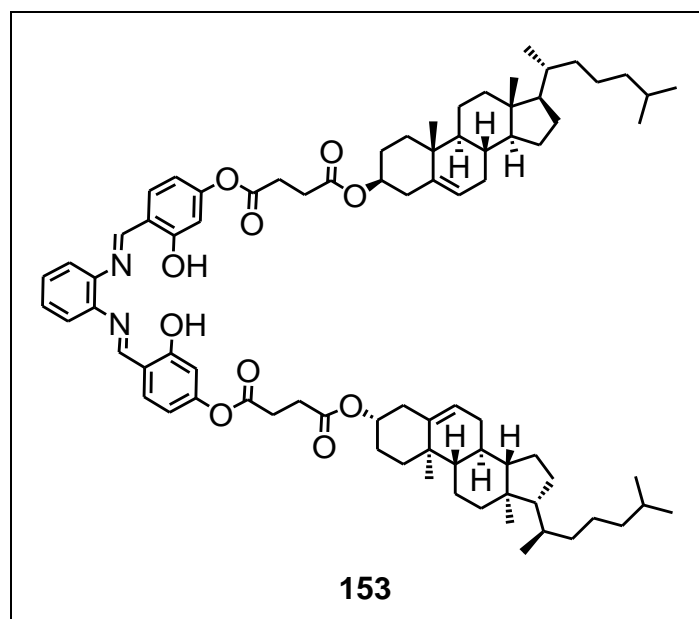


Figure 29. Salen-based cholesterol organogelator **153**.

Yagai, Ishii, Karatsu, and Kitamura have studied the organogelation of a pair of merocyanine compounds **154** & **155** which each have two cholesterol tail groups (Figure 30).⁹¹ The methyl analogue **154** was found to gelate cyclohexane, while the butyl compound **155** gelled acetone. The gels were found to differ greatly in their morphology, as observed by SEM and AFM, and in their absorption and fluorescence spectra. While the SEM images of the acetone gel of butyl compound **155** showed clearly fibrous structures, the cyclohexane gel of the methyl analogue **154** appeared to have an irregular structure; however, the higher resolution AFM images revealed thin fibers ~4 nm in width, which is on the order of the length of the molecule. Interestingly, the cyclohexane gel of **154** appeared to be more stable than the acetone gel of **155**, as a result of its higher gel-to-sol transition temperature and its lower minimum gelation concentration.

Comparison of the absorption and fluorescence spectra of the dilute solutions with the gels showed that organogelation can be used to tune the optical properties of the chromophoric

merocyanine unit. The absorption spectra of the gel of the methyl derivative **154** in cyclohexane exhibited a bathochromic shift to 460 nm (from 440 nm in solution), while the gel of the butyl compound **155** in acetone exhibited a hypsochromic shift to 425 nm (from 460 nm in solution). The fluorescence spectra of the gels were also both bathochromically shifted significantly, with the acetone gel of the butyl compound exhibiting a more pronounced shift, suggesting stronger exciton coupling due to enhanced aggregation. Fluorescence microscopy of the pristine (undried) gels of **154** and **155** showed that the fibers exhibited green and red fluorescence, respectively. In addition, it was found that the acetone gel of the butyl compound was only metastable, and evolved over time, exhibiting a different gel morphology and different fluorescence. Thus, the authors have shown that organogelation can be used to alter the optical properties of a chromophore by altering the excitonic coupling of the molecules as a result of their aggregation.

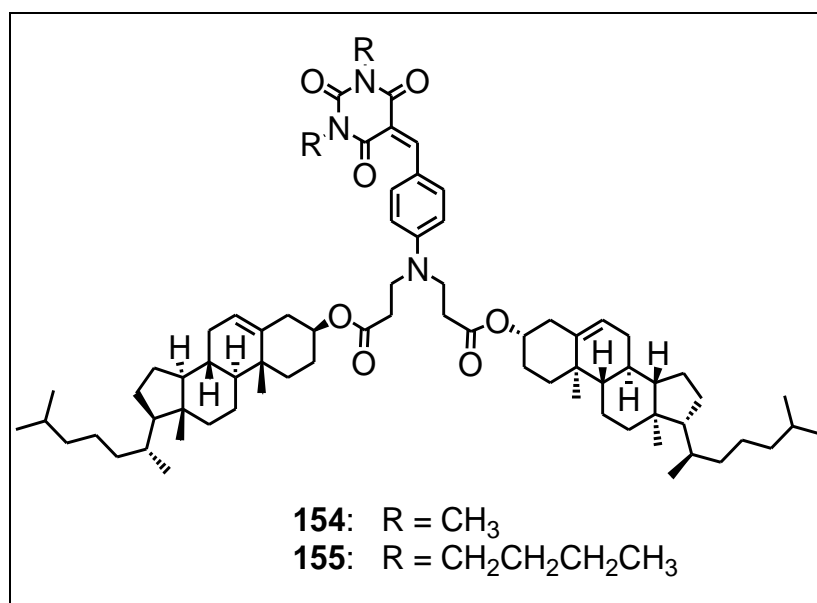


Figure 30. Structure of merocyanine cholesterol organogelators **154-155**.

III. Conclusion

Research of low molecular weight gelators is a rapidly expanding field which bridges the disciplines of organic chemistry, analytical chemistry, and materials chemistry. These unique, functional materials have been utilized in a diverse range of applications, including use as vehicles for drug delivery and controlled release, nanoelectronic and photonic devices, cell growth culture media, and cytotoxic or bacteriostatic agents for treating cancer or bacterial infections. Past efforts to understand how the structures of these small molecules influence the complex, intermolecular processes which dictate gelation has led to the ability to predict gelation with some accuracy, and even to efficiently design supramolecular gelators. In addition, these materials can be designed to include the functionalities which allow for their utility in the aforementioned applications.

Because of their biocompatibility, natural abundance, and proclivity for self-assembly, biomolecules continue to serve as a useful template for the design and synthesis of low molecular weight gelators. Depending on the desired gelation medium and application, steroids, peptides, or carbohydrates can be appropriately functionalized to afford low molecular weight gelators. The biological compatibility of these materials will continue to lend their use to an ever-increasing list of important biological and biomedical applications, which can aid in saving lives and improving our quality of life. As our understanding of these systems improves, supramolecular gels may provide us with the necessary tools for addressing a variety of humanity's largest problems, from the development of improved therapeutic agents and delivery vectors for treating disease and illness, to the generation and sustainability of clean, solar energy. The potential applications of low molecular weight gelators are limited only by our creativity.

References:

- 1) Gel. 2010. In *Merriam-Webster Online Dictionary*. Retrieved September 28th, 2010 from <http://www.merriam-webster.com/dictionary/gel>.
- 2) Flory, P. J.; *Faraday Discuss. Chem. Soc.*, **1974**, 57, 7.
- 3) Terech, P.; Weiss, R. G.; *Chem. Rev.*, **1997**, 97(8), 3133-3159.
- 4) Estroff, L. A.; Hamilton, A. D.; *Chem. Rev.*, **2004**, 104(3), 1201-1217.
- 5) A SciFinder Database search was conducted (9/23/10) using the keywords “low molecular weight gelators”, “low molecular mass gelators”, and “supramolecular gelators”, limiting the document type to preprint, journal, letter, report, and review. The search produced 1021 references. While the keywords used in the search ensure that only relevant papers are returned (replacing the word gelator with gel in the above keywords produced nearly 7000 references, but many were not relevant), they also serve to exclude some of the relevant papers. A search using the same limiters for document type, but instead utilizing the keywords “covalent gel” and “polymer gel” produced nearly 29,000 references, while using the keywords “covalent gelator” and “polymer gelator” yielded ~5700 references.
- 6) Shome, A.; Debnath, S.; Das, P. K.; *Langmuir*, **2008**, 24(8), 4280-4288.
- 7) Yan, Y.; de Keizer, A.; Martens, A. A.; Oliviera, C. L. P.; Pedersen, J. S.; de Wolf, F. A.; Drechsler, M.; Stuart, M. A. C.; Besseling, N. A. M.; *Langmuir*, **2009**, 25(22), 12899-12908.
- 8) Yang, Z.; Gu, H.; Zhang, Y.; Wang, L.; Xu, B.; *Chem. Commun.* **2004**, 2, 208-209.
- 9) Ghosh, A.; Dey, J.; *Langmuir*, **2009**, 25(15), 8466-8472.
- 10) Kar, T.; Debnath, S.; Das, D.; Shome, A.; Das, P. K.; *Langmuir*, **2009**, 25(15), 8639-8648.
- 11) Greenfield, M. A.; Hoffman, J. R.; de la Cruz, M. O.; Stupp, S. I.; *Langmuir*, **2010**, 26(5), 3641-3647.

- 12) 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*(13), 1663-1667.
- 13) Yang, Z.; Liang, G.; Xu, B.; *Acc. Chem. Res.*, **2008**, *41*(2), 315-326.
- 14) Zhao, F.; Ma, M. L.; Xu, B.; *Chem. Soc. Rev.*, **2009**, *38*, 883-891.
- 15) Kawano, S.; Fujita, N.; Shinkai, S.; *J. Am. Chem. Soc.*, **2004**, *126*(28), 8592-8593.
- 16) Peng, F.; Li, G.; Liu, X.; Wu, S.; Tong, Z.; *J. Am. Chem. Soc.*, **2008**, *130*(48), 16166-16167.
- 17) Sangeetha, N. M.; Maitra, U.; *Chem. Soc. Rev.*, **2005**, *34*(10), 821-836.
- 18) Viau, L.; Tourne-Peteilh, C.; Devoisselle, J.-M.; Vioux, A.; *Chem. Commun.*, **2010**, *46*, 228-230.
- 19) Bhuniya, S.; Park, S. M.; Kim, B. H.; *Org. Lett.*, **2005**, *7*(9), 1741-1744.
- 20) Rodriguez-Llansola, F.; Escuder, B.; Miravet, J. F.; *J. Am. Chem. Soc.*, **2009**, *131*(32), 11478-11484.
- 21) Sugiyasu, K.; Fujita, N.; Shinkai, S.; *Angew. Chem. Int. Ed.*, **2004**, *43*, 1229-1233.
- 22) Sugiyasu, K.; Fujita, N.; Shinkai, S.; *J. Mater. Chem.*, **2005**, *15*, 2747-2754.
- 23) Dutta, S.; Das, D.; Dasgupta, A.; Das, P. K.; *Chem. Eur. J.*, **2010**, *16*, 1493-1505.
- 24) Tiller, J. C.; *Angew. Chem. Int. Ed.*, **2003**, *42*, 3072-3075.
- 25) Yang, Z.; Xu, K.; Guo, Z.; Guo, Z.; Xu, B.; *Adv. Mater.*, **2007**, *19*, 3152-3156.
- 26) Khan, F.; Tare, R. S.; Oreffo, R. O. C.; Bradley, M.; *Angew. Chem. Int. Ed.*, **2009**, *48*(5), 978-982.
- 27) Liao, S. W.; Yu, T.-B.; Guan, Z.; *J. Am. Chem. Soc.*, **2009**, *131*(48), 17638-17646.
- 28) Silva, G. A.; Czeisler, C.; Niece, K. L.; Beniash, E.; Harrington, D. A.; Kessler, J. A.; Stupp, S. I.; *Science*, **2004**, *303*, 1352-1355.
- 29) Jayawarna, V.; Ali, M.; Jowitt, T. A.; Miller, A. F.; Saiani, A.; Gough, J. E.; Ulijn, R. V.; *Adv. Mater.*, **2006**, *18*(5), 611-614.

- 30) Tritt-Goc, J.; Bielejewski, M.; Luboradzki, R.; Łapiński, A.; *Langmuir*, **2008**, *24*(2), 534-540.
- 31) Yang, Z.; Liang, G.; Wang, L.; Xu, B.; *J. Am. Chem. Soc.*, **2006**, *128*(9), 3038-3043.
- 32) Yang, Z.; Ho, P.-L.; Liang, G.; Chow, K. H.; Wang, Q.; Cao, Y.; Guo, G.; Xu, B.; *J. Am. Chem. Soc.*, **2007**, *129*(2), 266-267.
- 33) Yang, Z.; Liang, G.; Xu, B.; *Acc. Chem. Res.*, **2008**, *41*(2), 315-326.
- 34) Yang, Z.; Xu, K.; Guo, Z.; Guo, Z.; Xu, B.; *Adv. Mater.*, **2007**, *19*(20), 3152-3156.
- 35) Yang, Z.; Liang, G.; Guo, Z.; Guo, Z.; Xu, B.; *Angew. Chem. Int. Ed.*, **2007**, *46*(43), 8216-8219.
- 36) Liang, G.; Xu, K.; Li, L.; Wang, L.; Kuang, Y.; Yang, Z.; Xu, B.; *Chem. Commun.*, **2007**, *40*, 4096-4098.
- 37) Yang, Z.; Gu, H.; Zhang, Y.; Wang, L.; Xu, B.; *Chem. Commun.* **2004**, *2*, 208-209.
- 38) Yang, Z.; Xu, K.; Wang, L.; Gu, H.; Wei, H.; Zhang, M.; Xu, B.; *Chem. Commun.*, **2005**, *35*, 4414-4416.
- 39) Liang, G.; Yang, Z.; Zhang, R.; Li, L.; Fan, Y.; Kuang, Y.; Gao, Y.; Wang, T.; Lu, W. W.; Xu, B.; *Langmuir*, **2009**, *25*(15), 8419-8422.
- 40) Bing Xu. *Langmuir*, **2009**, *25*(15), 8375-8377.
- 41) Burch, R. M.; Weitzburg, M.; Blok, N.; Muhlhauser, R.; Martin, D.; Farmer, S. G.; Bator, J. M.; Connor, J. R.; Ko, C.; Kuhn, W.; McMillan, A.; Raynor, M.; Shearer, B. G.; Tiffany, C.; Wilkins, D. E.; *Proc. Natl. Acad. Sci.*, **1991**, *88*(2), 355.
- 42) Wang, Q.; Yang, Z.; Ma, M.; Chang, C. K.; Xu, B.; *Chem. Eur. J.*, **2008**, *14*(16), 5073-5078.
- 43) Krajewska, B.; *J. Chem. Technol. Biotechnol.*, **2001**, *76*(6), 636-642.
- 44) Suzuki, M.; Sato, T.; Kurose, A.; Shirai, H.; Hanabusa, K.; *Tet. Lett.*, **2005**, *46*(16), 2741-2745.
- 45) Suzuki, M.; Nanbu, M.; Yumoto, M.; Shirai, H.; Hanabusa, K.; *New J. Chem.*, **2005**, *29*(11), 1439-1444.

- 46) Suzuki, M.; Yumoto, M.; Shirai, H.; Hanabusa, K.; *Tetrahedron*, **2008**, *64*(45), 10395-10400.
- 47) Suzuki, M.; Saito, H.; Hanabusa, K.; *Langmuir*, **2009**, *25*(15), 8579-8585.
- 48) Wu, X.; Ji, S.; Li, Y.; Li, B.; Zhu, X.; Hanabusa, K.; Yang, Y.; *J. Am. Chem. Soc.*, 2009, *131* (16), pp 5986–5993.
- 49) Suzuki, M.; Hanabusa, K.; *Chem. Soc. Rev.*, **2009**, *38*(4), 967-965.
- 50) Roy, S.; Dasgupta, A.; Das, P. K.; *Langmuir*, **2007**, *23*(23), 11769-11776.
- 51) Shome, A.; Debnath, S.; Das, P. K.; *Langmuir*, **2008**, *24*(8), 4280-4288.
- 52) Kar, T.; Debnath, S.; Das, D.; Shome, A.; Das, P. K.; *Langmuir*, **2009**, *25*(15), 8639-8648.
- 53) Duuta, S.; Das, D.; Dasgupta, A.; Das, P. K.; *Chem. Eur. J.*, **2010**, *16*(5), 1493-1505.
- 54) Escuder, B.; Miravet, J. F.; *Langmuir*, **2006**, *22*(18), 7793-7797.
- 55) Hirst, A. R.; Coates, I. A.; Boucheteau, T. R.; Miravet, J. F.; Escuder, B.; Castelletto, V.; Hamley, I. W.; Smith, D. K.; *J. Am. Chem. Soc.*, **2008**, *130*(28), 9113-9121.
- 56) Rodriguez-Llansola, F.; Escuder, B.; Miravet, J. F.; *J. Am. Chem. Soc.*, **2009**, *131*(32), 11478-11484.
- 57) Dawn, A.; Fujita, N.; Haraguchi, S.; Sada, K.; Shinkai, S.; *Chem. Commun.*, **2009**, *16*, 2100-2102.
- 58) Dawn, A.; Fujita, N.; Haraguchi, S.; Sada, K.; Tamaru, S.; Shinkai, S.; *Org. Biomol. Chem.*, **2009**, *7*(21), 4378-4385.
- 59) Brizard, A.; Stuart, M.; van Bommel, K.; Friggeri, A.; de Jong, M.; van Esch, J.; *Angew. Chem. Int. Ed.*, **2008**, *47*(11), 2063-2066.
- 60) Dowling, M. B.; Lee, J.-H.; Raghavan, S. R.; *Langmuir*, **2009**, *25*(15), 8519-8525.
- 61) Varghese, O. P.; Sun, W.; Hilborn, J.; Ossipov, D. A.; *J. Am. Chem. Soc.*, 2009, *131* (25), 8781–8783.

- 62) Frasconi, M.; Rea, S.; Matricardi, P.; Favero, G.; Mazzci, F.; *Langmuir*, **2009**, *25*(18), 11097-11104.
- 63) Krebs, M. D.; Jeon, O.; Alsberg, E.; *J. Am. Chem. Soc.*, **2009**, *131*(26), 9204-9206.
- 64) Ho, H. L. T.; Dryfe, R. A. W.; *Langmuir*, **2009**, *25*(21), 12757-12765.
- 65) Zhang, F.; Wu, Q.; Chen, Z.-C.; Li, X.; Jiang, X.-M.; Lin, X.-F.; *Langmuir*, **2006**, *22*(20), 8458-8464.
- 66) Haraguchi, S.; Numata, M.; Kaneko, K.; Shinkai, S.; *Bull. Chem. Soc. Jpn.*, **2008**, *81*(8), 1002-1006.
- 67) Tritt-Goc, J.; Bielejewski, M.; Luboradzki, R.; Łapiński, A.; *Langmuir*, **2008**, *24*(2), 534-540.
- 68) Karinaga, R.; Jeong, Y.; Shinkai, S.; Kaneko, K.; Sakurai, K.; *Langmuir*, **2005**, *21*(21), 9398-9401.
- 69) Yang, Z.; Liang, G.; Ma, M.; Abbah, A. S.; Lu, W. W.; Xu, B.; *Chem. Commun.*, **2007**, *8*, 843-845.
- 70) John, G.; Jung, J. H.; Masuda, M.; Shimizu, T.; *Langmuir*, **2004**, *20*(6), 2060-2065.
- 71) Cui, J.; Shen, Z.; Wan, X.; *Langmuir*, **2010**, *26*(1), 97-103.
- 72) Yan, N.; He, G.; Zhang, H.; Ding, L.; Fang, Y.; *Langmuir*, **2010**, *26*(8), 5909-5917.
- 73) Kimizuka, N.; Nakashima, T.; *Langmuir*, **2001**, *17*(22), 6759-6761.
- 74) Chen, Q.; Lv, Y.; Zhang, D.; Zhang, G.; Liu, C.; Zhu, D.; *Langmuir*, **2010**, *26*(5), 3165-3168.
- 75) Vemula, P. K.; Li, J.; John, G.; *J. Am. Chem. Soc.*, **2006**, *128*(27), 8932-8938.
- 76) Srivastava, A.; Ghorai, S.; Bhattacharijya, A.; Bhattacharya, S.; *J. Org. Chem.*, **2005**, *70*(17), 6574-6582.
- 77) Xing, B.; Yu, C.-W.; Chow, K.-H.; Ho, P.-L.; Fu, D.; Xu, B.; *J. Am. Chem. Soc.*, **2002**, *124*(50), 14846-14847.

- 78) Zhao, Y.-L.; Stoddart, J. F.; *Langmuir*, **2009**, *25*(15), 8442-8446.
- 79) Khan, F.; Tare, R. S.; Oreffo, R. O. C.; Bradley, M.; *Angew. Chem. Int. Ed.*, **2009**, *48*(5), 978-982.
- 80) Liao, S. W.; Yu, T.-B.; Guan, Z.; *J. Am. Chem. Soc.*, **2009**, *131*(48), 17638-17646.
- 81) Kawano, S.; Fujita, N.; Shinkai, S.; *J. Am. Chem. Soc.*, **2004**, *126*(28), 8592-8593.
- 82) Sugiyasu, K.; Fujita, N.; Shinkai, S.; *Angew. Chem. Int. Ed.*, **2004**, *43*(10), 1229-1233.
- 83) Sugiyasu, K.; Fujita, N.; Shinkai, S.; *J. Mater. Chem.*, **2005**, *15*(27-28), 2747-2754.
- 84) Kawano, S.; Fujita, N.; Shinkai, S.; *Chem. Eur. J.*, **2005**, *11*(16), 4735-4742.
- 85) Malik, S.; Kawano, S.; Fujita, N.; Shinkai, S.; *Tetrahedron*, **2007**, *63*(31), 7326-7333.
- 86) Huang, X.; Terech, P.; Raghavan, S. R.; Weiss, R. G.; *J. Am. Chem. Soc.*, **2005**, *127*(12), 4336-4344.
- 87) George, M.; Weiss, R. G.; *Acc. Chem. Res.*, **2006**, *39*(8), 489-497.
- 88) Bag, B. G.; Dinda, S. K.; Dey, P. P.; Mallia, V. A.; Weiss, R. G.; *Langmuir*, **2009**, *25*(15), 8663-8671.
- 89) Chen, Q.; Zhang, D.; Zhang, G.; Zhu, D.; *Langmuir*, **2009**, *25*(19), 11436-11441.
- 90) Chen, P.; Lu, R.; Xue, P.; Xu, T.; Chen, G.; Zhao, Y.; *Langmuir*, **2009**, *25*(15), 8395-8399.
- 91) Yagai, S.; Ishii, M.; Karatsu, T.; Kitamura, A.; *Angew. Chem. Int. Ed.*, **2007**, *46*(42), 8005-8009.

Chapter II. Probing the Effect of the Anomeric Group on Gelation: Supramolecular Organogelators and Hydrogelators from D-Glucose

Abstract: Low molecular weight gelators are unique soft materials which have come under a great deal of attention over the past several years. Their unique properties lend them to a variety of different applications, such as drug delivery and controlled release agents, media for cell growth, photoelectronic materials, and chemical sensors. Biomolecules make excellent templates for low molecular weight gelators, due to their natural propensity for self-assembly. Carbohydrates, in particular, make excellent scaffolds for supramolecular gelators, as they possess a multitude of chirally-arranged hydroxyl groups that can be harnessed for self-assembly. In the past, we have extensively studied how acylation of the C2 and C3 hydroxyl groups of the 4,6-O-benzylidene-methyl- α -D-glucopyranoside head group with various acyl chlorides and isocyanates affects its gelation. We wanted to further explore the structure gelation relationship of D-glucose derivatives by studying the effect of changing the anomeric group on gelation. To this end, we synthesized two new head groups, 4,6-O-benzylidene-ethyl- α -D-glucopyranoside and 4,6-O-benzylidene-ethyl- β -D-glucopyranoside, and acylated them with a variety of different acyl groups. The synthesis and characterization of the head groups and their ester derivatives, including the gel testing results, are presented herein.

Keywords: low molecular weight gelator, supramolecular gelator, organogelator, hydrogelator, monosaccharide, D-glucose

Introduction

Over the past several years, a great deal of research regarding low molecular weight gelators has been conducted. Many different research groups have expended great effort into elucidating how the structural features of supramolecular gelators promote their gelation, and how these molecules can be designed and applied to solving everyday problems. Although our understanding of supramolecular gels has progressed a great deal over the past few decades, most new classes of low molecular weight gelators are still discovered serendipitously. However, once a structural class of supramolecular gelators has been discovered, structural modification studies are typically carried out to determine what types of functional groups are necessary for gelation and which groups can be tolerated.

Once a structure-gelation relationship is established for a class of compounds, it is possible to predict, with some degree of accuracy, whether a new molecule within that class will act as a supramolecular gelator. This makes it possible to discover gelators which contain functional groups that allow for added utility. With so much past research aimed at understanding the relationship between the structure of a low molecular weight gelator and its gelation efficacy, the current trend in the literature is to showcase the functionality of the gel, in terms of its potential applications. Thus, the design of supramolecular gelators with secondary functions is becoming increasingly important.

However, many questions regarding some of the phenomenon that take place during gelation still remain. In addition, while some structural scaffolds used in gelator design have been thoroughly explored, namely amino acid and steroidal supramolecular gelators, other templates, such as carbohydrates, have been less actively researched. With this in mind, we set

out to more thoroughly explore monosaccharides as a template for supramolecular gelator design. Monosaccharides have been explored as low molecular weight gelators in the past. Between 2000 and 2002, Shinkai's group published several papers which set out to ascertain how the configuration of a series of 4,6-O-benzylidene methyl- α -D-glycopyranosides **1a-6** influenced their gelation ability (Figure 1)¹⁻³. The triprotected glycosides of glucose (**1a,b**), mannose (**2a,b**), allose (**3a,b**), altrose (**4a,b**), galactose (**5a,b**), and idose (**6**) were screened for gelation in water and a diverse range of organic solvents and water. Only the α -methoxy glucose, mannose, and galactose derivatives (**1a**, **2a**, and **5a**, respectively) and the β -methoxy mannose and galactose analogues **2b** and **5b** were able to form gels; all of the other compounds were able to form self-supporting precipitates or partially self-supporting precipitates, however.

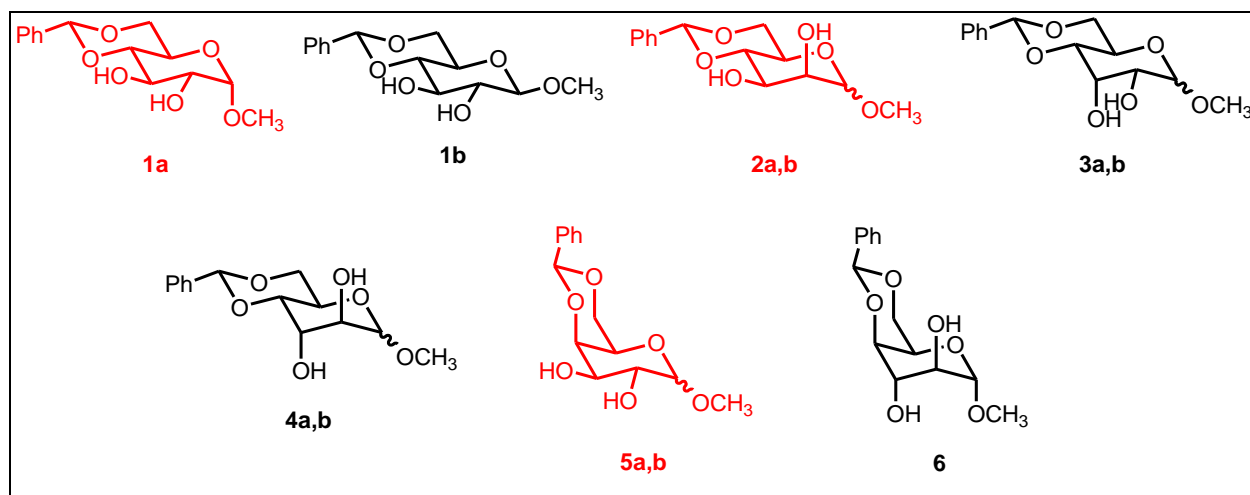


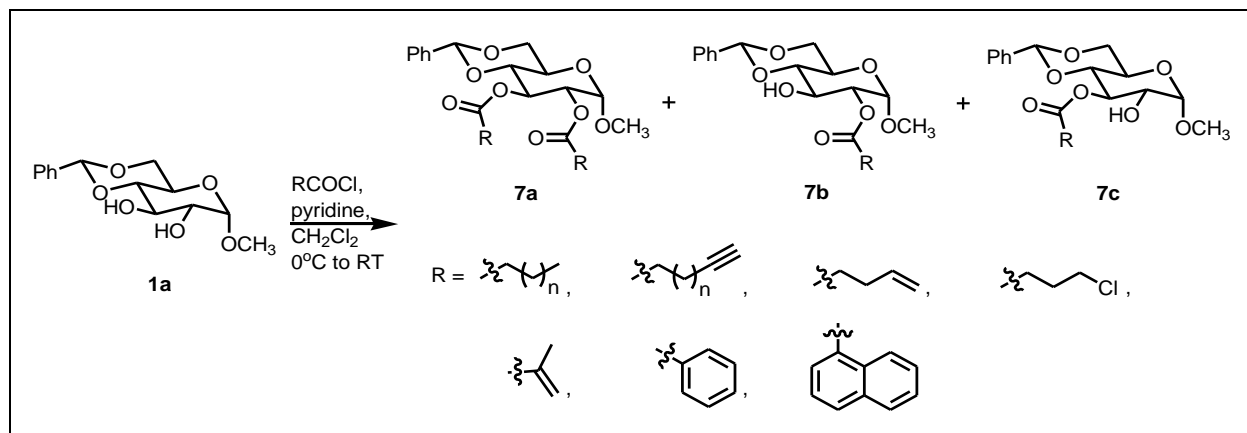
Figure 1. Structures of 4,6-O-benzylidene acetal protected methyl glycosides **1a-6**.

Comparison of the x-ray single crystal structures of glucose derivative **1a**, allose analogue **3a**, altrose equivalent **4a**, and idose product **6** gave some insight as to why the α -methoxy derivatives of glucose, mannose, and galactose derivatives were able to gelate while those of allose, altrose, and idose compounds could not.¹ The crystal structure of the glucose derivative **1a** was able to form a stronger, more one-dimensional hydrogen bonding array than the other compounds. The equatorial arrangement of the 3-OH in the glucose compound allowed for an additional intermolecular hydrogen bond to take place; in the other three compounds (**3a**, **4a**, and **6**) the 3-OH is axial, and prefers to form an intramolecular hydrogen bond with the anomeric methoxy group, weakening the intermolecular hydrogen bonding array.

Although the β -methoxy mannose and galactose gelators **2b** and **5b** were able to form more stable gels (as indicated by the gel-sol transition temperature and DSC measurements), the α anomer gelators tend to gelate at lower concentration, indicating that the α -anomers are more efficient gelators. Thus, Shinkai and coworkers have elucidated two important structural requirements for the gelation of monosaccharides: and equatorial hydroxyl group at the 3-position, and (to a lesser degree) an axial group at the anomeric center. Glucose, mannose, and galactose all meet these criteria, and coincidentally, they also happen to be more naturally abundant and generally, more well studied. This proves to be fortuitous for us, from both a synthetic and an economic perspective.

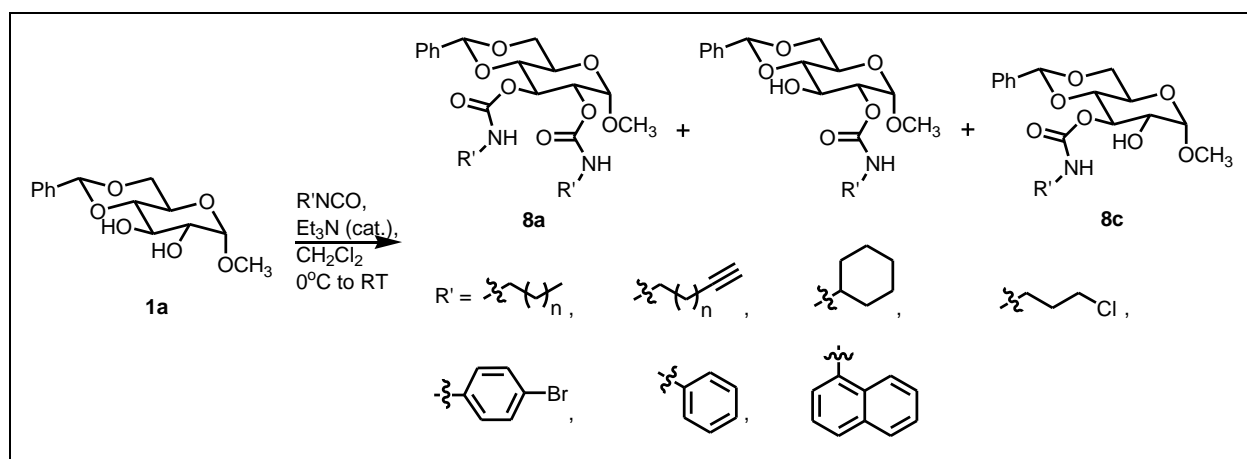
Unfortunately, the monosaccharides studied by Shinkai were inefficient gelators, and were only able to gelate a few of organic solvents at relatively high concentrations. However, since these monosaccharides showed some gelation ability, they seemed like a good starting point for further exploration of low molecular weight gelators. Over the past decade, our laboratory has focused on the synthesis and characterization of low molecular weight gelators

which are derived from acylation of the above-mentioned 4,6-O-benzylidene acetal protected methyl glycosides.⁴⁻⁷ Our reason for this was two-fold: 1) we wanted to better understand the structural requirements for gelation of monosaccharides, especially how functionalization of the hydroxyl groups at C2 and C3 affects gelation; and 2) we believed that modification of the existing framework with hydrophobic tail groups would afford compounds with improved and unique gelation properties, such as compounds that could gelate water and aqueous mixtures, which would allow us to explore biomedical applications for the gels, such as cell growth⁸⁻¹⁰ or wound healing¹¹⁻¹². We began by making simple ester derivatives of 4,6-O-benzylidene-methyl- α -D-glucopyranoside **1a** by reacting the monosaccharide with a slight excess of acyl chloride to obtain a mixture of three products (diester, 2-ester, and 3-ester), which could be purified by flash chromatography (Scheme 1). A variety of different acyl chlorides were used, and it was found that the monoester derivatives **7b** and **7c** with the terminal alkyne tail groups could gelate water and hexane at low concentrations.^{4,6}



Scheme 1. Synthesis of diester and monoester derivatives with general structure **7a-c** starting from **1a**.

By using isocyanates instead of acyl chlorides, we obtained carbamate derivatives **8a-8c**, which contain an additional hydrogen bonding amido group that we believed would improve gelation (Scheme 2). Many carbamates were able to gelate aqueous DMSO and aqueous ethanol mixtures effectively, and the short saturated derivatives were also found to gelate water.^{5,7}



Scheme 2. Synthesis of carbamate derivatives with general structure **8a-8c** starting from **1a**.

The results obtained by acylation of 4,6-O-benzylidene-methyl- α -D-glucopyranoside provided a great deal of information about what types of side chains would afford better gelators, and several efficient gelators for water and organic solvents were obtained, as shown in Figure 2.⁴⁻⁷

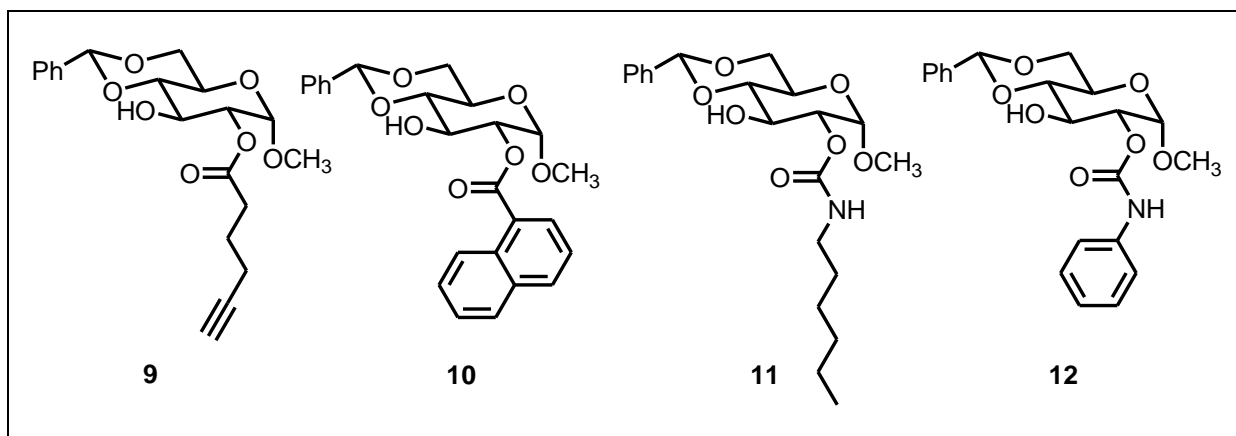


Figure 2. Structures of the some of the most efficient gelators obtained by acylation of **1a**.

With this information in hand, we wanted to further explore this monosaccharide core structure and determine how changing the functionality at the anomeric position would alter its gelation ability. By replacing the α -methoxy group with either an α -ethoxy or β -ethoxy group (Figure 3), we hoped to obtain more efficient gelators and better understand the structure-gelation relationship of D-glucose-based low molecular weight gelators. The results we obtained are discussed below.

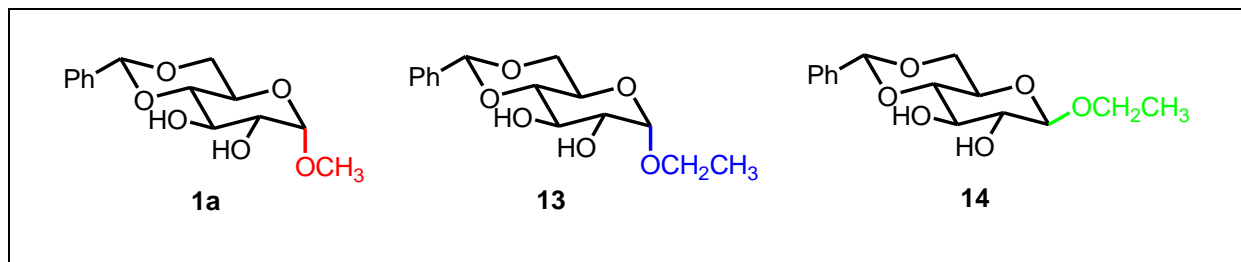
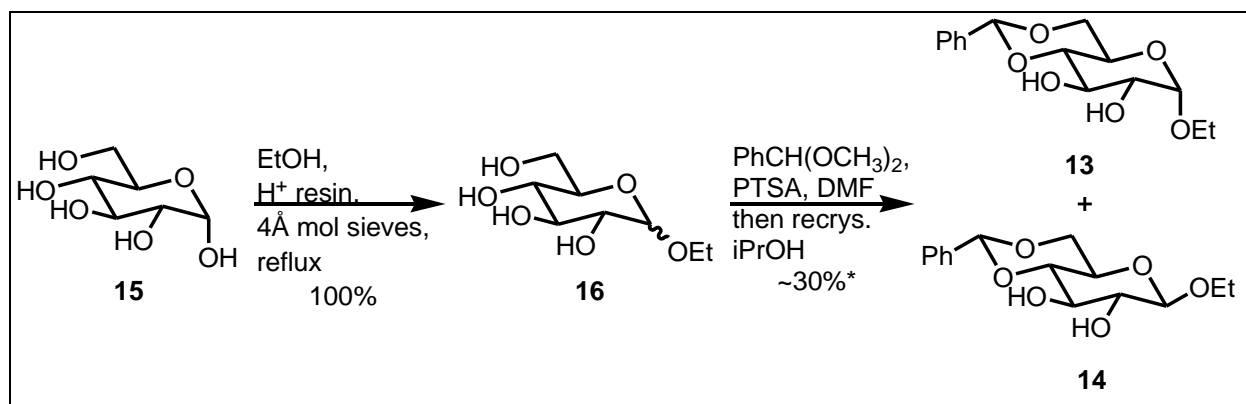


Figure 3. 4,6-O-benzylidene-methyl- α -D-glucopyranoside **1**, and its anomeric analogs **13** and **14**.

Results and Discussion

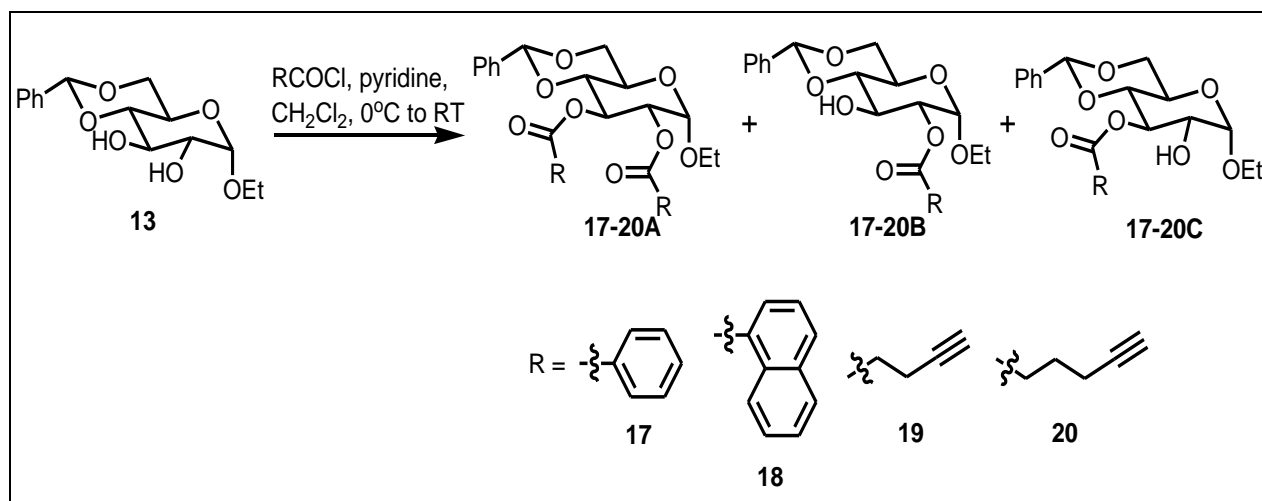
In our quest to better understand the correlation between the molecular structure of D-glucopyranoside derivatives and their gelation ability, we set out to synthesize derivatives with different anomeric groups. Because even small changes in structure can have a large effect on the gelation ability of a compound, we decided to proceed cautiously, making a very incremental change in going from the methoxyl group of the parent compound **1a** to an ethoxyl group. We wanted to obtain acyl derivatives of both anomers **13** and **14** so that we could understand how the stereochemical configuration affects gelation as well. Thus, compounds **13** and **14** were synthesized from α -D-glucose **15** in two steps, as shown in Scheme 3.

Fischer glycosylation in ethanol in the presence of acidic ion exchange resin and molecular sieves gave the ethyl glycoside **16** as a mixture of anomers. Conversion to the 4,6-O-benzylidene acetal was carried out using benzaldehyde dimethyl acetal in N,N-dimethyl formamide in the presence of a catalytic amount of p-toluenesulfonic acid. While the conversion of **16** to **13** and **14** was in excess of 80%, isolation of the two compounds was problematic (R_f values in hexanes:ethyl acetate differed by only ~5%, making column purification difficult), and was carried out using fractional recrystallization in isopropanol to give a combined yield of about 30% for both anomers (**13** and **14** were obtained in ~22% and 7% yields, respectively). Though a large portion of the material remained unresolved, enough of compounds **13** and **14** were obtained to carry out the esterification reactions.



Scheme 3. Synthesis of 4,6-O-Benzylidene-Ethyl- α -D-Glucopyranoside Head Group

With the head group compounds **13** and **14** in hand, we set out to synthesize a series of ester derivatives using the corresponding acyl chlorides. Acyl groups which gave the best gelation results for the analogous α -methoxy head group **1a** were chosen, so that a direct comparison between the two head groups could be made. We began with the α -ethoxy derivatives, and the naphthoyl, benzoyl, 4-pentynoyl, and 5-hexynoyl derivatives, compounds **17A-20C** were synthesized (Scheme 4). While the naphthoyl and benzoyl chlorides were commercially available, the terminal alkynoyl chlorides had to be prepared from the corresponding carboxylic acids using oxalyl chloride and DMF as catalyst. The standard reaction conditions for the ester syntheses called for the starting material to be dissolved in anhydrous dichloromethane and cooled to 0°C, at which point 1.3 equivalents of the corresponding acyl chloride and 5 equivalents of anhydrous pyridine were added (alternatively, the pyridine could be added to the head group solution prior to the acyl chloride addition).



Scheme 4. Synthesis of esters **17A-20C** derived from 4,6-O-benzylidene-ethyl- α -D-glucopyranoside **13**.

A mixture of products was obtained, which was separated by flash chromatography using a gradient solvent system starting with hexanes: ethyl acetate 9:1 or 12:1. ¹H and ¹³C NMR was used to identify the products, and based on the assignment, it was found that the 2-ester **B** was the major product, the diester **A** was the minor product, and the 3-ester **C** was observed only in trace quantities (naphthoyl derivative **21** gave only a small amount of diester **A**). In addition to ¹H and ¹³C NMR, the compounds were characterized by melting point measurement and screened for gelation. The ¹H and ¹³C NMR spectra for compounds **17A**, **17B**, and **17C** are shown below (Figures 4, 5 & 6).

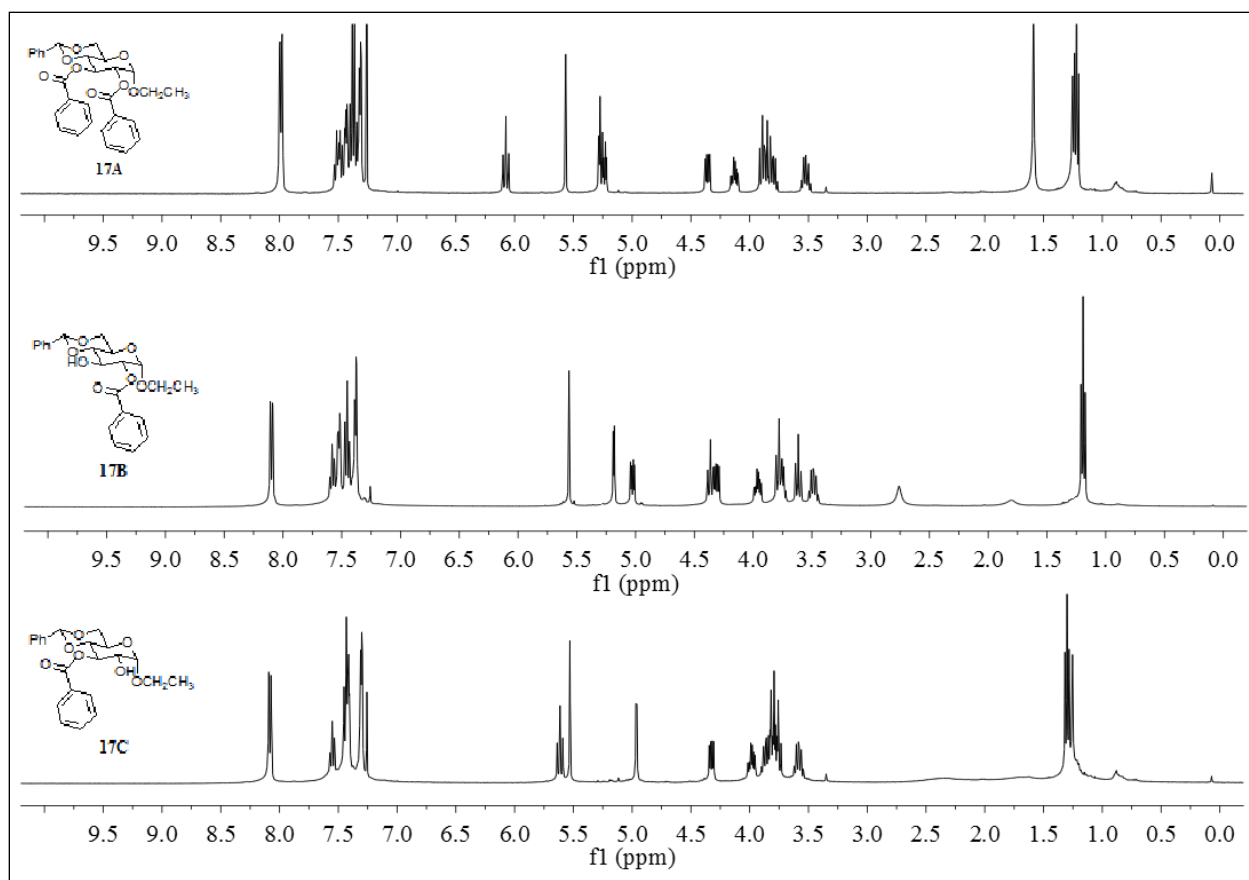


Figure 5. Comparison of ^1H NMR of **17A**, **17B**, and **17C**.

Assignments of the compounds **17A-C** were based on a side-by-side comparison of the ^1H and ^{13}C NMR spectra. The splitting patterns of the ^1H NMR spectra differ significantly from one another in the 3.0-6.0 ppm region, especially between 5.0 and 6.0 ppm. Because of the difference in dihedral angles, it is fairly easy to distinguish between the resonances corresponding to the protons at the C2 and C3 positions. Since the dihedral angle between H2 and H3 is 180° , and the dihedral angle between H1 and H2 is only 60° , the two coupling constants of H2 should be quite different, and the resonance should therefore appear as a doublet-of-doublets. Since the H3-H4 dihedral angle and the H2-H3 dihedral angle are both

180°, the difference in the coupling constants of H3 would be much less, and the resonance should appear as a pseudotriplet.

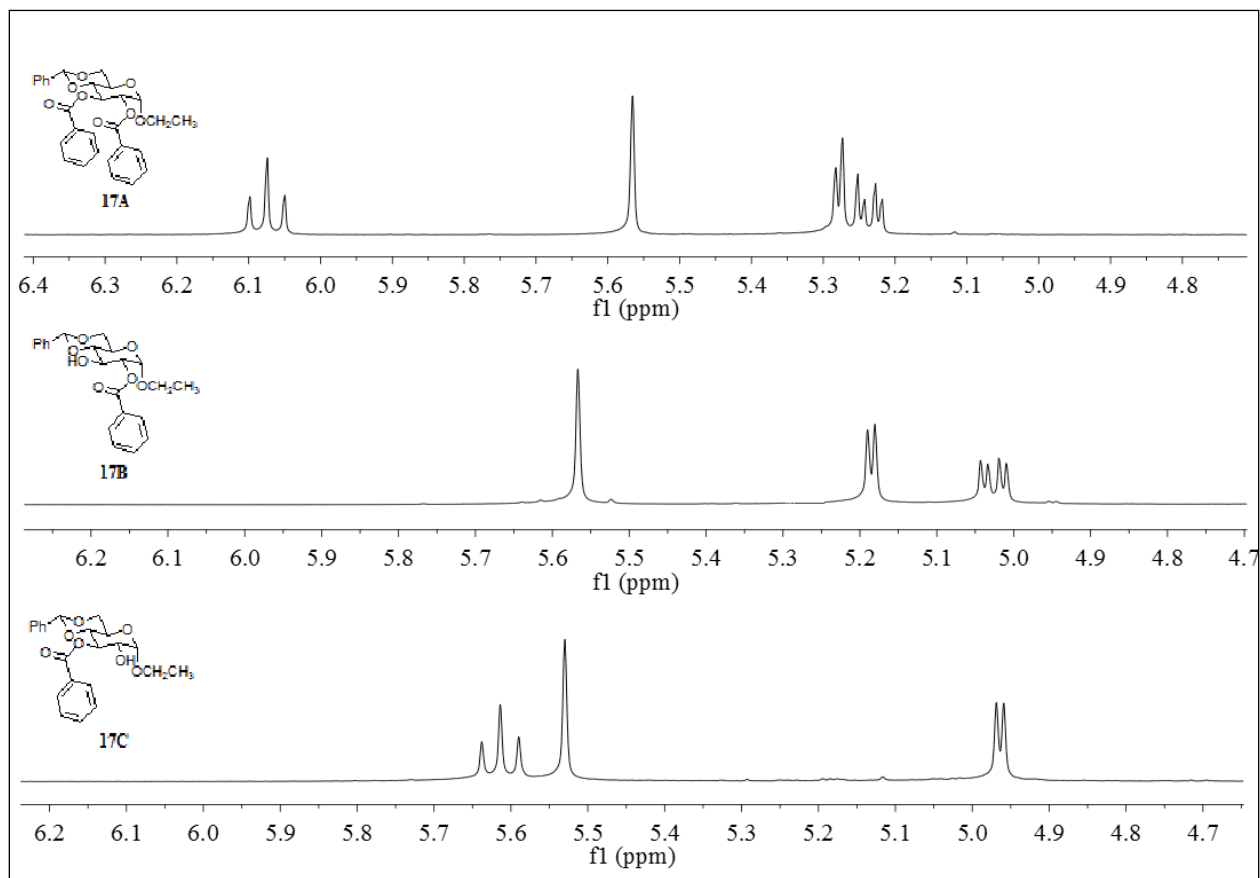


Figure 5. Close up comparison of 5.0-6.0 ppm range of ¹H NMR of **17A**, **17B**, and **17C**.

This was observed to be the case, as the diester **17A** exhibited a significant downfield shift of both the H2 (dd) and H3 (t) resonances, as shown in Figures 4 and 5. Meanwhile, the 2-ester **17B** and the 3-ester **17C** exhibited only the downfield shifting of the H2 doublet of doublets and H3 pseudotriplet, respectively (Figures 4 & 5). In addition, comparison of the ¹³C NMR

spectra helped to confirm the isomeric assignment. The diester **17A** exhibited two carbonyl resonances around ~ 165 ppm, whereas the 2-ester **17B** and 3-ester **17C** exhibit only one signal in this region. There is also a downfield shift of the anomeric carbon resonance in the spectrum of 3-ester **17C**, which results from the different electronic influence of the neighboring free hydroxyl group at C2 (the C2 hydroxyl is acylated in both the diester **17A** and 2-ester **17B**).

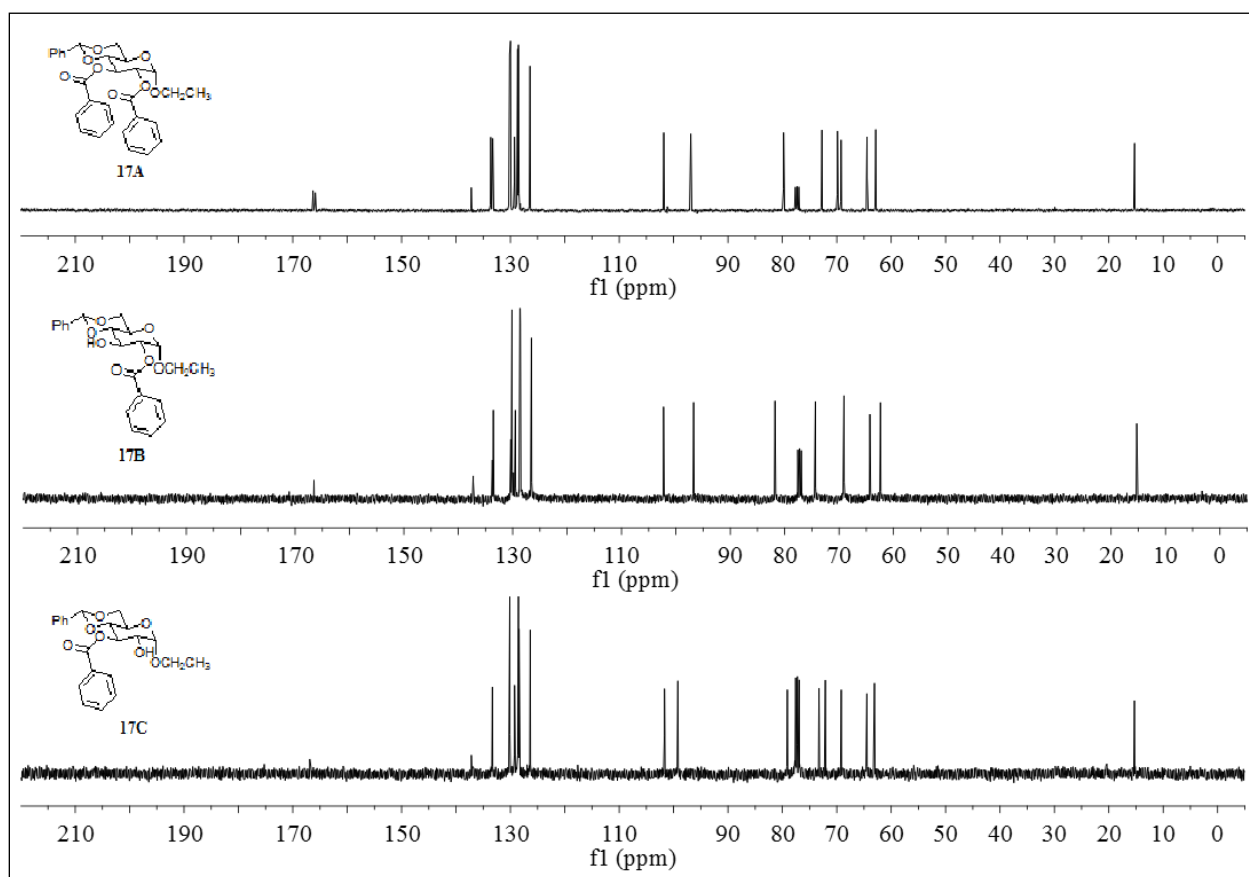
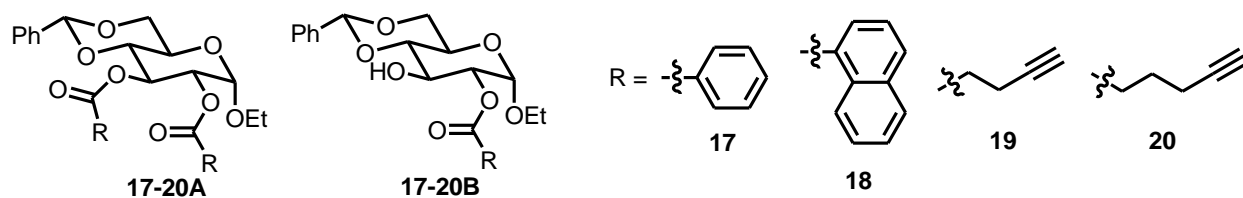


Figure 6. Comparison of ^{13}C NMR of **17A**, **17B**, and **17C**.

Upon isolation, the compounds were screened for gelation in hexanes, ethanol, water, and aqueous mixtures of DMSO and ethanol (both 1:2 organic: water). The results were tabulated and are shown below, in Table 1. It was found that the diesters were poor gelators overall, with only the terminal alkynyl derivatives **19A** and **20A** able to gel hexane at the initial screening concentration of 20 mg/mL. The 2-esters proved to be better gelators, with the benzoyl derivative **17B** gelling aqueous DMSO (MGC = 7.1 mg/mL), and the 4-pentynoyl derivative **19B** forming opaque gels in water, aqueous ethanol, and aqueous DMSO at fairly low concentrations (MGCs at or below 3.8 mg/mL). While the 5-hexynoyl derivative **20B** was unable to gel any of the aqueous solvents, it was found to form a transparent gel in hexane (MGC = 6.0 mg/mL). Compared to the corresponding esters obtained from α -methoxy head group **1a**, the esters obtained from **16** were slightly less efficient gelators.

The ClogP values for each of the compounds were also calculated using ChemDraw Ultra v.9.0, in order to determine if there was any correlation between the gelation and the relative solubility of the compounds. These values are also shown in Table 1. While it appears as if there may be some correlation between the ClogP values and the gelation efficacy of the diester compounds in hexanes, there is not enough data to identify a discernable trend. For the 2-esters, a similar correlation appears to be present between the ClogP values and the gelation efficacy in aqueous DMSO, but the 5-hexynyl derivative **20B** appears to violate this trend (it fails to form a gel in aqueous DMSO despite its ClogP value falling between that **17B** and **19B**, which do form gels). While the initial results seem to indicate some promise in establishing a correlation of ClogP value and gelation, more data is needed before any substantiated claim can be made.

Table 1. Gel testing results for compounds **17-203A** and **17-20B**.

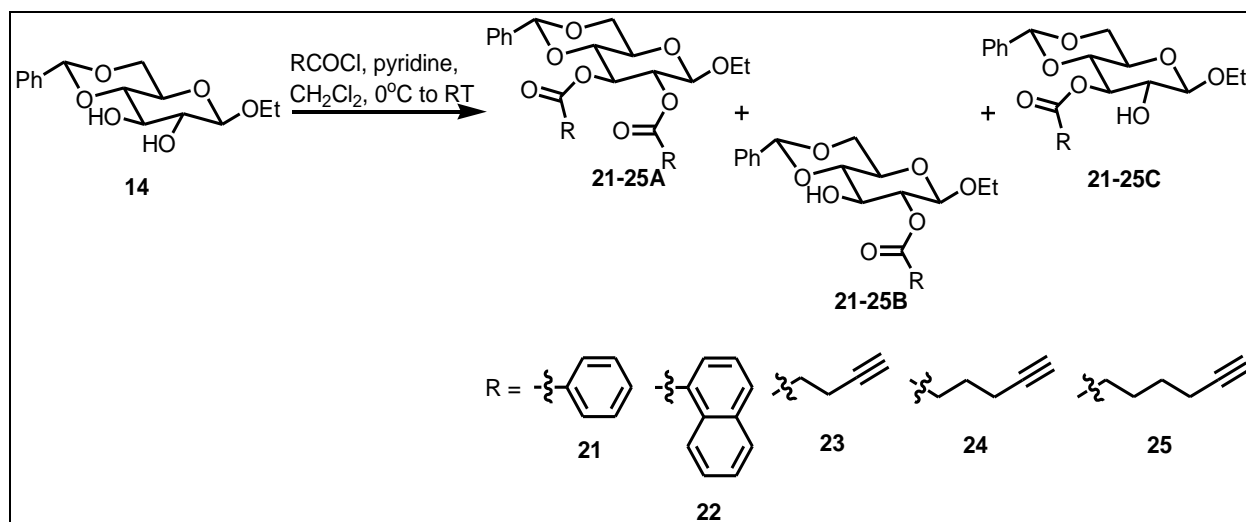


Compound	ClogP	m.p. (°C)	Hexanes	Ethanol	Water	Water: DMSO 2:1	Water: EtOH 2:1
17A	4.56	210 (decomp)	P	R	I	I	I
19A	2.64	66	G_T (20)	S	I	P	P
20A	3.29	84	G_O (20)	S	I	I	I
17B	2.11	Oil	I	R	I	G_O (7.1)	I
18B	3.28	216	I	R	I	I	I
19B	1.20	105	R	S	G_O (3.3)	G_O (3.7)	G_O (3.8)
20B	1.53	60	G_T (6.0)	S	P	P	P

All compounds tested at an initial concentration of ~20 mg/mL. Legend: I = insoluble, P = precipitate, R = recrystallization, S = soluble, UG = unstable gel, G = stable gel. Transparent/translucent gels are denoted with a subscript of T; opaque gels are denoted with a subscript of O. Numbers in parentheses correspond to concentration in mg/mL.

Next, we synthesized the esters of the β -ethoxy head group **14** (Scheme 5). In addition to the four acyl groups used for the previous α -ethoxy series, an additional terminal alkynoyl

chloride, 6-heptynyl chloride, was used. The syntheses and purifications were carried out in the same way as the α -ethoxy derivatives **17-20**. In the case of the β -ethoxy derivatives **21-25**, the 3-ester **C** was the major product, the diester **A** was the minor product, and the minor monoester, which in this case was the 2-ester **B**, was again observed only in trace quantities. Again, the assignments were made based on a comparison of the NMR spectra obtained for each isolated compound. Since the dihedral angles between H-1 and H-2, H-2 and H-3, and H-3 and H-4 are all 180° , the resonances for both H-2 and H-3 give pseudotriplets, making it difficult to make assignments based on the ^1H NMR spectra. However, the ^{13}C NMR spectrum of the 3-ester again allowed for the assignment to be made, as it showed shifts for the anomeric carbon that were not present in the diester or 2-ester spectra (while 3-ester compounds of the α -ethoxy series **17-20C** exhibited a downfield shift relative to the diester compounds **17-20A** and the 2-ester compounds **17-20B**, the β -ethoxy 3-ester compounds **21-25C** exhibited an upfield shift relative to its diester and 2-ester counterparts **21-25A** and **21-25B**). Upon isolation, the compounds were characterized by melting point and screened for gelation. For the 5-hexynyl and 6-heptynyl derivatives, the diesters **24A** and **25A** were not isolated in appreciable quantities due to problems with the purification.



Scheme 5. Synthesis of Esters **21A-25C** derived from 4,6-O-benzylidene-ethyl-β-D-glucopyranoside **14**.

As mentioned above, the diester and 3-ester compounds **21-23A** and **21-25C** were screened for gelation in hexanes, ethanol, water, aqueous DMSO, and aqueous ethanol (Table 2). Of the diesters that were tested, only the 4-pentynyl derivative **23A** showed any gelation ability, forming an unstable gel in hexane at the initial testing concentration of 20 mg/mL. The 3-esters showed good gelation for aqueous solvents. Benzoyl 3-ester **21C** was found to form an efficient gel in aqueous DMSO (MGC = 5.0 mg/mL), while the 4-pentynyl 3-ester **23C** was able to form gels in water, aqueous ethanol, and aqueous DMSO, all at minimum gelation concentrations below 10 mg/mL. The 5-hexynyl 3-ester **24C** was also found to gel aqueous DMSO and aqueous ethanol, albeit less efficiently (MGCs of 15 and 10 mg/mL, respectively). The ClogP values for each of the compounds were also calculated, in order to determine if there was any correlation between the relative solubility of the compounds and their gelation ability. For the diesters, since only three compounds were obtained, and only one of those compounds was able to form a gel, there was not enough data to identify any trend. While there wasn't enough data to

identify a trend among the diesters, the MGC values for the 3-esters in water, aqueous DMSO, and aqueous ethanol were plotted against the ClogP values (Figure 7). For water and aqueous ethanol, there seems to be a correlation between ClogP and gelation ability, though more data is needed to reach a definitive conclusion.

Table 2. Gel testing Results for β -esters **21-23A** and **21-25C**.

Compound	ClogP	m.p.	Hexanes	Ethanol	Water	H₂O: DMSO 2:1	H₂O: EtOH 2:1
21a	4.56	n.a.	I	R	I	I	I
22a	6.91	n.a.	I	I/R	I	I	I
23a	2.64	105	UG (20.0)	S	P	P	P
21c	2.12	187	I/R	R	I	G₀ (5.0)	I
22c	3.30	176	I/R	P	I	I	I
23c	1.21	146	I/P	S	G₀ (9.4)	G₀ (6.0)	G₀ (5.0)
24c	1.54	n.a.	R	S	P	G₀ (15)	G₀ (10)
25c	1.92	n.a.	R	S	I	R	R

All compounds tested at an initial concentration of ~20 mg/mL. Legend: I = insoluble, P = precipitate, R = recrystallization, S = soluble, UG = unstable gel, G = stable gel.

Transparent/translucent gels are denoted with a subscript of T; opaque gels are denoted with a subscript of O. Numbers in parentheses correspond to concentration in mg/mL.

Conclusion

Two new series of low molecular weight gelators were synthesized by acylation of 4,6-O-benzylidene-ethyl- α -D-glucopyranoside **13** and 4,6-O-benzylidene-ethyl- β -D-glucopyranoside **14**. Several efficient gelators for water and aqueous mixtures were obtained, as well as a few good gelators for hexanes. Compared to the corresponding derivatives from 4,6-O-benzylidene-methyl- α -D-glucopyranoside **1**, the ethoxy derivatives **17A-25C** were slightly less efficient and less versatile gelators. The terminal alkynyl diesters showed a mild propensity for gelling hexanes, with the α derivatives **19A** and **20A** behaving slightly better than the β derivative **23A**. The monoesters proved to be good gelators as well, gelling water and aqueous solvents. For the aromatic analogs, only the benzoyl compounds **17B** and **21C** were able to gel aqueous DMSO, with the β derivative **21C** proving slightly more efficient than α analog **17B**. The terminal alkynyl compounds showed the opposite trend, with the α analogs gelling more efficiently than the β compounds, though the 5-hexynyl β compound **24C** was able to form gels at higher concentrations while the corresponding α derivative **20B** did not form gels. The ClogP values for each of the compounds was also calculated, and though there was not enough data to establish a discernable trend for the α analogs, an apparent correlation between solubility and gelation for the β derivatives was found. However, more analogs will need to be synthesized and tested in order to reach a definitive conclusion.

Experimental Section:

General method and materials: Reagents and solvents were used as they were received from the supplier. NMR analysis was conducted using a 400 MHz Varian NMR spectrometer. Melting point measurements were carried out using a Fisherbrand Fisher-Johns melting point apparatus, and were uncorrected. For optical microscopy, a small amount of the gel was placed on a clean glass slide and was air-dried overnight. 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.

Gel Testing: Gel testing was conducted in 1 dram glass screw thread vials with black phenolic caps. Two milligrams of the dried compound was placed in the vial, and the corresponding solvent was added to obtain a concentration of ~20 mg/mL. The suspension was then heated until the solids were fully dissolved, and the resulting solution was briefly sonicated, and then the solution was allowed to cool to room temperature, undisturbed, for fifteen minutes. Compounds which appeared to be insoluble at the initial concentration were heated and sonicated several times, to ensure that the compound was truly insoluble (some compounds were resistant to solvation, suggesting a relatively high lattice energy or endothermic heat of solvation). After the compounds had cooled back to ambient temperature, the resulting phenomenon (recrystallization, precipitation, gelation, etc.) was then recorded. If the compound appeared to form a gel, the vial was inverted and shaken gently to determine if there was any flow; compounds which did not flow and which retained all of the solvent within the gel matrix were recorded as stable gels, while those which showed some loss of solvent or fell apart were recorded as unstable gels. Serial dilution was performed at increments of ~5 mg/mL for all

phenomenon other than gelation (precipitation, recrystallization, and compounds which were insoluble), down to a final concentration of ~5 mg/mL. Compounds which formed stable gels were serially diluted in increments of 1-2 mg/mL, until the gel was found to be unstable (by the above criteria). Compounds which were found to be soluble were not further diluted.

General method for synthesis: All reactions were performed using anhydrous solvents and reagents, and the anhydrous dichloromethane and pyridine were further dried over freshly activated 4Å molecular sieves prior to their use, to ensure their dryness. All reactions were conducted in flame dried scintillation vials cooled under a stream of dry nitrogen gas. All purification was conducted by flash chromatography using 230-400 mesh silica gel (SiO₂) obtained from Natland International Corporation, unless otherwise noted.

Synthesis of Ethyl-D-Glucopyranoside 16. α-D-Glucose **15** (5.15 g, 28.6 mmol), 5.03 g of DOWEX IR-120 acidic ion exchange resin, and 125 mL of absolute ethanol were heated to reflux in the presence of 4Å molecular sieves for 24 hours. ¹H NMR in D₂O indicated that all of the α-D-glucose **5** had been completely consumed, and that the ethyl glycoside was formed as a mixture of anomers (~3:2 α:β). The reaction was cooled to room temperature, filtered, and rinsed thoroughly with hot ethanol. The filtrate was then concentrated on the rotary evaporator and dried under vacuum for several hours to give 5.95 g of Ethyl-D-Glucopyranoside **16** as a golden, glass-like solid.

Synthesis of 4,6-O-Benzylidene-Ethyl- α -D-Glucopyranoside 13 and 4,6-O-Benzylidene-Ethyl- β -D-Glucopyranoside 14. Ethyl D-Glucopyranoside **16** (6.53 g, 31.4 mmol) and 307 mg of p-toluenesulfonic acid monohydrate (1.58 mmol) were dissolved in 6 mL of anhydrous N,N-dimethylformamide, 5.7 mL of benzaldehyde dimethyl acetal (37.8 mmol) was added, and the reaction was stirred at room temperature. ^1H NMR was used to monitor the reaction conversion, which had been determined to have ceased at 26.5 hours, so another 5.0 mL of benzaldehyde dimethyl acetal (33.2 mmol) was added, and the reaction was stirred for another 15 hours. The reaction was determined to have reached ~80-85% conversion, so it was placed on the rotary evaporator at 58°C briefly to remove methanol and drive the reaction to completion. The reaction was stirred at room temperature for another four hours, at which point 720 mg of sodium bicarbonate (8.57 mmol) was added to quench the reaction. After thirty minutes of stirring, the reaction was diluted with 100 mL of ice water, causing precipitation to occur. The water and solids were washed twice with 150 mL portions of hexane to remove the excess benzaldehyde dimethyl acetal, and then the water and solids were extracted with 200 mL of dichloromethane, causing the solids to dissolve. The water phase was extracted with two more 100 mL portions of dichloromethane, followed by two 100 mL portions of chloroform. The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated on the rotary evaporator. The resulting crude white solid was fractionally recrystallized in isopropanol to afford 2.06 g of pure α anomer **13** and 0.61 g of pure β anomer **14**, in ~22% and 7% yields, respectively.

General Method for the Synthesis of Benzoyl Esters 17A-C and Naphthoyl Esters 18A-C of 4,6-O-Benzylidene-Ethyl- α -D-Glucopyranoside 13. To a solution of 4,6-O-Benzylidene-Ethyl- α -D-Glucopyranoside **13** (75 mg, 0.282 mmol) in 2 mL of anhydrous dichloromethane, 1.2-1.4 equivalents of the corresponding acyl chloride (benzoyl or naphthoyl) was added dropwise at 0°C, followed by 9-18 equivalents of anhydrous pyridine. The reaction was warmed to room temperature within a few minutes, and stirred for 18-30 hours. The reaction was diluted with dichloromethane, washed with cold 5% sodium bicarbonate solution, then water, and dried over anhydrous sodium sulfate. The solution was filtered and concentrated then purified by flash chromatography.

General Method for the Synthesis of Terminal Alkynyl Esters 19A-20C of 4,6-O-Benzylidene-Ethyl- α -D-Glucopyranoside 13. A solution was made by dissolving 1.3 equivalents of the corresponding carboxylic acid (relative to 75-100 mg of 4,6-O-Benzylidene-Ethyl- α -D-Glucopyranoside **13**) in ~1 mL of anhydrous dichloromethane, and then adding 1.1 equivalents of oxalyl chloride and a single drop of anhydrous N,N-dimethylformamide at 0°C. The reaction was stirred at 0°C for about one to two hours, until ¹H NMR shows that all the acid has been completely converted to the corresponding acyl chloride. A solution of 4,6-O-Benzylidene-Ethyl- α -D-Glucopyranoside **13** (75-100 mg) in anhydrous dichloromethane and 5-20 equivalents of anhydrous pyridine were then added rapidly, and the reaction was stirred briefly at 0°C before being warmed to room temperature for 12-24 hours. Purification was conducted via flash chromatography, usually using a hexanes:ethyl acetate gradient.

General Method for the Synthesis of Benzoyl Esters 21A-C and Naphthoyl Esters 22A-C of 4,6-O-Benzylidene-Ethyl- β -D-Glucopyranoside 14. A solution of 4,6-O-Benzylidene-Ethyl- β -D-Glucopyranoside **14** (50-100 mg) was dissolved in anhydrous dichloromethane and cooled to 0°C. 1.3 equivalents of benzoyl or naphthoyl chloride and 5 equivalents of pyridine were then added sequentially, and the reaction was stirred at 0°C for 30 minutes before being warmed to room temperature for 16 hours. The reaction was diluted with dichloromethane and washed with cold 10% sodium bicarbonate solution. The aqueous phase was then extracted three times with dichloromethane, and the organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product, which was purified by flash chromatography using a gradient solvent system of hexanes:ethyl acetate 9:1.

General Method for the Synthesis of Terminal Alkynyl Esters 23A-C, 24A-C, and 25A-C of 4,6-O-Benzylidene-Ethyl- β -D-Glucopyranoside 14. A solution was made by dissolving 1.3 equivalents of the corresponding carboxylic acid (relative to 75-100 mg of 4,6-O-Benzylidene-Ethyl- β -D-Glucopyranoside **14**) in ~1 mL of anhydrous dichloromethane, and adding 1.1 equivalents of oxalyl chloride and a single drop of anhydrous N,N-dimethylformamide at 0°C. The reaction was stirred at 0°C for about one to two hours, until ^1H NMR shows that all the acid has been completely converted to the corresponding acyl chloride. A solution of 4,6-O-Benzylidene-Ethyl- β -D-Glucopyranoside **14** (75-100 mg) in anhydrous dichloromethane and 5-20 equivalents of anhydrous pyridine were then added rapidly, and the reaction was stirred briefly at 0°C before being warmed to room temperature for 12-24 hours. Purification was conducted via flash chromatography, usually using a hexanes:ethyl acetate gradient.

Characterization Data for Compounds **17-25A**, **17-20B**, and **21-25C**:

2,3-Dibenzoyl-4,6-O-Benzylidene-Ethyl- α -D-Glucopyranoside 17A. 9% yield. White solid. m.p. = 210°C (decomp.). R_f = 0.73 (hexanes: ethyl acetate 3:1). ^1H NMR (400 MHz, CDCl_3) δ 8.06 – 7.92 (m, 4H), 7.61 – 7.28 (m, 11H), 6.07 (t, J = 9.7, 1H), 5.57 (s, 1H), 5.30 – 5.20 (m, 2H), 4.36 (dd, J = 10.3, 4.9, 1H), 4.13 (td, J = 9.9, 4.9, 1H), 3.97 – 3.70 (m, 3H), 3.60 – 3.44 (m, 1H), 1.22 (t, J = 7.1, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 166.2, 165.8, 137.1, 133.5, 133.2, 130.1, 129.9, 129.3, 129.2, 128.6, 128.5, 128.4, 126.3, 101.7, 96.8, 79.7, 72.7, 69.8, 69.2, 64.4, 62.8, 15.2.

2-Benzoyl-4,6-O-Benzylidene-Ethyl- α -D-Glucopyranoside 17B. 32% yield. Colorless oil. R_f = 0.42 (hexanes: ethyl acetate 3:1). 400 MHz, CDCl_3) δ 8.16 – 8.03 (m, 2H), 7.68 – 7.28 (m, 8H), 5.59 (s, 1H), 5.19 (d, J = 3.8, 1H), 5.02 (dt, J = 18.4, 9.2, 1H), 4.43 – 4.25 (m, 2H), 3.96 (td, J = 9.9, 4.9, 1H), 3.84 – 3.71 (m, 2H), 3.60 (t, J = 9.8, 1H), 3.54 – 3.43 (m, 1H), 2.76 (s, 1H), 1.19 (t, J = 7.0, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 166.8, 137.5, 134.0, 133.8, 130.6, 130.4, 130.1, 129.8, 128.9, 128.9, 126.8, 102.6, 97.0, 82.1, 74.6, 69.5, 69.4, 64.6, 62.7, 15.6.

3-Benzoyl-4,6-O-Benzylidene-Ethyl- α -D-Glucopyranoside 17C. 7% yield. White solid. m.p. = 192-194°C. R_f = 0.27 (hexanes: ethyl acetate 3:1). ^1H NMR (400 MHz, CDCl_3) δ 8.08 (d, J = 7.4, 2H), 7.66 – 7.27 (m, 8H), 5.61 (t, J = 9.6, 1H), 5.53 (s, 1H), 4.96 (d, J = 3.8, 1H), 4.33 (dd, J = 10.3, 4.8, 1H), 3.98 (td, J = 9.9, 4.8, 1H), 3.92 – 3.69 (m, 4H), 3.69 – 3.50 (m, 1H), 1.30 (t, J = 7.1, 4H). ^{13}C NMR (101 MHz, CDCl_3) δ 166.9, 137.2, 133.3, 130.2, 130.1, 129.2, 128.5, 128.4, 126.3, 101.7, 99.2, 79.1, 73.3, 72.1, 69.2, 64.5, 63.1, 15.3.

2-Naphthoyl-4,6-O-Benzylidene-Ethyl- α -D-Glucopyranoside 18B. 55% yield. White solid. m.p = 216-217°C. R_f = 0.57 (hexanes: ethyl acetate 3:1). ^1H NMR (400 MHz, CDCl_3) δ 8.92 (t, J = 16.0, 1H), 8.24 (t, J = 14.0, 1H), 8.04 (d, J = 8.2, 1H), 7.90 (d, J = 8.1, 1H), 7.72 – 7.30 (m, 8H), 5.57 (s, 1H), 5.34 (d, J = 3.8, 1H), 5.12 (dd, J = 9.6, 3.9, 1H), 4.41 (t, J = 9.5, 1H), 4.33 (dd, J = 10.2, 4.9, 1H), 3.99 (td, J = 10.0, 4.9, 1H), 3.91 – 3.70 (m, 2H), 3.63 (t, J = 7.2, 1H), 3.59 – 3.48 (m, 1H), 2.74 (s, 1H), 1.26 (t, J = 6.0, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 167.5, 137.2, 134.0, 133.8, 131.4, 130.9, 129.5, 128.7, 128.5, 128.0, 127.0, 126.5, 126.5, 126.0, 124.7, 102.2, 96.6, 81.6, 74.6, 69.1, 69.0, 64.2, 62.3, 15.3.

2,3-di(4-pentynoyl)-4,6-O-Benzylidene-Ethyl- α -D-Glucopyranoside 19A. 5% yield. White solid. R_f = 0.41 (hexanes:ethyl acetate 4:1). m.p. = 65.5-67°C. ^1H NMR (400 MHz, CDCl_3) δ 7.47 – 7.41 (m, 2H), 7.38 – 7.31 (m, 3H), 5.64 (t, J = 9.8, 1H), 5.50 (s, 1H), 5.07 (d, J = 3.7, 1H), 4.90 (dd, J = 9.9, 3.8, 1H), 4.29 (dd, J = 10.3, 4.9, 1H), 3.97 (td, J = 9.9, 4.8, 1H), 3.81 – 3.69 (m, 2H), 3.65 (t, J = 9.6, 1H), 3.55 – 3.43 (m, 1H), 2.62 – 2.42 (m, 9H), 1.98 (t, J = 2.5, 1H), 1.88 (t, J = 2.4, 1H), 1.23 (t, J = 7.1, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 171.1, 170.5, 136.9, 129.0, 128.2, 126.1, 101.5, 96.2, 82.3, 82.1, 79.2, 71.8, 69.2, 69.2, 69.1, 68.8, 64.0, 62.3, 33.2, 33.2, 14.9, 14.4, 14.3.

2-(4-pentynoyl)-4,6-O-Benzylidene-Ethyl- α -D-Glucopyranoside 19B. 13% yield. White solid. R_f = 0.20 (hexanes:ethyl acetate 4:1). m.p. = 104.5-105.5°C. ^1H NMR (400 MHz, CDCl_3) δ 7.50 (dd, J = 6.6, 2.7, 2H), 7.42 – 7.32 (m, 3H), 5.55 (s, 1H), 5.08 (d, J = 3.8, 1H), 4.79 (dd, J = 9.6, 3.8, 1H), 4.28 (dd, J = 10.2, 4.8, 1H), 4.22 (t, J = 9.5, 1H), 3.89 (td, J = 9.9, 4.8, 1H), 3.81 –

3.70 (m, 2H), 3.62 – 3.44 (m, 2H), 2.74 – 2.46 (m, 5H), 1.99 (t, $J = 2.5$, 1H), 1.23 (t, $J = 7.1$, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 171.6, 137.2, 129.5, 128.6, 126.5, 102.2, 96.4, 82.6, 81.5, 74.2, 69.4, 69.1, 68.8, 64.2, 62.3, 33.5, 15.2, 14.7.

2,3-di(5-hexynoyl)-4,6-O-Benzylidene-Ethyl- α -D-Glucopyranoside 20A. 25% yield. White solid. m.p. = 83.5-85°C. ^1H NMR (400 MHz, CDCl_3) δ 7.50 – 7.40 (m, 2H), 7.40 – 7.30 (m, 3H), 5.64 (t, $J = 9.8$, 1H), 5.51 (s, 1H), 5.08 (d, $J = 3.7$, 1H), 4.87 (dd, $J = 9.9$, 3.8, 1H), 4.29 (dd, $J = 10.1$, 4.8, 1H), 3.97 (td, $J = 9.9$, 4.8, 1H), 3.83 – 3.70 (m, 2H), 3.64 (t, $J = 9.7$, 1H), 3.50 (dq, $J = 14.2$, 7.0, 1H), 2.55 – 2.42 (m, 4H), 2.26 (td, $J = 6.8$, 2.5, 2H), 2.21 (td, $J = 7.0$, 2.6, 2H), 1.97 (t, $J = 2.4$, 1H), 1.94 (d, $J = 2.6$, 1H), 1.88 – 1.77 (m, 4H), 1.23 (t, $J = 7.1$, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 172.4, 171.8, 136.9, 129.0, 128.2, 126.1, 101.5, 96.2, 83.1, 82.9, 79.3, 71.6, 69.3, 69.1, 68.9, 68.8, 64.0, 62.3, 32.7, 32.7, 23.7, 23.5, 17.7, 17.6, 14.9.

2-(5-hexynoyl)-4,6-O-Benzylidene-Ethyl- α -D-Glucopyranoside 20B. 8% yield. White solid. m.p. = 60-62°C. ^1H NMR (400 MHz, CDCl_3) δ 7.50 (dd, $J = 6.6$, 2.9, 2H), 7.42 – 7.32 (m, 3H), 5.56 (s, 1H), 5.09 (d, $J = 3.8$, 1H), 4.77 (dd, $J = 9.7$, 3.8, 1H), 4.28 (dd, $J = 10.2$, 4.8, 1H), 4.21 (t, $J = 9.5$, 1H), 3.89 (td, $J = 9.9$, 4.8, 1H), 3.80 – 3.70 (m, 2H), 3.56 (t, $J = 9.4$, 1H), 3.53 – 3.45 (m, 1H), 2.56 (t, $J = 7.3$, 2H), 2.29 (td, $J = 7.0$, 2.6, 2H), 1.98 (t, $J = 2.6$, 1H), 1.93 – 1.83 (m, 2H), 1.23 (t, $J = 7.1$, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 172.7, 137.0, 129.3, 128.3, 126.3, 102.0, 96.1, 83.1, 81.4, 73.7, 69.2, 68.9, 68.7, 63.9, 62.1, 32.8, 23.6, 17.7, 15.0.

2,3-dibenzoyl-4,6-O-Benzylidene-Ethyl-β-D-Glucopyranoside 21A. 5% yield. No m.p. reported. ¹H NMR (400 MHz, CDCl₃) δ 7.96 (dd, *J* = 7.4, 1.6, 4H), 7.59 – 7.45 (m, 2H), 7.45 – 7.27 (m, 9H), 5.78 (t, *J* = 9.6, 1H), 5.55 (s, 1H), 5.46 (dd, *J* = 9.3, 8.0, 1H), 4.81 (d, *J* = 7.9, 1H), 4.44 (dd, *J* = 10.5, 4.9, 1H), 4.00 – 3.84 (m, 4H), 3.77 – 3.56 (m, 2H), 1.15 (t, *J* = 7.1, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 165.6, 165.2, 136.8, 133.1, 133.1, 129.8, 129.8, 129.4, 129.4, 129.0, 128.3, 128.3, 128.2, 126.1, 101.5, 101.5, 78.8, 72.5, 72.1, 68.7, 66.6, 66.0, 15.1.

3-benzoyl-4,6-O-Benzylidene-Ethyl-β-D-Glucopyranoside 21C. 30 % yield. White solid. m.p. = 186.5-188°C. ¹H NMR (400 MHz, CDCl₃) δ 8.09 (dd, *J* = 8.2, 1.0, 2H), 7.61 – 7.52 (m, 1H), 7.49 – 7.38 (m, 4H), 7.35 – 7.28 (m, 3H), 5.58 – 5.45 (m, 2H), 4.55 (d, *J* = 7.7, 1H), 4.40 (dd, *J* = 10.5, 5.0, 1H), 4.00 (dq, *J* = 9.4, 7.1, 1H), 3.83 (q, *J* = 9.9, 2H), 3.77 – 3.65 (m, 2H), 3.60 (td, *J* = 9.6, 4.9, 1H), 2.76 (s, 1H), 1.28 (t, *J* = 5.0, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 166.5, 136.9, 133.2, 129.9, 129.7, 129.0, 128.3, 128.2, 126.1, 103.4, 101.4, 78.6, 74.2, 73.5, 68.7, 66.5, 66.1, 15.1.

2,3-dinaphthoyl-4,6-O-Benzylidene-Ethyl-β-D-Glucopyranoside 22A. 12% yield. White solid. ¹H NMR (400 MHz, CDCl₃) δ 8.70 (dd, *J* = 6.1, 3.6, 1H), 8.63 (d, *J* = 8.5, 1H), 8.15 – 8.06 (m, 2H), 7.97 (dd, *J* = 13.1, 8.2, 2H), 7.89 – 7.77 (m, 2H), 7.57 – 7.30 (m, 11H), 5.95 (t, *J* = 9.6, 1H), 5.69 – 5.56 (m, 2H), 4.91 (d, *J* = 7.9, 1H), 4.48 (dd, *J* = 10.5, 4.9, 1H), 4.09 – 3.88 (m, 3H), 3.81 – 3.63 (m, 2H), 1.22 (t, *J* = 7.0, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 167.0, 166.4, 137.0, 133.9, 133.8, 133.6, 133.4, 131.4, 131.3, 130.0, 129.9, 129.3, 128.6, 128.6, 128.4, 127.9, 127.8, 127.2,

127.1, 126.5, 126.4, 126.3, 125.8, 125.8, 124.8, 101.9, 101.7, 79.1, 72.8, 72.5, 68.9, 66.9, 66.3, 15.4.

3-naphthoyl-4,6-O-Benzylidene-Ethyl-β-D-Glucopyranoside 22C. 44% yield. White solid. m.p. = 176-178°C. ¹H NMR (400 MHz, CDCl₃) δ 8.86 – 8.75 (m, 1H), 8.14 (d, *J* = 11.2, 1H), 8.01 (d, *J* = 8.2, 1H), 7.92 – 7.82 (m, 1H), 7.63 – 7.41 (m, 5H), 7.41 – 7.28 (m, 3H), 5.70 – 5.52 (m, 2H), 4.60 (d, *J* = 7.6, 1H), 4.43 (dd, *J* = 10.5, 4.9, 1H), 4.09 – 3.94 (m, 1H), 3.93 – 3.59 (m, 5H), 2.93 (s, 1H), 1.29 (t, *J* = 5.6, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 167.8, 136.9, 133.7, 133.3, 131.1, 129.8, 129.0, 128.4, 128.2, 127.7, 127.4, 126.3, 126.1, 125.8, 124.5, 103.4, 101.4, 78.7, 74.3, 73.5, 68.7, 66.5, 66.1, 15.1.

2,3-di(4-pentynoyl)-4,6-O-Benzylidene-Ethyl-β-D-Glucopyranoside 23A. 30% yield of white solid. M.p. = 105-106.5°C. ¹H NMR (400 MHz, CDCl₃) δ 7.43 (dd, *J* = 6.6, 2.9, 2H), 7.35 (dd, *J* = 9.0, 5.7, 3H), 5.47 (s, 1H), 5.35 (t, *J* = 9.5, 1H), 5.02 (dd, *J* = 9.3, 8.0, 1H), 4.60 (d, *J* = 7.9, 1H), 4.36 (dd, *J* = 10.5, 5.0, 1H), 3.90 (dq, *J* = 9.7, 7.1, 1H), 3.80 (t, *J* = 10.3, 1H), 3.71 (t, *J* = 9.6, 1H), 3.65 – 3.47 (m, 2H), 2.60 – 2.41 (m, 8H), 1.98 (t, *J* = 2.4, 1H), 1.88 (t, *J* = 2.5, 1H), 1.20 (t, *J* = 7.1, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 170.8, 170.3, 136.7, 129.1, 128.2, 126.1, 101.4, 101.1, 82.2, 82.1, 78.3, 72.4, 71.9, 69.1, 69.1, 68.5, 66.3, 65.9, 33.1, 15.1, 14.2.

3-(4-pentynoyl)-4,6-O-Benzylidene-Ethyl-β-D-Glucopyranoside 23C. 12 yield of white solid. M.p. = 145.5-147°C. ¹H NMR (400 MHz, CDCl₃) δ 7.44 (dd, *J* = 6.4, 3.0, 2H), 7.38 – 7.31 (m,

3H), 5.49 (s, 1H), 5.27 (t, $J = 9.4$, 1H), 4.47 (d, $J = 7.7$, 1H), 4.35 (dd, $J = 10.5$, 4.9, 1H), 3.96 (dq, $J = 9.6$, 7.1, 1H), 3.84 – 3.73 (m, 1H), 3.71 – 3.48 (m, 4H), 2.70 – 2.60 (m, 2H), 2.55 – 2.48 (m, 2H), 1.89 (t, $J = 2.6$, 1H), 1.27 (t, $J = 7.1$, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 171.4, 136.8, 129.0, 128.2, 126.1, 103.2, 101.4, 82.3, 78.4, 73.7, 73.2, 69.1, 68.6, 66.4, 66.0, 33.3, 15.1, 14.4.

2,3-di(5-hexynoyl)-4,6-O-Benzylidene-Ethyl- β -D-Glucopyranoside 24A. 15% yield. m.p. = 70–72°C. ^1H NMR (400 MHz, CDCl_3) δ 7.43 (dd, $J = 6.5$, 2.9, 2H), 7.39 – 7.31 (m, 3H), 5.50 (s, 1H), 5.34 (t, $J = 9.5$, 1H), 5.02 (dd, $J = 9.3$, 8.0, 1H), 4.59 (d, $J = 7.9$, 1H), 4.37 (dd, $J = 10.5$, 4.9, 1H), 3.91 (dq, $J = 9.7$, 7.1, 1H), 3.81 (t, $J = 10.3$, 1H), 3.70 (t, $J = 9.5$, 1H), 3.65 – 3.48 (m, 2H), 2.50 – 2.40 (m, 4H), 2.26 (td, $J = 7.0$, 2.6, 2H), 2.20 (td, $J = 7.0$, 2.6, 2H), 1.97 (t, $J = 2.6$, 1H), 1.93 (t, $J = 2.6$, 1H), 1.88 – 1.75 (m, 4H), 1.21 (t, $J = 7.1$, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 172.1, 171.6, 136.8, 129.1, 128.2, 126.1, 101.4, 101.2, 83.0, 78.5, 72.1, 71.7, 69.2, 69.2, 68.6, 66.4, 65.9, 32.7, 32.7, 23.6, 17.7, 17.6, 15.1.

3-(5-hexynoyl)-4,6-O-Benzylidene-Ethyl- β -D-Glucopyranoside 25C. 24% yield. White solid. m.p. = 112–113.5°C. ^1H NMR (400 MHz, CDCl_3) δ 7.44 (dd, $J = 6.6$, 2.9, 2H), 7.40 – 7.30 (m, 3H), 5.49 (s, 1H), 5.25 (t, $J = 9.5$, 1H), 4.46 (d, $J = 7.7$, 1H), 4.35 (dd, $J = 10.5$, 4.9, 1H), 3.96 (dq, $J = 9.5$, 7.1, 1H), 3.79 (t, $J = 10.2$, 1H), 3.71 – 3.60 (m, 2H), 3.53 (ddd, $J = 14.5$, 11.7, 6.6, 2H), 2.65 (s, 1H), 2.53 (t, $J = 7.3$, 2H), 2.24 (td, $J = 7.0$, 2.6, 2H), 1.94 (t, $J = 2.6$, 1H), 1.86 (p, $J = 7.1$, 2H), 1.27 (t, $J = 7.1$, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 172.9, 136.9, 129.0, 128.2, 126.1, 103.3, 101.4, 83.2, 78.5, 73.4, 73.3, 69.1, 68.6, 66.4, 66.0, 32.9, 23.7, 17.6, 15.1.

2,3-di(6-heptynoyl)-4,6-O-Benzylidene-Ethyl-β-D-Glucopyranoside 25A. 28% yield. Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.45 – 7.39 (m, 2H), 7.38 – 7.30 (m, 3H), 5.50 (s, 1H), 5.33 (t, *J* = 9.5, 1H), 5.05 – 4.97 (m, 1H), 4.59 (d, *J* = 7.9, 1H), 4.36 (dd, *J* = 10.5, 4.9, 1H), 3.95 – 3.85 (m, 1H), 3.80 (t, *J* = 10.3, 1H), 3.69 (t, *J* = 9.5, 1H), 3.66 – 3.47 (m, 2H), 2.40 – 2.25 (m, 3H), 2.20 (td, *J* = 7.0, 2.4, 2H), 2.11 (td, *J* = 6.9, 2.4, 2H), 1.95 (t, *J* = 2.3, 1H), 1.91 (t, *J* = 2.3, 1H), 1.79 – 1.64 (m, 4H), 1.60 – 1.43 (m, 4H), 1.20 (t, *J* = 7.0, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 172.4, 171.8, 136.8, 129.1, 128.2, 126.1, 101.4, 101.2, 83.8, 83.7, 78.5, 72.0, 71.6, 68.7, 68.6, 68.6, 66.3, 65.8, 33.6, 33.5, 27.6, 27.5, 23.9, 23.9, 18.1, 18.0, 15.1.

3-(6-heptynoyl)-4,6-O-Benzylidene-Ethyl-β-D-Glucopyranoside 25C. 22% yield. White solid. ¹H NMR (400 MHz, CDCl₃) δ 7.49 (dd, *J* = 6.5, 3.0, 2H), 7.42 – 7.34 (m, 3H), 5.55 (s, 1H), 4.94 (dd, *J* = 9.1, 8.0, 1H), 4.53 (d, *J* = 7.9, 1H), 4.36 (dd, *J* = 10.5, 5.0, 1H), 3.97 – 3.85 (m, 2H), 3.81 (t, *J* = 10.3, 1H), 3.59 (ddd, *J* = 14.0, 10.2, 6.5, 2H), 3.46 (td, *J* = 9.7, 5.0, 1H), 2.55 (d, *J* = 3.4, 1H), 2.46 – 2.39 (m, 2H), 2.22 (td, *J* = 7.0, 2.6, 2H), 1.95 (t, *J* = 2.6, 1H), 1.80 (dt, *J* = 14.8, 7.6, 2H), 1.60 (p, *J* = 8.3, 2H), 1.21 (t, *J* = 7.1, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 173.3, 136.9, 129.1, 128.2, 126.1, 103.3, 101.5, 84.0, 78.5, 75.6, 73.4, 73.3, 68.7, 68.6, 66.5, 66.1, 33.8, 27.5, 24.0, 18.0, 15.1.

References

- 1) Luboradzki, R.; Gronwald, O.; Ikeda, M.; Shinkai, S.; Reinhouldt, D.; *Tetrahedron*, **2000**, *56*, 9595-9599.

- 2) Gronwald, O.; Sakurai, K.; Luboradzki, R.; Kimura, T.; Shinkai, S.; *Carbohydr. Res.*, **2001**, *331*, 307-318.
- 3) Gronwald, O.; Shinkai, S.; *Chem. Eur. J.*, **2001**, *7*, 4329-4334.
- 4) Wang, G.; Cheuk, S.; Williams, K.; Sharma, V.; Dakessian, L.; Thorton, Z.; *Carbohydr. Res.*, **2006**, *341*, 705-716.
- 5) Wang, G.; Cheuk, S.; Yang, H.; Goyal, N.; Reddy, P. V. N.; Hopkinson, B.; *Langmuir*, **2009**, *25*, 8696-8705.
- 6) Cheuk, S.; Stevens, E.; Wang, G.; *Carbohydr. Res.*, **2009**, *344*, 417-425.
- 7) Goyal, N.; Cheuk, S.; Wang, G.; *Tetrahedron*, **2010**, *66*, 5962-5971.
- 8) Lee, K. Y.; Mooney, D. J.; *Chem. Rev.*, **2001**, *101*(7), 1869-1879.
- 9) Liao, S. W.; Yu, T.-B.; Guan, Z.; *J. Am. Chem. Soc.*, **2009**, *131*(48), 17638-17646.
- 10) Khan, F.; Tare, R. S.; Oreffo, R. O. C.; Bradley, M.; *Angew. Chem. Int. Ed.*, **2009**, *48*, 978-982.
- 11) Yang, Z.; Xu, K.; Wang, L.; Gu, H.; Wei, H.; Zhang, M.; Xu, B.; *Chem. Commun.*, **2005**, 4414-4416.
- 12) Yang, Z.; Liang, G.; Ma, M.; Abbah, A. S.; Lu, W. W.; Xu, B.; *Chem. Commun.*, **2007**, 843-845.

Chapter III: Synthesis and Characterization of Low Molecular Weight Hydrogelators Derived from D-Galactose.

Abstract: Low molecular weight gelators are a novel class of materials that have received an increasing amount of attention over the past two decades. The interesting and complex supramolecular behavior of these molecules, along with their seemingly limitless potential applications, have helped to spur their interest. Our laboratory has synthesized several series of compounds derived from D-glucose and D-glucosamine, and we have found that monosaccharides make excellent templates for low molecular weight gelators. In an effort to better understand how changes to the monosaccharide core affect gelation, we wanted to understand how changing the stereochemistry would attenuate gelation. Hence, we decided to synthesize a series of analogs from D-galactose that directly paralleled our original D-glucose-based compounds. The synthesis, characterization, and gel testing of these compounds are discussed herein.

Keywords: gel, low molecular weight gelator, supramolecular gelator, hydrogel, monosaccharide, D-galactose

Introduction

Gelators are important soft materials with a variety of useful applications. Among the various classes of gelators, low molecular weight hydrogelators are especially desirable materials, due to several, unique properties, including: 1) thermoreversibility, 2) the ability to easily and uniformly synthesize the compounds (as opposed to traditional, polymer-based gelators), and 3) the potential for biocompatibility. The applications of these materials are wide-ranging¹, but some of the most remarkable breakthroughs have been in the development of low molecular weight hydrogelators for biological and biomedical uses, including drug delivery²⁻⁴, enzyme immobilization⁵, tissue engineering⁶, and wound healing⁷. As such, a great deal of effort has been devoted recently to the development of novel low molecular weight hydrogelators which can undertake specific applications.

Typically, gels are formed by fibrous networks which trap solvent within their frameworks⁸; this requires that the gelator molecules self-assemble anisotropically. The supramolecular networks formed by low molecular weight gelators are typically held together by a variety of weak, noncovalent forces, such as hydrogen bonding, π - π stacking, electrostatic interactions, and various Van der Waal's interactions, such as dipole-dipole interactions and hydrophobic forces⁹. As such, low molecular weight gelators must find a delicate balance between solubility and insolubility in the desired solvent; if the molecules are too soluble, the solvent effectively breaks up these intermolecular interactions, disrupting self-assembly indefinitely, whereas if the molecules are too insoluble, the molecules remain unsolvated in the solid phase, and are not free to rearrange and self-assemble into the fibrous gel network and trap the solvent. A great deal of effort has been put forth by a number of research groups to determine how to functionalize small molecules in order to promote gelation, and it is now

possible to predict with some accuracy whether or not a small molecule will act as a low molecular weight gelator.

Since self-assembly is widely utilized by nature, biomolecules make excellent templates for the design and synthesis of low molecular weight gelators. Biomolecules are abundant, readily available, biocompatible, and often contain the types of functionalities which promote self-assembly; if the self-assembly of the molecules can be directed in an anisotropic manner, good gelators can often be obtained. Many research groups have shown that functionalization of amino acids¹⁰ or steroids¹¹ can generate efficient low molecular weight gelators for water or organic solvents. Although carbohydrate-based supramolecular gelators⁹ aren't as thoroughly explored, they are often utilized as templates for low molecular weight gelators as well. Depending on the functionalization of these molecules, biomolecular templates can often be designed and synthesized to carry out a specific function in addition to gelation. This provides a means to design novel smart materials with a specific purpose.

Our laboratory's interest lies in the synthesis and characterization of novel hydrogelators and organogelators derived from monosaccharides. Shinkai and coworkers have shown that several 4,6-O-benzylidene protected methyl glycosides **1-4** (Figure 1) can act as low molecular weight gelators for water or organic solvents¹²⁻¹⁴. Inspired by these findings, our laboratory set out to determine how modifying the structures of these monosaccharide derivatives would alter their gelation. Using 4,6-O-benzylidene-methyl- α -D-glucopyranoside **1** as our archetype, we synthesized a series of esters with the general structures **5A-C** by acylating the free hydroxyl groups at the 2- and 3-positions of **1**^{15,16}, as shown in Scheme 1. We found that the 2-esters **5B** with terminal acetylene or aromatic functionalities were good gelators for water or aqueous mixtures.

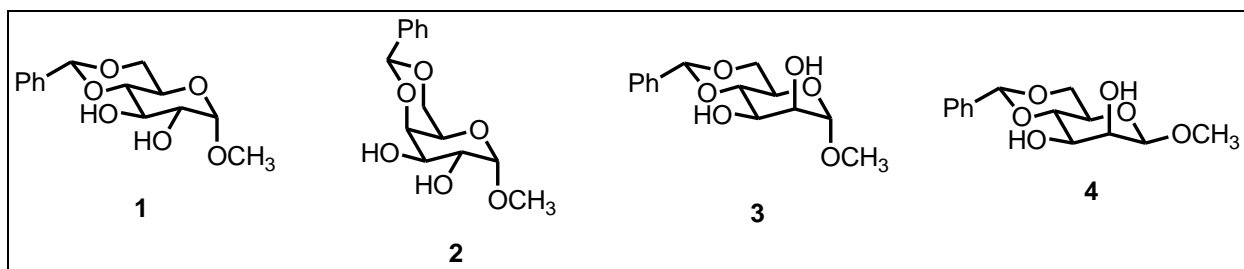
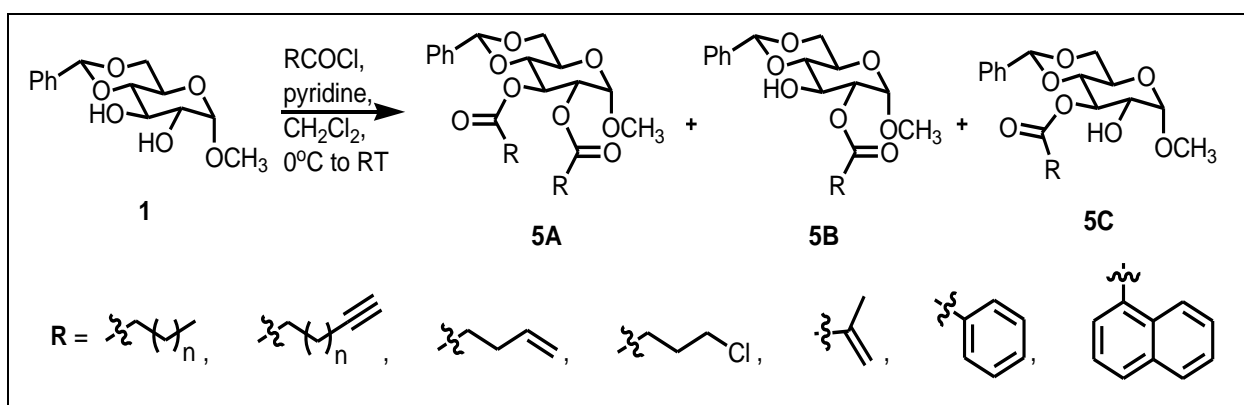


Figure 1. Structures of monosaccharide-based organogelators **1-4**.



Scheme 1. Synthesis of gelators **5A-C** by esterification of **1**.

We wanted to find gelators which were more efficient and that had special gelation properties, such as a propensity for gelling water and aqueous solvent mixtures in preference to organic solvents, as well as explore how changing the functionality at other sites of the monosaccharide core would affect gelation. Therefore, we decided to investigate how changes to the stereochemistry might affect gelation. Looking back to Shinkai's work in the area, one can see that of the common monosaccharides studied, only the D-glucose, D-mannose, and D-galactose derivatives were able to effectively gelate the organic solvents screened. With this in mind, we decided to synthesize an analogous series of esters starting from 4,6-O-benzylidene-

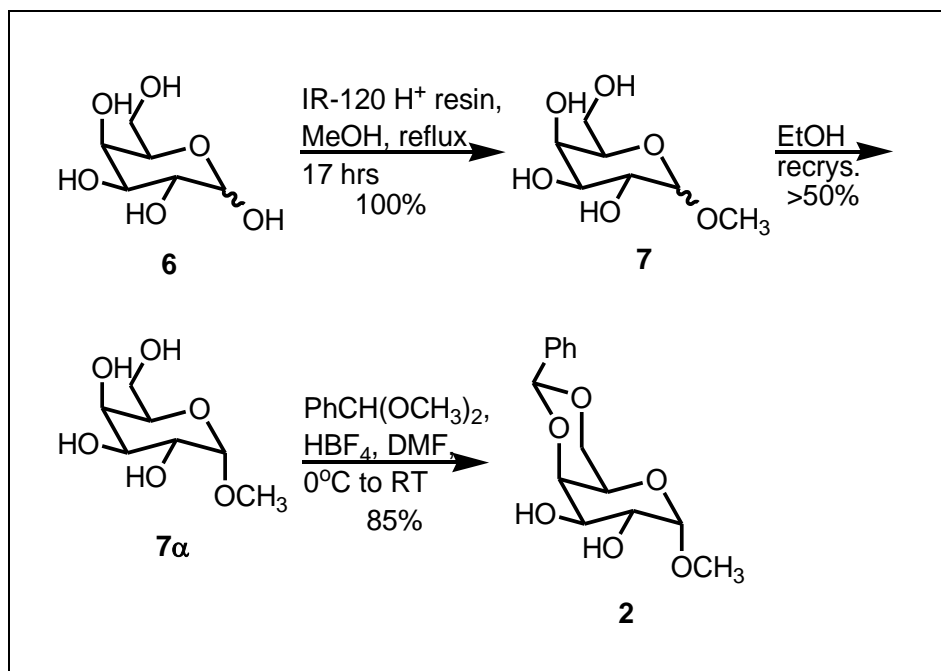
methyl- α -D-galactopyranoside **2** in order to see how the change in stereochemistry would affect the gelation ability of the compounds. The results that were obtained are described herein.

Results and Discussion

Because of the success that our laboratory has achieved in synthesizing efficient hydrogelators and organogelators obtained from the acylation of 4,6-O-benzylidene-methyl- α -D-glucopyranoside **1** and 4,6-O-benzylidene-2-deoxy-2-amino-methyl- α -D-glucopyranoside **9**, we hoped to expound on that success by synthesizing a similar series of analogues starting from 4,6-O-benzylidene-methyl- α -D-galactopyranoside **2**. This series of analogues was meant to parallel the ester series derived from 4,6-O-benzylidene-methyl- α -D-glucopyranoside **1**, in an attempt to understand how changing the stereochemistry would affect the gelation behavior of these esters. To this end, 4,6-O-benzylidene-methyl- α -D-galactopyranoside **3** was synthesized in two steps from D-galactose **6** (Scheme 2).

D-galactose **6** was methylated at the anomeric position under Fisher glycosylation conditions, affording methyl-D-galactopyranoside **7** as a mixture of anomers (~3:2). This mixture of anomers was resolved by recrystallization in ethanol, which afforded the α anomer **7 α** in good yield (~83% based on conversion to desired anomer). The methyl- α -D-galactopyranoside **7 α** was then protected with benzylidene dimethyl acetal in the presence of tetrafluoroboric acid to give the desired product. It was found that the clean product could be obtained without recrystallization or column purification; the product was obtained by simply quenching the reaction with saturated sodium bicarbonate solution, extracting the unreacted

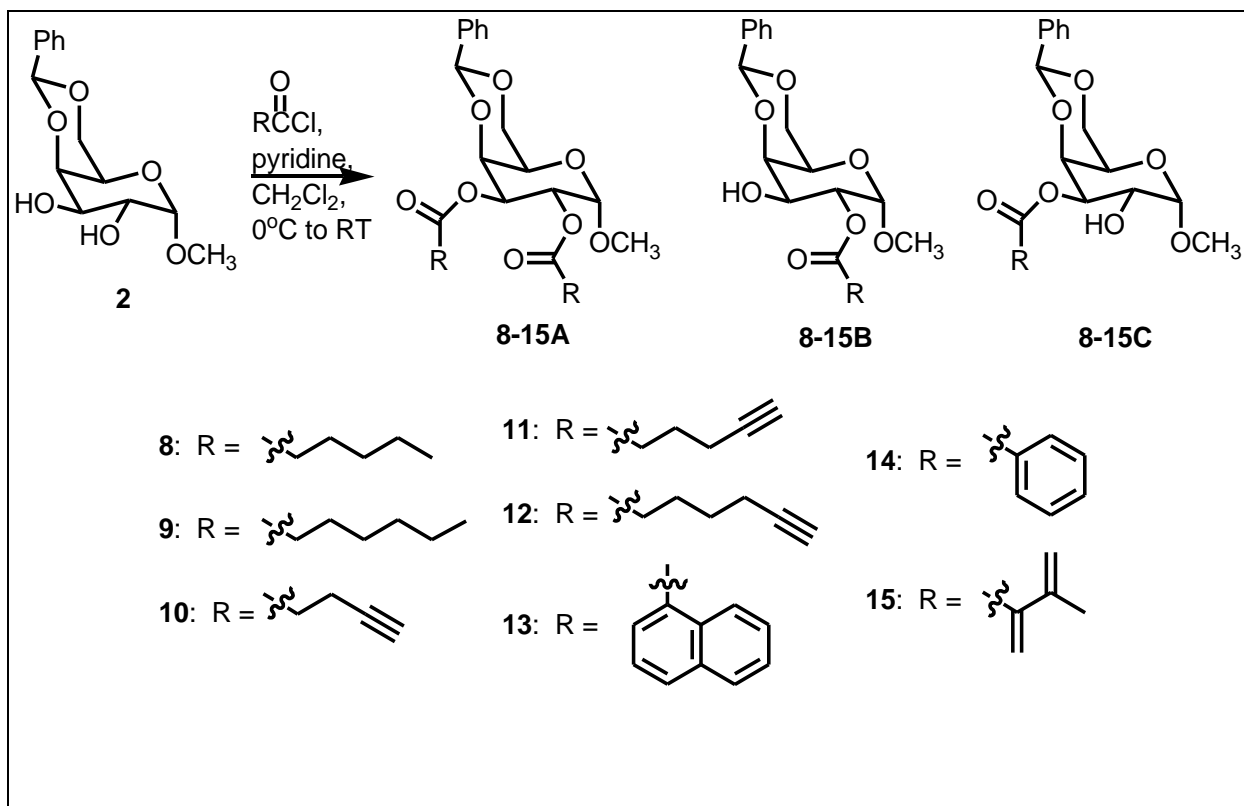
benzaldehyde dimethyl acetal with hexane, and then extracting the product with dichloromethane. In this way, the product **2** was obtained as a pure white solid in 85% yield.



Scheme 2. Synthesis of 4,6-O-benzylidene-methyl- α -D-galactopyranoside **2**.

With the desired 4,6-O-benzylidene-methyl- α -D-galactopyranoside **2** in hand, we then carried out a series of esterification reactions with nine different acyl chlorides, in the presence of pyridine, to give 18 different compounds; the hexanoate analogs **8A** and **8C**, heptanoate compounds **9A** and **9C**, 4-pentynoates **10A** and **10C**, 5-hexynoate derivatives **11A** and **11C**, 6-heptynoate esters **12A** and **12C**, naphthoates **13A** and **13C**, benzoate analogs **14A** and **14C**, and methacrylates **15A** and **15C** were all obtained (Scheme 3). The benzoyl, hexanoyl, and heptanoyl chlorides were used directly, but the remaining acyl chlorides were synthesized in situ

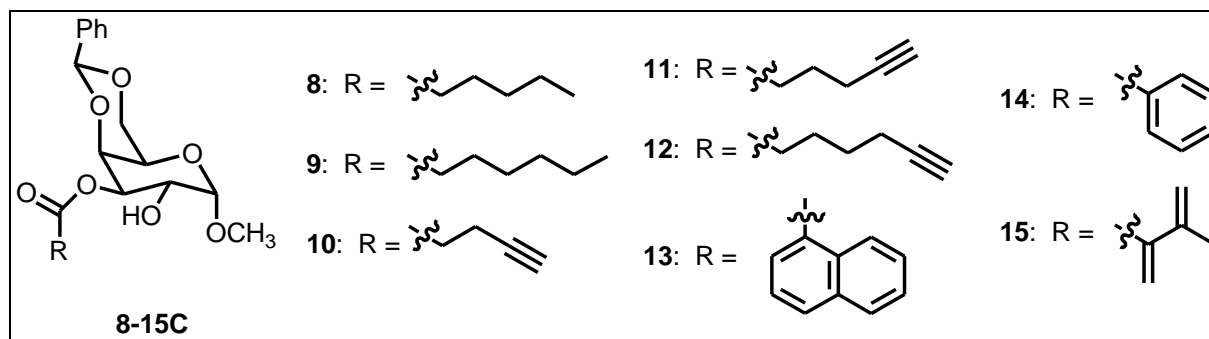
from the corresponding carboxylic acids, using anhydrous N,N-dimethylformamide as a catalyst in most cases. The reaction typically gave a mixture of products; the 3-ester was the major product, and varying quantities of the diester and the 2-ester were afforded as minor products. The products were separated using flash chromatography with a gradient solvent system of hexane, dichloromethane, and acetone. The 2-isomer was typically not isolated due to the low conversion and difficulty in separating it from the major product (R_f values for the 2-ester and 3-ester were typically within 5% or less of one another).



Scheme 3. Synthesis of D-Galactose Based Esters **8-15A** and **8-15C**.

Upon isolation, the compounds were characterized by ^1H and ^{13}C NMR, and the compounds were tested for their gelation ability. The compounds were tested in hexanes, ethanol, water, water:DMSO 2:1, and water:ethanol 2:1, starting at concentrations of about 20-25 mg/mL. Of the 18 compounds tested, only four compounds were found to be gelators within the concentration range tested (~ 25 mg/mL to 5 mg/mL): the 4-pentynoyl diester **10A**, the 5-hexynoyl 3-ester **11C**, the naphthoyl 3-ester **13C**, and the benzoyl 3-ester **14C**. Interestingly enough, all of the compounds were found to be hydrogelators, though the minimum gelation concentrations were all around 20 mg/mL. ClogP values were calculated for all of the compounds using ChemDraw Ultra v9.0, but no discernable trend could be obtained from the data. For the diesters, too few compounds gelled to observe a trend, while the slightly better performing 3-esters failed to exhibit any correlation. The gel testing results for the diesters and 3-esters are shown below (Tables 1 & 2).

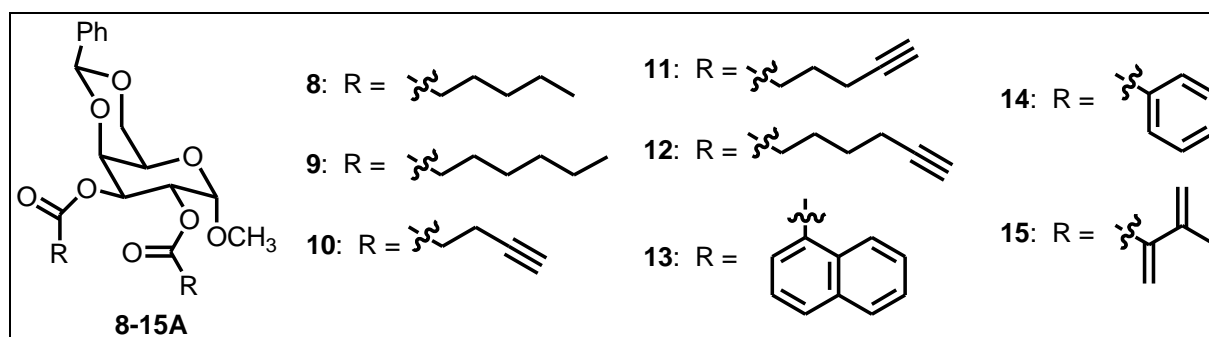
Table 1. Gel testing data for D-galactose diesters **8-15A**.



Compound	ClogP	m.p. (°C)	Water	EtOH	Hexanes	H ₂ O: DMSO 1:2	H ₂ O: EtOH 1:2	H ₂ O: EtOH 1:1
8A	5.32	Oil	I	P	P	P	P	n.t.
9A	6.38	Oil	P	S	S	P	P	P
10A	2.25	n.t.	G(25); UG(12.5)	S	R	P	P	P
11A	2.91	Oil	P	S	P	P	P	P
12A	3.66	Oil	I	S	P	P	P	P
13A	6.52	162	I	S	P	I	I	P
14A	4.17	n.t.	I	R	I	I	I	I
15A	2.37	n.t.	P	S	I	P	I	P

All compounds tested at an initial concentration of ~20 mg/mL. Legend: I = insoluble, P = precipitate, R = recrystallization, S = soluble, UG = unstable gel, G = stable gel, n.t. = not tested. Transparent/translucent gels are denoted with a subscript of T; opaque gels are denoted with a subscript of O. Numbers in parentheses correspond to concentration in mg/mL.

Table 2. Gel testing data for D-galactose diesters **8-15C**.



Compound	ClogP	m.p.	Water	EtOH	Hexanes	H ₂ O: DMSO 1:2	H ₂ O: EtOH 1:2	H ₂ O: EtOH 1:1
8C	2.36	n.t.	P	S	P	P	P	n.t.
9C	2.88	n.t.	I	S	S	P	P	S
10C	0.82	110	R	S	R	S	P	S
11C	1.15	80	G (23)	S	R	P	P	S
12C	1.53	Oil	P	S	P	P	P	P
13C	2.91	n.t.	G(12)	S	P	P	P	P
14C	1.73	n.t.	G (21)	S	R	P	I/G (20); UG(10.0)	S
15C	0.88	n.t.	P	S	I	I	P	S

All compounds tested at an initial concentration of ~20 mg/mL. Legend: I = insoluble, P = precipitate, R = recrystallization, S = soluble, UG = unstable gel, G = stable gel, n.t. = not tested. Transparent/translucent gels are denoted with a subscript of T; opaque gels are denoted with a subscript of O. Numbers in parentheses correspond to concentration in mg/mL.

Conclusion

A new series of monosaccharide esters derived from D-galactose was synthesized and characterized in order to better understand how the stereochemistry of these monosaccharides affects their ability to perform as low molecular weight gelators. It was found that while the D-galactose esters were much less efficient gelators than the analogs derived from D-glucose, four of the compounds, **10A**, **11C**, **13C**, and **14C**, were found to act as low molecular weight gelators for water. Calculation of the ClogP values of the compounds offered no evidence of a correlation between solubility and gelation. It appears that the stereochemical configuration of these D-galactose-based esters is not as suitable for supramolecular gelation as that of the analogous compounds derived from D-glucose. It is likely that the axial configuration of the benzylidene acetal interferes with the ability of the molecules to self-assemble one-dimensionally. While the galactose esters are inefficient overall, it is quite interesting to note that the four compounds which were found to be gelators were hydrogelators. As previously mentioned, low molecular weight gelators for water have the potential to be used in a variety of biomedical applications. Further structural modification of the compounds reported here might afford some derivatives with improved efficiency that could find use in enzyme immobilization, tissue growth, drug delivery, or other biomedical applications.

Experimental Section:

General method and materials: Reagents and solvents were used as they were received from the supplier. NMR analysis was conducted using a 400 MHz Varian NMR spectrometer. Melting point measurements were carried out using a Fisherbrand Fisher-Johns melting point apparatus,

and were uncorrected. For optical microscopy, a small amount of the gel was placed on a clean glass slide and was air-dried overnight. 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.

Gel Testing: Gel testing was conducted in 1 dram glass screw thread vials with black phenolic caps. ~2 mg of the dried compound was placed in the vial, and the corresponding solvent was added to obtain a concentration of ~20 mg/mL. The suspension was then heated until the solids were fully dissolved, and the resulting solution was briefly sonicated, and then the solution was allowed to cool to room temperature, undisturbed, for fifteen minutes. Compounds which appeared to be insoluble at the initial concentration were heated and sonicated several times, to ensure that the compound was truly insoluble (some compounds were resistant to solvation, suggesting a relatively high lattice energy or endothermic heat of solvation). After the compounds had cooled back to ambient temperature, the resulting phenomenon (recrystallization, precipitation, gelation, etc.) was then recorded. If the compound appeared to form a gel, the vial was inverted and shaken gently to determine if there was any flow; compounds which did not flow and which retained all of the solvent within the gel matrix were recorded as stable gels, while those which showed some loss of solvent or fell apart were recorded as unstable gels. Serial dilution was performed at increments of ~5 mg/mL for all phenomenon other than gelation (precipitation, recrystallization, and compounds which were insoluble), down to a final concentration of ~5 mg/mL. Compounds which formed stable gels were serially diluted in increments of 1-2 mg/mL, until the gel was found to be unstable (by the above criteria). Compounds which were found to be soluble were not further diluted.

General method for synthesis: All reactions were performed using anhydrous solvents and reagents, and the anhydrous dichloromethane and pyridine were further dried over freshly activated 4Å molecular sieves prior to their use, to ensure their dryness. All reactions were conducted in flame dried scintillation vials cooled under a stream of dry nitrogen gas. All purification was conducted by flash chromatography using 230-400 mesh silica gel (SiO₂) obtained from Natland International Corporation, unless otherwise noted.

Synthesis of Methyl- α -D-Galactopyranoside 7a. D-galactose **6** (15.26 g, 82.2 mmol), 15.25 g of IR-120 H⁺ ion exchange resin, and 175 mL of anhydrous methanol were heated to a vigorous reflux (100°C) in the presence of 4Å molecular sieves. After 20 hours, all of the D-galactose had been consumed, and the reaction was warmed to room temperature, filtered, the resin and molecular sieves were rinsed thoroughly, and the reaction solution was concentrated on the rotary evaporator to give a yellow solid in quantitative yield. Recrystallization in ethanol gave colorless crystals. ¹H NMR (D₂O, 400 MHz) δ ppm: 4.9 (d, J=2.4 Hz, 1H), 3.81 (s, 1H), 3.75 (t, J=6.4 Hz, 1H), 3.67 (t, J=1.2 Hz, 2H), 3.60 (d, J=6 Hz, 2H), 3.27 (s, 3H).

Synthesis of 4,6-O-benzylidene methyl- α -D-galactopyranoside 2. Methyl α -D-galactopyranoside monohydrate **7a** (1.03 g, 4.85 mmol) was dissolved in 3 mL of anhydrous N,N-dimethylformamide and cooled to 0°C. To this solution, 2.5 mL of benzaldehyde dimethyl acetal (16.5 mmol, 3.4 equivalents) was added, followed by the dropwise addition of 0.22 mL of tetrafluoroboric acid (1.30 mmol, 0.27 equivalents), and the reaction was left to stir for fifteen minutes before being warmed to room temperature. After fourteen hours, the reaction flask was

placed on the rotary evaporator, which was preheated to 50°C, for five minutes, in order to remove the methanol that is formed during the course of the reaction and drive the reaction to completion. The reaction was then stirred for an additional hour at room temperature before being quenched with 5 mL of saturated sodium bicarbonate solution. The reaction was diluted with water, extracted once with hexane to remove the excess benzaldehyde dimethyl acetal, and then extracted three times with dichloromethane. The combined dichloromethane layers were dried over sodium sulfate, filtered, and concentrated on the rotary evaporator and placed on the vacuum line to remove the DMF that was carried over from the extraction. 1.17 g of clean white solid was obtained for an 85.4% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.54 – 7.45 (m, 2H), 7.40 – 7.31 (m, 3H), 5.55 (s, 1H), 4.93 (d, *J* = 3.1, 1H), 4.34 – 4.21 (m, 2H), 4.08 (dd, *J* = 1.8, 12.6, 1H), 3.98 – 3.84 (m, 2H), 3.70 (s, 1H), 3.47 (s, *J* = 14.2, 3H).

(Note: if necessary, recrystallization in isopropanol can also be used to purify product.)

General Procedure for Esterification of 4,6-O-Benzylidene-Methyl-α-D-Galactopyranoside 2:

Part I: Synthesis of Acyl chlorides. Acyl chlorides which were commercially available (benzoyl, 1-naphthoyl, hexanoyl, heptanoyl) were used directly. The others were generated from the corresponding carboxylic acids prior to use in the esterification reactions. Two methods were typically used for the synthesis of the acyl chlorides.

Method A: The acid was dissolved in dichloromethane (usually one mL), 3-5 equivalents of oxalyl chloride were added at 0°C, and the reaction was stirred for 1-4 hours, until ¹H NMR analysis indicated that the reaction was completed. The reaction solution was then concentrated on the rotary evaporator or blown under a stream of dry nitrogen, and then codistilled with

hexane to remove the excess oxalyl chloride. The acyl chloride was then dissolved once again in dichloromethane and added to the head group dropwise.

Method B: The acid was dissolved in dichloromethane (usually one mL), and cooled to 0°C. An equimolar quantity of oxalyl chloride was added to the acid solution, in the presence of one drop of anhydrous DMF as the catalyst, and stirred for 30 minutes to one hour. Once ¹H NMR indicated that the conversion of the acid to the corresponding acyl chloride was complete, the solution was added directly to the head group solution.

Part II. Esterification of Sugar Head Group 2 with Acyl Chlorides: About 50-100 mg of the head group was dissolved in 1-2 mL of anhydrous dichloromethane, along with 3-5 equivalents of anhydrous pyridine, and the solution was then cooled to 0°C. A dropwise addition of 1.1-1.3 equivalents of the acyl chloride was then made to the solution at 0°C, and the reaction was warmed to room temperature after a brief time (typically 15 minutes to one hour). The reaction was stirred at room temperature for 10 to 24 hours, until the reaction was deemed to be complete according to ¹H NMR and TLC analysis. The reaction was diluted with dichloromethane, washed with water once or twice, and depending on the polarity of the compounds being synthesized, the aqueous layer was extracted several times with dichloromethane. The (combined) organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated on the rotary evaporator, and then transferred to a tared glass scintillation vial and blown under nitrogen to give the crude product. The products were purified by flash chromatography. (Note: in some cases, the addition of pyridine to the reaction was carried out after the addition of the acyl chloride rather than at the outset)

Characterization Data for compounds **8-15A** and **8-15C**:

2,3-di- and 3-hexanoate esters of 4,6-O-benzylidene-methyl-alpha-D-galactopyranoside (8a and 8c). Diester **8a** was obtained in 16% yield (22 mg), along with 31 mg of 3-ester **8c** for a 28% yield, 19 mg of 2-ester **8b** for 17% yield, and 20 mg mixture of 2-ester **8b** and 3-ester **8c** (18% yield). Total yield of 79% (44% of desired compounds).

Diester **8a**: Colorless oil. $R_f = 0.68$ (hexanes:dichloromethane:acetone 4:1:1). NMR spectra matched data previously reported by our group.¹⁷

3-ester **8c**: $R_f = 0.41$ (hexanes:dichloromethane:acetone 4:1:1). NMR spectra matched data previously reported by our group.¹⁷

2,3-diheptanoate ester of 4,6-O-benzylidene-methyl-alpha-D-galactopyranoside (9a). A colorless oil was obtained for a 87% yield (177 mg). $R_f = 0.56$ (hexanes:ethyl acetate 3:1). ¹H NMR (400 MHz, CDCl₃) δ 7.50 (dd, $J = 7.4, 2.0, 2H$), 7.39 – 7.29 (m, 3H), 5.50 (s, 1H), 5.34 (qd, $J = 10.9, 3.2, 2H$), 5.05 (t, $J = 9.8, 1H$), 4.45 (d, $J = 2.8, 1H$), 4.25 (dd, $J = 12.5, 1.2, 1H$), 4.04 (dd, $J = 12.5, 1.4, 1H$), 3.73 (s, 1H), 3.40 (s, 3H), 2.40 – 2.22 (m, 4H), 1.66 – 1.52 (m, 4H), 1.36 – 1.16 (m, 12H), 0.93 – 0.77 (m, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 173.5, 173.1, 137.7, 129.1, 128.2, 126.3, 100.9, 98.0, 74.0, 69.2, 68.5, 68.0, 62.1, 55.6, 34.4, 34.3, 31.5, 31.4, 28.8, 25.1, 25.0, 24.8, 22.6, 22.5, 14.1, 14.0.

2-heptanoate- and 3-heptanoate-4,6-O-benzylidene-methyl-alpha-D-galactopyranoside 9b and 9c. The reaction afforded 59 mg of 2-ester **9b** for a 14% yield, 73 mg of 3-ester **9c** for a 17%

yield, and 26 mg of the beta monoester (R_f value of 0.31 in H:D:A 4:1:1) for a 6% yield. In addition, 121 mg of overlapping monoesters were obtained for a 28% yield, as well as 20 mg of overlapping 3-ester and beta monoester for 5% yield, and 57 mg of unreacted 4,6-O-benzylidene-methyl- α -D-galactopyranoside **2** (18.5%). This gave an overall yield of 70% (85% based on recovered starting material). No diester was obtained.

2-ester **9b**: R_f = 0.46 (hexanes:dichloromethane:acetone 4:1:1). ^1H NMR (CDCl_3 , 400 MHz) δ ppm: 7.53-7.49 (m, 2H), 7.41-7.35 (m, 3H), 5.57 (s, 1H), 5.16 (dd, J = 10.3, 3.5 Hz, 1H), 4.98 (d, J = 3.5 Hz, 1H), 4.33 (m, 2H), 4.09 (dd, J = 12.5, 1.6 Hz, 2H), 3.73 (s, 1H), 3.42 (s, 3H), 2.40 (t, J = 7.5, 2H), 1.70 – 1.58 (m, 2H), 1.40 – 1.19 (m, 6H), 0.88 (t, J = 6.7, 3H). ^{13}C NMR (CDCl_3 , 125 MHz) δ ppm: 174.2, 137.6, 129.5, 128.5, 126.6, 101.6, 98.5, 76.3, 71.3, 67.5, 62.6, 55.8, 34.4, 31.6, 28.9, 25.1, 22.7, 14.2.

3-ester **9c**: R_f = 0.41 (hexanes:dichloromethane:acetone 4:1:1). ^1H NMR (400 MHz, CDCl_3) δ ppm: 7.53 – 7.46 (m, 2H), 7.40 – 7.32 (m, 3H), 5.51 (s, 1H), 5.12 (dd, J = 10.4, 3.5 Hz, 1H), 4.95 (d, J = 3.7 Hz, 1H), 4.37 (d, J = 5.2 Hz, 1H), 4.28 (dd, J = 12.5, 1.5 Hz, 1H), 4.17 (td, J = 10.2, 3.7 Hz, 1H), 4.06 (dd, J = 12.5, 1.6 Hz, 1H), 3.72 (s, 1H), 3.47 (s, 3H), 2.39 (t, J = 7.5 Hz, 2H), 2.01 (d, J = 10.3 Hz, 1H), 1.72 – 1.56 (m, 3H), 1.39 – 1.17 (m, 9H), 0.84 (t, J = 6.8 Hz, 4H). ^{13}C NMR (125 MHz, CDCl_3) δ ppm: 174.5, 137.9, 129.2, 128.4, 126.3, 101.0, 100.5, 74.5, 71.7, 69.4, 67.0, 62.7, 55.9, 34.6, 31.6, 28.9, 25.2, 22.6, 14.2.

*2,3-di- and 3-(4-pentynoate) esters of 4,6-O-benzylidene-methyl- α -D-galactopyranoside (**10a** and **10c**).* The reaction afforded 42 mg of clean diester **10a** (8% yield) and 28 mg of clean 3-ester **10c** (6% yield), along with 148 mg of overlapping 2-ester **10b** and 3-ester **10c**. R_f values (hexanes:dichloromethane: acetone 4:1:1): **10a** = 0.45, **10b** = 0.26, **10c** = 0.26, β isomer = 0.19.

Diester **10a**: ^1H NMR (400 MHz, CDCl_3) δ 7.54 – 7.47 (m, 2H), 7.41 – 7.32 (m, 3H), 5.52 (s, 1H), 5.40 (qd, $J = 10.8, 3.3, 2\text{H}$), 5.08 (d, $J = 3.2, 1\text{H}$), 4.48 (d, $J = 3.1, 1\text{H}$), 4.29 (d, $J = 12.6, 1\text{H}$), 4.07 (d, $J = 11.6, 1\text{H}$), 3.77 (s, 1H), 3.42 (s, 3H), 2.65 – 2.54 (m, 4H), 2.54 – 2.44 (m, 4H), 1.98 (t, $J = 2.6, 1\text{H}$), 1.93 (t, $J = 2.6, 1\text{H}$). ^{13}C NMR (101 MHz, CDCl_3) δ 171.5, 171.2, 137.7, 129.3, 128.4, 126.4, 101.1, 98.0, 82.4, 82.4 74.1, 69.4, 69.3, 69.2, 69.0, 68.5, 62.2, 55.8, 33.6, 33.5, 14.6, 14.5.

3-ester **10c**: mp: 109.5-111°C. ^1H NMR (400 MHz, CDCl_3) δ 7.50 (dd, $J = 7.4, 2.0, 2\text{H}$), 7.41 – 7.32 (m, 3H), 5.52 (s, 1H), 5.17 (dd, $J = 10.4, 3.5, 1\text{H}$), 4.96 (d, $J = 3.7, 1\text{H}$), 4.39 (d, $J = 3.3, 1\text{H}$), 4.29 (d, $J = 12.5, 1\text{H}$), 4.19 (d, $J = 10.3, 1\text{H}$), 4.07 (d, $J = 12.4, 1\text{H}$), 3.74 (s, 1H), 3.48 (s, 3H), 2.66 (t, $J = 7.0, 2\text{H}$), 2.58 – 2.46 (m, 2H), 1.94 (t, $J = 2.6, 1\text{H}$).

2,3-di- and 3-(5-hexynoate) esters of 4,6-O-benzylidene-methyl-alpha-D-galactopyranoside (11a and 11c). The reaction afforded 38 mg of clean diester **11a** (4% yield), 36 mg of β anomer (5% yield) and 300 mg of overlapping mixed monoesters (**11b**, **11c**, and β anomer).

Diester **11a**: Product is an oil (no m.p.). ^1H NMR (400 MHz, CDCl_3) δ 7.51 (dd, $J = 7.3, 2.0, 2\text{H}$), 7.41 – 7.31 (m, 3H), 5.52 (s, 1H), 5.36 (qd, $J = 10.9, 3.1, 2\text{H}$), 5.09 (d, $J = 3.1, 1\text{H}$), 4.48 (d, $J = 2.6, 1\text{H}$), 4.29 (d, $J = 12.6, 1\text{H}$), 4.07 (d, $J = 12.5, 1\text{H}$), 3.77 (s, 1H), 3.43 (s, 3H), 2.55 – 2.42 (m, 4H), 2.32 – 2.18 (m, 4H), 1.96 (t, $J = 2.6, 1\text{H}$), 1.94 (t, $J = 2.6, 1\text{H}$), 1.90 – 1.76 (m, 4H). ^{13}C NMR (101 MHz, CDCl_3) δ 172.9, 172.5, 137.7, 129.3, 128.4, 126.4, 101.1, 98.0, 83.3 77.5, 77.2, 76.9, 74.1, 69.5, 69.3, 68.8, 68.3, 62.2, 55.8, 33.1, 32.9, 29.9, 23.8, 23.8, 17.9.

3-ester **11c**: m.p.: 80-81.5°C. ^1H NMR (400 MHz, CDCl_3) δ 7.49 (dd, $J = 17.3, 11.1, 2\text{H}$), 7.44 – 7.29 (m, 3H), 5.52 (s, 1H), 5.13 (dd, $J = 10.4, 3.4, 1\text{H}$), 4.92 (d, $J = 18.1, 1\text{H}$), 4.38 (d, $J = 3.4,$

1H), 4.28 (d, $J = 12.5$, 1H), 4.17 (td, $J = 10.4$, 3.7, 1H), 4.07 (d, $J = 12.3$, 1H), 3.73 (s, 1H), 3.47 (s, 3H), 2.55 (t, $J = 7.4$, 2H), 2.26 (td, $J = 7.0$, 2.6, 2H), 2.02 – 1.92 (m, 1H), 1.92 – 1.81 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 173.6, 137.8, 129.2, 128.4, 126.4, 101.0 100.5, 83.5, 74.5, 71.9, 69.4, 69.4, 67.0, 62.7, 56.0, 33.2, 23.9, 17.9.

2,3-di- and 3-(6-heptynoate) esters of 4,6-O-benzylidene-methyl-alpha-D-galactopyranoside (12a and 12c). The reaction afforded 18 mg of diester (4% yield), along with various portions of mixed monoesters mixed with side products from beta anomer.

Diester **12a**: Product is oil (no m.p.). ^1H NMR (400 MHz, CDCl_3) δ 7.50 (dd, $J = 7.4$, 2.0, 2H), 7.44 – 7.28 (m, 3H), 5.51 (s, 1H), 5.34 (qd, $J = 10.9$, 3.3, 2H), 5.08 (d, $J = 3.2$, 1H), 4.47 (d, 1H), 4.28 (dd, $J = 12.5$, 1.4, 1H), 4.07 (dd, $J = 12.5$, 1.5, 1H), 3.75 (s, 1H), 3.42 (s, 3H), 2.45 – 2.27 (m, 4H), 2.19 (td, $J = 8.7$, 4.3, 2H), 2.12 (td, $J = 7.0$, 2.6, 2H), 1.94 (t, $J = 2.6$, 1H), 1.91 (t, $J = 2.6$, 1H), 1.79 – 1.66 (m, 4H), 1.63 – 1.45 (m, 4H). ^{13}C NMR (101 MHz, CDCl_3) δ 173.2, 172.8, 137.7, 129.3, 128.4, 126.5, 101.1, 98.0, 84.0, 74.1, 69.3, 68.9, 68.9, 68.8, 68.2, 62.2, 55.8, 34.0, 33.8, 27.9, 27.8, 24.3, 24.2, 18.3, 18.3.

3-ester **12c**: Product is an oil (no m.p.). ^1H NMR (400 MHz, CDCl_3) δ 7.50 (dd, $J = 7.4$, 2.0, 2H), 7.43 – 7.30 (m, 3H), 5.52 (s, 1H), 5.13 (dd, $J = 10.4$, 3.5, 1H), 4.95 (d, $J = 3.7$, 1H), 4.39 (d, $J = 3.2$, 1H), 4.29 (dd, $J = 12.5$, 1.4, 1H), 4.18 (d, $J = 7.5$, 1H), 4.07 (dd, $J = 12.5$, 1.6, 1H), 3.73 (s, 1H), 3.48 (s, 3H), 2.43 (t, $J = 7.4$, 2H), 2.16 (td, $J = 7.0$, 2.6, 2H), 1.92 (t, $J = 2.6$, 1H), 1.83 – 1.71 (m, 2H), 1.62 – 1.51 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 174.0, 137.8, 129.2, 128.4, 126.4, 101.0, 100.5, 75.8, 74.4, 71.8, 69.4, 68.8, 67.0, 62.7, 56.0, 34.0, 27.9, 24.2, 18.3.

2,3-di(1-naphthoate)-, 2-(1-naphthoate)-, and 3-(1-naphthoate)-4,6-O-benzylidene-methyl- α -D-galactopyranosides **13a** and **13c**. The reaction yielded 89 mg of clean diester **13a** (15% yield), 24 mg of clean 2-ester **13b** (6% yield), 33 mg of clean 3-ester **13c** (8% yield), and 192 mg of mixed monoesters **13b** and **13c** (45% yield), for a total of 73% overall yield (29% total isolated yield). R_f values (hexanes:dichloromethane:acetone 4:1:1): diester **13a**=0.50, 2-ester **13b**=0.34, 3-ester **13c**=0.29.

Diester **13a**: mp:162-165°C. ^1H NMR (CDCl_3 , 400 MHz) δ ppm 8.89 (d, 1H, $J=8.79$ Hz), 8.81 (d, 1H, $J=8.42$ Hz), 8.17 (ddd, 2H, $J=1.10$ Hz, 7.33 Hz, 20.51 Hz), 7.95 (d, 2H, $J=8.06$ Hz), 7.81 (d, 2H, 8.06 Hz), 7.62-7.60 (m, 2H), 7.47-7.32 (m, 9H), 5.98-5.91 (m, 2H), 5.66 (s, 1H), 5.44 (d, 1H, $J=3.30$ Hz), 4.82 (d, 1H, $J=2.56$ Hz), 4.42 (dd, 2H, $J=1.47$ Hz, 12.45 Hz), 4.20 (dd, 2H, $J=1.47$ Hz, 12.45 Hz), 3.99 (s, 1H), 3.53 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) 167.6, 167.1, 137.8, 135.4, 133.9, 133.8, 131.5, 131.2, 130.9, 129.3, 128.7, 128.5, 128.0, 126.8, 126.7, 126.5, 126.4, 126.0, 125.9, 124.8, 124.7, 101.2, 98.4, 74.5, 69.7, 69.5, 69.2, 62.5, 56.1.

2-ester **13b**: ^1H NMR (400 MHz, CDCl_3) δ ppm: 8.92 (d, $J = 8.6$, 1H), 8.28 (d, 1H), 8.03 (d, $J = 8.1$, 1H), 7.88 (d, $J = 8.0$, 1H), 7.65 – 7.35 (m, 10H), 5.62 (s, 1H), 5.49 (dd, $J = 10.0$, 3.6, 1H), 5.23 (d, $J = 3.5$, 1H), 4.41 – 4.30 (m, 3H), 4.13 (dd, $J = 12.5$, 1.5, 1H), 3.81 (s, 1H), 3.46 (d, $J = 10.8$, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 167.8, 137.6, 134.0, 133.8, 131.6, 131.0, 129.6, 128.8, 128.6, 128.0, 127.0, 126.6, 126.4, 126.0, 124.8, 101.7, 98.6, 76.4, 72.3, 69.5, 67.6, 62.7, 56.0.

3-ester **13c**: ^1H NMR (400 MHz, CDCl_3) δ ppm: 8.90 (d, $J = 8.6$, 1H), 8.25 (d, $J = 7.2$, 1H), 8.00 (d, $J = 8.1$, 1H), 7.86 (d, $J = 8.1$, 1H), 7.62 – 7.32 (m, 9H), 5.59 (s, 1H), 5.50 (dd, $J = 10.3$, 3.5, 1H), 5.03 (d, $J = 3.7$, 1H), 4.63 (d, $J = 3.4$, 1H), 4.40 (dd, $J = 10.4$, 3.7, 1H), 4.33 (d, $J = 12.4$, 1H), 4.12 (d, $J = 12.4$, 1H), 3.83 (s, 1H), 3.52 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ

ppm: 168.0, 137.6, 133.7, 133.6, 131.2, 130.8, 128.9, 128.5, 128.1, 127.7, 127.1, 126.1, 125.9, 124.5, 100.7, 100.4, 74.3, 72.5, 69.2, 66.8, 62.5, 55.7.

2,3-di- and 3-benzoate esters of 4,6-O-Benzylidene-Methyl-Alpha-D-Galactopyranoside (14a, 14b, and 14c). The reaction afforded 24 mg of diester **14a** (6% yield), 17 mg of 3-ester **14c** (5%), and 109 mg of mixed monoesters **21b** and **21c** (32%) for a total yield of 43% (isolated yield = 11%). 34 mg of clean 4,6-O-benzylidene-methyl- α -D-galactopyranoside **3** (14%) was also obtained.

Diester **14a**: ^1H NMR (400 MHz, CDCl_3) δ 8.00 (dd, $J = 7.1, 6.1$, 4H), 7.58 – 7.46 (m, 4H), 7.41 – 7.30 (m, 7H), 5.83 – 5.75 (m, 2H), 5.58 (s, 1H), 5.28 (s, 1H), 4.66 (s, 1H), 4.36 (d, $J = 12.5$, 1H), 4.15 (d, $J = 12.4$, 1H), 3.91 (s, 1H), 3.47 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 166.2, 165.9, 137.6, 133.2, 133.2, 129.8, 129.8, 129.5, 129.5, 128.9, 128.4, 128.1, 126.1, 100.7, 98.1, 74.2, 69.2, 69.2, 68.8, 62.2, 55.7.

2-ester **14b**: ^1H NMR (CDCl_3 , 400 MHz) δ ppm: 8.12-8.08 (m, 2H), 7.60-7.52 (m, 3H), 7.47-7.37 (m, 5H), 5.61 (s, 1H), 5.38 (dd, $J=10.26$ Hz, 3.57 Hz, 1H), 5.12 (d, $J=3.48$ Hz, 1H), 4.39-4.26 (m, 3H), 4.13 (dd, $J=1.74, 12.54$ Hz, 1H), 3.81 (s, 1H), 3.44 (s, 3H).

3-ester **14c**: ^1H NMR (400 MHz, CDCl_3) δ 8.18 – 8.04 (m, 2H), 7.62 – 7.50 (m, 3H), 7.50 – 7.35 (m, 5H), 5.61 (s, 1H), 5.38 (dd, $J = 10.3, 3.6$, 1H), 5.12 (d, $J = 3.5$, 1H), 4.38 – 4.26 (m, 3H), 4.17 – 4.08 (m, 1H), 3.81 (s, 1H), 3.44 (s, 3H).

2,3-dimethacrylate- and 3-methacrylate-4,6-O-benzylidene-methyl- α -D-galactopyranosides 15a and 15c. Use of 2.5 equivalents of methacryloyl chloride (made in situ from methacrylic acid) gave 40 mg of diester in 26% yield.

Diester **15a**: ^1H NMR (400 MHz, CDCl_3) δ 7.63 – 7.44 (m, 2H), 7.42 – 7.28 (m, 3H), 6.10 (d, $J = 9.0$, 2H), 5.59 – 5.43 (m, 5H), 5.14 (d, $J = 2.1$, 1H), 4.50 (s, 1H), 4.29 (d, $J = 12.3$, 1H), 4.09 (d, $J = 11.7$, 1H), 3.79 (s, 1H), 3.42 (s, 3H), 1.90 (s, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ ppm: 166.8, 166.6, 137.6, 135.6, 135.6, 128.8, 128.1, 126.6, 126.4, 126.0, 100.4, 97.9, 74.0, 69.1, 68.7, 68.5, 62.1, 55.5, 18.1, 18.0.

3-ester **15c**: ^1H NMR (400 MHz, CDCl_3) δ 7.49 (dd, $J = 7.5$, 2.0, 2H), 7.40 – 7.31 (m, 3H), 6.22 (s, 1H), 5.62 (t, $J = 1.5$, 1H), 5.53 (s, 1H), 5.20 (dd, $J = 10.3$, 3.5, 1H), 4.96 (d, $J = 3.7$, 1H), 4.41 (d, $J = 3.4$, 1H), 4.29 (dd, $J = 8.5$, 4.2, 1H), 4.08 (dd, $J = 12.5$, 1.5, 1H), 3.76 (s, 1H), 3.49 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 167.7, 137.9, 136.1, 129.1, 128.3, 126.9, 126.2, 100.7, 100.5, 74.5, 72.1, 69.4, 67.1, 62.8, 55.9, 18.5.

References:

- 1) Sangeetha, N. M.; Maitra, U.; *Chem. Soc. Rev.*, **2005**, *34*, 821-836.
- 2) Vintiloiu, A.; Leroux, J.-C.; *J. Controlled Release*, **2008**, *125*, 179-192.
- 3) Vemula, P. K.; Li, J.; John, G.; *J. Am. Chem. Soc.*, **2006**, *128*(27), 8932-8938.
- 4) Lim, P. F. C.; Liu, X. Y.; Kang, L.; Ho, P. C. L.; Chan, S. Y.; *Int. J. Pharm.*, **2008**, *358*, 102-107.

- 5) Kiyonaka, S.; Sada, K.; Yoshimura, I.; Shinkai, S.; Kato, N.; Hamachi, I.; *Nat. Mater.*, **2004**, *3*(1), 58-64.
- 6) Silva, G. A.; Czeisler, C.; Niece, K. L.; Beniash, E.; Harrington, D. A.; Kessler, J. A.; Stupp, S. I.; *Science*, 2004, *303*, 1352-1355.
- 7) Pratoomsoot, C.; Tanioka, H.; Hori, K.; Kawasaki, S.; Kinoshita, S.; Tighe, P. J.; Dua, H.; Shakesheff, K. M.; Rose, F. R. A. J.; *Biomaterials*, **2008**, *29*, 272-281.
- 8) Estroff, L. A.; Hamilton, A. D.; *Chem. Rev.*, **2004**, *104*(3), 1201-1218.
- 9) Terech, P.; Weiss, R. G.; *Chem. Rev.*, **1997**, *97*(8), 3133-3159.
- 10) Suzuki, M.; Hanabusa, K.; *Chem. Soc. Rev.*, **2009**, *38*, 967-975.
- 11) George, M.; Weiss, R. G.; *Acc. Chem. Res.*, **2006**, *39*(8), 489-497.
- 12) Luboradzki, R.; Gronwald, O.; Ikeda, M.; Shinkai, S.; Reinhouldt, D. N.; *Tetrahedron*, **2000**, *56*, 9595-9599.
- 13) Gronwald, O.; Sakurai, K.; Luboradzki, R.; Kimura, T.; Shinkai, S.; *Carbohydr. Res.*, **2001**, *331*, 307-318.
- 14) Gronwald, O.; Shinkai, S.; *Chem. Eur. J.*, **2001**, *7*(20), 4329-4334.
- 15) Wang, G.; Cheuk, S.; Williams, K.; Sharma, V.; Dakessian, L.; Thorton, Z.; *Carbohydr. Res.*, **2006**, *341*, 705-716.
- 16) Cheuk, S.; Stevens, E. D.; Wang, G.; *Carbohydr. Res.*, **2009**, *344*, 417-425.
- 17) Unpublished data. Nie, X.; Wang, G.

Chapter IV: Synthesis and Characterization of Organogelators Derived from D-Glucosamine and Their Potential Applications

Abstract: Research of supramolecular gelators has become an increasingly popular field over the past few decades. A great deal of effort has gone into studying how changes in the functionalization of low molecular weight gelators affect their gelation ability. With several structural classes of low molecular weight gelators having been thoroughly explored, researchers have a reasonably accurate understanding of how the structure of these molecules affect their ability to act as gelators. With this knowledge, many researchers have placed a greater emphasis on adapting the structure of a well-studied class of gelator to incorporate additional functionality into the gel, giving rise to new supramolecular gelators which can act as chemical sensors, controlled delivery agents, novel photoelectronic materials, etc. Our laboratory has spent the past decade synthesizing and characterizing monosaccharide derivatives which can act as low molecular weight gelators for water or organic solvents. In an effort to better understand the influence of the core structure on gelation, two new series of amide gelators were derived from acylation of glucosamine, in which the anomeric group and 4,6-acetal protecting group were altered. The synthesis and characterization of these compounds, along with some potential applications are discussed herein.

Keywords: low molecular weight gelator, supramolecular gelator, organogel, hydrogel, monosaccharide, glucosamine, oil gelation

Introduction

Low molecular weight gelators are an important class of compounds with a variety of useful applications, including use as drug delivery¹ or controlled release agents², chemical sensors³, cell culture media⁴, or light harvesting smart materials⁵. These molecules self-assemble in solution to form supramolecular assemblies which entangle to trap the solvent molecules within their matrix. Because the forces which dictate gelation of LMWGs are noncovalent in nature (Van der Waals, hydrogen bonding, electrostatic, pi stacking, etc.), the resulting gels are typically thermoreversible, and can often be designed to include functional groups which will allow for phase transitions to occur in response to other stimuli, including changes in pH⁶, photoisomerization⁷, or treatment with enzymes⁸.

Biomolecules often serve as templates for the synthesis of supramolecular gelators, as their self-assembly processes have been well studied in the past, and are driven by the same forces that promote gelation. In addition, biomolecules tend to be readily available and abundant, and the chemistry regarding their functionalization is well known. Amino acid and steroidal gelators have been extensively studied, and several reviews have been recently published^{9,10}. Meanwhile, carbohydrates have often been overlooked as starting materials for the synthesis of low molecular weight gelators. This is unfortunate, as carbohydrates are abundant natural resources with inherent, built-in chirality. The chiral arrangement of the multiple hydroxyl groups present in carbohydrates allows for directed, intermolecular hydrogen bonding to take place, which can be harnessed to afford supramolecular gelation.

Although they are not as thoroughly studied, many research groups have successfully used carbohydrates, and more specifically, monosaccharides, as templates for designing and synthesizing low molecular weight gelators. One of the most active research groups in the field

of monosaccharide-based low molecular weight gelators is the group of Seiji Shinkai, whose work has inspired our own research in the field. His research group has worked extensively to elucidate the role that the stereochemical configurations of 4,6-O-benzylidene-protected α -methyl glycosides of monosaccharides play on their gelation.¹¹⁻¹³ While the compounds reported by Shinkai and coworkers were able to gelate several organic solvents, the gelation efficacy was fairly low. Our research group wanted to further explore these monosaccharides as templates for supramolecular gelators, and improve their efficiency. We started by synthesizing ester and carbamate derivatives **2A-C** and **3A-C** of 4,6-O-benzylidene-methyl- α -D-glucopyranoside **1** (Figure 1).¹⁴⁻¹⁷ Upon screening for gelation, several efficient gelators (**4-8**) were obtained (Figure 2). It was found that the carbamate derivatives in particular were versatile and efficient gelators, likely as a result of the amido group, which could act as an additional hydrogen bond donor.

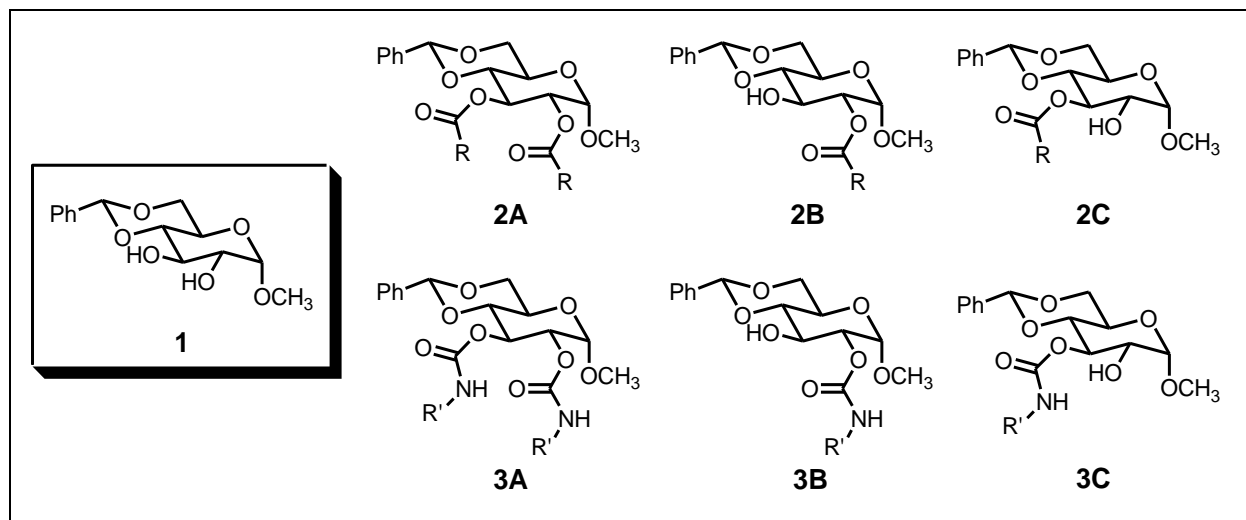


Figure 1. Structure of head group **1** and its ester analogs (**2A-C**) and carbamate derivatives (**3A-C**).

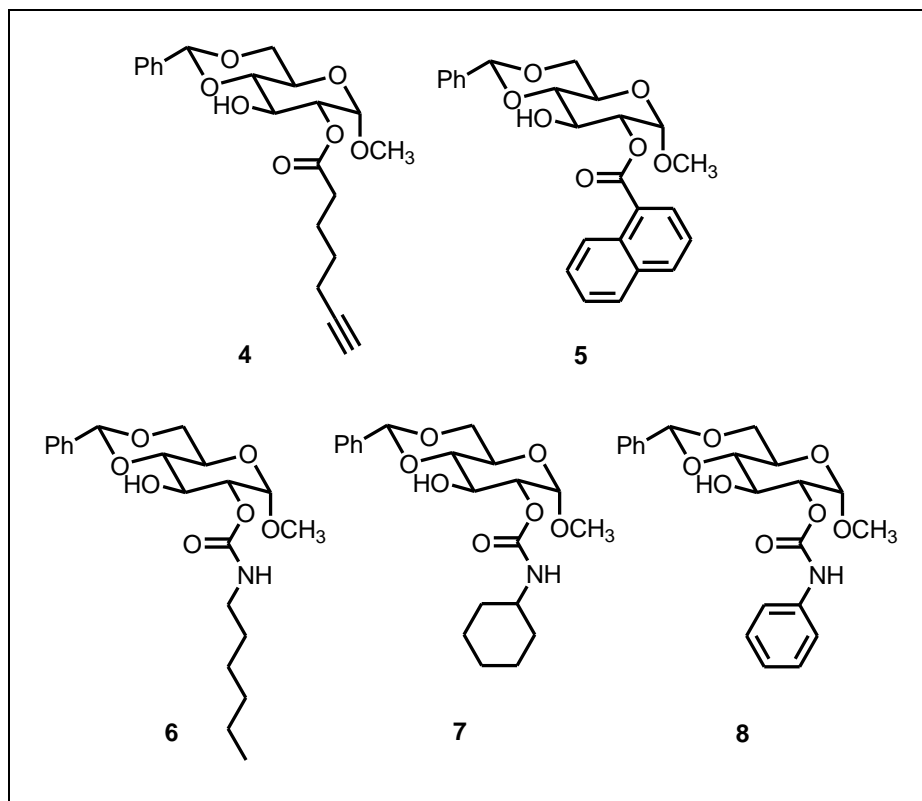
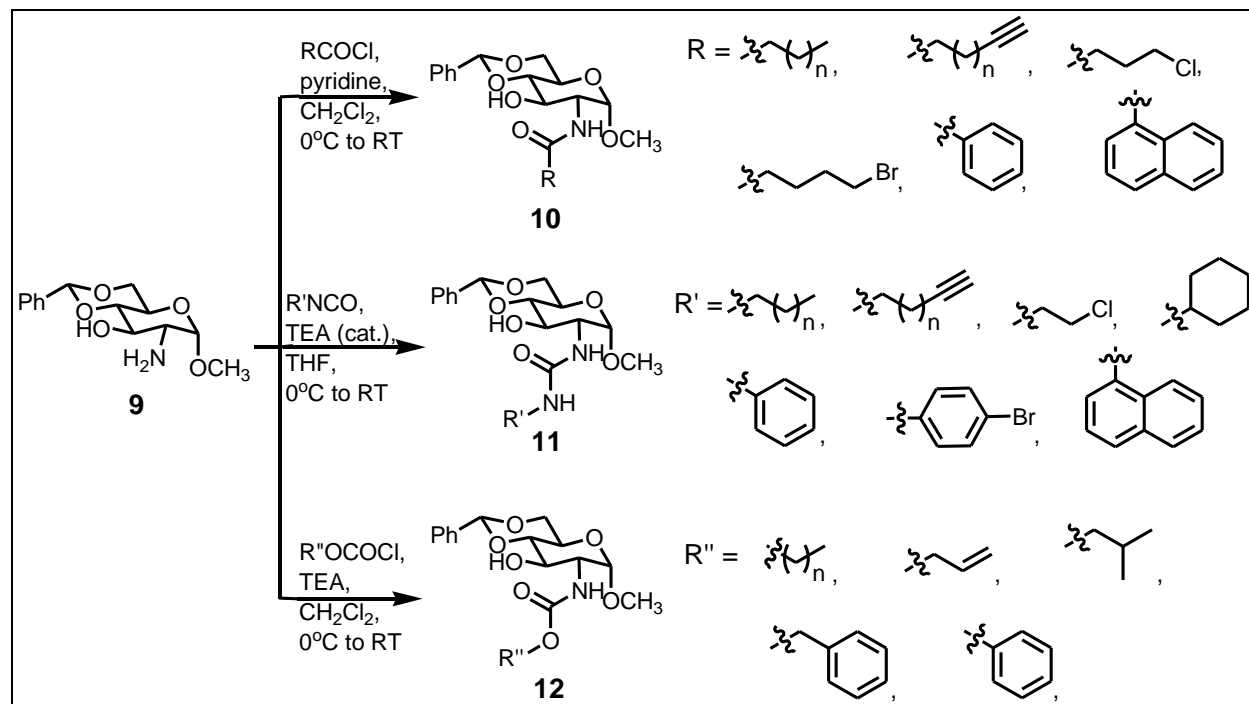


Figure 2. Several of the most efficient gelators derived from D-glucose.

We thought to further improve gelation by incorporating an additional hydrogen bonding group into the head group directly. In addition, since it was found that the monoacylated products **7b** and **8b** were better gelators than the 3-monoacylated or diacylated compounds, we wanted to focus on obtaining products which could be acylated selectively at the 2-position. Thus, D-glucosamine, which is naturally abundant and readily available, was used to synthesize the analogous head group **9**, which differs only from **1a** by the amino group at the 2-position. This head group was used to synthesize amides **10**, ureas **11**, and carbamates **12** from the corresponding acyl chlorides, isocyanates, and chloroformates (Scheme 1). Overall, gelation was improved in the glucosamine analogues, with the amides, carbamates, and ureas gelling

more of the organic solvents and more efficiently gelating aqueous DMSO and aqueous ethanol, in most cases. In addition, several hydrogelators with minimum gelation concentrations below 5 mg/mL were also obtained.



Scheme 1. Synthesis of amides **10**, ureas **11**, and carbamates **12** from glucosamine head group **9**.

To date, our study of monosaccharide-based low molecular weight gelators has focused mainly on the affect that changing the functionalization at the 2-position has on gelation. However, our laboratory was also interested in determining how changing the anomeric group or the acetal at the 4- and 6-positions would affect the gelation. With this in mind, we set out to modify the head group accordingly. We decided to use D-glucosamine as our template, since the D-glucosamine-derived head group **9** exhibited better gelation than the D-glucose-derived head

group **1**. Since even small modifications to the structures of gelators can greatly change their gelation ability, we decided to implement incremental changes to the previous head group **9**, leading to head groups **13** and **14** (Figure 3). Head groups **13** and **14** could also be synthesized using the same three step sequence that was used to synthesize head group **9** from N-acetyl D-glucosamine, and would only require that we change the reagents for one of the steps.

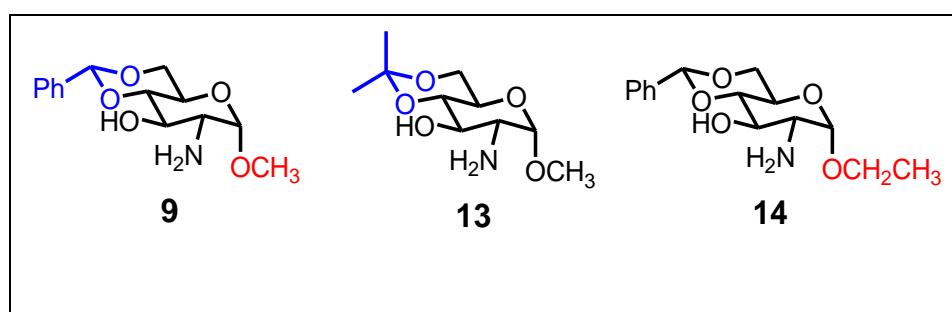


Figure 3. Structures of previous glucosamine-based headgroup **9** and modified head groups **13** and **14**.

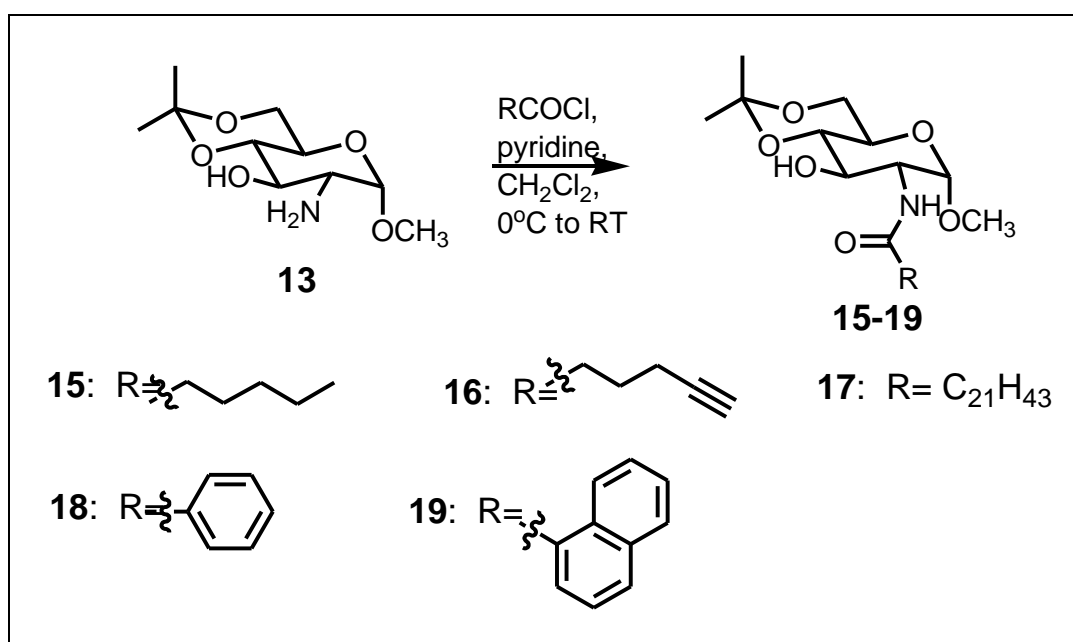
Thus, we set out to synthesize head groups **13** and **14** and acylate them with various acyl chlorides like those used in the previous studies. The compounds were synthesized, characterized, and screened for their gelation ability in water, ethanol, hexanes, aqueous ethanol, and aqueous DMSO (some of the compounds were also screened for gelation in additional organic solvents, like toluene and isopropanol). The compounds which were able to form gels were further studied by optical microscopy. The results which were obtained are described and discussed below.

Results and Discussion

We wanted to probe the effect of changing the 4,6-protecting group of the monosaccharide head group **9** by synthesizing a small library of amides using the isopropylidene-appended glucosamine derivative **13** as our head group (**13** was prepared by another member of our lab in a sequence that is analogous to that used to prepare **9** and **14**, using dimethoxypropane in place of benzylidene dimethyl acetal). Our rationale behind choosing the isopropylidene group was twofold: it is significantly different in structure from the benzylidene acetal, and it can be hydrolyzed much easier. We planned to screen the compounds for their gelation ability before and after the removal of the acetal, and compare the results with those obtained from the analogous benzylidene-protected compounds. In this way, we hoped to get a more definitive understanding of how the functionalization at the 4- and 6-positions of the monosaccharide affects its gelation.

We synthesized a series of amides comprised of the five isopropylidene-protected compounds **15-19**, as shown in Scheme 2. We chose acyl groups which were diverse in structure so that we could do a quick screening of the isopropylidene analogues. The hexanoyl, 5-hexynoyl, benzoyl, and 1-naphthoyl derivatives can be used to directly compare the isopropylidene analogues with their benzylidene counterparts; the docosanoyl analogue **17** was also synthesized to help compensate for the increased polarity and loss of a pi-stacking group (gelation would be promoted by Van der Waals interactions instead) when going from a benzylidene to an isopropylidene acetal. The reactions were carried out by adding the corresponding acyl chloride in a dropwise fashion to a solution of the glucosamine and pyridine in dichloromethane at 0°C, and then warming the reaction to room temperature for 12 hours. After a standard phase-phase extraction workup, the compounds were purified by flash

chromatography and dried under vacuum to afford the pure compounds **15-19**. Yields ranged from 15-69%, but they are not optimized, and will need to be repeated before the results can be published. The compounds were characterized by ^1H and ^{13}C NMR and melting point (compound **16** was extremely hygroscopic, so the melting point could not be obtained for this compound) before being screened for gelation.

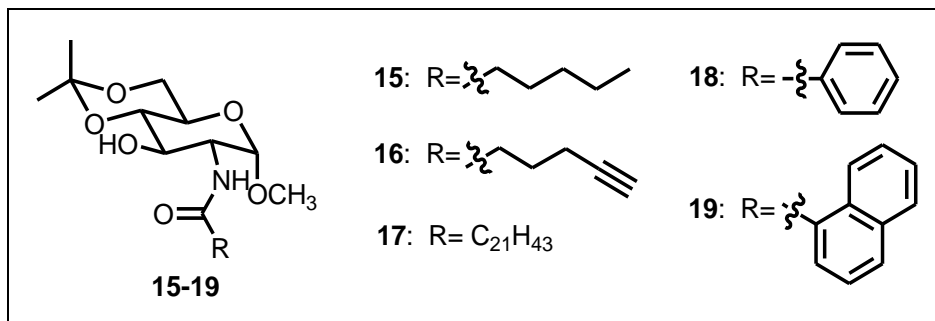


Scheme 2. Synthesis of amide derivatives **15-19** of 4,6-O-benzylidene-2-deoxy-2-amino-methyl- α -D-glucopyranoside **13**.

After the compounds were isolated, they were screened for gelation in several organic solvents, water, and a few aqueous mixtures (Table 1). Unfortunately, the isopropylidene analogues **15-19** proved to be poor gelators, as the only stable gel was afforded by the docosanoyl compound **17** in toluene at high concentration. It is likely that the phenyl ring of the

benzylidene protected compounds with general structure **10** participates in some pi stacking or hydrophobic interactions which are crucial for gelation.

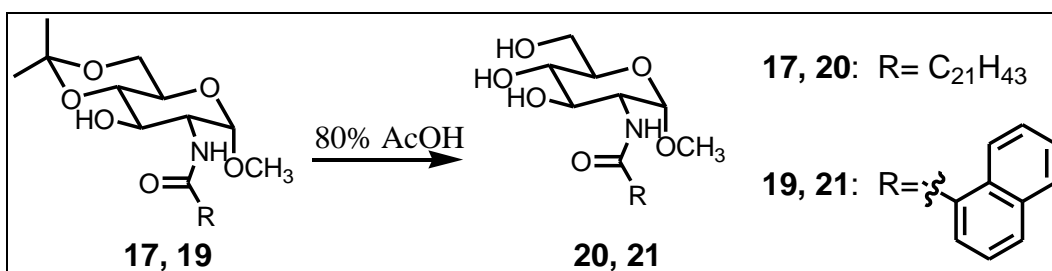
Table 1. Gel Testing Data for Compounds **15-19**.



Cpd	ClogP	m.p. (°C)	H ₂ O	EtOH	iPrOH	Hex	Acetone	Toluene	DCM	EtOH :H ₂ O 1:2	DMSO :H ₂ O 1:2
15	1.60	107	S	S	P	R	S	S	P/S	S	S
16	0.39	n.t.	S	S	I	I	I	UG(21.1)	I	S	S
17	>9.00	97	I	S	P	P	P	G (20.0) UG(12.5)	S	I	I
18	0.97	75	S	S	n.t.	P	n.t.	n.t.	n.t.	S	S
19	2.14	198	P	S	I	I	I	R	I	S	S

All compounds tested at an initial concentration of ~20 mg/mL. Legend: C = recrystallization, I = insoluble, P = precipitate, S = soluble, P/S = precipitate then soluble at lower concentrations, UG = unstable gel, G = stable gel, n.t. = not tested. Transparent/translucent gels are denoted with a subscript of T; opaque gels are denoted with a subscript of O. Numbers in parentheses correspond to concentration in mg/mL.

Despite the poor gelation of most of the isopropylidene analogues, two of the isopropylidene compounds were subsequently deprotected and studied: the docosanoyl derivative **20**, which was obtained by deprotection of **17**, and the naphthoyl derivative **21**, which was obtained from **19** (Scheme 3). The deprotection of the 4,6-O-isopropylidene acetal in the presence of the methyl acetal at the anomeric position was carried out by treatment with 80-85% acetic acid at room temperature. The docosanoyl compound proved a bit tricky to deprotect, due to some issues with solubility, but after the conditions were worked out, the deprotected product **20** was obtained in 84% yield; the naphthoyl derivative proved easier to deprotect, giving a quantitative yield of deprotected triol **21**. The compounds were blown dry under nitrogen and dried thoroughly on the pump before being characterized by ^1H and ^{13}C NMR, high resolution mass spectroscopy, and melting point measurement.

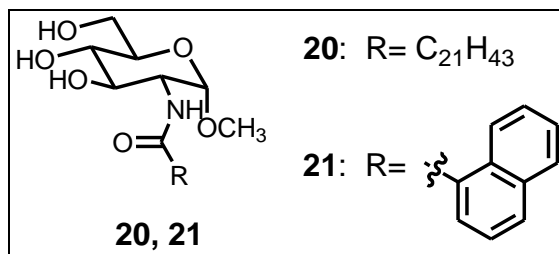


Scheme 3. Hydrolysis of Isopropylidene Acetals of Glucosamine Amides

The gelation ability of the deprotected triols **20** and **21** was then assayed in a screen of our standard five solvent systems, as shown in Table 3. While the naphthoyl derivative **21** was not able to gelate any of the solvents, we were delighted to find that docosanoyl triol **20** was able

to form stable gels in ethanol, as well as aqueous ethanol and aqueous DMSO. An unstable gel was also formed by **20** in hexanes.

Table 2. Gel Testing Data for Compounds **20** and **21**.



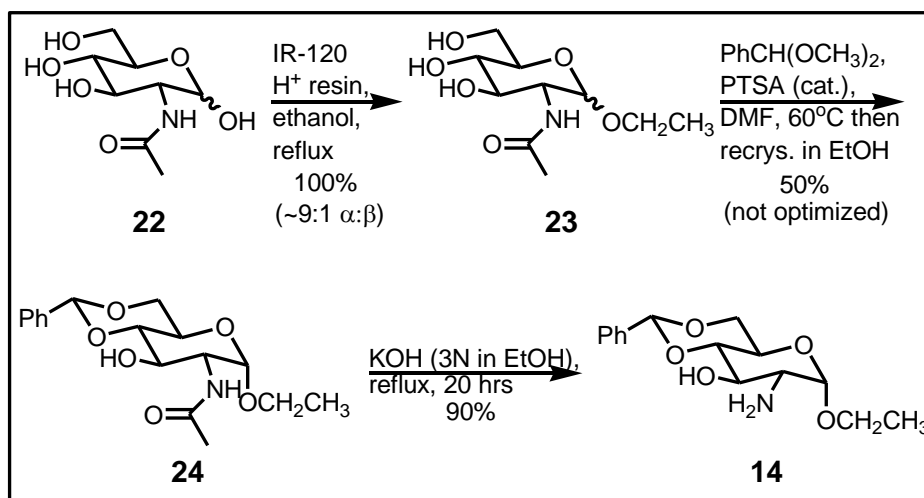
Cpd.	H ₂ O	EtOH	Hexanes	EtOH:H ₂ O 1:2	DMSO:H ₂ O 1:2
20	I	G (9.2); UG (6.5)	UG (12.5)	G (8.3); UG (6.7)	G (5.0); UG (4.0)
21	P	P	I	S	S

All compounds tested at an initial concentration of ~20 mg/mL. Legend: I = insoluble, P = precipitate, S = soluble, UG = unstable gel, G = stable gel, n.t. = not tested. Transparent/translucent gels are denoted with a subscript of T; opaque gels are denoted with a subscript of O. Numbers in parentheses correspond to concentration in mg/mL.

The deprotection of the other three analogues (**15**, **16** and **18**) must be carried out before we can analyze the trend, but it appears that the benzylidene acetal is necessary for gelation, unless another suitable functional group, like a long alkyl chain, can make up for the loss of hydrophobicity and pi stacking capability. It seems likely that the docosanoyl analogue can

compensate for the loss of the phenyl ring by promoting self-assembly through increased Van der Waals interactions of the side chains. It is also likely that intermolecular hydrogen bonding between hydroxyl groups and the amide carbonyl are taking place as well. However, IR or NMR studies will need to be conducted to substantiate these claims.

In order to probe the effect of changing the anomeric group on gelation, we synthesized 4,6-O-benzylidene-2-deoxy-2-amino-ethyl- α -D-glucopyranoside **14**, starting from N-acetyl-D-glucosamine **22**, as shown in Scheme 4. Fischer glycosylation of **22** with ethanol in the presence of acidic ion exchange resin gave the ethyl glycoside **23** as a mixture of anomers (\sim 9:1 α : β). Acetal protection of the ethyl glycoside **23**, followed by recrystallization to resolve the anomers, gave the corresponding N-acetyl-4,6-O-benzylidene-2-deoxy-2-amino-ethyl- α -D-glucopyranoside **24** in about 50% yield (yield is unoptimized). Deacetylation of **24** was carried out by refluxing the compound in 3N potassium hydroxide in ethanol for 20 hours. Column purification of the crude afforded the desired head group **14** in 90% yield.

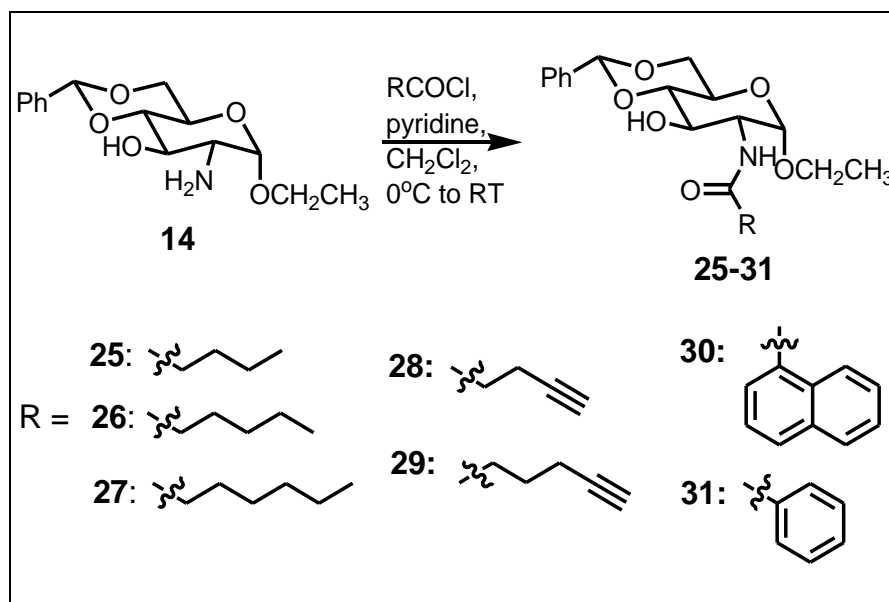


Scheme 4. Synthesis of 4,6-O-benzylidene-2-deoxy-2-amino-ethyl- α -D-glucopyranoside **14**.

Head group **14** differs from the previously reported glucosamine-based head group **9** in that it contains an ethoxyl group rather than a methoxyl group at the anomeric position (Figure 3). From compound **14**, a new series of organogelators **25-31** was synthesized by N-acylation of the 2-amino group with various acyl chlorides (Scheme 5). Compounds **25-31** were obtained by adding the corresponding acyl chloride dropwise to a solution of the monosaccharide and pyridine in dichloromethane at 0°C, and then warming the reaction mixture to room temperature for twelve hours. Workup and column purification afforded the desired amides **25-31**. In some cases, the diacylated side product (**25b-31b**) was obtained, but the conversion was typically less than 10%. For compounds **25**, **27**, **28**, and **29**, the acyl chlorides had to be made in situ from the corresponding carboxylic acids before the addition to the head group. The acyl chlorides which were found to impart good gelation in the previous series of amides derived from glucosamine (compound **10**, Scheme 2) were used so that a direct comparison could be drawn between the two head groups **9** and **14**.

The yields ranged from 57-86%, with the saturated alkanoyl compounds **25-27** being obtained in lower yields than the other analogues. The exact reason for this is unknown, but is likely a result of experimental error, due to those derivatives being among the first to be synthesized. Gel testing was conducted for all of the compounds, and several excellent gelators were obtained; the results are shown in Table 4. The saturated alkanoyl derivatives **25-27** gave excellent results for aqueous mixtures of both DMSO and ethanol, forming gels at concentrations at or below 3.0 mg/mL. The pentanoyl derivative **25** and the hexanoyl derivative **26** were also able to form organogels in toluene and hexane, respectively, at more moderate concentrations. The 4-pentynoyl derivative **28** was able to form a translucent organogel in toluene, at 7.8 mg/mL; it also formed an unstable gel in water, at 3.0 mg/mL, despite its poor solubility at that

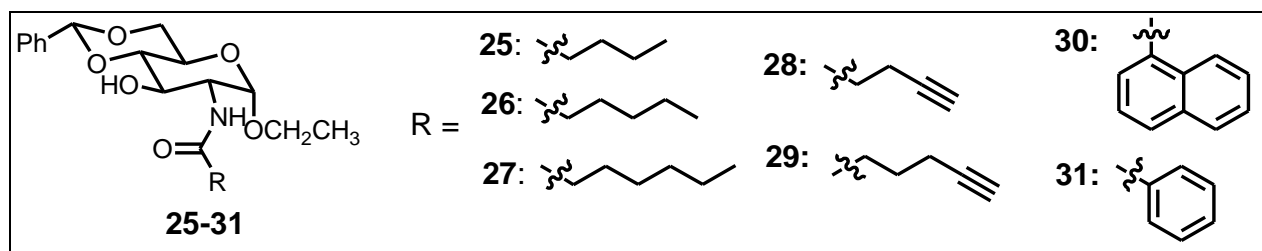
concentration. The 5-hexynoic amide **29** also formed an unstable, translucent gel in toluene at 10.0 mg/mL, and while it was insoluble in water, it did form opaque gels in ethanol:water 1:2 and DMSO:water 1:2, at concentrations of 8.0 mg/mL and 7.0 mg/mL, respectively.



Scheme 5. Library of Amides (**25-31**) Derived from 4,6-O-benzylidene-2-deoxy-2-amino-ethyl- α -D-glucopyranoside **14**.

Some of the gels which were formed by the compounds were only metastable or exhibited polymorphism. For instance, the naphthoyl derivative **30**, which was insoluble or recrystallized in most of the solvents, formed a metastable gel at 15.4 mg/mL in isopropanol; the gel collapsed into a precipitate upon setting for 1-2 hours. The benzoyl derivative **31** also exhibited some metastability, forming a polymorphic gel in aqueous DMSO. The gel fluxuated from being completely transparent to being completely opaque; in some instances, the reverse

Table 3. Gel Testing Data for Compounds 25-31.



Cpd	ClogP	m.p. (°C)	Hexanes	Toluene	iPrOH	EtOH	Water	EtOH: H ₂ O 1:2	DMSO: H ₂ O 1:2
25	1.59	210	I	G (10.0)	S	S	I	G _T (2.5)	G _T (3.0)
26	2.12	203	UG _O (5.0)	C	S	S	I	G _T (0.7)	G _T (1.5)
27	2.65	197	I/C	C	S	S	I	G _T (0.8)	G _T (0.8)
28	0.58	209	I	G _T (7.8)	C	C	I/G _O (5.0)	C	C
29	0.91	176	I	UG _T (10.0)	I/C	S	I	G _O (8.0)	G _O (7.0)
30	1.49	216	I	C	C	C	I	I	G _{TO} (1.0)
31	2.66	219	I	C	G _T (15.4)*	C	I	I	I

All compounds tested at an initial concentration of ~20 mg/mL. Legend: I=insoluble, SI=partially insoluble,

P=precipitate, S=soluble, C=recrystallization, UG=unstable gel, G=stable gel. Transparent/translucent gels are

denoted with a subscript of T; opaque gels are denoted with a subscript of O. Numbers in parentheses correspond

to concentration in mg/mL.

behavior was observed. Upon standing, the opacity grew from the bottom to the top, until the whole matrix was opaque. Compound **31** also formed a polymorphic gel in toluene at 6.0 mg/mL, in which some localized crystalline areas formed within the matrix.

A comparison of the gelation of compounds **25-31** with the corresponding analogues derived from head group **9**, which contains a methoxyl group at the anomeric position, gave some insight into how the anomeric group affects gelation. Like the methoxy series, the ethoxy compounds were generally poor hydrogelators; only the 4-pentynoyl amide **28** was able to gelate water at 5.0 mg/mL, and even at that concentration, it was not completely soluble. In comparison, the only methoxyl analogue to gelate water was the benzoyl derivative, and it was able to gelate water at 2.0 mg/mL. Similarly, gelation of hexane and isopropanol was poor for both the ethyl and methyl series, with only one or two compounds from each series being able to gelate either solvent, though the methyl analogue was slightly more efficient in both cases. While the saturated and terminal alkynyl five carbon analogues of the methoxy compounds were able to gelate ethanol, none of the ethoxy series were able to do so.

For the aqueous ethanol and aqueous DMSO mixtures, the ethyl series derivatives with saturated alkanoyl chains **25-27** performed more efficiently than the corresponding methoxyl analogues, exhibiting lower minimum gelation concentrations. Puzzlingly enough, the terminal alkynyl and aromatic derivatives **28-31** exhibited the opposite behavior in the aqueous DMSO and aqueous ethanol mixtures, proving to be less efficient than the corresponding methoxy analogues. Overall, the methoxy series proved to be more efficient for the amides which contained terminal alkyne or aromatic groups, while the saturated alkanoyl derivatives of the ethyl series proved superior to their methoxyl counterparts. These findings are significant when considering the relative costs of scaling up the syntheses of these materials for a real world

application, such as environmental cleanup; the cost of the saturated carboxylic acids and acid chlorides is much lower than that of their terminal alkynyl or naphthoyl counterparts.

Some of the compounds which were able to form gels were then observed using optical microscopy. Images of the wet gels, as well as the air dried xerogels, were obtained (Figure 3). Different morphologies were present in different solvent systems, and most of the gels exhibited birefringence, which is typical of our monosaccharide gelators. The wet gel formed by the heptanoyl amide **27** in aqueous DMSO at 1.0 mg/mL (Figure 3C) exhibited densely branched, thin fibers, while the gel formed by the 5-hexynoyl amide **29** in aqueous ethanol at 9.0 mg/mL (Figure 4A,B) exhibited birefringent, fibrous assemblies which were thicker and appeared to be more crystalline in nature. These birefringent fibers were observed in both the wet gel and the air-dried xerogel, suggesting that the morphology of this compound doesn't change much during the drying process. The gel formed by the naphthoyl amide **30** exhibited many different types of morphologies, in both the wet gel and dried xerogel (Figure 4D-F). Globular assemblies, fibrous networks, and starburst crystalline regions were all observed in the same gel, before and after drying. In addition, regularly spaced ridged regions were also observed in the isopropanol gel of **30**, but these regions may have resulted from the drying process rather than being a natural morphology of the gel (the lighted stage of the microscope rapidly dried the wet gel). In any case, the extreme polymorphism of the isopropanol gel formed by naphthoyl amide **30** may explain why it is only metastable, and collapses into a precipitate upon standing.

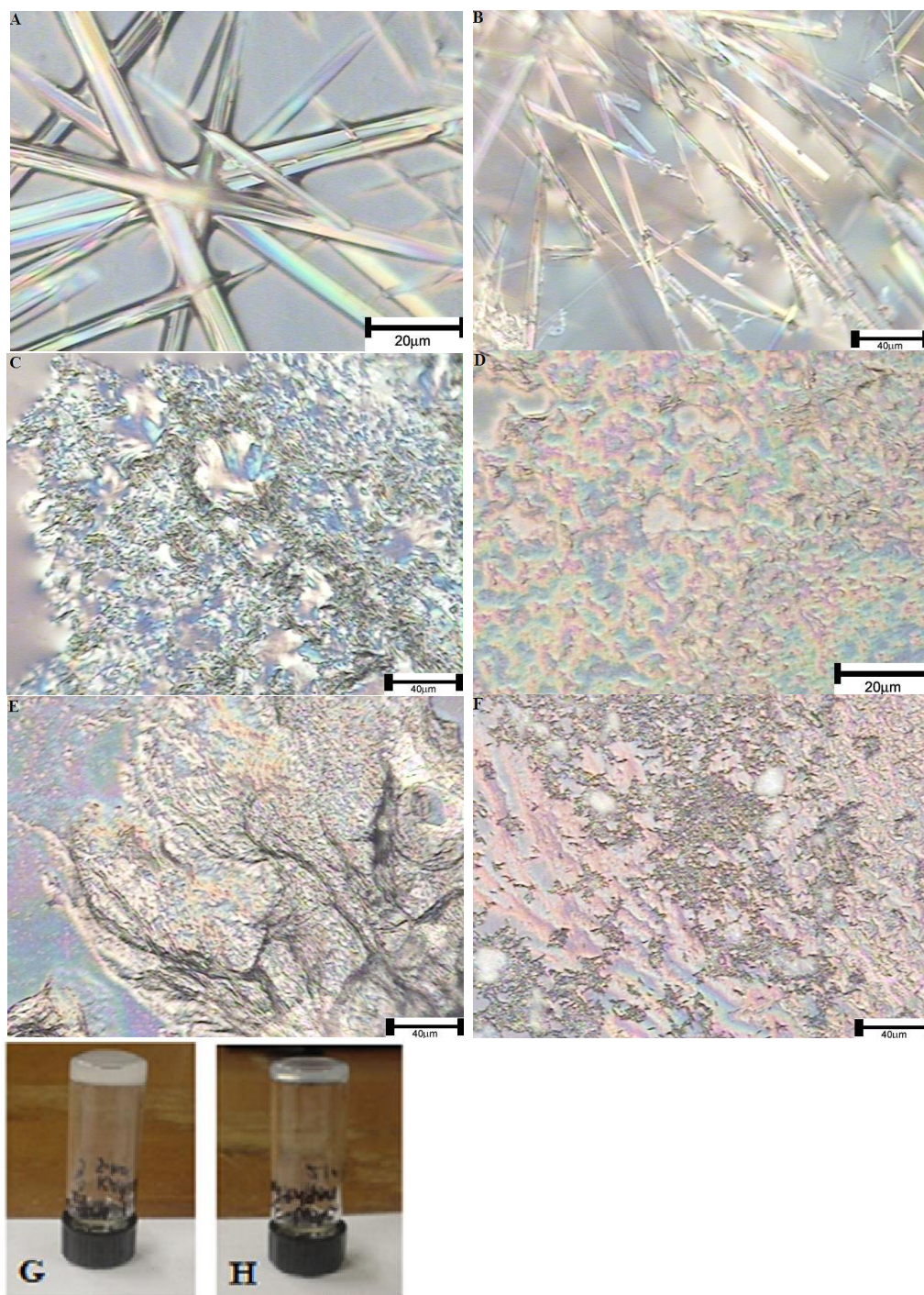


Figure 4. Optical microscopy images and photographs of the gels formed by **27**, **29**, and **30**. A) Dried gel of **29** in DMSO:H₂O 1:2 at 8.0 mg/mL (500x magnification). B) Wet gel of **29** in EtOH:H₂O 1:2 at 9.0 mg/mL (200x magnification). C) Wet gel of **27** in DMSO:H₂O 1:2 at 1.0 mg/mL (200x magnification). D) Dried gel of **30** in iPrOH at 17.5 mg/mL (500x magnification). E) Wet gel of **30** in iPrOH at 17.5 mg/mL (200x magnification). F) Dried gel of **30** in iPrOH at 17.5 mg/mL (200x magnification). G) H)

magnification). G) Photograph of gel formed by **29** in DMSO:H₂O 1:2 at 8.0 mg/mL. H) Photograph of gel formed by **30** in iPrOH at 17.5 mg/mL.

Since several of the glucosamine-based compounds were capable of forming gels in organic solvent, we decided to screen the compounds for their ability to gelate crude oil (Table 4). Several of the compounds from the benzylidene series were found to gelate crude oil (Scheme 5), along with the deprotected docosanoyl compound **20** from the isopropylidene series. The compounds which gelated crude oil were also screened for gelation in engine oil and marvel oil (a transparent red oil similar in consistency to the main organic components of crude oil). All of the compounds which gelated the crude oil were also able to gelate the marvel oil at similar concentrations, but only the pentanoyl compound **25** of the benzylidene series could gelate the engine oil, albeit at a higher concentration (below 15.4 mg/mL, precipitation occurred).

Table 4. Oil Gel Testing Data for Compounds **15-21** & **25-31**.

Cpd.	Crude oil	Engine oil	Marvel oil
15	NG	n.t	n.t
16	NG	n.t	n.t
17	NG	n.t	n.t
18	n.t.	n.t	n.t
19	NG	n.t	n.t
20	G (2.0)	P	G (2.5)
21	NG	n.t	n.t
25	NG	G (15.4)	G (7.8)
26	G (6.1)	P	G (6.1)
27	G (13.1)	P	G (6.1)
28	G (6.0)	P	G (8.1)
29	NG	n.t	n.t
30	NG	n.t	n.t
31	G (5.0)	P	G (7.8)

All compound tested at an initial concentration of ~20 mg/mL. Legend: NG = no gel, G = gel, P = precipitate, n.t. = not tested. Because of the

opaque nature of the crude oil, if a compound did not form a gel, it could not be determined if the compound was soluble, or if precipitation or recrystallization was occurring, so compounds that did not gel were simply recorded as not gelling (NG). The gels in marvel oil were typically translucent rather than opaque, though it was difficult to determine in some cases due to the color of the oil.

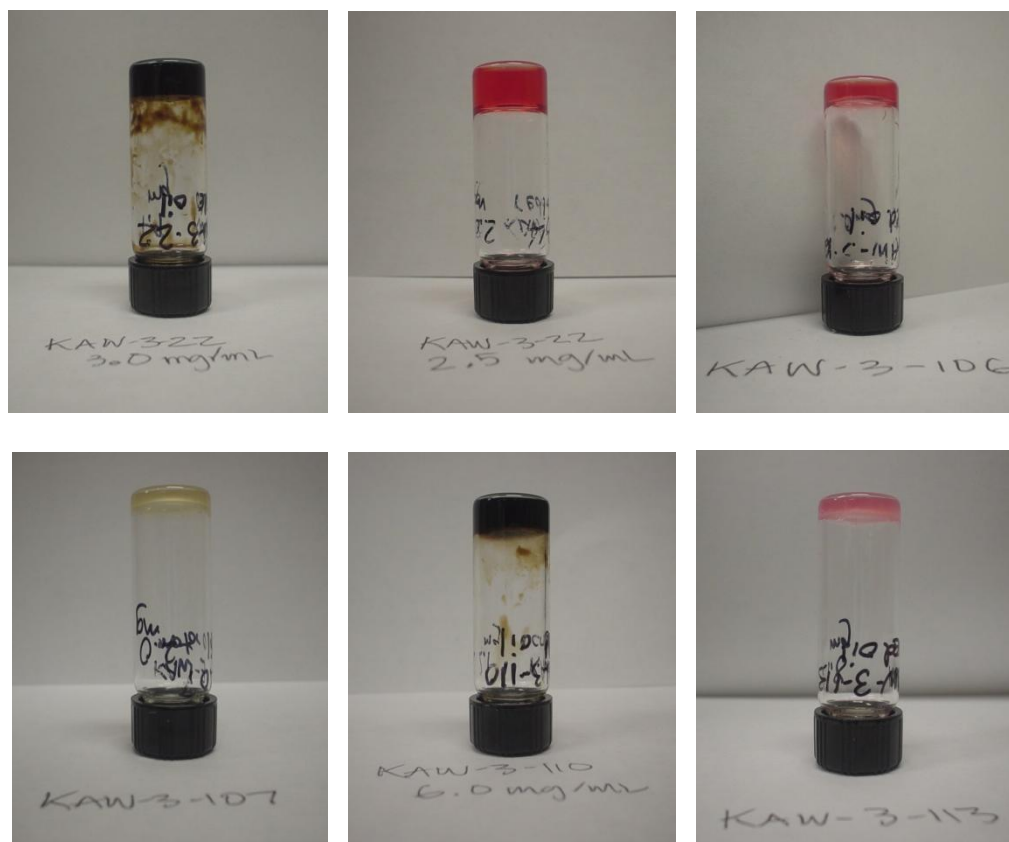


Figure 4. Photographs of amide compounds gelling oil. A) Gel of **20** in crude oil at 3.0 mg/mL. B) Gel of **20** in marvel oil at 2.5 mg/mL. C) Gel of **31** in marvel oil at 6.1 mg/mL. D) Gel of **25** in engine oil at 15.4 mg/mL. E) Gel of **28** in crude oil at 6.0 mg/mL. F) Gel of **31** in marvel oil at 12.0 mg/mL.

We also conducted some experiments to determine if we could get phase selective gelation to occur. In order to apply our compounds to real world applications involving recovery of crude oil after a spill, the gelator must be able to selectively gelate the oil in the presence of water. In addition, since our library of gelators are typically all solid compounds, we must find a way to homogeneously disperse them in the oil phase. Therefore, we conducted a series of experiments where we made 1:1 or 1:2 mixtures of marvel oil and water, in which the salinity of the water had been adjusted to match the average salinity of the ocean, which is about 35 g/L. The quantity of the gelator which would give a concentration of twice the minimum gelation concentration in the oil was then dissolved in a minimum amount of ethanol and added to either the top of the oil/water mixture, or at the interface. Three of the compounds, **20**, **26**, and **31** were tested, and among them, it was found that the hexanoyl derivative **26** could selectively gelate the oil in the presence of the water (Figure 5).

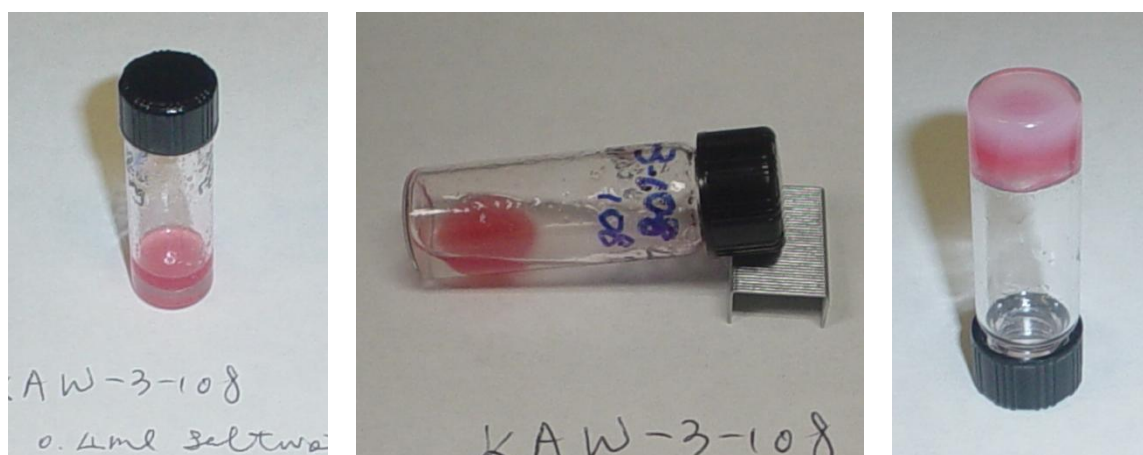


Figure 5. Photographs from phase selective gelation experiments. A, B) Phase selective gelation of **26** in 1:1 oil:water mixture at 5 mg/mL (relative to only marvel oil). C)

Gelation of both oil and water by **26** at 5 mg/mL (relative to oil), after heating and sonication.

However, when the mixture was heated and sonicated, the **26** was not phase selective, and gelled the entire mixture instead. Further work in the practical application of our compounds is needed, but these initial studies show that our compounds have the potential to act as phase selective gelators for cleaning up oil spills.

Conclusions:

We have successfully synthesized and characterized two series of compounds by acylation of head groups **13** and **14**, which are both derived from D-glucosamine. Several of these compounds have been found to be low molecular weight gelators for organic solvents or aqueous mixtures. The compounds have been synthesized in fair yields, which may need to be optimized, and they have been characterized by ^1H and ^{13}C NMR and melting point, and screened for gelation in several organic solvents and water, though additional characterization and screening is needed. In particular, IR spectroscopy and rheological characterization of the compounds would aid us in better understanding the supramolecular packing order and mechanical properties of the gels, and additional solvent screening might produce additional positive gelation results. We have also shown that several of the compounds are able to gelate crude oil and similar oils, and that at least one compound, **26**, can do so in a phase selective manner, gelling oil in the presence of water. This preliminary study demonstrates the potential

of our low molecular weight gelators to act as phase selective gelators for use in environmental clean-up scenarios, such as oil spills.

In light of the recent oil spill disaster in the Gulf of Mexico, the need for improved environmental cleanup agents is greater than ever. Ideally, these materials would be cheap, readily available, efficient, easy to administer, environmentally benign, and would allow for the recovery of the contaminant. Our gelators fit most, if not all, of these criteria. Because they are derived from glucosamine and require only a few synthetic steps for preparation, they meet the requirement for being cheap and readily available. Though some testing is needed, sugars and their simpler derivatives are typically biocompatible, so our compounds should be safe for the environment. Because of their ability to trap large quantities of solvent within their matrices and their inherent thermoreversibility, low molecular weight gelators are efficient and allow for recovery of the contaminant. Our phase selective gelation studies show that our compounds have the potential to be easily administered to an oil slick or other chemical spill, and we will continue to work to improve this aspect of our gelator systems in the future.

Experimental Section:

General method and materials: Reagents and solvents were used as they were received from the supplier. NMR analysis was conducted using a 400 MHz Varian NMR spectrometer. Melting point measurements were carried out using a Fisherbrand Fisher-Johns melting point apparatus, and were uncorrected. For optical microscopy, a small amount of the gel was placed on a clean glass slide and was air-dried overnight. 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.

Gel Testing: Gel testing was conducted in 1 dram glass screw thread vials with black phenolic caps. ~2 mg of the dried compound was placed in the vial, and the corresponding solvent was added to obtain a concentration of ~20 mg/mL. The suspension was then heated until the solids were fully dissolved, and the resulting solution was briefly sonicated, and then the solution was allowed to cool to room temperature, undisturbed, for fifteen minutes. Compounds which appeared to be insoluble at the initial concentration were heated and sonicated several times, to ensure that the compound was truly insoluble (some compounds were resistant to solvation, suggesting a relatively high lattice energy or endothermic heat of solvation). After the compounds had cooled back to ambient temperature, the resulting phenomenon (recrystallization, precipitation, gelation, etc.) was then recorded. If the compound appeared to form a gel, the vial was inverted and shaken gently to determine if there was any flow; compounds which did not flow and which retained all of the solvent within the gel matrix were recorded as stable gels, while those which showed some loss of solvent or fell apart were recorded as unstable gels. Serial dilution was performed at increments of ~5 mg/mL for all phenomenon other than gelation (precipitation, recrystallization, and compounds which were insoluble), down to a final concentration of ~5 mg/mL. Compounds which formed stable gels were serially diluted in increments of 1-2 mg/mL, until the gel was found to be unstable (by the above criteria). Compounds which were found to be soluble were not further diluted.

General method for synthesis: All reactions were performed using anhydrous solvents and reagents, and the anhydrous dichloromethane and pyridine were further dried over freshly activated 4Å molecular sieves prior to their use, to ensure their dryness. All reactions were conducted in flame dried scintillation vials cooled under a stream of dry nitrogen gas. All purification was conducted by flash chromatography using 230-400 mesh silica gel (SiO₂) obtained from Natland International Corporation, unless otherwise noted. A hexanes: ethyl acetate 6:1 solvent gradient was typically used to elute the compounds **17-24** (in some cases, a 3:1 gradient was used, but resolution was generally not as good; the diacyl side products typically eluted in 6:1, and the desired amide products **17-24** began eluting in either 3:1 or 1:1).

Yields were calculated using the glucosamine derivative **13** as the limiting reagent, even for the diacyl compounds, in which the actual limiting reagent was the acyl chloride (this was done for the sake of easily tracking the conversion of the starting material **13** to product). All NMR data was obtained using a Varian Unity 400 MHz spectrometer, and all spectra are referenced to the residual solvent peak: 7.26 ppm (s) and 77.00 ppm (t) for ¹H and ¹³C, respectively, in CDCl₃; spectra taken in CDCl₃/CD₃OD were referenced to the residual solvent peak of methanol at 4.87 ppm (bs) for ¹H, and to the residual solvent peak of chloroform at 77.00 ppm for ¹³C spectra (s=singlet, t=triplet, bs=broad singlet).

Synthesis of N-Hexanoyl-4,6-O-Isopropylidene-Methyl-α-D-Glucosamine 15. A solution of 55 mg of 4,6-O-isopropylidene-methyl-α-D-glucosamine **13** (0.236 mmol) in 1 mL of anhydrous dichloromethane and 0.2 mL of anhydrous pyridine (2.48 mmol, 10.5 equivalents) was cooled to 0°C, and 0.04 mL of hexanoyl chloride (0.291 mmol, 1.2 equivalents) was then added. The

reaction was stirred at 0°C for about two hours before being warmed to room temperature and stirred for an additional 15 hours. At this point, ¹H NMR indicated that the head group **1** had been completely consumed. The reaction was concentrated, rediluted with dichloromethane, washed with saturated sodium bicarbonate solution, and the aqueous phase was extracted three times with dichloromethane. The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated to give 73 mg of crude yellow oil. Purification was conducted using flash chromatography with a gradient solvent system of hexanes:ethyl acetate 3:1 to 1:3 to give 46 mg of clean product as a white solid for a 59% yield. Mp = 107-108.5°C. R_f = 0.20 (hexanes:ethyl acetate 1:1). ¹H NMR (400 MHz, CDCl₃) δ 5.92 (d, J = 8.6, 1H), 4.66 (d, J = 3.8, 1H), 4.13 (td, J = 9.3, 3.8, 1H), 3.84 (dd, J = 10.6, 4.5, 1H), 3.79 – 3.65 (m, 2H), 3.65 – 3.52 (m, 2H), 3.34 (s, 3H), 2.21 (t, J=7.3, 2H), 1.61 (quintet, J=7.3, 2H), 1.50 (s, 3H), 1.41 (s, 3H), 1.38 – 1.21 (m, 5H), 0.87 (t, J = 6.8, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 174.9, 100.0, 99.0, 77.6 77.2, 76.9, 74.9, 71.2, 63.4, 62.4, 55.3, 54.3, 36.7, 31.5, 29.3, 25.4, 22.5, 19.2, 14.1.

Synthesis of N-5-hexynoyl-4,6-O-Isopropylidene-Methyl-α-D-Glucosamine 16. A solution of 0.03 mL of 5-hexynoic acid (0.261 mmol) in 1 mL anhydrous dichloromethane was cooled to 0°C, and 0.03 mL of oxalyl chloride (0.343 mmol, 1.3 equivalents) was then added, followed by a single drop of anhydrous DMF, and the reaction was stirred for four hours at 0°C. Anhydrous pyridine (0.2 mL, 2.48 mmol, 9.5 equivalents) was then added, followed by 58 mg of 4,6-O-Isopropylidene-Methyl-α-D-Glucosamine **13** (0.249 mmol, 0.95 equivalents), and the reaction was stirred at 0°C for an additional 30 minutes before being warmed to room temperature and stirred for another 13 hours. ¹H NMR and TLC analysis showed complete consumption of the starting material, so the reaction was diluted with dichloromethane, washed with saturated

sodium bicarbonate solution, and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated to give 80 mg of crude, yellow-brown oil which was purified by flash chromatography using a gradient of hexanes:ethyl acetate 7:3 to 2:3. 29 mg of pure white solid were obtained for a 36% yield (upon drying under vacuum). Compound is extremely hygroscopic, and absorbs moisture to become a gummy oil within a few minutes. Thus, melting point could not be obtained. $R_f=0.18$ (hexanes:ethyl acetate 2:3). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.98 (d, $J = 8.7$, 1H), 4.66 (d, $J = 3.8$, 1H), 4.15 (td, $J = 9.4, 3.8$, 1H), 3.84 (dd, $J = 10.6, 4.5$, 1H), 3.80 – 3.66 (m, 2H), 3.66 – 3.53 (m, 2H), 3.38 (s, 3H), 2.38 (t, $J = 7.3$, 2H), 2.29-2.23 (m, 2H), 1.98 (t, $J = 2.6$, 1H), 1.92 – 1.80 (m, 2H), 1.51 (s, 3H), 1.42 (s, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 173.8, 100.0, 99.0, 83.6, 74.9, 71.1, 69.5, 63.5, 62.4, 55.9, 55.4, 54.3, 35.1, 29.3, 24.1, 19.3, 17.8.

Synthesis of N-Docosanoyl-4,6-O-Isopropylidene-Methyl- α -D-Glucosamine 17. Docosanoic acid (80 mg, 0.233 mmol) was suspended in 1.5 mL of anhydrous dichloromethane and 1 mL of anhydrous hexane and cooled to 0°C. Oxalyl chloride (0.025 mL, 0.286 mmol, 1.2 equivalents) was then added, followed by a single drop of anhydrous DMF, causing the suspension to immediately go into solution. After 1.5 hours, $^1\text{H NMR}$ showed ~90% conversion to the acyl chloride, so the reaction was warmed to room temperature and stirred for another 1.5 hours to ensure complete conversion to the acyl chloride. The solution was then cooled to 0°C, and 0.10 mL of anhydrous pyridine (1.24 mmol, 5.3 equivalents) was added, followed by 46 mg of 4,6-O-Isopropylidene-Methyl- α -D-Glucosamine **13** (0.197 mmol, 0.85 equivalents), and the reaction was stirred for 45 minutes at 0°C before being warmed to room temperature. After 16 hours, ^1H

NMR showed complete conversion of the starting material, so the reaction was diluted with dichloromethane, washed with saturated sodium bicarbonate solution, and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated to give 240 mg of crude off-white solid. Purification via flash chromatography using a gradient of hexanes:ethyl acetate 4:1 to 1:1 afforded 54 mg of amide as a white solid in 49% yield. Mp = 97-98°C. $R_f=0.25$ (hexanes:ethyl acetate 3:2). ^1H NMR (400 MHz, CDCl_3) δ 5.88 (d, $J = 8.5$, 1H), 4.66 (d, $J = 3.8$, 1H), 4.15 (td, $J = 9.3$, 3.8, 1H), 3.85 (dd, $J = 10.7$, 4.3, 1H), 3.80 – 3.65 (m, 2H), 3.65 – 3.52 (m, 2H), 3.35 (s, 3H), 3.20 (s, 1H), 2.22 (t, $J = 7.5$, 2H), 1.61 (dd, $J = 13.9$, 6.9, 2H), 1.52 (s, 3H), 1.42 (s, 3H), 1.24 (s, 36H), 0.86 (t, $J = 6.7$, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 175.0, 100.0, 99.0, 74.9, 71.4, 63.4, 62.4, 55.3, 54.3, 36.8, 32.1, 29.9, 29.83, 29.81, 29.7, 29.5, 29.4, 29.3, 25.8, 22.9, 19.3, 14.3.

Synthesis of N-Benzoyl-4,6-O-Isopropylidene-Methyl- α -D-Glucosamine 18. A solution of 49 mg of 4,6-O-Isopropylidene-Methyl- α -D-Glucosamine **13** (0.210 mmol) in 0.6 mL of anhydrous dichloromethane and 0.2 mL of anhydrous pyridine (2.48 mmol, 11.8 equivalents) was cooled to 0°C, and 0.025 mL of benzoyl chloride (0.217 mmol, 1.03 equivalents) was added. The reaction was warmed to room temperature and stirred for 24 hours, at which point the reaction was diluted with dichloromethane, washed with saturated sodium bicarbonate solution, and the aqueous phase was extracted four times with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated to give 121 mg of brown oil. Purification via flash chromatography using a gradient of hexanes:ethyl acetate 7:3 to 3:2 gave 11 mg of white solid for a 15% yield. Mp = 74.5-76°C. $R_f=0.23$ (hexanes:ethyl acetate

1:1). ^1H NMR (400 MHz, CDCl_3) δ 7.77 (d, $J = 7.3$, 2H), 7.48 (t, $J = 7.4$, 1H), 7.40 (t, $J = 7.5$, 2H), 6.59 (d, $J = 8.6$, 1H), 4.79 (d, $J = 3.8$, 1H), 4.37 (td, $J = 9.3$, 3.8, 1H), 3.94 – 3.73 (m, 3H), 3.70 – 3.59 (m, 2H), 3.38 (s, 3H), 1.52 (s, 3H), 1.43 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 168.7, 133.9, 132.0, 128.7, 127.4, 100.1, 99.1, 74.9, 71.1, 63.5, 62.4, 55.4, 54.8, 29.3, 19.3.

Synthesis of N-Naphthoyl-4,6-O-Isopropylidene-Methyl- α -D-Glucosamine 19. A solution of 50 mg of 4,6-O-Isopropylidene-Methyl- α -D-Glucosamine **13** (0.214 mmol) in 1 mL of anhydrous dichloromethane and 0.10 mL of anhydrous pyridine (1.24 mmol, 5.8 equivalents) was cooled to 0°C, and 0.035 mL of 1-naphthoyl chloride (0.226 mmol, 1.06 equivalents) was then added. The reaction was warmed to room temperature after five minutes and then stirred for an additional eight hours. ^1H NMR showed the reaction to be completed at this time, so the reaction was diluted with dichloromethane, washed with saturated sodium bicarbonate solution, and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated to give ~130 mg of yellow-brown solid. Purification was conducted using flash chromatography using a gradient of hexanes:ethyl acetate 4:1 to 3:2 to give 57 mg of white solid for a 69% yield. Mp = 198-199°C. $R_f = 0.26$ (hexanes:ethyl acetate 3:2). ^1H NMR (400 MHz, CDCl_3) δ 8.26 – 8.16 (m, 1H), 7.82 – 7.71 (m, 2H), 7.52 (dd, $J = 7.0$, 1.0, 1H), 7.45 – 7.38 (m, 2H), 7.32 – 7.27 (m, 1H), 6.36 (d, $J = 8.8$, 1H), 4.77 (d, $J = 8.1$, 1H), 4.37 (td, $J = 9.6$, 4.0, 1H), 3.82 – 3.65 (m, 3H), 3.63 – 3.47 (m, 2H), 3.33 – 3.22 (m, 4H), 1.42 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.7, 134.0, 133.7, 130.9, 130.2, 128.4, 127.4, 126.6, 125.5, 125.4, 124.8, 100.0, 99.1, 74.9, 71.0, 63.6, 62.4, 55.4, 54.7, 29.2, 19.2.

Synthesis of N-Docosanoyl-Methyl- α -D-Glucosamine 20. Acetal protected docosanoyl amide **17** (34 mg) was suspended in 1 mL of 85% v/v aqueous acetic acid and stirred for 8.25 hours, but TLC analysis indicated that only partial hydrolysis had taken place, so the compound was dissolved in 5 mL of tetrahydrofuran and 1 mL of 85% v/v aqueous acetic acid and stirred for an additional 12 hours. The reaction was still sluggish, so another 2 mL of 50% v/v aqueous acetic acid was added, and the reaction was stirred for another 66 hours, at which point the reaction was deemed to have reached completion by TLC (H:EA 3:1) and ^1H NMR analysis. The reaction was diluted with tetrahydrofuran and concentrated under a stream of nitrogen, and then dried thoroughly under vacuum to afford 27 mg of triol **20** in 84% yield. HRMS (ESI) m/z calculated for $\text{C}_{29}\text{H}_{58}\text{NO}_6$ $\{\text{M}+\text{H}\}$, 516.4264; found, 516.4272.

Synthesis of N-Naphthoyl-Methyl- α -D-Glucosamine 21. Isopropylidene-protected naphthoyl amide **19** (20 mg) was dissolved in 1 mL of 85% v/v aqueous acetic acid and stirred for eight hours at room temperature. TLC and ^1H NMR indicated that the reaction was complete, so the compound was dried under a stream of nitrogen and then dried on the vacuum line to afford the desired triol **21** in quantitative yield. The compound decomposed upon heating, so no melting point could be obtained. HRMS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{21}\text{NO}_6\text{Na}^+$ $[\text{M}+\text{Na}]$, 370.1267; found, 370.1269.

Synthesis of 4,6-O-Benzylidene-Ethyl- α -D-Glucosamine 24. N-Acetyl-4,6-O-Benzylidene-Ethyl- α -D-Glucosamine (650 mg, 1.93 mmol) was suspended in 25 mL of absolute ethanol and then heated to reflux. At this point, 4.07 g of potassium hydroxide (72.5 mmol) was then added, causing the starting material to go into solution. After fifteen minutes, the potassium hydroxide had also gone into solution, causing the solution to become brown in color. At 20 hours, ^1H NMR ($\text{CDCl}_3/\text{CD}_3\text{OD}$, 400 MHz) showed that all of the acetamide had been consumed, so the reaction was concentrated on the rotary evaporator to remove the ethanol, and then diluted with water, and extracted three times with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated to give 541 mg of brown solid for a 95.1% crude yield. Purification via gravitational column chromatography using 100-200 mesh silica gel and a gradient of methanol in dichloromethane, 0% to 10%, afforded 510 mg of the product as an orange solid for an 90% yield.

^1H NMR (400 MHz, CDCl_3) δ 7.49 (dd, $J = 6.7, 2.7$, 2H), 7.42 – 7.31 (m, 3H), 5.52 (s, 1H), 4.76 (d, $J = 3.4$, 1H), 4.24 (dd, $J = 10.0, 4.7$, 1H), 3.87 – 3.61 (m, 4H), 3.53 – 3.37 (m, 2H), 2.81 – 2.68 (m, 1H), 2.29 (s, 3H), 1.23 (t, $J = 7.1$, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 137.2, 129.1, 128.3, 126.3, 101.8, 99.9, 82.1, 71.6, 69.1, 63.7, 62.6, 56.5, 15.0.

Synthesis of N-Pentanoyl-4,6-O-Benzylidene-Ethyl- α -D-Glucosamine 25. Valeric (pentanoic) acid (0.02 mL, 0.182 mmol) was added to 0.8 mL of anhydrous dichloromethane and cooled to 0°C , and then 0.02 mL of oxalyl chloride (0.233 mmol) was then added, followed by two drops of anhydrous DMF, and the reaction was stirred at 0°C for one hour. Anhydrous pyridine (0.1 mL, 1.24 mmol) was then added to the solution, followed by 48 mg of the benzylidene-protected ethyl glucosamine **14** (0.163 mmol), and the reaction was stirred at 0°C for an additional 1.5 hours before being warmed to room temperature for 17.5 hours. ^1H NMR of the crude was was

obtained, and showed that the starting material **14** had been completely consumed, so the reaction was diluted with dichloromethane and quenched by the addition of saturated sodium bicarbonate solution, and after fifteen minutes, the layers were separated, and the aqueous layer was extracted twice with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude solid, which was purified by flash chromatography to give 40 mg of the amide **17** for a yield of 65% (18 mg of the diacylated product was also obtained, for a 24% yield). M.p. = 210-211.5°C. ¹H NMR (400 MHz, CDCl₃) δ 7.54 – 7.45 (m, 2H), 7.39 – 7.30 (m, 3H), 5.92 (d, *J* = 8.6, 1H), 5.54 (s, 1H), 4.81 (d, *J* = 3.7, 1H), 4.30 – 4.13 (m, 2H), 3.89 (t, *J* = 9.5, 1H), 3.85 – 3.68 (m, 3H), 3.56 (t, *J* = 9.1, 1H), 3.52 – 3.35 (m, 2H), 2.31 – 2.15 (m, 2H), 1.69 – 1.53 (m, 2H), 1.42 – 1.28 (m, 2H), 1.22 (t, *J* = 7.0, 3H), 0.90 (t, *J* = 7.3, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 174.5, 137.1, 129.1, 128.2, 126.3, 115.3, 101.7, 97.5, 82.0, 70.5, 68.8, 63.6, 62.4, 53.9, 36.3, 27.6, 22.2, 14.9, 13.7.

Synthesis of N-Hexanoyl-4,6-O-Benzylidene-Ethyl-α-D-Glucosamine 26. The benzylidene-protected ethyl glucosamine **14** (42 mg, 0.142 mmol) was dissolved in 1 mL of anhydrous dichloromethane and 0.10 mL of anhydrous pyridine (1.24 mmol), and the solution was cooled to 0°C. Hexanoyl chloride (0.02 mL, 0.142 mmol) was then added, and the reaction was stirred at 0°C for two hours, and then warmed to room temperature for 18 hours. ¹H NMR of the crude was obtained, and showed that the starting material **14** had been completely consumed, so the reaction was diluted with dichloromethane and quenched by the addition of saturated sodium bicarbonate solution, and after fifteen minutes, the layers were separated, and the aqueous layer was then extracted twice with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated to give 55 mg of the crude solid (98% crude

yield). Purification of the crude by flash chromatography gave 32 mg of the amide **26** and 8 mg of the diacyl product for a yield of 57% (8 mg of diacylated product was also obtained for 11% yield). M.p. = 202.5-204°C. ¹H NMR (400 MHz, CDCl₃) δ 7.50 (dd, *J* = 6.7, 2.7, 2H), 7.40 – 7.32 (m, 3H), 5.87 (d, *J* = 8.4, 1H), 5.55 (s, 1H), 4.82 (d, *J* = 3.9, 1H), 4.31 – 4.14 (m, 2H), 3.90 (t, *J* = 9.6, 1H), 3.86 – 3.68 (m, 3H), 3.57 (dd, *J* = 17.9, 8.7, 1H), 3.53 – 3.42 (m, 1H), 3.27 (s, 1H), 2.31 – 2.17 (m, 2H), 1.70 – 1.57 (m, 2H), 1.39 – 1.27 (m, 4H), 1.24 (t, *J* = 7.1, 3H), 0.89 (t, *J* = 6.8, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 174.6, 137.1, 129.1, 128.2, 126.3, 101.8, 97.5, 82.1, 70.7, 68.8, 63.6, 62.4, 53.9, 36.6, 31.3, 25.2, 22.3, 14.9, 13.9.

Diacylated compound: No m.p. was obtained. ¹H NMR (400 MHz, CDCl₃) δ 7.44 (dd, *J* = 6.5, 2.9, 2H), 7.38 – 7.31 (m, 3H), 5.78 (d, *J* = 9.5, 1H), 5.53 (s, 1H), 5.34 (t, *J* = 10.1, 1H), 4.83 (d, *J* = 3.7, 1H), 4.38 – 4.23 (m, 2H), 3.91 (td, *J* = 9.9, 4.7, 1H), 3.82 – 3.65 (m, 3H), 3.53 – 3.42 (m, 1H), 2.39 – 2.21 (m, 2H), 2.20 – 2.06 (m, 2H), 1.67 – 1.51 (m, 3H), 1.37 – 1.18 (m, 12H), 0.89 (t, *J* = 6.9, 3H), 0.82 (t, *J* = 6.8, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 174.3, 173.1, 137.1, 129.0, 128.2, 126.1, 101.4, 97.8, 79.2, 69.8, 68.9, 63.8, 62.9, 52.4, 36.7, 34.2, 31.3, 31.1, 25.3, 24.7, 22.3, 22.2, 15.0, 13.9, 13.8.

Synthesis of N-Heptanoyl-4,6-O-Benzylidene-Ethyl-α-D-Glucosamine 27. A solution of 48 mg of 4,6-O-benzylidene-ethyl-α-D-glucosamine **14** (0.163 mmol) in 1 mL of anhydrous dichloromethane and 0.2 mL of anhydrous pyridine (2.48 mmol) was cooled to 0°C, 0.03 mL of heptanoyl chloride (0.195 mmol) was added, and the reaction was stirred at 0°C for 1.5 hours, and then warmed to room temperature for an additional 19.5 hours. ¹H NMR of the crude was obtained, and showed that the starting material **14** had been completely consumed, so the

reaction was diluted with dichloromethane and quenched by the addition of saturated sodium bicarbonate solution, and after 45 minutes, the layers were separated, and the aqueous layer was then extracted twice with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated to give 125 mg of light brown crude solid. Purification via flash chromatography gave 39 mg of the amide **27** in 59% yield (17 mg of the diacyl compound was also obtained for a yield of 20%). M.p. = 197-198.5°C. ¹H NMR (400 MHz, CDCl₃) δ 7.50 (dd, *J* = 7.0, 2.5, 2H), 7.39 – 7.32 (m, 3H), 5.87 (d, *J* = 8.6, 1H), 5.56 (s, 1H), 4.82 (d, *J* = 3.8, 1H), 4.30 – 4.16 (m, 2H), 3.90 (td, *J* = 9.8, 2.7, 1H), 3.86 – 3.70 (m, 3H), 3.58 (t, *J* = 9.1, 1H), 3.49 (dq, *J* = 9.9, 7.0, 1H), 3.25 (s, 1H), 2.31 – 2.17 (m, 2H), 1.70 – 1.56 (m, 2H), 1.38 – 1.20 (m, 9H), 0.88 (t, *J* = 6.6, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 174.6, 137.1, 129.1, 128.2, 126.3, 101.8, 97.5, 82.1, 70.7, 68.8, 63.6, 62.4, 53.9, 36.6, 31.5, 28.8, 25.5, 22.4, 15.0, 14.0.

Diacylated compound: ¹H NMR (400 MHz, CDCl₃) δ 7.44 (dd, *J* = 6.5, 3.0, 2H), 7.38 – 7.31 (m, 3H), 5.78 (d, *J* = 9.4, 1H), 5.53 (s, 1H), 5.33 (t, *J* = 10.1, 1H), 4.82 (d, *J* = 3.7, 1H), 4.37 – 4.23 (m, 2H), 3.91 (td, *J* = 9.9, 4.7, 1H), 3.82 – 3.67 (m, 3H), 3.52 – 3.41 (m, 1H), 2.39 – 2.21 (m, 2H), 2.21 – 2.06 (m, 2H), 1.63 – 1.51 (m, 3H), 1.35 – 1.16 (m, 16H), 0.94 – 0.77 (m, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 174.3, 173.0, 137.0, 129.0, 128.2, 126.1, 101.4, 97.8, 79.2, 69.8, 68.9, 63.8, 62.8, 52.4, 36.7, 34.3, 31.5, 31.4, 28.9, 28.6, 25.6, 24.9, 22.5, 22.4, 15.0, 13.98, 13.96.

Synthesis of N-(4-pentynoyl)-4,6-O-Benzylidene-Ethyl-α-D-Glucosamine 28. A solution of 17 mg of 4-pentynoic acid (0.170 mmol) in 1 mL of anhydrous dichloromethane was cooled to 0°C, 1 drop of anhydrous DMF and 0.015 mL of oxalyl chloride (0.173 mmol) were then added, and

the reaction was stirred at 0°C for 1.25 hours. The acyl chloride solution was then added dropwise to a 0.8 mL solution of 50 mg of 4,6-O-benzylidene-ethyl- α -D-glucosamine **14** (0.169 mmol) and 0.08 mL of anhydrous pyridine (0.989 mmol) in anhydrous dichloromethane at 0°C. The reaction was then stirred at 0°C for one hour and then warmed to room temperature for 17 hours. ^1H NMR of the crude was obtained, and showed that the starting material **14** had been completely consumed, so the reaction was diluted with dichloromethane and quenched by the addition of saturated sodium bicarbonate solution, and after 45 minutes, the layers were separated, and the aqueous layer was then extracted twice with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated to give 65 mg of crude yellow solid, which was then purified by flash chromatography to afford 47 mg of amide **28** as a white solid, for a 74% yield. m.p. = 209-210.5°C. ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 7.43 (dd, $J = 6.6, 2.9, 2\text{H}$), 7.33 – 7.26 (m, 3H), 6.72 (d, $J = 8.9, 1\text{H}$), 5.50 (s, 1H), 4.76 (d, $J = 3.7, 1\text{H}$), 4.18 (dd, $J = 9.8, 4.4, 1\text{H}$), 4.11 – 4.04 (m, 1H), 3.85 – 3.73 (m, 2H), 3.73 – 3.64 (m, 2H), 3.51 (t, $J = 9.2, 1\text{H}$), 3.42 (dq, $J = 9.8, 7.1, 1\text{H}$), 2.50 – 2.32 (m, 4H), 1.97 (t, $J = 2.4, 1\text{H}$), 1.17 (t, $J = 7.1, 3\text{H}$). ^{13}C NMR (101 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 172.8, 137.2, 129.3, 128.3, 126.4, 102.0, 97.8, 82.9, 82.1, 69.4, 69.3, 68.9, 63.9, 62.8, 54.2, 35.1, 15.0, 14.8.

Synthesis of N-(5-Hexynoyl)-4,6-O-Benzylidene-Ethyl- α -D-Glucosamine 29. A solution of 0.02 mL of 5-hexynoic acid (0.174 mmol) in 0.8 mL of anhydrous dichloromethane was cooled to 0°C, 0.02 mL of oxalyl chloride (0.236 mmol) and 2 drops of anhydrous DMF were then added, and the reaction was stirred at 0°C for 1.75 hours. The acyl chloride solution was then added dropwise to a 0.5 mL solution of 48 mg of 4,6-O-benzylidene-ethyl- α -D-glucosamine **14** (0.163 mmol) in anhydrous dichloromethane at 0°C, and 0.07 mL of anhydrous pyridine (0.867 mmol)

was then added. The reaction was then stirred at 0°C for two hours and then warmed to room temperature for 16 hours. ¹H NMR of the crude was obtained, and showed that the starting material **14** had been completely consumed, so the reaction was diluted with dichloromethane and quenched by the addition of saturated sodium bicarbonate solution, and after 15 minutes, the layers were separated, and the aqueous layer was then extracted twice with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude yellow-brown solid, which was then purified by flash chromatography to give 45 mg of **29** as a white solid, in 71% yield. The diacylated compound was formed, but not isolated. M.p. = 175.5-177°C. ¹H NMR (400 MHz, CDCl₃) δ 7.50 (dd, *J* = 6.6, 2.6, 2H), 7.41 – 7.31 (m, 3H), 5.94 (d, *J* = 8.7, 1H), 5.56 (s, 1H), 4.82 (d, *J* = 3.8, 1H), 4.23 (ddd, *J* = 13.0, 9.5, 4.1, 2H), 3.91 (t, *J* = 8.8, 1H), 3.87 – 3.71 (m, 3H), 3.58 (t, *J* = 9.1, 1H), 3.49 (dq, *J* = 9.9, 7.1, 1H), 3.16 (d, *J* = 2.6, 1H), 2.40 (t, *J* = 7.3, 2H), 2.27 (ddd, *J* = 9.6, 6.5, 3.2, 2H), 1.99 (t, *J* = 2.6, 1H), 1.92 – 1.82 (m, 2H), 1.24 (t, *J* = 7.0, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 173.6, 137.1, 129.2, 128.3, 126.3, 101.9, 97.5, 83.4, 82.1, 70.7, 69.3, 68.8, 63.7, 62.4, 53.9, 34.9, 23.9, 17.6, 15.0.

Synthesis of N-Naphthoyl-4,6-O-Benzylidene-Ethyl-α-D-Glucosamine 30. A solution of 42 mg of 4,6-O-benzylidene-ethyl-α-D-glucosamine **14** (0.142 mmol) in 1 mL of anhydrous dichloromethane and 0.1 mL of anhydrous pyridine (1.24 mmol) was cooled to 0°C., 0.025 mL of naphthoyl chloride (0.162 mmol) was then added, and the reaction was stirred at 0°C for 1.5 hours before being warmed to room temperature for 16 hours. ¹H NMR of the crude was obtained, and showed that the starting material **14** had been completely consumed, so the reaction was diluted with dichloromethane and quenched by the addition of saturated sodium

bicarbonate solution, and after fifteen minutes, the layers were separated, and the aqueous layer was extracted twice with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated to give ~65 mg of crude solid, which was then purified by flash chromatography. 55 mg of product **30** was obtained for a yield of 86%. M.p. = 216-217.5°C. ¹H NMR (400 MHz, CDCl₃/CD₃OD) δ 8.27 (d, *J* = 7.6, 1H), 7.91 (d, *J* = 8.2, 1H), 7.85 (d, *J* = 7.2, 1H), 7.65 (d, *J* = 6.8, 1H), 7.56 – 7.40 (m, 7H), 7.37 – 7.30 (m, 3H), 5.57 (s, 1H), 5.12 (d, *J* = 3.7, 1H), 4.26 (dd, *J* = 9.8, 4.4, 1H), 3.98 (t, *J* = 9.6, 2H), 3.91 – 3.84 (m, 1H), 3.84 – 3.75 (m, 2H), 3.62 (t, *J* = 9.2, 1H), 3.59 – 3.50 (m, 1H), 1.23 (t, *J* = 7.1, 3H). ¹³C NMR (101 MHz, CDCl₃/CD₃OD) δ 171.6, 137.8, 134.5, 134.2, 131.3, 130.5, 129.7, 128.9, 128.7, 127.6, 126.9, 126.8, 125.9, 125.7, 125.3, 102.5, 98.2, 82.8, 69.4, 69.3, 64.4, 63.4, 55.5, 15.4.

Synthesis of N-Benzoyl-4,6-O-Benzylidene-Ethyl-α-D-Glucosamine 31. A solution of 50 mg of 4,6-O-benzylidene-ethyl-α-D-glucosamine **14** (0.169 mmol) in 1 mL of anhydrous dichloromethane was cooled to 0°C, and 0.02 mL of benzoyl chloride (0.172 mmol) and 0.07 mL of anhydrous pyridine (0.866 mmol) was then added. The resulting solution was stirred at 0°C for fifteen minutes, at which point the reaction was allowed to warm to ambient temperature. After fifteen hours, the reaction was diluted with dichloromethane, washed with ~70% sodium bicarbonate solution, and the aqueous phase was extracted twice with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product as a yellow-brown solid, which was purified by flash chromatography to give 46 mg of **31** as a white solid for a 68% yield. m.p. = 219-220°C. ¹H NMR (400 MHz, CDCl₃/CD₃OD) δ 7.79 – 7.73 (m, 2H), 7.51 – 7.43 (m, 3H), 7.41 – 7.28 (m, 5H), 6.87 (d, *J* =

8.7, 1H), 5.52 (s, 1H), 4.92 (d, $J = 3.8$, 1H), 4.37 – 4.29 (m, 1H), 4.23 (dd, $J = 10.1$, 4.7, 1H), 3.98 (t, $J = 8.7$, 1H), 3.83 (td, $J = 11.8$, 6.0, 1H), 3.78 – 3.69 (m, 2H), 3.58 (t, $J = 9.3$, 1H), 3.46 (dq, $J = 10.0$, 7.0, 1H), 1.19 (t, $J = 7.1$, 3H). ^{13}C NMR (101 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 168.8, 137.2, 133.9, 131.9, 129.3, 128.7, 128.4, 127.3, 126.4, 102.0, 97.8, 82.2, 69.7, 68.9, 63.9, 62.8, 54.6, 15.1.

References

- 1) Vintiloiu, A.; Leroux, J.-C.; *J. Controlled Release*, 2008, 125, 179-192.
- 2) Komatsu, H.; Matsumoto, S.; Tamaru, S.-I.; Kaneko, K.; Ikeda, M.; Hamachi, I.; *J. Am. Chem. Soc.*, 2009, 131(15), 5580-5585.
- 3) Chen, J.; McNeil, A. J.; *J. Am. Chem. Soc.*, 2008, 130(49), 16496-16497.
- 4) Silva, G. A.; Czeisler, C.; Niece, K. L.; Beniash, E.; Harrington, D. A.; Kessler, J. A.; Stupp, S. I.; *Science*, 2004, 303, 1352-1355.
- 5) Sugiyasu, K.; Fujita, N.; Shinkai, S.; *Angew. Chem. Int. Ed.*, 2004, 43, 1229-1233.
- 6) Hwang, I.; Jeon, W. S.; Kim, H.-J.; Kim, D.; Kim, H.; Selvapalam, N.; Fujita, N.; Shinkai, S.; Kim, K.; *Angew. Chem. Int. Ed.*, 2007, 46, 210-213.
- 7) Zhao, Y.-L.; Stoddart, J. F.; *Langmuir*, 2009, 25(15), 8442-8446.
- 8) Yang, Z.; Liang, G.; Wang, L.; Xu, B.; *J. Am. Chem. Soc.*, 2006, 128, 3038-3043.
- 9) Suzuki, M.; Hanabusa, K.; *Chem. Soc. Rev.*, 2009, 38, 967-975.

- 10) George, M.; Weiss, R. G.; *Acc. Chem. Res.*, **2006**, 39(8), 489-497.
- 11) Luboradzki, R.; Gronwald, O.; Ikeda, M.; Shinkai, S.; Reinholdt, D. N.; *Tetrahedron*, **2000**, 56, 9595-9599.
- 12) Gronwald, O.; Sakurai, K.; Luboradzki, R.; Kimura, T.; Shinkai, S.; *Carbohydr. Res.*, **2001**, 331, 307-318.
- 13) Gronwald, O.; Shinkai, S.; *Chem. Eur. J.*, **2001**, 7(20), 4329-4334.
- 14) Wang, G.; Cheuk, S.; Williams, K.; Sharma, V.; Dakessian, L.; Thorton, Z.; *Carbohydr. Res.*, **2006**, 341, 705-716.
- 15) Cheuk, S.; Stevens, E. D.; Wang, G.; *Carbohydr. Res.*, **2009**, 344, 417-425.
- 16) Wang, G.; Cheuk, S.; Yang, H.; Goyal, N.; Reddy, P. V. N.; Hopkinson, B.; *Langmuir*, **2009**, 25(15), 8696-8705.
- 17) Goyal, N.; Cheuk, S.; Wang, G.; *Tetrahedron*, **2010**, 66, 5962-5971.

Vita

The author was born in Marrerro, Louisiana, in September, 1980. He obtained his Bachelor's Degree (B.S.) in Chemistry from the University of New Orleans in 2005. He joined the Department of Chemistry's graduate program at the University of New Orleans in August 2005, to pursue a doctorate degree in organic chemistry under the guidance of Dr. Guijun Wang, whose research group he joined later that year.