Synthesis, Characterization, and Drug Delivery Applications of Carbohydrate Based Low Molecular Weight Gelators

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SYNTHESIS, CHARACTERIZATION, AND DRUG DELIVERY APPLICATIONS OF CARBOHYDRATE BASED LOW MOLECULAR WEIGHT GELATORS

by

Kristen Elizabeth Bashaw
M.S. December 2015, Old Dominion University
B.S. May 2012, Longwood University

A Dissertation Submitted to the Faculty of Old Dominion University in the Partial Fulfillment of the Requirements for the Degree of

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Kristen Elizabeth Bashaw

Old Dominion University, 2019

Director: Dr. Guijun Wang

The main aim of the research focuses on the study of self-assembly and gelation by several classes of simple sugar derivatives and the potential applications of them as drug delivery vehicles. Since carbohydrates are naturally abundant renewable resources and are therefore readily available and many of them are inexpensive compared to other raw materials. They are also biocompatible which makes them suitable for a wide variety of applications. Combining the use of carbohydrates with low molecular weight gelators (LMWGs) we can introduce a new class of soft materials that are able to self-assemble into spheres, fibers, sheets, and micelles in a wide variety of solvents. The self-assembly occurs through non-covalent forces such as hydrogen bonding, π-π stacking, and van der Waals forces. The entrapment of the solvent in the fibrous network results in a gel formation. There are many applications for these soft materials such as drug delivery, environmental clean-up, and even for reaction catalysis. Previously, our lab has reported that several series of 4,6-O-benzylidene protected D-glucose and N-acetyl-D-glucosamine are effective molecular gelators. In order to probe the effect whether the benzylidene functional group is a structural requirement for gelation, in this research, the phenyl group was replaced with aliphatic functional group. Therefore, a series of 4,6-O-alkylidene protected N-acetyl-D-glucosamine and α-D-methyl glucoside were synthesized and their gelation properties were studied. Depending on the structures of these derivatives, effective LMWGs in aqueous and organic solvents were obtained. The effective hydrogelators obtained from this study were used as drug delivery carriers for naproxen etc. The release profiles of naproxen from the gel-drug matrix were studied carefully using UV-vis spectroscopy. Different methods of preparing the gel with the model drugs were also studied and compared. Several covalently linked drug-gelator conjugates were synthesized and analyzed in the attempt of designing prodrug-based drug delivery systems.
This dissertation is dedicated to:

My husband, Robert Burns

My grandparents, Frank and Bonnie and Marie and Lloyd

My Mom, Tracey

My dad, Thomas

My sister, Sarah
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NOMENCLATURE

LWMGs low molecular weight gelators

Ac acetyl

Ar aryl

PEG polyethylene glycol

NSAID nonsteroidal anti-inflammatory drugs

TTF tetrathiafulvalene

DCM dichloromethane

DI deionized

DMF N, N-dimethylformamide

DMSO dimethyl sulfoxide

EG ethylene glycol

EtOH ethanol

HCl hydrochloric acid

NaOH sodium hydroxide

PTSA p-toluenesulfonic acid

TEA trimethylamine

THF tetrahydrofuran

Ts toluene sulfonyl
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CHAPTER 1. BACKGROUND AND LITERATURE REVIEW

1.1 INTRODUCTION

The study of gels goes all the way back to 1926 when D. Jordan Lloyd wrote “The colloidal condition, the ‘gel’, is one which is easier to recognize than to define…”,¹ this means that many gels are found through serendipity not through a scientific approach, therefore from this time forward many researchers decided to study the structure analysis in relationship to the gelation ability.² Gels have many properties.³ Gels can be solid like where they can sustain shear stress, returning to original form when relieved.⁴ Also, gels can undergo liquid to solid transitions to form the gels, they appear solid but are composed of mostly liquids at the micro scale.⁵ These multicomponent systems have different dynamics on different time scales to make gels heterogeneous.⁶ These gels can be defined as chemical or physical gels.⁷ Chemical gels are irreversible and in previous decades were polymers either reacting monomers or cross-linked polymers.⁸ There are two types of gels chemical gels and physical gels.⁹ Chemical gels are chemically cross-linked where as physical gels are reversible physical cross links.¹⁰ These gels are reversible when an external stimulus is applied such as temperature, pH, or change in salt concentration.¹¹ From here the gelation can occur in organic solvents, water, or aqueous mixtures.² Those gels that form in organic solvents are called organogels and those that gelate in water are termed hydrogels.¹² Organogels and hydrogels are on the rise to use as smart materials in environmental for pollutant removal and biological applications for wound dressing, drug reservoirs and even temporary scaffolds for cells.¹² Organo or hydrogels are prepared by warming the gelator in an organic liquid or water until the solid dissolves, and then cooling the solution to a temperature where there is no more liquid flow.¹³ The material that is obtained is gel like depending on the properties.¹¹ The 3D network that is formed immobilizes the liquid

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tension. The focus of this review will be on the use of gels as biological materials from drug delivery to environmental remediation. The research done in this area for many years focuses on polymeric networks or swollen gels. The downside to these gels are that when stress is applied they begin to degrade and are unable to reform, therefore localized delivery of drugs is impossible. In the previous decades’ polymer gels were extensively studied but the upcoming research is using low molecular weight gelators (LMWGs).

1.2 POLYMER GELS
Polymer gels are solid liquid co-systems in which a matrix is formed chemically or physically which is cross-linked in order to form a 3D network which is swollen by the uptake of liquids. The degree of swelling depends on the nature of the polymer and the density of the cross-linking. Hydrogels are a cross-linked network of hydrophilic polymers, which can swell by absorbing water or shrink when water is released, like when it encounters aqueous solutions, such as biological fluids. Polymers from natural, synthetic, or semisynthetic sources, containing hydroxyl, amine, amide, ether, carboxylate, and sulfonate as functional groups in their side chains are used for synthesizing hydrogels for delivery of both hydrophilic and hydrophobic drug macromolecules. These gels are very attractive to many applications but we are interested in low molecular weight gelators which will be described further.

1.3 LOW MOLECULAR WEIGHT GELS
LMWGs often self-assemble through non-covalent interactions, such as π-π interactions, van der Waals forces, and hydrogen bonding. The discussion of these forces, examples of the gels and their applications are to be discussed next. The classes of LWMGs span from fatty acid to amino
acids, steroids, saccharides, and even some organometallic gelators have been studied, examples of these structures can be shown in Figure 1.\textsuperscript{13,23,24}

After looking at Figure 1, one may notice that there is a wide structure diversity in the structure of each gelating molecule. During the last decade, there are many examples of these organo and hydrogelators.

Fig. 1 Classes of LMWGs. a. fatty acid derivative, b. STNH, a steroid derivative, c. DDOA, anthyrl derivative, d. organometallic derivative, copper complex

The structure of the gelation is that the single molecule first forms fibers and then these fibers form a fibrous network.\textsuperscript{25} These entangled networks are completely reversible via a gelation to solution mechanism, but you must have the gelator and solvent balance which is why there is such a structure diversity in these molecules.\textsuperscript{24} As previously discussed the two different types of gels are polymer gels and LMWGs the gelation of LMWGs is by molecular crosslinking formed by entanglement, but the polymers are cross linked but can be permanent chemical bonds or
entanglements. To characterize these gels, you can use a wide variety of techniques such as infrared spectroscopy or circular dichroism, and oncoming microscopic techniques such as electron microscopy or small angle scattering which will show whether these morphologies are cylinders or hollow tubes. Rheology is also an option to study the mechanical properties to ensure that the gel is a viscoelastic solid like material. The examples of those systems in the literature and their structure will be discussed next.

1.3.1 PEPTIDE BASED LMWGS

Peptides are used as low molecular weight gelators to form these hydrogels due to their inherent biocompatibility and biodegradability. Incorporating the amino acids into the materials facilitates the possibility of bio-functionality, biodegradability, and biocompatibility into these small molecule gels. The main application of these gels is for wound healing, sustained release of drugs and biomolecules, cell culture media, tissue engineering, and pollutant removal. Figure 2 shows examples of amino acid derivatives used as hydrogelators.

![Peptide gel structural example](image-url)

Fig. 2 Peptide gel structural example
1.3.2 CARBOHYDRATE BASED LMWGS

Sugars can be used as energy sources by various living organisms. Therefore, as a substrate, glucose is fundamental in the metabolism of various life forms. Other sugars also occur in nature. These include deoxyribose in DNA, ribose in RNA, starch in plants, and cellulose in the cell walls of plants and algae, and glycogen in animals. Chemists try to follow the same pathway in the construction of biological pathways. The main driving force of self-assembly of gelators are non-covalent interactions. Based on the nature of the driving force for the molecular aggregation, the gelator molecules defined by certain functionalities may be classified into the following categories. Primarily, the amides and ureas can form self-complementary hydrogen bonding interactions. Next, the carbohydrates contain multiple hydroxyl groups and display broad hydrogen bonding interactions. Third, nucleobases used in biological systems utilize hydrogen bonding and π-π stacking interactions. Last, the aliphatic hydrocarbons, use a significant amount of van der Waals forces and solvophobic interactions. Among the various non-covalent interactions, intermolecular and intramolecular hydrogen bonding interactions have been utilized in the production of complex organized systems due to the reversibility, specificity, directionality and cooperativity of such interactions. Hydrogen bond forming gelators generally include amides, commonly using amino acids, ureas, nucleobases and carbohydrates. Carbohydrates are far superior to amides, urea, and nucleobases in hydrogen bonding mediated self-assembly processes because of their significantly greater number of hydrogen bonding sites. Initially, the investigation of hydrogen bond forming gelators was limited to a few amino acid and urea derivatives. In recent scientific advances, the use of bioactive small molecules is more common, owing to their biomedical applications in three-dimensional cell cultures, biomolecular screening, wound healing, and drug delivery. The self-assembly of sugar derived
LMWGs has received attention for various reasons. Sugar-derived LMWGs are often biodegradable, non-toxic and eco-friendly, which makes them ideal building blocks for the regeneration of tissues and organs. Carbohydrate–protein interactions are extremely important in numerous biological phenomena, such as blood coagulation, immune response, viral infection, inflammation, embryogenesis and inter-cellular signal transfer. Furthermore, the design and synthesis of carbohydrate-derived systems that imitate the organization at the cell surface and is also a fertile approach to investigate and intervene in various carbohydrate mediated interactions. Yamanaka et al. reported a pale-yellow transparent hydrogel derived from a carbohydrate amphiphiles. Since the surface of the resultant fibers was enriched with densely packed glucosides, this hydrogel exhibited selective responsiveness to lectins such as concanavalin A (ConA). Dr. Wang’s lab is a main contributor to the carbohydrate gelator field of study. Studying the effects of monosaccharides on gelation and their derivatives can be quite challenging as there is no incite on structural necessities with these gelators. Beginning in 2006, Wang et al. were able to show the gelation properties of the structures shown in Figure 3. If you look at the structures you can see that there were monomers, dimers, carbamates, esters, and the like. After using these compounds to predict structural necessities for gelators it was noticed that the molecules that contained nitrogen moieties were potentially better gelators, since this is the case the next series instead of using glucose, it was of interest to use N-acetyl-D-glucosamine.
After synthesizing the glucose derivatives, the N-acetyl-D-glucosamine derivatives were extensively studied with incorporation of triazole, diacetylene, and even disaccharides.49-55

1.4 STIMULI RESPONSIVE GELATORS

Stimuli responsive gelators will be discussed in detail due to their rising importance. These gels that have been previously discussed are capable to undergo external stimuli due to their ability to self-assemble. The external stimuli can be temperature, light, and pH.56-58

1.4.1 TEMPERATURE RESPONSIVE GELATORS

Temperature-sensitive hydrogels have been studied most extensively and their unique applications have been reviewed in many details.59 During a step wise temperature change a triggered release profile can be obtain to enhance a thermosensitive hydrogel system. There are a wide range of molecular structures used for these studies however, polymers are extensively used.60 Yong Qiu et. al. synthesized a NIPAAm gels where a hydrophobic co-monomer BMA was introduced into to increase their mechanical strength.61 The system was able to release drug molecules from the gel matrix. The matrix was on at lower temperature and off at higher temperatures. This on-off switch was explained by the formation of a skin like barrier. The skin like barrier is a dense, less permeable surface layer of gel. The formation of this barrier was due to a sudden temperature
change. Which was due to the ability of the gel surface to collapse faster than that of the gel interior. The variation in the length of the methacrylate alky sidechain attributed to the surface shrinking process. Also, the results were able to suggest that the entrapped drug in the polymeric matrices diffused from the inside to the surface even when no drug release was visible. The hydrogels that have temperature controllability can also be placed inside a capsule that has holes or openings. The drug release rate was found to be proportional to the rate of squeezing from the capsule system when the drug loaded polymer was used. When placing the temperature-sensitive hydrogels on a rigid surface such as a rigid membrane it can be secured. The tunability of temperature release drug delivery systems is quite phenomenal however the variation in temperature in the body is very small compared to other stimuli. In addition to temperature, hydrogels can be made to respond to other stimuli, such as pH or light. Not only are thermoresponsive gelators used in drug delivery but also environmental remediation. Figure 4 shows the structure of 4, 4’-dihydroxybiphenyl linked polymers which are used by Tang et. al. for the study of thermoresponsive gelators. The gels exhibited a resiliency through swelling and deswelling cycles, with complete reversibility.
1.4.2 pH RESPONSIVE GELATORS

The major part of the study done was using pH responsive gelators to be used as drug delivery system. There are two types of pH responsive systems. The first type is through protonation and deprotonation is shown in Figure 5.\textsuperscript{34} If the structure contains an acid or base then with addition of acid or base it can be positively charged from protonation, negatively charged from deprotonation, or neutral. Looking at Figure 5, the top figure shows a carboxylic acid at low pH is neutral but upon addition of base (OH\textsuperscript{-}), the neutral molecule becomes deprotonated, on the other hand the lower portion of the figure has a base, and at basic pH the molecule is neutral, but upon the addition of acid (H\textsuperscript{+}) the molecule becomes protonated.\textsuperscript{67} During the protonation/deprotonation process the gel can be transformed from gel to solution and back to gel upon addition.
of acid or base. The second class of pH responsive gelators are to incorporate pH labile functional
groups in the structure of the molecules, so instead of protonation and deprotonation the molecule
will break apart into a different class of functional groups, as seen in Table 1.⁶⁸

![Chemical Structures](image)

**Fig. 5 First class of pH responsive systems by protonation and deprotonation**

Most functional groups cannot withstand mildly acidic conditions. Therefore, the incorporation of
these molecules into the gelation structure can assisting in their trigger ability in delivery
mechanisms, which is shown in Table 1.
Table 1 Second class of pH responsive systems by cleavage of acid labile groups

<table>
<thead>
<tr>
<th>Name</th>
<th>Reaction Under Acidic Conditions</th>
<th>Cleavable pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ester</td>
<td><img src="image1" alt="Ester Reaction" /></td>
<td>6-8</td>
</tr>
<tr>
<td>Hydrazone</td>
<td><img src="image2" alt="Hydrazone Reaction" /></td>
<td>5-6</td>
</tr>
<tr>
<td>Carboxy dimethyl maleic amide</td>
<td><img src="image3" alt="Carboxy Dimethyl Maleic Amide" /></td>
<td>5.8-6.6</td>
</tr>
<tr>
<td>Orthoester</td>
<td><img src="image4" alt="Orthoester Reaction" /></td>
<td>5-6</td>
</tr>
<tr>
<td>Imine</td>
<td><img src="image5" alt="Imine Reaction" /></td>
<td>5-7</td>
</tr>
<tr>
<td>β-thiopropionate</td>
<td><img src="image6" alt="β-Thiopropionate Reaction" /></td>
<td>3-5</td>
</tr>
<tr>
<td>Vinylether</td>
<td><img src="image7" alt="Vinylether Reaction" /></td>
<td>4.5-5.5</td>
</tr>
<tr>
<td>Acetal/ketal</td>
<td><img src="image8" alt="Acetal/Ketal Reaction" /></td>
<td>5.0-6.5</td>
</tr>
</tbody>
</table>

Certain functional groups are labile at various pH in order to make this drug delivery system successful it is important to know the pH of the certain body area of each infection, for example the stomach has a pH of 1-3 so you want to incorporate a functional group that has a cleavable pH at or around the same pH as the stomach. In theory if you can obtain this relationship the gel will break down at the pH of the stomach but not at the pH of other parts of the body so the drug would be delivered just to the stomach. A disease that this would be useful for would be diabetes, since...
insulin must be injected throughout the day when eating it would be beneficial for a patient to inject the insulin once per day and it have a triggered release.\textsuperscript{69} To show this phenomenon research examples will be discussed.\textsuperscript{70} Polymers have been extensively studied for their self-assembling properties in order to function as supramolecular gels.\textsuperscript{71,72} Supramolecular polymers can be random and entangled coils with the mechanical properties of plastics and elastomers.\textsuperscript{73} Polymers also have a great capacity for recycling, and self-healing due to their reversible transitions.\textsuperscript{74,75} At the other extreme, supramolecular polymers can be formed by self-assembly among designed subunits to yield shaped and highly ordered fibers.\textsuperscript{76} They can resemble the ordered and dynamic one-dimensional supramolecular assemblies of the cell cytoskeleton and possess useful biological functions.\textsuperscript{65} As previously mentioned, polymers were used prior to the use of LMWGs, to extensively study controlled release systems. In 2014, Singh et. al. introduced an injectable external stimuli responsive biodegradable block copolymer hydrogel for the controlled release of drugs\textsuperscript{77}. Singh and her coworkers synthesized a pH and temperature sensitive negatively charged pentablock copolymer composed of acidic sulfamethazine oligomers (OSMs), poly(\(\varepsilon\)-caprolactone-co-lactide) (PCLA), and polyethylene glycol (PEG), the copolymer is shown in Figure 6, with a formula of OSM-PCLA-PEG-PCLA-OSMs. This copolymer was able to form gels in acidic solution and not in basic solutions which would help with drug delivery in various parts of the body.\textsuperscript{78}
The colon drug delivery systems have been studied extensively in the past decade. The colon was of interest because it is considered a less hostile environment, which means it is a suitable organ for absorption of drugs because of the lack of digestive enzymes when compared to the stomach and small intestines. It has been known that the colon can digest low molecular weight compounds to treat diseases such as ulcerative colitis, diarrhea, and colon cancer. With the design of the colon and need for a drug delivery system one can turn to a system that has a high swelling ability. If you incorporate carboxylic acid groups to the structure of the molecule, these molecules will be compact at low pH, but as the pH increases the gel will have swelling abilities. After the swelling if an azo bond is incorporated in the structure will break, but it will only be broken in the colon. The colon has an enzyme, azoreductase that can degrade the azo bond therefore releasing the drug molecule being trapped in the gel.\textsuperscript{34} Due to the variation of pH in the body, the study of pH sensitive drug delivery systems is of increasing importance.

1.4.3 REDUCTION-OXIDATION RESPONSIVE GELATORS

Reduction-oxidation responsive gels are those gels that are triggered on and off during the reductions and oxidation process. Zhang and Zhu et al. subtly designed a multi-stimulus responsive
organogelator containing electroactive tetrathiafulvalene (TTF) and photo responsive azobenzene groups, which are shown in figure 7.79

![Chemical structure of TTF and TTF²⁺ with oxidation-reduction reactions]

**Fig. 7 Oxidation reduction of tetrathiafulvalene (TTF)**

This organogel responded not only to thermal stimuli but also to redox reactions and light irradiation. The gel–sol transition for this organogel could be reversibly changed by either chemical or electrochemical oxidation–reduction reactions of the TTF group. The oxidation-reduction has been achieved by reductively degradable micelles from self-assembled amphiphilic copolymers containing disulfide links within the hydrophobic backbone or bearing a single disulfide bond at the connection of the two polymer blocks.

### 1.4.4 PHOTO RESPONSIVE GELATORS

The use of UV light as a treatment mechanism has been of rising importance for cancer therapy; however, the harshness of the UV light for the human body creates many side effects. Therefore, if you were able to introduce a photo triggered system where you can implant the drug and carrier into the tumor itself and then pulse light to trigger the gel matrix to release the drug, then the side effects could be weakened and there would be an effective system. Many variations in the structure...
can attribute to a photo responsive molecule. Figure 8 below of \( trans \)-\( C_n \)-Chol shows an example of a photo responsive gelator. Cholesterol has been studied as an effective gelator which is incorporated in \( trans \)-\( C_n \)-Chol. Also incorporated in the molecule is an azo bond which is the photo switch moiety in the molecule. Finally, tetraphenyl ethylene (TPE) was incorporated because it contains aggregation induced emission properties which assists with photodynamic therapy.

The goals of using gelators as photo triggered drug delivery systems will continue to be investigated for the rising importance in cancer therapy.59

![trans-C_n-Chol](image)

Fig. 8 Photoresponsive cholesterol gelator

### 1.5 APPLICATIONS OF GELATORS

LMWG\( s\) and the resulting gels are used for a wide range of applications. These applications will be discussed in detail as follows.

#### 1.5.1 DRUG DELIVERY APPLICATIONS

Both polymers and low molecular weight gelators have been utilized as effective drug delivery systems. Cardonol, a naturally occurring product from cashew nutshell liquid, was used as the starting material to synthesize coumarin-tris amphiphiles. These derivatives formed through a self-
assembling mechanism. These hydrogels are then used in drug delivery applications. These gels are of interest to my research because of their pH induced ability to go through a gelation to solution transition. Figure 9 below shows the coumarin derivatives that were synthesized by Lalitha et al.  

![ coumarin derivatives ]

**A1.** $R=H$

<table>
<thead>
<tr>
<th>Compound</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2, $R=\text{A}$</td>
<td>15:1 50%</td>
</tr>
<tr>
<td>$\text{A}$</td>
<td>15:2 16%</td>
</tr>
<tr>
<td></td>
<td>15:3 29%</td>
</tr>
<tr>
<td></td>
<td>15:0 5%</td>
</tr>
</tbody>
</table>

**A3, $R=\text{A}$**

<table>
<thead>
<tr>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15:0 100%</td>
</tr>
</tbody>
</table>

Fig. 9 Coumarin derivatives

After synthesizing these derivatives and completing full characterization via NMR and mass spectrometry, the gelation properties were studied. The gelation was studied in both hydrophilic and hydrophobic solvents. Compound **A3** showed excellent gelation in DMSO-water (1-2) mixture with heating and sonication. The minimum gelation concentration was 0.8% (wt/v), which was stable at room temperature even for lengths as long as ten months. As mentioned previously it is very important to have an exact balance of hydrophobic groups and hydrophilic groups on the molecule so that the molecule will have good self-assembly in order to have gelation abilities
similar to A3. A1 and A2 were unable to perform gels due to the lack of hydrophobic groups in A1 and the kink in the structure of A2. After the study of the gelation properties, it was important to study the effect of pH on the gelation. A pH 4 buffer was added to the gel. With this addition, there is a slow conversion from the gel to the solution. This is said to be due to the disruption of the hydrogen bonding enabled by the amide group. Although this transition is visible through the naked eye, the morphological network must be explained using microscopy. The reason behind testing the gelation ability at various pH is to be able to help with the encapsulation of curcumin (drug, Figure 10) into the hydrophobic portion of the gelator molecule. In fact, these composite gels (gelator + drug) were reversible via pH and temperature. The release of the model drug is occurring via disassembly of the gel matrix, and this can be monitored via ultraviolet-visible (UV-Vis) spectroscopy. The researchers explained that there was no absorbance at 0 minutes but as time increased the absorbance of curcumin became visible, and the solution became yellow in color. Thus showing the drug release took a time course of up to 55 hours, this would be good for certain diseases, or infections that need a lot of medication over a long period of time.

![Curcumin](image)

**Fig. 10 Curcumin**

Due to the rising importance of carbohydrates as drug delivery vehicles, the next examples show them in use. Using a synthesized methylated N-acetyl galctosamine (Figure 11, 2) as the gelator was discussed previous for thermally reversible gel, therefore, to become a pH-dependent hydrogel
a carboxylic acid moiety should be introduced (Figure 11, 3). The self-assembled network can transition from gels to solutions in neutral pH, but under acidic pH the gels can have a volume phase transition.

![Chemical structures](image)

Fig. 11 N-acetyl galactosamine (2) with introduction of carboxylic acid derivative (3)

The major key to visualizing this phase transition is via microscopy. The images can qualitatively tell you the swelling and shrinkage of the gel. As mentioned, that the originally synthesized gelator was not pH labile prior to the addition of carboxylic acid, therefore it was important for the researchers to study the ratio of carboxylic acid moiety to the original gelator. Zhou et al. concluded that there should be a 1:1 molar ratio of the hydrogel with the carboxylic acid to form the best swelling and shrinking ability under various pH levels. Another aspect of this dual component hydrogel is the ability for it to cycle through the swelling and shrinking, this gel could go through the cycle 6 times, which shows this is not happening through decomposition but
through a reversible physical chemical property. The introduction of the acid groups could produce a pH induced volume changing gel with controlled drug release properties.\textsuperscript{84} The pH sensitivity of the gel matrix was studied by many researchers where the findings were able to show effective drug delivery. Not only can these systems be pH sensitive some of the systems can be sensitive to glucose for instance. Zhou \textit{et. al.} was able to incorporate both phenomenon into one system. The system they were able to synthesize is both pH and glucose sensitive.\textsuperscript{15,19} Their system is based on a phenylboronic acid (PBA), and is a small molecular mass gelator (Figure 12).\textsuperscript{85} Prior to this study, in 2012, Li \textit{et. al.} was able to incorporate boronate esters into their already synthesized polyethylene glycol polymer structure. They determined that the addition of the boronate esters were chosen because of their ability to be stable at physiologically pH values, even when carbohydrates that generally compete are present, and the self-assembly results in the micelles.\textsuperscript{57,86}

![Fig. 12 Phenylboronic acid LMWG used for glucose and pH sensitive drug delivery system](image)

The gelation of the PBA gelator is shown in Table 2.\textsuperscript{87} This table shows that the gel was mainly formed in nonpolar organic solvents. The glucose binding was able to be shown via UV-Vis spectroscopy, since the formation of the PBA-glucose complex will dissolve the gel the absorbance will change based on the amount of gel that has dissolved. After the study of the glucose sensitivity of the PBA-glucose complex, the pH sensitivity should be studied due to the acid moiety in PBA.
<table>
<thead>
<tr>
<th>Solvent</th>
<th>MGC at 25°C (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclohexane</td>
<td>G (24.4)</td>
</tr>
<tr>
<td>Toluene</td>
<td>G (30.0)</td>
</tr>
<tr>
<td>Xylene</td>
<td>G (30.7)</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>G (100.2)</td>
</tr>
<tr>
<td>Chloroform</td>
<td>G (100.8)</td>
</tr>
<tr>
<td>Tetrachloromethane</td>
<td>G (24.9)</td>
</tr>
<tr>
<td>Diethyl ether</td>
<td>P</td>
</tr>
<tr>
<td>Ethanol</td>
<td>S</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>S</td>
</tr>
<tr>
<td>Isopropanol</td>
<td>S</td>
</tr>
<tr>
<td>Acetic ether</td>
<td>S</td>
</tr>
<tr>
<td>Acetone</td>
<td>S</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>S</td>
</tr>
<tr>
<td>Dimethyl Sulfoxide</td>
<td>S</td>
</tr>
<tr>
<td>Water</td>
<td>I</td>
</tr>
</tbody>
</table>

MGC- maximum gelation concentration (mg/mL), G (gel), P (precipitate), S (soluble), and I (insoluble)
Zhou et. al. used UV-Vis spectroscopy to study the effect of pH on the system. At pH 11 and 13 the PBA-glucose systems show the greatest sensitivity, meaning the gel had trouble forming, on the other hand from pH 5-9 the spectra had little deviation. This means that the gel would be stable through this transition, this may be attributed to the pKa of the gelator. The researchers were able to create a reversible system that can be reused which is very much convenient for diabetic patients and the insulin delivery. Peptide based hydrogels have also been studied by Lange et. al. The structure pictured in Figure 13 shows a thiol group attached to the molecule. These thiol groups can participate in disulfide bonding. These bonds are incorporated into structures because in nature cysteine residues contain the thiol groups, these amino acids are rare so the ability for these to form disulfide bonds are even rarer. If you break the disulfide bonds then you are denaturing the protein, despite their strength they can be broken. Figure 13 shows a tripeptide Fmoc-\textit{l}-Cys(\textit{Acm})-\textit{l}-His-\textit{l}-Cys and also a tripeptide with the structure Fmoc-\textit{l}-Cys-\textit{l}-His-\textit{l}-Cys. One may notice that Fmoc (N-flouroenyl-9-methoxycarbonyl) is used in the structures of the tripeptides, this is introduced in order to help with self-assembly into $\pi$-$\pi$ interlocked $\beta$ sheets. The researchers discovered previously synthesized compound 4, and it was found by serendipity to form a hydrogel. The researchers were able to discover these molecules were pH responsive and fully able to be functionalized at the thiol groups, which were able to form a drug delivery system with model drugs.
In 2013, Kim et al. synthesized a novel pH-responsive assembly (PEG-lipid: DOPE liposomes), shown in Figure 14, which were said to contain a tunable and bifunctional phenyl-substituted vinyl ether (PIVE) cross-linker. The PIVE linkage was introduced to the structure in order to be hydrolyzed under acidic conditions. The researchers extensively studied the hydrolysis of these linkers at pH 4.2, 5.4, and 7.4, along with the pH distribution the study was conducted to determine if there was an effect based on the electron donating or electron withdrawing groups on the phenyl ring in the linker. The drug release is done by the destabilization of the acid labile linkers. The results showed that the dePEGylation was dependent on the acidity and correlated with the PIVE proton affinity of the phenyl group. Using PIVE, a new class of acid-sensitive, tunable, and bifunctional cross linkers, a novel pH-sensitive gene delivery system was constructed. PIVEs allow for using the intrinsic electronic effects on phenyl substituents of vinyl ethers and thus offer the
control over the pH-sensitivity, which can be used for drug and gene delivery purposes. It was found that these linkers were degraded under acidic conditions, while they were stable at pH 7.4. The rate of acid-catalyzed hydrolysis could be controlled simply by changing electron donating/withdrawing groups of the phenyl ring. This makes it possible to design novel pH-responsive delivery carriers based on the concept of functional group selection. Here, the acid-sensitive PEG-lipid conjugates were used to create gene delivery vectors, which can be triggered by acid-catalyzed dePEGylation. The observed content release using acid-triggered dePEGylation correlated well with the acid-catalyzed degradation of PIVE. This result confirmed that the rate of acid-catalyzed dePEGylation could be adjusted by controlling the hydrolysis of the cross linker.

In vitro transfection efficiency of mPEGPIVE-lipid: DOPE liposomes/PS/DNA complexes was influenced by introducing different functional groups onto the phenyl ring. The complex with mPEG-(4-MeO-PIVE)-DOG: DOPE loaded with PS/DNA was higher in transfection efficiency in HEK 293 and COS-7 cells but lower in cytotoxicity than the positive control, PEI. These results suggest that the mPEG-PIVE-lipid: DOPE liposomes can be a promising non-viral vehicle for the drug and gene deliveries that require more precisely controllable acid-triggering.80
1.5.2 ENVIRONMENTAL APPLICATIONS

The environmental impacts of the gels that have been previously discussed are of great importance due to water being a resource that is needed for daily survival. Many of the previous examples that have been described are for biomedical applications, although these materials are very useful for those applications, it is important to discuss other uses for these materials. The soft materials made by self-assembling low molecular weight building blocks are able to immobilize oil spills, remove dyes, extract heavy metals or toxic anions, and even detect or remove chemical weapons. These
examples of environmental uses for the gels will be discussed.\textsuperscript{96} Due to the cost effectiveness of carbohydrates and when functionalized their inability to dissolve in water they are good candidates for oil spills in larger bodies of water. Figure 15 below shows an example of a synthesized N-Acetyl glucosamine derivative. Narayana \textit{et. al.} synthesized this derivative in hopes for a gelator useful for environmental remediation. The researchers discovered the gelator was effective in oils such as diesel and petrol. Being that these gels were formed in oil it can be used to remove oil with leaving the water phase unaffected.\textsuperscript{91}

\begin{center}
\begin{tikzpicture}
\node at (0,0) [label=right:OH, draw, circle] (a) {OH};
\node at (1,-0.5) [label=right:BnO, draw, circle] (b) {BnO};
\node at (0.5,-1) [label=right:BnO, draw, circle] (c) {BnO};
\node at (0.5,-1.5) [label=right:AcHN, draw, circle] (d) {AcHN};
\node at (1,-2) [label=right:OMe, draw, circle] (e) {OMe};
\end{tikzpicture}
\end{center}

Fig. 15 N-acetyl glucosamine derivative used as a LMWG

Another example of using N-acetyl glucosamine was researched by Mukherjee \textit{et. al.} The researchers effectively reported two new carbohydrate derived efficient organogelators. These are very cost effective and synthesized in one step. Their structures are depicted in Figure 16 below. The compounds had gelation abilities in various oils and oil: water mixtures which would be an ideal system for environmental remediation. An effective quality of this system is that it can be recycled and reused which in turn makes it more cost effective for large spills. Based on these examples, gelators have an exciting prospect in oil spill recovery.\textsuperscript{97}
1.5.3 ENZYME TRIGGERED GELATION APPLICATIONS

The process of gelation can be described using external stimuli, therefore in the recent decade researchers have been studying the ability for self-assembly and gelation to be enzymatically controlled. The ability to functionalize the hydrogels to obtain the balance between hydrophobicity and hydrophilicity would be properly balanced. Difficulties arise when creating drug delivery systems, due to enzymatic instability. In presence of enzymes many gelators do not have the strength of stability to withstand the enzymatic degradation. Therefore, it would be pertinent to synthesize a gelator molecule that can withstand the enzymes that are in the forefront of drug delivery. McDougall et. al. synthesized the dipeptide in Figure 17 below. This dipeptide withstood the presence of enzymes which shows that the synthesized gelators could potentially be used in an effective drug delivery system.
1.6 MY RESEARCH RATIONALE

The research discussed in this dissertation is developed based on the previous work in the lab of Dr. Guijun Wang. Carbohydrate low molecular weight gelators have been extensively studied in our lab for the past two decades. Both monosaccharides and disaccharides have been explored as potential gelators. Effective gelators have been exposed to various external stimuli to study their effect. Many of the effective gelators have been explored for drug delivery and dye removal. The effective gelators are shown in Figure 18 below.

![Structures of several classes of sugar derived LMWGs](image)

Fig. 18 Structures of several classes of sugar derived LMWGs

Our group has been working on the rational design of carbohydrate based low molecular weight gelators. Several monosaccharide derivatives have been studied and the general structures for effective LMWGs are shown in Figure 19. These include the 2-O-ester derivatives 1, 2-O-linked carbamate derivatives 2, amide derivatives 3, 3-O-ester derivatives 4, and 4,6-O-(2-phenylethylidene)-functionalized D-glucosamine derivatives 5. These various classes of carbohydrate based low molecular weight gelators expressed gelation ability in various solvents, both organic and aqueous mixtures. Previous research by the Wang group showed that D-glucose can be used as the starting material for the construction of effective low molecular weight gelators. However, a systematic study on the influence of 4,6 acetal protective functional group to gelation properties have not be carried out yet. Therefore, we synthesized and analyzed a series of
alkylidene acetal and arylidene acetal derivatives of methyl α-D-glucopyranoside. The synthesis and characterizations of these derivatives are discussed. In many different monosaccharide derivatives, the benzylidene acetal functional group seemed to play an important role in gelation and molecular self-assembly. The phenyl acetaldehyde derivatives 5 also showed effective gelation, however, these compounds also contain a phenyl ring in the 4,6-substituents.49

Figure 19 shows compounds which were able to effectively form co-gel systems with drug molecules. External stimuli were applied to these co-gel systems to study their drug delivery properties.50,100

![Fig. 19 Various carbohydrate based LMWGs synthesized by Wang Lab](image)

Goyal et. al synthesized a series of pH labile gelators which showed under acidic conditions it can be used as an effective drug delivery system. If a pH labile functional group is introduced into the gelator structure, the drug will effectively release from the gel matrix at a faster rate.100 To further investigate the functional group effect on the drug delivery systems Chen et. al synthesized a series of triazole derivatives on the first position of the sugar ring. These derivatives formed gels in a variety of solvents majority of the solvents were aqueous mixtures. The drug delivery profile was studied with Naproxen which was fully released from the gel matrix at 24 hours. The final series was a series which studied the third position of the sugar ring.53 Also, Chen et. al. synthesized a
series of 3-O-esters of N-acetyl-D-glucosamine derivatives. The drug delivery profile was studied using naproxen as the drug molecule. This drug delivery system was able to release 75% of the drug at 48 hours. The systems studied in our lab could effectively prove to release drug molecules from the self-assembled matrix to solution. Encapsulation of the drug molecules in the gel itself using some form of external stimuli as the source for release has been studied extensively in our lab, but covalently attaching a drug molecule to the gelator and using chemical reactions to release the drug has not been investigated in detail.

In order to probe the effective of the benzylidene acetal functional group and the structure and gelation correlation of sugar derivatives, in this study, we replaced the phenyl functional group with alkyl groups. We studied the effect of introducing the 4,6 position with alkyl groups ranging from 6 carbons to 10 carbons in chain length. Since the gelation process is often found via serendipity, we used the alkyl chain in hopes to find the perfect balance between hydrophobic and hydrophilic functional groups in order to create strong and effective hydrogels. These are the main goals for the studies in chapters 2 and 3. And for chapter 4, a series of covalently linked drug-gelator conjugates were synthesized and studied, these can be considered as prodrug-based systems.
CHAPTER 2. SYNTHESIS AND CHARACTERIZATION OF 4,6-O-ACETAL PROTECTED α-D-METHYL GLUCOSIDE LOW MOLECULAR WEIGHT GELATORS

2.1 ABSTRACT

The use of low molecular gelators as smart materials have been under extensive investigation. They can act as drug delivery mechanism which is why the study of the structural arrangement is important. The introduction of various functional groups is needed in order to have the most affective drug delivery system. The use of carbohydrates gives striking interest due to their bioavailability, cost effectiveness, and ability to functionalize. Various 4,6-benzylidene acetal protected α-methyl 2-D-glucosamine derivatives have been uncovered and proven be efficient low-molecular-weight gelators. During the structural analysis of the α-methyl 2-D-glucosamine alkyl protected derivatives it was noticed to not have the hydrophobic and hydrophilic balance in order to produce effective gelators. In comparison to the alkyl derivatives, aromatic derivatives were synthesized and proved to be significantly better gelators. However, in the future studies we will use alkyl protected N-acetyl-D-glucosamine derivatives to determine if these molecules can be used as effective low molecular weight gelators.
2.2 INTRODUCTION

Low molecular weight gelators have been of rising interest due to their wide range of versatility. Many have studied the use of low molecular weight gelators for biological applications, along with environmental remediation. These gelators produce supramolecular gels which use noncovalent forces as the building blocks for their gelation abilities. The non-covalent forces mainly said to attribute to the self-assembly are π-π stacking, hydrogen bonding, hydrophobic interactions, also CH-π interactions, and van der Waals forces. Carbohydrates have been used as the basis of low-molecular weight gelators due to their structural diversity, cost effectiveness, and bioavailability. In the early 2000’s an extensive study was done on a glycoside library to determine a way to predict structures that will have gelating properties. Previous studies have used glucose as building blocks for phase selective organic gelators (PSOG). These phase selective gelators are mainly used for environmental remediation. If the gelator can form gels in oils. Figure 20 shown below is an example of a PSOG. These gelators for efficient gels in benzene and can gel oil in water/oil mixtures. Due to the cost effectiveness of the glucose building block, these could be used on large scale oil spills.

![Fig. 20 Structure of phase selective organogelator](image)

After many years of investigations, it is still termed serendipitous to find a structure that has efficient gelation properties. In previous research it was shown that when protecting the 6 position of glucose with aniline derivative show that glycolipids in general do not show the gelation
properties. However, the aniline substituted glycolipid derivatives display gelation properties in various polar and nonpolar solvents. Figure 21 shows the structural building block of the effective glycolipid derivatives.  

![Structural representation of aniline glycolipid derivative](image)

Fig. 21 Structural representation of aniline glycolipid derivative

Previous research by the Wang group and other research labs showed that D-glucose can be used as the starting material for the construction of effective low molecular weight gelators. However, a systematic study on the influence of 4,6 acetal protective functional group to gelation properties have not be carried out yet. Therefore, we synthesized and analyzed a series of alkylidene acetal and arylidene acetal derivatives of methyl α-D-glucopyranoside. The synthesis and characterizations of these derivatives are discussed. Due to the rising importance of these materials, it is important to thoroughly study the functionalization of the structure to determine the structural characteristics to ensure the gelators have good gelation properties.
2.3 RESULTS AND DISCUSSION

Methylated glucose was used as the starting material for this study in order to determine if the acetyl group on the sugar ring was necessary for gelation properties as studied by previous students. The synthesis is shown in Scheme 1. Comparing to previous studies, the protection of the 4,6 position on the sugar is very important for gelation. In other studies, the 4,6 position was protected using benzyl derivatives, therefore alkyl protecting group were used to study the effect of the benzyl group on gelation properties. As previously discussed, it is important to have a balance of hydrophobic and hydrophilic functionality on the molecule, along with hydrogen bond donors and acceptors.

![Scheme 1 – Synthesis of 4,6 acetal protected glucose derived gelators](image)

The introduction of the alkylidene production presents more hydrophobicity on the molecule. The gelation properties were studied in various solvents, both polar and non-polar. Table 1 describes the gelation properties of the synthesized compounds. The table below shows we can conclude
that the 4,6-O-alkylidene protected α-D-methyl glucoside compounds are not expected to be suitable as gelators. However, the introduction of an aromatic group on the 4,6 position increases the gelation ability. Based on the gelation table results it can be determined that the structure must incorporate a benzene functional group to attribute to gelation. Figure 22 shows the photos of the gels in various solvents. Figure 23 shows the optical micrographs of the gels. From the micrographs we can determine the gel morphology. Based on these micrographs it is shown that these gels have a fibrous micellar like morphology.

Table 3 Gelation results of 4,6 acetal protected glucose derivatives.

<table>
<thead>
<tr>
<th>Solvent/ Compound</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<th>5</th>
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<td>S</td>
<td>S</td>
<td>G10</td>
<td>G20</td>
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<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>G20</td>
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<tr>
<td>EtOH: H₂O 1:2</td>
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</table>

G, gelation, for compounds forming gels, their MGCs are given in mg of gelator/mL of solvent, I-insoluble, P-precipitate, and S-soluble at 20 mg/mL, Cr-crystallizes. Gelation solvents are in v/v ratio.
Fig. 22 Gel Photos of Compound 8 (a) 20 mg/mL, DMSO:H₂O 1:1 (v/v) (b) 20 mg/mL, EtOH:H₂O 1:1 (v/v) (c) 6.7 mg/mL, EtOH:H₂O 1:2 (v/v)
Fig. 23 a. Optical micrograph of the gels formed by compound 8, EtOH:H₂O 1:2 6.67 mg/mL 50X. b. Optical micrograph of the gels formed by compound 8, EtOH:H₂O 1:2 6.67 mg/mL 20X.
Based on the gelation abilities we can determine the $T_{gel}$ of the gelators by using the ball drop method. The gels were prepared at the MGC value in an NMR tube. Then a small metal ball was added to the top of the gel in the NMR tube. The tube was placed in a water bath a heated. When the gel was started to melt $T_1$ measurement was taken. $T_2$ measurement was at the halfway point of the gelation process. The final measurement, $T_3$, was taken when the gel was fully melted and then the ball dropped to the bottom of the tube.

Table 4 $T_{gel}$ of compound 8.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Concentration (mg mL$^{-1}$)</th>
<th>Solvent System</th>
<th>$T_1$ (ºC)</th>
<th>$T_2$ (ºC)</th>
<th>$T_3$ (ºC)</th>
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<tr>
<td>9</td>
<td>20</td>
<td>DMSO:H$_2$O 1:1</td>
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<td>63.1</td>
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<tr>
<td>9</td>
<td>6.7</td>
<td>EtOH:H$_2$O 1:2</td>
<td>53.2</td>
<td>55.1</td>
<td>63.2</td>
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<tr>
<td>9</td>
<td>20</td>
<td>EtOH:H$_2$O 1:1</td>
<td>42.1</td>
<td>45.2</td>
<td>46.3</td>
</tr>
</tbody>
</table>

The minimum gelation concentration was used to prepare the gels for gel–sol phase transition studies. $T_1$: initial melting temperature when the liquid was first seen. $T_2$: temperature when the gel is half melted. $T_3$: the temperature of the entire gel turned into a colorless liquid and the ball reached the bottom of the tube.

To ensure determine the compound purity we confirmed using NMR ($^1$H, and $^{13}$C). Figure 24 and 25 show the spectrum of compound 8. Detailed procedure and data of all the compound synthesized are presented in the experimental section.
Fig. 24 $^1$H NMR of compound 8 in CDCl$_3$

Fig. 25 $^{13}$C NMR of compound 8 in CDCl$_3$
Figure 26 shows the IR spectra of the solid and gel of compound 8. The IR spectrum shows that in gel phase majority of the self-assembly is due to the solvent versus the solid sample. We can see ample CH stretching within the solid and O-H stretch in the gel form.

Fig. 26 IR spectra of compound 8, solid and gel (6.67 mg/mL, EtOH:H₂O 1:2 v/v)

2.4 CONCLUSIONS

We have designed and synthesized a series of 4,6-O-acetal protected α-D-methyl glucoside and studied their gelator properties in organic solvents. However, only aromatic aldehyde derivatives were able to form gels in several solvents, the aliphatic aldehyde derivatives didn’t form gels in the selected solvents. The phenyl, benzyl, and naphthyl containing compounds formed gels in toluene and pump oils. The best performing compound was the naphthylidene acetal derivative 8, forming gels toluene as well as aqueous mixtures. The results indicate that further functionalization of the 4,6 position with other functional groups to include aromatic functions should be further investigated.
2.5 EXPERIMENTAL SECTION

**General Methods and Materials:** The solvents and reagents were used straight as they were received from the merchants. Purification was done by flash chromatography on a conventional column using 230-400 mesh silica gel. The solvent systems used for chromatography are all in a volume ratio. The solvent mixtures for all gelation tests are also in volume ratios. NMR analysis was conducted using a 400 MHz Bruker NMR spectrometer. Melting point measurements were carried out using a Stuart SMP40 automatic melting-point apparatus.

**Gelation Testing:** On average, about 2 mg of a previously dried compound was placed in a vial, 1 dram in size. A series of solvents was then added until a concentration of 20 mg/mL was obtained. Once the vial is capped, heat the solution until the dried compound is completely dissolved. During certain cases the mixture should be sonicated in order to ensure a homogenous solution is formed. Once the compound is dissolved, let the mixture cool to room temperature. After fifteen minutes, if there is a clear solution still present in the vial it is said to be soluble. If the vial can be inverted without flow of solvent, the sample is said to be a stable gel, otherwise it is said to be unstable. In order to determine the minimum gelation concentration (MGC), a serial dilution was performed on the stable gels. The minimum gelation concentration is defined as the concentration prior to unstable gelation.

**FTIR Spectroscopy:** FTIR measurement was performed on a Bruker ALPHA Platinum ATR FTIR Spectrometer. The solid sample (gelator or a piece of gel scooped from the gel matrix) was placed onto the ATR crystal, and then pressure was gently applied to the solid sample by anvil before the measurement was taken. For the liquid sample, a droplet of the liquid sample was spread
on the ATR crystal before the measurement was carried out. The operating software for spectrum acquisition is OPUS 7.5. The absorption spectra of gelator, gel form of the gelator in solvent and the solvent were obtained at room temperature in the range of 400-4000 cm⁻¹.

**General Synthesis of 4,6-O-alkylidene protected α-D-methylglucoside:**

To a small round both flask, 500 mg (1 equivalent) of an alkane aldehyde ranging from six to ten carbons in length, or aromatic substituent was added. To the mixture trimethyl orthoformate (1.2 equivalents), para toluene sulfonic acid (PTSA) (0.1 equivalent), and 2 mL of anhydrous methanol as solvent. The reaction mixture was stirred at 70 °C for on average five hours. After the five hours, sodium bicarbonate solid (0.05 equivalents) was added to the mixture and stirred for 30 minutes to remove residual acid. Then the mixture was filtered and concentrated using rotary evaporator. The crude product was used directly for the next step.

To a 50 mL round bottom flask, 500 mg (1 equivalent) methylated glucose, 1.2 equivalents of the previously synthesized acetal, and 0.1 equivalent PTSA were added, with 5mL of dimethylformamide (anhydrous). The mixture was heated to 70 °C for 12 hours, then quenched with sodium bicarbonate (solid, 0.05 equivalent) to remove any residual acid. The reaction mixture was filtered, the filtrate was concentrated directly to remove all solvents to afford the crude product. Phase-phase extraction was done using DCM: Water (20 mL x 3: 15mL). DMF (anhydrous) was left over so the product was washed with 3mL of cold deionized water 3 times and filtered using vacuum filtration method. Recrystallization was done using EtOH: Hexane to afford the pure alpha product.
Synthesis of 4,6-O-hexyl protected α-D-methyl glucoside 1:

Hexanal (500 mg, 1 equivalent, 4.99 mmol), trimethyl orthoformate (635 mg, 1.2 equivalents, 5.99 mmol), p-Toluenesulfonic Acid (85.9 mg, 0.1 equivalent, 0.499 mmol) were added to a 50 mL round bottom flask, along with 2 mL of methanol (anhydrous) as solvent. The reaction mixture was stirred at 70ºC for five hours. After the five hours, sodium bicarbonate solid (0.05 equivalents) was added to the mixture and stirred for 30 minutes to remove residual acid. Then the mixture was filtered and concentrated using rotary evaporator. The crude product was used directly for the next step. To a 50 mL round bottom flask, 500 mg (1 equivalent, 2.57 mmol) methylated glucose (pre-co-distilled with toluene), 451 mg (1.2 equivalents, 3.084 mmol) of C$_5$H$_{11}$CH(OMe)$_2$, and 44.2 mg (0.1 equivalents, 0.257 mmol) PTSA were added, with 5mL of dimethylformamide (DMF, anhydrous). The mixture was heated to 70ºC for 12 hours, then quenched with sodium bicarbonate (solid, 0.05 equivalents) to remove any residual acid. The reaction mixture was filtered, the filtrate was concentrated directly to remove all solvents to afford the crude product. Work up was done using dichloromethane (DCM, 20 mL, 3 times). DMF was left over so the product was washed with 3mL of cold deionized water 3 times and filtered using vacuum filtration method. Recrystallization was done using EtOH: Hexane to afford the pure product. The desired product was a white solid (502 mg, 71%), R$_f$ = 0.48 in solvent. 3% MeOH:DCM. mp 241-243 ºC. $^1$H NMR (400 MHz, CDCl$_3$) δ 4.78 (d, $J = 3.9$ Hz, 1H), 4.57 (t, $J = 5.1$ Hz, 1H), 4.15 (dd, $J = 10.1$, 4.8 Hz, 1H), 3.87 (t, $J = 9.2$ Hz, 1H), 3.68 (d, $J = 4.8$ Hz, 1H), 3.65 (dd, $J = 9.7$, 4.8 Hz, 1H), 3.59 (dd, $J = 9.1$, 3.9 Hz, 1H), 3.56-3.49 (m, 1H), 3.45 (s, 3H), 3.28 (t, $J = 9.4$ Hz, 1H), 1.76-1.60 (m, 2H), 1.47-1.25 (m, 6H), 0.91 (t, $J = 6.9$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 102.7, 99.7, 80.3, 73.0, 71.9, 68.5, 62.5, 55.5, 34.2, 31.6, 23.7, 22.5, 14.0.
Synthesis of 4,6-O-heptyl protected α-D-methylglucoside 2:

Heptanal (500 mg, 1 equivalent, 4.38 mmol), trimethyl orthoformate (557 mg, 1.2 equivalents, 5.25 mmol), p-Toluenesulfonic Acid (75.4 mg, 0.1 equivalent, 0.438 mmol) were added to a 50 mL round bottom flask, along with 2 mL of methanol (anhydrous) as solvent. The reaction mixture was stirred at 70 ºC for five hours. After the five hours, sodium bicarbonate solid (0.05 equivalents) was added to the mixture and stirred for 30 minutes to remove residual acid. Then the mixture was filtered and concentrated using rotary evaporator. The crude product was used directly for the next step. To a 50 mL round bottom flask, 500 mg (1 equivalent, 2.57 mmol) methylated glucose (pre-co-distilled with toluene), 494 mg (1.2 equivalents, 3.084 mmol) of C₆H₁₃CH(OMe)₂, and 48 mg (0.1 equivalent, 0.257 mmol) PTSA were added, with 5 mL of dimethylformamide (DMF, anhydrous). The mixture was heated at 70 ºC for 12 hours, then quenched with sodium bicarbonate (solid, 0.5 equivalent) to remove any residual acid. The reaction mixture was filtered, the filtrate was concentrated directly to remove all solvents to afford the crude product. Work up was done using dichloromethane (DCM, 20mL, 3 times). DMF was left over so the product was washed with 3mL of cold deionized water 3 times and filtered using vacuum filtration method. Recrystallization was done using EtOH: Hexane to afford the pure product. White solid (555 mg, 74%). Rf = 0.44 in 3% MeOH:DCM. mp 243-244 ºC, ¹H NMR (400 MHz, CDCl₃) δ 4.77 (d, J = 3.8 Hz, 1H), 4.55 (t, J = 5.1 Hz, 1H), 4.13 (dd, J = 10.1, 4.8 Hz, 1H), 3.86 (t, J = 9.2 Hz, 1H), 3.68-3.56 (m, 2H), 3.5-3.48 (m, 1H), 3.44 (s, 3H), 3.26 (t, J = 9.4 Hz, 1H), 1.74-1.57 (m, 2H), 1.46-1.23 (m, 8H), 0.86 (t, J = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 102.7, 99.7, 80.4, 72.9, 73.0, 71.8, 68.5, 62.5, 55.4, 34.2, 31.7, 29.1, 24.0, 22.5, 14.0.
**Synthesis of 4,6-O-octyl protected α-D-methylglucoside 3:**

Octanal (500 mg, 1 equivalent, 3.90 mmol), trimethyl orthoformate (497 mg, 1.2 equivalents, 4.68 mmol), p-Toluenesulfonic Acid (67.2 mg, 0.1 equivalent, 0.390 mmol) were added to a 50 mL round bottom flask, along with 2 mL of methanol (anhydrous) as solvent. The reaction mixture was stirred at 70°C for five hours. After the five hours, sodium bicarbonate solid (0.05 equivalents) was added to the mixture and stirred for 30 minutes to remove residual acid. Then the mixture was filtered and concentrated using rotary evaporator. The crude product was used directly for the next step. To a 50 mL round bottom flask, 500 mg (1 equivalent, 2.57 mmol) methylated glucose (pre-co-distilled with toluene), 537 mg (1.2 equivalents, 3.084 mmol) of C7H15CH(OMe)2, and 48 mg (0.1 equivalent, 0.257 mmol) PTSA were added, with 5 mL of dimethylformamide (DMF, anhydrous). The mixture was heated at 70 °C for 12 hours, then quenched with sodium bicarbonate (solid, 0.05 equivalent) to remove any residual acid. The reaction mixture was filtered, the filtrate was concentrated directly to remove all solvents to afford the crude product. Work up was done using dichloromethane (DCM, 20mL, 3 times). DMF was left over so the product was washed with 3mL of cold deionized water 3 times and filtered using vacuum filtration method. Recrystallization was done using EtOH: Hexane to afford the pure product. White solid (500 mg, 64%). \( R_f = 0.37 \) in 3% MeOH:DCM. mp 248-249 °C, \( ^1\text{H NMR} \) (400 MHz, CDCl3) \( \delta \) 4.78 (d, \( J = 3.9 \text{ Hz}, 1\text{H} \)), 4.56 (t, \( J = 5.1 \text{ Hz}, 1\text{H} \)), 4.14 (dd, \( J = 10.1, 4.8 \text{ Hz}, 1\text{H} \)), 3.90 (t, \( J = 9.2 \text{ Hz}, 1\text{H} \)), 3.70-3.62 (m, 1H), 3.56-3.49 (m, 1H), 3.45 (s, 3H), 3.30 (t, \( J = 9.4 \text{ Hz}, 1\text{H} \)), 1.77-1.54 (m, 2H), 1.49-1.18 (m, 10H), 0.99-0.83 (m, 3H). \( ^{13}\text{C NMR} \) (100 MHz, CDCl3) \( \delta \) 102.7, 99.7, 80.3, 62.5, 55.5, 34.2, 31.7, 29.4, 29.1, 24.1, 22.6, 14.0.
Synthesis of 4,6-O-nonyl protected α-D-methylglucoside 4:

Nonal (500 mg, 1 equivalent, 3.52 mmol), trimethyl orthoformate (448 mg, 1.2 equivalents, 4.22 mmol), p-Toluenesulfonic Acid (60.6 mg, 0.1 equivalent, 0.352 mmol) were added to a 50 mL round bottom flask, along with 2 mL of methanol (anhydrous) as solvent. The reaction mixture was stirred at 70°C for five hours. After the five hours, sodium bicarbonate solid (0.05 equivalents) was added to the mixture and stirred for 30 minutes to remove residual acid. Then the mixture was filtered and concentrated using rotary evaporator. The crude product was used directly for the next step. To a 50 mL round bottom flask, 500 mg (1 equivalent, 2.57 mmol) methylated glucose (pre-co-distilled with toluene), 581 mg (1.2 equivalents, 3.084 mmol) of C₈H₁₇CH(OMe)₂, and 48 mg (0.1 equivalent, 0.257 mmol) PTSA were added, with 5 mL of dimethylformamide (DMF, anhydrous). The mixture was heated at 70°C for 12 hours, then quenched with sodium bicarbonate (solid, 0.05 equivalent) to remove any residual acid. The reaction mixture was filtered, the filtrate was concentrated directly to remove all solvents to afford the crude product. Work up was done using dichloromethane (DCM, 20mL, 3 times). DMF was left over so the product was washed with 3mL of cold deionized water 3 times and filtered using vacuum filtration method. Recrystallization was done using EtOH: Hexane to afford the pure product. White solid (444 mg, 54%). Rᵢ = 0.37 in 3% MeOH:DCM. mp 251-253 °C, ¹H NMR (400 MHz, CDCl₃) δ 4.75 (d, J = 3.9 Hz, 1H), 4.54 (t, J = 5.0 Hz, 1H), 4.12 (dd, J = 10.1, 4.8 Hz, 1H), 3.85 (t, J = 9.3 Hz, 1H), 3.67-3.60 (m, 1H), 3.60-3.55 (m, 1H), 3.53-3.47 (m, 1H), 3.43 (s, 3H), 3.25 (t, J = 9.4 Hz, 1H), 2.92 (bs, 1H), 1.74-1.58 (m, 2H), 1.44-1.19 (m, 12H), 0.90-0.85 (m, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 102.7, 99.8, 80.4, 72.9, 71.6, 68.5, 62.5, 55.4, 34.2, 31.8, 29.4, 24.1, 22.6, 18.3, 14.0.
Synthesis of 4,6-O-decyl protected α-D-methylglucoside 5:
Decanal (500 mg, 1 equivalent, 3.20 mmol), trimethyl orthoformate (407 mg, 1.2 equivalents, 4.22 mmol), p-Toluenesulfonic Acid (55.1 mg, 0.1 equivalent, 0.320 mmol) were added to a 50 mL round bottom flask, along with 2 mL of methanol (anhydrous) as solvent. The reaction mixture was stirred at 70°C for five hours. After the five hours, sodium bicarbonate solid (0.05 equivalents) was added to the mixture and stirred for 30 minutes to remove residual acid. Then the mixture was filtered and concentrated using rotary evaporator. The crude product was used directly for the next step. To a 50 mL round bottom flask, 500 mg (1 equivalent, 2.57 mmol) methylated glucose (pre-co-distilled with toluene), 624 mg (1.2 equivalents, 3.084 mmol) of C\textsubscript{9}H\textsubscript{19}CH(OMe)\textsubscript{2}, and 48 mg (0.1 equivalent, 0.257 mmol) PTSA were added, with 5 mL of dimethylformamide (DMF, anhydrous). The mixture was heated at 70°C for 12 hours, then quenched with sodium bicarbonate (solid, 0.05 equivalent) to remove any residual acid. The reaction mixture was filtered, the filtrate was concentrated directly to remove all solvents to afford the crude product. Work up was done using dichloromethane (DCM, 20mL, 3 times). DMF was left over so the product was washed with 3mL of cold deionized water 3 times and filtered using vacuum filtration method. Recrystallization was done using EtOH: Hexane to afford the pure product. White solid (452 mg, 53%). R\textsubscript{f} = 0.34 in 3% MeOH:DCM. mp 254-255 °C, \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 4.78 (d, J = 3.9 Hz, 1H), 4.57 (t, J = 5.1 Hz, 1H), 4.15 (dd, J = 10.1, 4.8 Hz, 1H), 3.87 (t, J = 9.3 Hz, 1H), 3.70-3.62 (m, 1H), 3.60 (dd, J = 9.1, 4.0, 1H), 3.56-3.50 (m, 1H), 3.46 (s, 3H), 3.28 (t, J = 9.4 1H), 1.86 (bs, 1H), 1.72-1.63 (m, 2H), 1.47-1.22 (m, 16H), 0.93-0.87 (m, 3H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 102.7, 99.7, 80.3, 73.0, 72.0, 68.5, 62.5, 55.5, 34.3, 31.9, 29.4, 29.3, 24.1, 23.5, 22.7, 14.1.
Synthesis of 4,6-O-phenyl protected α-D-methylglucoside 6:

To a 50 mL round bottom flask, 500 mg (1 equivalent, 2.57 mmol) methylated glucose (pre-co-distilled with toluene), 512 mg (1.3 equivalents, 3.34 mmol) of C₆H₅CH(OMe)₂, and 44 mg (0.1 equivalent, 0.257 mmol) PTSA were added, with 5 mL of dimethylformamide (DMF, anhydrous). The mixture was heated at 70°C for 12 hours, then quenched with sodium bicarbonate (solid, 0.05 equivalent) to remove any residual acid. The reaction mixture was filtered, the filtrate was concentrated directly to remove all solvents to afford the crude product. Work up was done using dichloromethane (DCM, 20 mL, 3 times). DMF was left over so the product was washed with 3mL of cold deionized water 3 times and the precipitate was filtered using vacuum filtration method. White solid (506 mg, 70%). Rᵣ =0.51 in 3% MeOH:DCM. mp 225.8-227.2°C, ¹H NMR (400 MHz, CDCl₃) δ 7.54-7.49 (m, 2H), 7.42-7.35 (m, 3H), 5.53 (bs, 1H), 4.77 (d, J = 3.9 Hz, 1H), 4.29 (dd, J = 13.9, 5.36 Hz, 1H), 3.93 (t, J = 9.2 Hz, 1H), 3.84 - 3.77 (m, 1H), 3.77-3.71 (m, 1H), 3.51-3.48 (m, 1H), 3.45 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 137.09, 129.2, 128.3, 126.3, 101.9, 99.9, 81.0, 72.8, 71.6, 68.9, 62.4, 55.5.

Synthesis of 4,6-O-benzyl protected α-D-methylglucoside 7:

To a 50 mL round bottom flask, 500 mg (1 equivalent, 2.57mmol) methylated glucose (pre-co-distilled with toluene), 560 mg (1.3 equivalents, 3.34 mmol) of C₆H₅CH₂CH(OMe)₂, and 44 mg (0.1 equivalent, 0.257 mmol) PTSA were added, with 3 mL of dimethylformamide (DMF, anhydrous). The mixture was heated at 70°C for hours, then quenched with sodium bicarbonate (solid, 0.05 equivalent) to remove any residual acid. The reaction mixture was filtered, the filtrate was concentrated directly to remove all solvents to afford the crude product. Work up was done using dichloromethane (DCM, 20mL, 3 times). DMF was left over so the product was washed
with 3mL of cold deionized water 3 times and the precipitate was filtered using vacuum filtration method. The crude product was purified using column chromatography with an eluent of 75% EtOAc:Hexane to afford the pure product. White solid (400 mg, 52 %). R\textsubscript{f} = 0.53 in 50% EtOAc:Hexanes. mp 182.9-184.1°C, \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.36-7.21 (m, 5H), 4.79-4.74 (m, 2H), 4.14 (dd, \( J = 5.4, 15.2 \) Hz, 1H), 3.89 (t, \( J = 9.2 \) Hz, 1H), 3.73-3.66 (m, 1H), 3.63-3.56 (bs, 1H), 3.52-3.46 (m, 1H), 3.46 (s, 3H), 3.30 (t, \( J = 9.4 \) Hz, 1H), 3.10-2.94 (m, 2H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 136.1, 129.6, 128.3, 126.6, 102.8, 99.7, 80.4, 73.0, 72.0, 68.5, 62.4, 55.5, 40.9.

**Synthesis of 4,6-O-2-naphyl protected α-D-methyl glucoside 8:**

2-napthylaldehyde (526 mg, 1 equivalent, 3.37 mmol), trimethyl orthoformate (0.83 mL, 2.25 equivalents, 7.56 mmol), 1 drop of conc. H\textsubscript{2}SO\textsubscript{4} were added to a 50 mL round bottom flask, along with 2 mL of methanol (anhydrous) as solvent. The reaction mixture was stirred at 70°C for 1 hour. After the 1 hr., sodium bicarbonate solid (0.05 equivalents) was added to the mixture and stirred for 30 minutes to remove residual acid. Then the mixture was filtered and concentrated using rotary evaporator. The crude product was used directly for the next step. To a 50 mL round bottom flask, 500 mg (1 equivalent, 2.57 mmol) methylated glucose (pre-co-distilled with toluene), 681 mg (1.3 equivalents, 3.34 mmol) of the acetal synthesized above C\textsubscript{10}H\textsubscript{7}CH(OMe)\textsubscript{2}, and 44 mg (0.1 equivalent, 0.257 mmol) PTSA were added, with 5 mL of dimethylformamide (DMF, anhydrous). The mixture was heated at 70°C for 12 hours, then quenched with sodium bicarbonate (solid, 0.05 equivalent) to remove any residual acid. The reaction mixture was filtered, the filtrate was concentrated directly to remove all solvents to afford the crude product. Work up was done using dichloromethane (DCM, 20 mL, 3 times). DMF was left over so the product was washed with 3
mL of cold deionized water 3 times and the precipitate was filtered using vacuum filtration method. White solid (425 mg, 50%). Rf = 0.52 in 3% MeOH:DCM. mp 184.2-185.6ºC. $^1$H NMR (400 MHz, CDCl₃) δ 7.99 (bs, 1H), 7.90-7.84 (m, 3H), 7.63 (dd, $J = 8.5$, 1.6 Hz, 1H), 7.54-7.48 (m, 2H), 5.72 (bs, 1H), 4.85 (d, $J = 3.9$ Hz, 1H), 4.40-4.35 (m, 1H), 4.00 (t, $J = 9.2$, 1H), 3.93-3.79 (m, 2H), 3.69 (bs, 1H), 3.59 (t, $J = 9.2$ 1H), 3.51 (s, 3H). $^{13}$C NMR (100 MHz, CDCl₃) δ 134.4, 133.8, 132.9, 128.4, 128.2, 127.7, 126.5, 126.2, 125.8, 123.8, 102.0, 99.8, 81.0, 72.9, 71.8, 69.0, 62.4, 55.6.
CHAPTER 3. SYNTHESIS AND CHARACTERIZATION OF 4,6-O-ALKYLDENE PROTECTED N-ACETYL-D-GLUCOSAMINE LOW MOLECULAR WEIGHT GELATORS

3.1 ABSTRACT

Carbohydrate based low molecular weight gelators (LMWGs) have attracted increasing attention due to their potential applications in many fields spanning from biomedical research to advanced materials. Previously we have found that 4,6-O-benzylidene acetal protected D-glucose and D-glucosamine derivatives form robust organogels and hydrogels. In order to understand the factors affecting gelation properties of monosaccharide derivatives, in this study, we replaced the 4,6 protective functional group with non-aromatic functions. A library of ten different derivatives of D-glucosamine with 4,6-O-alkylidene acetal functional group were synthesized and characterized. Their gelation properties were studied in several organic solvents and water. A few derivatives were found to be effective LMWGs for, organic solvents, aqueous mixtures, and water. Since these derivatives were able to form hydrogels, these were further studied for the controlled release of model drugs including naproxen and chloramphenicol. Some gelators were also studied for their dye absorption properties using Rhodamine and toluidine blue. The controlled release of the drug for the gel to the aqueous phase was done using UV-vis spectroscopy. This study showed that there was a positive effect of the alkyl group on the 4,6 protection of N-acetyl-D-glucosamine, which is a new feasible strategy to design hydrogelators.

Keywords: hydrogelators, carbohydrates, gelators, sugar, analysis

Note: This chapter is adapted from the following manuscript: “Synthesis and Characterization of 4,6-O-alkylidene protected N-acetyl-D-glucosamine Low Molecular Weight Hydrogelators”

3.2 INTRODUCTION

Carbohydrate derivatives have intrinsic biocompatibility and degradability there for they can form environment friendly new materials. LMWGs are small molecules that can self-assemble and form reversible gels in organic solvents or water. The driving forces of the formation of supramolecular gel networks are noncovalent interactions such as hydrogen bonding, hydrophobic interactions, π-π stacking, CH-π interactions, and van der Walls forces, etc. The resulting gels are fully reversible due to the noncovalent driving forces for gelation. As discussed in Chapter 1, the structures of LMWGs encompass a broad range of functionalities. Sugar based gelators are likely to be biocompatible, and they may find many applications as advanced materials. Figure 27 shows examples of carbohydrate based low molecular weight gelators and their applications are discussed. Rajkamal et. al. synthesized a series of partially acetylated or benzylated arabinose derivatives. These arabinose derivates were studied for the effect of the ester protection. These gels are stable in organic solvents, under ultrasound and photochemical irradiation which would be useful for the carrying out of reactions in the media which will be studied extensively in the future by the researchers. Narayana et. al. utilizes carbohydrate based LMWGs for oil water separation, and dye removal. The carbohydrate derivates reported were effective gelators in both organic solvents and water. These were also able to form gels in oils such as petrol and diesel which will ultimately assist with oil spill recovery applications. These gels also showed the ability to remove synthetic die which in turn helps with environmental remediations. Based on the current research there are a wide range of applications for these gelators.
Our group has been working on the rational design of carbohydrate based low molecular weight gelators. Several monosaccharide derivatives have been studied and the general structures for effective LMWGs are shown in Figure 28. These include the 2-O-ester derivatives 1, 2-O-linked carbamate derivatives 2, amide derivates 3, 3-O-ester derivatives 4, and 4,6-O-(2-phenylethylidene)-functionalized D-glucosamine derivatives 5. These various classes of carbohydrate based low molecular weight gelators expressed gelation ability in various solvents, both organic and aqueous mixtures.

In many different monosaccharide derivatives, the benzylidene acetal functional group seemed to play an important role in gelation and molecular self-assembly. The phenyl acetaldehyde derivatives 5 also showed effective gelation, however, these compounds also contain a phenyl ring in the 4,6-substituents. In order to probe the effective of the benzylidene acetal functional group
and the structure and gelation correlation of sugar derivatives, in this study, we replaced the phenyl functional group with alkyl groups. We studied the effect of introducing the 4,6 position with alkyl groups ranging from 6 carbons to 10 carbons in chain length. Since the gelation process is often found via serendipity, we used the alkyl chain in hopes to find the perfect balance between hydrophobic and hydrophilic functional groups in order to create strong and effective hydrogels.

### 3.3 RESULTS AND DISCUSSION

N-acetyl-D-glucosamine was used as the starting material for the study in order to focus on the intermolecular forces associated with self-assembly in low molecular weight gelators. The synthesis of the alkylidene derivatives of N-acetyl-D-glucosamine is shown in Scheme 1. Commercially available compound 6 was reacted with methanol and Amberlite IR120 acidic resin to afford the glycosylated product compound 7. Compound 7 reacted with various aliphatic acetals which protected the 4, 6 position on the sugar and resulted in compounds 8-12. Compounds 8-12 where then deacetylated on the 2 position of N-acetyl-D-glucosamine resulted in compounds 13-17. This synthesis shows the protection of the 4, 6 position of N-acetyl-D-glucosamine with acetal derivatives, varying in the number of carbons. After the synthetic route the proton and carbon NMR spectrum were obtained to ensure purity of the compound. Figure 29a shows the proton NMR spectra of compound 11, and Figure 29b shows the carbon NMR spectra of compound 11. These samples were obtained in CDCl₃. After the deacetylation of the second position of the sugar ring the proton and carbon spectrum are shown in Figure 30a and Figure 30b of compound 16. These spectra differ from the spectrum of 11 due to the NHAc group deacetylated and the carbonyl carbon no longer present in the carbon spectrum.
Scheme 2. Synthesis of 4,6-\(\text{O}\)-alkyldene protected monosaccharides A

Scheme 3. Synthesis of 4,6 alkylidene protected D-glucosamine derivatives B
Fig. 29a $^1$H NMR spectra of compound 11 in CDCl$_3$
Fig. 29b $^{13}$C NMR spectra of compound $\textbf{11}$ in CDCl$_3$
Fig. 30a $^1$H NMR spectra of compound 16 in CDCl$_3$
After the compounds were synthesized and purified, their gelation properties were tested. The results are shown in Table 1 for compounds 8-12 and Table 2 for compound 13-17. These results show that we have successfully synthesized a series of organo and hydrogels. Since these gels have a good performance in varying solvents when the gelator and solvent solution is heated. It was important for us to understand the effectiveness of the spontaneity gelation in Table 3. This experiment was done by dissolving 2 mg of the compound in 0.1 mL of DMSO and then heated, after heating all of the samples were soluble therefore, 0.2 mL of water was added to the hot solution to determine spontaneity. After adding 0.2 mL of water there were gels for, but an additional 0.2 mL of water only formed a gel after heating and not just sonication.

Fig. 30b $^{13}$C NMR spectra of compound 16 in CDCl$_3$
Table 5. Gelation test of 4,6 alkylidene protected N-acetyl-D-glucosamine

<table>
<thead>
<tr>
<th></th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
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<tr>
<td>H₂O</td>
<td>G 20.0</td>
<td>G 5.0</td>
<td>G 4.0</td>
<td>G 6.7</td>
<td>G 10.0</td>
</tr>
<tr>
<td>EtOH:H₂O 1:1</td>
<td>G 20.0</td>
<td>G 4.0</td>
<td>G 6.7</td>
<td>G 4.0</td>
<td>G 20.0</td>
</tr>
<tr>
<td>EtOH:H₂O 1:2</td>
<td>G 20.0</td>
<td>G 5.0</td>
<td>G 5.0</td>
<td>G 6.7</td>
<td>S</td>
</tr>
<tr>
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<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>DMSO:H₂O 1:1</td>
<td>G 10.0</td>
<td>G 6.7</td>
<td>G 5.0</td>
<td>G 6.7</td>
<td>S</td>
</tr>
<tr>
<td>DMSO:H₂O 1:2</td>
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<td>G 6.7</td>
<td>G 10.0</td>
<td>G 10.0</td>
<td>G 10.0</td>
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<td>I</td>
<td>I</td>
<td>S</td>
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<tr>
<td>IPA</td>
<td>S</td>
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</table>

For compounds forming gels, their MGCs are given in mg of gelator/mL of solvent, I-insoluble, P-precipitate, and S-soluble at 20 mg/mL, Cr-crystallizes.
Table 6. Gelation test 4,6 alkylidene protected deacetylated N-acetyl-D-glucosamine

<table>
<thead>
<tr>
<th>Solvent</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
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<tr>
<td>H₂O</td>
<td>G 10.0</td>
<td>G 5.0</td>
<td>G 5.0</td>
<td>G 5.0</td>
<td>P</td>
</tr>
<tr>
<td>EtOH:H₂O 1:1</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>G 10.0</td>
<td>G 6.7</td>
</tr>
<tr>
<td>EtOH:H₂O 1:2</td>
<td>G 4.0</td>
<td>G 5.0</td>
<td>G 6.7</td>
<td>G 6.7</td>
<td>G 10.0</td>
</tr>
<tr>
<td>EtOH</td>
<td>S</td>
<td>S</td>
<td>S</td>
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<tr>
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<td>S</td>
<td>S</td>
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<td>S</td>
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<tr>
<td>DMSO:H₂O 1:1</td>
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<td>G 6.7</td>
<td>G 10.0</td>
<td>G 2.8</td>
<td>G 3.3</td>
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<tr>
<td>DMSO:H₂O 1:2</td>
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<td>G 6.7</td>
<td>G 3.3</td>
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<tr>
<td>Hexane</td>
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<td>THF</td>
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<td>S</td>
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</tbody>
</table>

For compounds forming gels, their MGCs are given in mg of gelator/mL of solvent, I-insoluble, P-precipitate, and S-soluble at 20 mg/mL, Cr-crystallizes.

Table 7. Gelation test for DMSO and water mixtures

<table>
<thead>
<tr>
<th>Compound number</th>
<th>0.1 mL DMSO</th>
<th>1st addition of water</th>
<th>Appearance of gel</th>
<th>0.1 mL of water</th>
<th>0.1 mL of water</th>
<th>0.1 mL of water</th>
<th>Gelation conc.</th>
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<td>8</td>
<td>S</td>
<td>0.1 mL</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>S</td>
<td>0.6 mL</td>
<td>Gsᵀ</td>
<td>Gᵀ</td>
<td>Gᵀ</td>
<td>UGᵀ</td>
<td>2.2 mg/mL</td>
</tr>
<tr>
<td>10</td>
<td>S</td>
<td>0.4 mL</td>
<td>Gsᵀ</td>
<td>Gᵀ</td>
<td>UGᵀ</td>
<td>S</td>
<td>3.33 mg/mL</td>
</tr>
<tr>
<td>11</td>
<td>S</td>
<td>0.4 mL</td>
<td>Gsᵀ</td>
<td>Gᵀ</td>
<td>UGᵀ</td>
<td>S</td>
<td>3.33 mg/mL</td>
</tr>
<tr>
<td>12</td>
<td>S</td>
<td>0.4 mL</td>
<td>Gsᵀ</td>
<td>Gᵀ</td>
<td>UGᵀ</td>
<td>S</td>
<td>3.33 mg/mL</td>
</tr>
</tbody>
</table>
After the first addition of water you must use heat gun to allow for dissolution and for the gel to form again. Gs: spontaneous gelation, G: gelation after heating and sonication, T - translucent

To continue to the characterization Figure 31 shows gel photos formed by compound 11 at 6.7 mg/mL and compound 10 in water at 4.0 mg/mL. Figures 32 a and b. show the optical micrographs of the gels formed at 50x magnification. These optical micrographs show the fibrous morphology of the gels.

Fig. 31 a) A translucent/opaque clear gel formed by compound 11 in water at 6.7 mg/mL; b) A translucent/opaque gel formed by compound 10 in water at 4.0 mg/mL
Fig. 32 a) Optical micrograph of a translucent/opaque clear gel formed by compound 11 in water at 6.7 mg/mL at 50X
Fig. 32 b) Optical micrograph of a translucent/opaque gel formed by compound 10 in water at 4.0 mg/mL at 50X

Alternatively Figure 33 shows the gel picture of compound 16 in water at 5.0 mg/mL and in DMSO: Water 1:2 at 2.9 mg/mL. Figure 34 a and b show the optical images of these gels. At 50x magnification.
Fig. 33 a) An opaque gel formed by compound 16 in water at 5.0 mg/mL; b) an opaque gel formed by compound 16 in DMSO: Water 1:1 at 2.9 mg/mL
Fig. 34 a) Optical micrograph of an opaque gel formed by compound 16 in DMSO: H₂O 1:2 at 50X with a concentration of 3.3 mg/mL

Fig. 34 b) Optical micrograph of an opaque gel formed by compound 16 in EtOH: H₂O 1:2 at 50X with a concentration of 6.7 mg/mL
In order to understand the self-assembly of the compounds we can use a variable temperature study of compound 8 in DMSO-d6. The $^1$H NMR spectra of compound 8 are shown in Figure 35a for the select regions and Figure 35b for the full range. The amide N–H signal showed the most obvious shift among all signals, from 7.82 ppm shifted up field to 7.63 ppm upon heating from 30 to 60 °C, which indicates that the amide hydrogen bonding is important for gelation. Another important signal of discussion is the hydroxy hydrogen which had a slight up field shift from 4.99 ppm to 4.83 ppm which also shows the importance of the hydrogen bonding for self-assembly. In polar solvents as well as water, the intermolecular hydrogen bonding among the gelator molecules plays an important role in the gel stability and strength.

![1H NMR variable temperature study of compound 8 in DMSO-d6](image)

Fig. 35a $^1$H NMR variable temperature study of compound 8 in DMSO-d$_6$, 4-9 ppm.
In addition, we also carried out the time dependent NMR study for compound 8 after adding D₂O and acquired the ¹H spectrum right away. The time dependence ¹H NMR spectra are shown in Figure 36. As what to be expected, the proton signal of 3-OH disappeared upon addition of D₂O immediately, but the amide signal gradually exchanged with deuterium within 6 hours. The rate of the exchange with deuterium for amide functional group is fast. Addition of D₂O also led to chemical shift changes for several signals including the NH and OH proton. The rate constant of the exchange was calculated to be 0.00964, which indicated that the half-life was 71.9 minutes.
Fig. 36a – Time dependent $^1$H NMR spectra of compound 8 (1.6 mg in 0.40 mL d$_6$-DMSO) after addition of 0.10 mL D$_2$O to the sample. The NMR spectra were all acquired at 30 °C (4.5 – 8 ppm)
Fig. 36b - Time dependent $^1$H NMR spectra of compound 8 (1.6 mg in 0.40 mL d$_6$-DMSO) after addition of 0.10 mL D$_2$O to the sample. The NMR spectra were all acquired at 30 $^\circ$C (0-10 ppm)
Rheology was used in order to analyze the stability of the gels that were formed by compounds 9, 11, and 12 which are shown in Figure 37. For the oscillation frequency sweep in a range of different frequencies, the gels studied showed that the storage modulus $G'$ is always greater than loss modulus $G''$. This shows that the gels are stable and have elastic like properties. The storage modulus, $G'$ describes the solid like elastic properties of the gels, and the loss modulus is described with $G''$ explaining the liquid like viscous properties. Due to the increase in angular frequency we can describe the gels as viscoelastic and stable. The gels formed by water range in strength however, the strongest gel is formed by 12, and this gel has the longest alkyl chain protection which means there is a perfect balance between hydrophobicity and hydrophilicity to induce the self-assembly properties.
Rheology was used in order to analyze the stability of the gels that were formed by compounds 13, 14, 16 which are shown in Figure 38. For the oscillation frequency sweep in a range of different frequencies, the gels studied showed that the storage modulus $G'$ is always greater than loss modulus $G''$. This shows that the gels are stable and have elastic like properties. As previously mentioned, the storage modulus, $G'$ describes the solid like elastic properties of the gels, and the loss modulus is described with $G''$ explaining the liquid like viscous properties. Due to the increase in angular frequency we can describe the gels as viscoelastic and stable. The gels formed by water for compounds 13, 14, and 16 are very similar in strength.
Fig. 38 Rheological properties of the gels formed by 13 ● (10 mg/mL, H₂O), 14 ■ (5 mg/mL, H₂O), and 16 ▲ (5 mg/mL, H₂O) under 1% oscillation strain.

In order to test the strength of the gels, a gel aging experiment was done and the $G'/G''$ ratio was determined to show if the longer the gel aged influenced the strength of the gel. These results are shown in Figure 39 below. This experiment showed that as the gel aged the $G'/G''$ ratio varied. The ratio decreased from higher to lower angular frequency. The larger ratio indicates that the gel has a more solid like feature, and when the shear frequency increases the gel becomes more rigid. Therefore, the longer the gels are aged the stronger the gels become due to the self-assembling nature.
Fig. 39 Gel aging rheological experiment of the gels formed by 11 (6.7 mg/mL, DMSO:H₂O v/v 1:2) at 8 ▲, 24 ■, and 36 ● hours under 1% oscillation strain.

ATR-FTIR is a useful tool in understanding the gelation mechanism. Based on Figure 40, it is important to discuss the various peaks of interest. The first peak that is of interest is the amide C=O stretch at 1682 cm⁻¹ which is a sharp signal in the solid spectrum but as the solid becomes a gel the peak disappears and gives a very similar spectrum to the solvent which would make a clear conclusion since the gel is only composed of 10 mg solid versus the 1mL of solvent. The next peak that is corresponding to a functional group involved in gelation is the alkyl C-H stretch at 2949 cm⁻¹. This peak would play in the gelation properties due to the alkyl protecting group which will
assist in the hydrophobicity and hydrophilicity balance. The last peak to discuss is the amide N-H stretch at 3552 cm$^{-1}$. Which would assist in the hydrogen bonding of the gel matrix.

Fig. 40 ATR-FTIR spectrum of compound 10 in solid form (grey), gel form, 10 mg/mL DMSO: H$_2$O v/v 1:1 (blue), DMSO: H$_2$O v/v 1:1 solvent (orange).

As previously described the various peaks to describe the gelation properties in the hexane gel. Also shown in Figure 41, the amide N-H stretch at 3552 cm$^{-1}$ which would attribute to the hydrogen bonding assisting in the self-assembly of the molecules to induce the gel. Also, the peak at 2950 cm$^{-1}$ which corresponds to the alkyl C-H stretch. Which is predominant through all the spectrum which explains that these stretches are through the solvent and the solid which could play a role in the hydrophilicity and hydrophobicity balance in the self-assembly.
In order to use the gel matrix as a drug delivery system we must ensure that the gel will be strong when a certain amount of drug is entrapped. We completed a drug loading experiment using Naproxen sodium, an NSAID (non-steroidal anti-inflammatory drug) used for pain medication that relieves inflammation and joint stiffness. 4 mg compound of 10 with 1 mL of water (0.012M), 2 mg of naproxen sodium was added every 15 minutes to 1 hours to find the maximum amount of naproxen that was able to be loaded. At 36 mg the gel became unstable resulting in a final mol ratio of naproxen to gelator of 11.9. The photos in Figure 42 show these results.
Fig. 42 Gel photos of drug loading experiment. 4 mg of compound 10 with 1 mL H₂O, with ranging amounts of mg Naproxen. Left to right, (a.) 4 mg, (b.) 8 mg, (c.) 12 mg, (d.) 16 mg, (e.) 20 mg, (f.) 24 mg, (g.) 28 mg, (h.) 32 mg, and (i.) 36 mg.

After we determined a co-gel could be made with Naproxen sodium and the gelator. A gel was prepared in a 1-dram vial using 10 mg of compound 12, 0.5 mg/mL of naproxen sodium solution. After a stable gel formed and rested for 12 hours, 3 mL of water at pH 7 was added to the top of the gel carefully. Naproxen release from the gel was monitored by UV absorption at a certain time by transferring the supernatant with a pipet to a cuvette, and after each measurement, the aqueous phase was carefully transferred back to the vial and placed on top of the gel again until the next measurement. The UV spectra of the pure naproxen was also recorded and shown in Figure 43.
Fig. 43 Release of naproxen from gel to the aqueous phase. The gel was formed by 10 mg of compound 12 in 1 mL of 0.5 mg/mL naproxen solution, then 3 mL of pH 7 water was added to the top of the gel. The naproxen standard was prepared by 0.125 mg/mL H₂O.

Fig. 43a The percent release of naproxen at different times; this was calculated using absorbance at 331 nm at different times versus the standard.
The gel formed by compound 12 in H₂O was selected for testing the sustained release profile of trapped drugs from the gel phase to the solution phase due to the mimic of the biological systems. Naproxen was selected for the study due to the fluorophore that it contains within the molecule. The purpose of the characterization is to analyze the ability of the gelator to encapsulate drug molecules in the gel matrix. The drug release was monitored by UV absorption at a certain time by transferring the supernatant with a pipet to a cuvette, and after each measurement, the aqueous phase was carefully transferred back to the vial. From the spectrum shown in Figure 44 we can see that at 24 hours, 99% of Naproxen has been released from the gel matrix to the solution.

In order to compare the effectiveness of the NHAc moiety on the structure of the drug delivery systems a drug delivery system was done on the free amine compound 16. The gel was made using 5 mg of compound 16 and 1 mL of H₂O, 0.5 mg of naproxen sodium was added to the solution. The solution was heated and let to cool to ensure the gel was able to form with the naproxen sodium. The spectrum shown in Figure 45 shows the time course UV experiment of this study. The spectrum shows that the drug molecule was released at a much faster rate compared to Compound 12. We believe that the self-assembly for compound 12 is much stronger than that of 16 therefore the matrix is harder to break without introducing some external stimuli.
Fig. 44 Release of naproxen from gel to the aqueous phase. The gel was formed by 5 mg of compound 16 in 1 mL of 0.5 mg/mL naproxen solution, then 3 mL of pH 7 water was added to the top of the gel. The naproxen standard was prepared by 0.125 mg/mL H₂O.
Since we were able to successfully synthesize a hydrogelators. We investigated the treatment of base on the effectiveness of the drug delivery system. This experiment was done with compound 10 in pH 7 and pH 13 conditions. The experiments were conducted similarly to the conditions of above. The gel was made using 4 mg of compound 10 and 1 mL of H2O, and 0.5 mg of naproxen sodium was added to the solution. The solution was heated and let to cool to ensure the gel was able to form with the naproxen sodium. 2 mL of pH 7 solution was added to the top of the gel in the vial. The supernatant was studied via UV-Visible spectroscopy. The spectrum shown in Figure 45a shows the time course UV experiment of this study. The spectrum shows that the drug molecule was released very slowly at a release rate of 48 hours. In comparison the same gel was
made however, a pH 13 solution was placed on top of the gel to study the effective of the basic nature on the drug delivery mechanism. These results are shown in Figure 45b. Based on this experiment when basic conditions are introduced the release rate occurs faster by about 24 hours.

Fig. 45a Release of naproxen from gel to the aqueous phase under acidic (pH 5) conditions. The gel was formed by 4 mg of compound 10 in 1 mL of 0.5 mg/mL naproxen solution, then 3 mL of pH 5 solution was added to the top of the gel. The naproxen standard was prepared by 0.125 mg/mL H2O.
Fig. 45b The percent release of naproxen at different times; this was calculated using absorbance at 331 nm at different times versus the standard.

Not only can these gel matrices be used as a drug delivery system, they can be used as environmental remediation for dye removal. For the dye removal study, two different dyes were studied, Rhodamine B base and Toluidine blue. There absorption experiments are shown below. 13.4 mg of compound 11 was combined with 2 mL of water to create a gel at 6.7mg/mL, and 2 mL of 0.04 mM Rhodamine B solution was added to the top of the gel. A time course experiment was done using UV-Vis spectroscopy to determine the absorption of dye through the gel matrix. The dye absorption experiment was used to show the ability of the gel to absorb dye through the gel matrix. Based on the UV-spectra below in Figure 46 we can see that as time progresses the UV absorbance of the dye decreases. After 24 hours the maximum amount of dye is absorbed into the gel. There absorption experiments are shown below.
Fig. 46a Dye absorption study (A) time course UV-absorbance spectrum for dye absorption of Rhodamine B. 13.4 mg of compound \textit{11} was combined with 2mL of water to create a gel at 6.7mg/mL, and 2 mL of 0.04mM Rhodamine B solution was added to the top of the gel (B). gel photos of the absorption from 0 hour to 24 hours.
Fig. 46b The percent absorption of rhodamine B at different times; this was calculated using absorbance at 555 nm at different times versus the standard.

Similarly, toluidine blue absorption was also studied. The gel was prepared using 13.4 mg of compound 11 and 2 mL of water (6.7 mg/mL). A solution of 0.04 mM was made using Toluidine Blue. We added 2 mL of the Toluidine Blue solution on top of the gel and the absorption of the dye was measured using UV spectroscopy. The UV spectra are shown in Figure 47a below. We can conclude from Figure 47b the gel has a slow absorption for toluidine blue compared to rhodamine B.
Fig. 47a Dye absorption study (A) Time course UV-absorbance spectrum for dye absorption of Toluidine Blue. The gel was prepared using 13.4 mg of compound 11 and 2 mL of water (6.7 mg/mL), and 2 mL of 0.04 mM toluidine blue solution was added to the top of the gel. (B) gel photos of the absorption from 0 hour to 60 hours.
Fig. 47b The percent absorption of toluidine blue at different times; this was calculated using absorbance at 633 nm at different times versus the standard.

### 3.4 CONCLUSIONS

We have synthesized and characterized a series of 4,6-\(O\)-alkylidene protected monosaccharides and obtained several effective low molecular weight hydrogelators. This series of compounds had an overall good performance in a variety of solvents, especially for water solutions. The hydrogelators were used to encapsulate naproxen and the naproxen release profiles were analyzed using UV-Vis spectroscopy. The gel formed by compound 11 was also used to absorb two different dyes, rhodamine and toluidine blue, however the gels showed not-optimum absorption for the dyes. Further studies of different gelators and conditions of gel formations will be necessary to study dye absorption. The gel matrix showed good prospects as drug delivery profiles due to the sustained release over 24 hours. These glucosamine gelators are promising for a variety of potential applications.
3.5 EXPERIMENTAL SECTIONS

General Methods and Materials:

**Gelation test:** 2 mg of compound was added to a 1-dram vial, with 0.1 mL of the gelation testing solvent. The solution was heated until point of dissolving, if the solid did not dissolve it was concluded to be insoluble. If the solution was soluble it was placed on the bench for 30 min to cool to room temperature. If solid particles formed within the solvent, it was reported as a precipitate. If no solid particles formed and a homogenous solution was left, it resulted in soluble. If self-assembly occurred and a gel formed, the vial was inverted, and no flow of solvent was visible. At this point, it was further diluted with another 0.1 mL of the gelation solvent and followed through the same procedure until it was no longer forming a gel. The minimum gelation concentration (MGC) is the minimum concentration (mg/mL) that allows for gelation.

**FTIR Studies:** FTIR measurement was performed on a Bruker ALPHA Platinum ATR FTIR Spectrometer. The solid sample (gelator or a piece of gel scooped from the gel matrix) was placed onto the ATR crystal, and then pressure was gently applied to the solid sample by anvil before the measurement was taken. For the liquid sample, a droplet of the liquid sample was spread on the ATR crystal before the measurement was carried out. The operating software for spectrum acquisition is OPUS 7.5. The absorption spectra of gelator, gel form of the gelator in solvent and the solvent were obtained at room temperature in the range of 400-4000 cm\(^{-1}\).

**Naproxen trapping and release:** Naproxen release studies were done by encapsulating 0.5 mg of naproxen sodium in the gel matrix at MGC, with 2 mL of gelation solvent. After the gel was formed and stable, 2 mL of solution was added to the top of the gel matrix. The naproxen release was monitored by UV absorption at various time points. This was done by using a pipette to
carefully remove the supernatant from the gel into a cuvette. Then, after each measurement the supernatant was transferred carefully back to the gel matrix until the next time point. The naproxen standard and gelator were also reported.

**Dye absorption studies:** The dye absorption study was done using rhodamine B and toluidine blue. The experiments were carried out similarly. A 0.04 mM solution was made of both rhodamine B and toluidine blue. 13.4 mg of compound 11 was combined with 2mL of water to create a gel at 6.7 mg/mL. After a stable gel was formed, 2 mL of 0.04 mM rhodamine B solution was added to the top of the gel. The dye layer was tested via UV-Vis spectroscopy at various time points. Similarly, 13.4 mg of compound 11 was combined with 2mL of water to create a gel at 6.7 mg/mL. After a stable gel was formed, 2 mL of 0.04 mM toluidine blue solution was added to the top of the gel. The dye layer was tested via UV-Vis spectroscopy at various time points.

**Rheology studies:** The elastic behavior of the gels was studied via rheology. A HR-2 Discovery hybrid rheometer from TA Instruments with TRIOS software was used. A portion of the gel matrix around 1-1.5 mL was placed on the steel plate. The cone geometry is a 25 mm Peltier plate with a gap width of 100 µm. The experiment was carried out at 25 °C. The samples were applied with oscillation strain from 0.125 to 10%. After a frequency sweep was done for the sample in the range of 0.1 to 100.0 rad/s for the angular frequency. The results showed the storage modulus (G’) and loss modulus (G'”) as a function of angular frequency.
General synthesis of acetal:

To a small round both flask, 500 mg (1 equivalent) of an alkane aldehyde ranging from six to ten carbons in length was added. To the mixture trimethyl orthoformate (1.2 equivalents), para toluene sulfonic acid (PTSA) (0.1 equivalent), and 2 mL of anhydrous methanol as solvent. The reaction mixture was stirred at 70 °C for on average five hours. After the five hours, sodium bicarbonate solid (0.05 equivalents) was added to the mixture and stirred for 30 minutes to remove residual acid. Then the mixture was filtered and concentrated using rotary evaporator. The crude product was used directly for the next step.

General synthesis of 4,6 protected N-acetyl-D-glucosamine:

To a small round both flask, 500 mg (1 equivalent) of an N-acetyl-D-glucosamine. To the mixture the dimethyl acetal ranging from 6 carbon to 10 carbon length (1.2 equivalents) was added, para toluene sulfonic acid (PTSA) (0.1 equivalent), and 2 mL of anhydrous N,N-dimethylformamide as solvent. The reaction mixture was stirred at 70 °C for on average five hours. After the five hours, sodium bicarbonate solid (0.05 equivalents) was added to the mixture and stirred for 30 minutes to remove residual acid. Then the mixture was filtered and concentrated using rotary evaporator. Phase, phase extraction was done using DCM:H₂O (10mL, 3 times). The organic layer was extracted and concentrated. The crude product was purified with flash column chromatography (solvent will be mentioned for each analogue).
Synthesis of 4,6 hexyl protected N-acetyl-D-glucosamine derivative 8:

Hexanal (500 mg, 1 equivalent, 4.99 mmol), trimethyl orthoformate (635 mg, 1.2 equivalents, 5.99 mmol), p-Toluenesulfonic Acid (85.9 mg, 0.1 equivalent, 0.499 mmol) were added to a 50 mL round bottom flask, along with 2 mL of methanol (anhydrous) as solvent. The reaction mixture was stirred at 70 °C for five hours. After the five hours, sodium bicarbonate solid (0.05 equivalents) was added to the mixture and stirred for 30 minutes to remove residual acid. Then the mixture was filtered and concentrated using rotary evaporator. The crude product was used directly for the next step. N-acetyl-D-glucosamine (2 g, 1 equivalent, 8.5 mmol), hexyl aldehyde dimethyl acetal (C₅H₁₁CH(OMe)₂) (1.79 g, 1.2 eq, 10.2 mmol), p-Toluenesulfonic acid (PTSA) (0.146g, 0.1 equivalent, .85 mmol), and 2 mL of N,N-dimethylformamide was added to a small round bottom flask. The reaction mixture was stirred at 70 °C for about five hours. After the five hours, sodium bicarbonate solid (0.05 equivalents) was added to the mixture and stirred for 30 minutes to remove residual acid. Then the mixture was filtered and concentrated using rotary evaporator. Phase, phase extraction was done using DCM:H₂O (10 mL, 3 times). The organic layer was extracted and concentrated. The crude product was purified with flash column chromatography, final eluent (50% EtOAc/Hexane) be mentioned for each analogue). The desired product was a white solid (2.3 g, 84%), Rf = 0.32 in 1% MeOH/DCM. mp 154.2-155.9 °C. ¹H NMR (400 MHz, CDCl₃) 5.87 (d, J = 8.7 Hz, 1H), 4.69 (d, J = 3.9 Hz, 1H), 4.60 (t, J = 5.0 Hz, 1H), 4.22-4.11 (m, 2H), 3.83 (t, J = 9.6 Hz, 1H), 3.67-3.60 (m, 1H), 3.55 (t, J = 8.8 Hz, 1H), 3.40 (s, 3H), 3.36 (t, J = 9.2 Hz, 1H), 2.08 (s, 3H), 1.77-1.61 (m, 2H), 1.48-1.38 (m, 2H), 1.36-1.25 (m, 4H), 0.90 (t J = 6.9 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) 171.6, 102.8, 98.8, 81.6, 70.5, 68.4, 62.6, 55.2, 54.2, 34.2, 31.6, 23.7, 23.2, 22.5, 14. LC-MS m/z calculated for C₁₅H₂₇NO₆ [M + H]⁺ 317.2, found 317.2.
Synthesis of 4,6 hexyl protected N-acetyl-D-glucosamine derivative 9: Heptanal (500 mg, 1 equivalent, 4.38 mmol), trimethyl orthoformate (557 mg, 1.2 equivalents, 5.25 mmol), p-Toluenesulfonic Acid (75.4 mg, 0.1 equivalent, 0.438 mmol) were added to a 50 mL round bottom flask, along with 2 mL of methanol (anhydrous) as solvent. The reaction mixture was stirred at 70°C for five hours. After the five hours, sodium bicarbonate solid (0.05 equivalents) was added to the mixture and stirred for 30 minutes to remove residual acid. Then the mixture was filtered and concentrated using rotary evaporator. The crude product was used directly for the next step.

N-acetyl-D-glucosamine (2 g, 1 equivalent, 8.5 mmol), heptyl aldehyde dimethyl acetal (C₆H₁₁CH(OMe)₂) (1.63 g, 1.2 eq, 10.2 mmol), p-Toluenesulfonic acid (PTSA) (0.146 g, 0.1 equivalent, 0.85 mmol), and 2 mL of N,N-dimethylformamide was added to a small round bottom flask. The reaction mixture was stirred at 70°C for about five hours. After the five hours, sodium bicarbonate solid (0.05 equivalents) was added to the mixture and stirred for 30 minutes to remove residual acid. Then the mixture was filtered and concentrated using rotary evaporator. Phase, phase extraction was done using DCM:H₂O (10mL, 3 times). The organic layer was extracted and concentrated. The crude product was purified with flash column chromatography, final eluent 50% EtOAc/Hexane. The desired product was a white solid (2.21 g, 79%), Rᵣ = 0.38 in 50% EtOAc/Hexane. mp 156.5-157.9 °C. ¹H NMR (400 MHz, CDCl₃) 6.03 (d, J = 8.7 Hz, 1H), 4.68 (d, J = 3.8 Hz, 1H), 4.58 (t, J = 5.0 Hz, 1H), 4.19-4.15 (m, 1H), 4.14-4.09 (m, 1H), 3.81 (t, J = 9.7 Hz, 1H), 3.63 (ddd, J = 4.6, 4.7, 9.5 Hz, 1H), 3.56-3.51 (m, 1H), 3.38 (s, 3H), 3.36-3.31 (m, 1H), 2.06 (s, 3H), 1.74-1.85 (m, 2H), 1.46-1.37 (m, 2H), 1.27 (bs, 8H), 0.88 (t, J = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) 171.6, 102.8, 98.7, 81.6, 70.7, 68.4, 62.5, 55.2, 54.2, 34.3, 31.7, 29.4, 29.1, 24, 23.2, 22.6, 14.0. LC-MS m/z calculated for C₁₆H₂₉NO₆ [M + H]⁺ 331.2, found 331.2.
Synthesis of 4,6 octyl protected N-acetyl-D-glucosamine derivative 10: Octanal (500 mg, 1 equivalent, 3.90 mmol), trimethyl orthoformate (497 mg, 1.2 equivalents, 4.68 mmol), p-Toluenesulfonic Acid (67.2 mg, 0.1 equivalent, 0.390 mmol) were added to a 50 mL round bottom flask, along with 2 mL of methanol (anhydrous) as solvent. The reaction mixture was stirred at 70 °C for five hours. After the five hours, sodium bicarbonate solid (0.05 equivalents) was added to the mixture and stirred for 30 minutes to remove residual acid. Then the mixture was filtered and concentrated using rotary evaporator. The crude product was used directly for the next step. N-acetyl-D-glucosamine (2 g, 1 equivalent, 8.5 mmol), octyl aldehyde dimethyl acetal (C_{7}H_{11}CH(OMe)_{2}) (1.78 g, 1.2 eq, 10.2 mmol), p-Toluenesulfonic acid (PTSA) (0.146 g, 0.1 equivalent, 0.85 mmol), and 2 mL of N,N-dimethylformamide was added to a small round bottom flask. The reaction mixture was stirred at 70 °C for about five hours. After the five hours, sodium bicarbonate solid (0.05 equivalents) was added to the mixture and stirred for 30 minutes to remove residual acid. Then the mixture was filtered and concentrated using rotary evaporator. Phase, phase extraction was done using DCM:H₂O (10 mL, 3 times). The organic layer was extracted and concentrated. The crude product was purified with flash column chromatography, final eluent 50% EtOAc/Hexane. The desired product was a white solid (2.55 g, 87%), R_f = 0.4 in 50% EtOAc/Hexane. mp 157.9-159.1 °C. ^1H NMR (400 MHz, CDCl₃) 6.02 (d, J = 9 Hz, 1H), 4.69 (d, J = 4.1 Hz, 1H), 4.6 (t, J = 4.9 Hz, 1H), 4.23-4.17 (m, 1H), 4.15-4.11 (m, 1H), 3.81 (t, J = 10.1 Hz, 1H), 3.63 (ddd, J = 4.7 Hz, 4.8, 9.7, 1H), 3.56-3.51 (m, 1H), 3.42 (s, 3H), 3.35-3.29 (m, 1H), 2.1 (s, 3H), 1.74-1.85 (m, 2H), 1.50-1.42 (m, 2H), 1.3 (bs, 10H), 0.89 (t, J = 6.6 Hz, 3H). ^13C NMR (100 MHz, CDCl₃) 174.9, 109.3, 108.7, 86.8, 80.8, 73.1, 69.3, 60.3, 55.6, 34.2, 32, 29.9, 24.1, 23.5, 22.6, 14.2. LC-MS m/z calculated for C_{17}H_{31}NO_{6} [M + H]^+ 345.2, found 345.2.
Synthesis of 4,6 nonyl protected N-acetyl-D-glucosamine derivative 11:

Nonal (500 mg, 1 equivalent, 3.52 mmol), trimethyl orthoformate (448 mg, 1.2 equivalents, 4.22 mmol), p-Toluenesulfonic Acid (60.6 mg, 0.1 equivalent, 0.352 mmol) were added to a 50 mL round bottom flask, along with 2 mL of methanol (anhydrous) as solvent. The reaction mixture was stirred at 70°C for five hours. After the five hours, sodium bicarbonate solid (0.05 equivalents) was added to the mixture and stirred for 30 minutes to remove residual acid. Then the mixture was filtered and concentrated using rotary evaporator. The crude product was used directly for the next step. N-acetyl-D-glucosamine (2 g, 1 equivalent, 8.5 mmol), nonyl aldehyde dimethyl acetal (C₈H₁₁CH(OMe)₂) (1.92 g, 1.2 eq, 10.2 mmol), p-toluenesulfonic acid (PTSA) (0.146 g, 0.1 equivalent, 0.85 mmol), and 2 mL of N,N-dimethylformamide was added to a small round bottom flask. The reaction mixture was stirred at 70°C for about five hours. After the five hours, sodium bicarbonate solid (0.05 equivalents) was added to the mixture and stirred for 30 minutes to remove residual acid. Then the mixture was filtered and concentrated using rotary evaporator. Phase, phase extraction was done using DCM:H₂O (10 mL, 3 times). The organic layer was extracted and concentrated. The crude product was purified with flash column chromatography, final eluent 50% EtOAC/Hexane. The desired product was a white solid (2.29 g, 75%), Rᵣ = 0.4 in 50% EtOAc/Hexane. mp 160.1-161.8 °C. ¹H NMR (400 MHz, CDCl₃) 5.99 (d, J = 8.6 Hz, 1H), 4.69 (d, J = 3.8 Hz, 1H), 4.58 (t, J = 5 Hz, 1H), 4.22-4.09 (m, 2H), 3.82 (t, J = 9.6 Hz, 1H), 3.66-3.60 (m, 1H), 3.57-3.50 (m, 1H), 3.38 (s, 3H), 3.36-3.31 (m, 1H), 3.26 (bs, 1H), 2.06 (s, 3H), 1.74-1.58 (m, 2H), 1.46-1.36 (m, 2H), 1.33-1.22 (m, 12H), 0.89 (t, J = 6.5 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) 174.6, 109.4, 108.5, 87.0, 80.6, 73.2, 69.1, 60.5, 55.6, 34.4, 31.8, 29.8, 29.7, 29.2, 24.1, 23.5, 22.8, 14.0. LC-MS m/z calculated for C₁₈H₃₃NO₆ [M + H]+ 360.5, found 360.5.
**Synthesis of 4,6 decyl protected N-acetyl-D-glucosamine derivative 12:**

Decanal (500 mg, 1 equivalent, 3.20 mmol), trimethyl orthoformate (407 mg, 1.2 equivalents, 4.22 mmol), p-Toluenesulfonic Acid (55.1 mg, 0.1 equivalent, 0.320 mmol) were added to a 50 mL round bottom flask, along with 2 mL of methanol (anhydrous) as solvent. The reaction mixture was stirred at 70°C for five hours. After the five hours, sodium bicarbonate solid (0.05 equivalents) was added to the mixture and stirred for 30 minutes to remove residual acid. Then the mixture was filtered and concentrated using rotary evaporator. The crude product was used directly for the next step. N-acetyl-D-glucosamine (2 g, 1 equivalent, 8.5 mmol), decyl aldehyde dimethyl acetal (C₈H₁₁CH(OMe)₂) (2.06 g, 1.2 eq, 10.2 mmol), p-Toluenesulfonic acid (PTSA) (0.146 g, 0.1 equivalent, 0.85 mmol), and 2 mL of N,N-dimethylformamide was added to a small round bottom flask. The reaction mixture was stirred at 70°C for about five hours. After the five hours, sodium bicarbonate solid (0.05 equivalents) was added to the mixture and stirred for 30 minutes to remove residual acid. Then the mixture was filtered and concentrated using rotary evaporator. Phase, phase extraction was done using DCM: H₂O (10 mL, 3 times). The organic layer was extracted and concentrated. The crude product was purified with flash column chromatography, final eluent 50% EtOAc/Hexane. The desired product was a white solid (2.53 g, 85%), Rₚ = 0.4 in 50% EtOAc/Hexane. mp 162.1-163.7 °C. ¹H NMR (400 MHz, CDCl₃) 6.03 (d, J = 8.2 Hz, 1H), 4.68 (d, J = 3.4 Hz, 1H), 4.58 (t, J = 5.4 Hz, 1H), 4.19-4.15 (m, 1H), 4.14-4.09 (m, 1H), 3.81 (t, J = 9.7 Hz, 1H), 3.63 (ddd, J = 4.9 Hz, 5.1, 9.2, 1H), 3.56-3.51 (m, 1H), 3.39 (s, 3H), 3.36-3.31 (m, 1H), 2.08 (s, 3H), 1.72-1.5 (m, 2H), 1.51-1.45 (m, 2H), 1.29 (br s, 14H), 0.91 (t, J = 6.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) 174.4, 109.1, 108.2, 86.9, 80.3, 72.8, 69.0, 60.2, 55.3, 34.1, 31.7, 29.8, 29.3, 23.8, 23.4, 22.5, 13.9. LC-MS m/z calculated for C₁₉H₃₅NO₆ [M + H]+ 374.3, found 374.2.
Synthesis of 4,6 hexyl protected deacetylated N-acetyl-D-glucosamine derivative 13:

750 mg of starting material 8 was added to Chemglass tube for the microwave, along with 5 mL of 1M NaOH in ethanol solution. This reaction ramped to 150°C for 10 minutes then remained there for an additional 40 minutes. After the reaction was complete ethanol was removed and work up was done using DCM: Water (20 mL x 10 mL), the organic layer was dried and concentrated. The desired product was a white solid (579 mg, 89%), \( R_f = 0.41 \) in 5% DCM: MeOH. mp 184.2-185.9°C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) 4.66 (d, \( J = 3.6 \) Hz, 1H), 4.58 (t, \( J = 5.1 \) Hz, 1H), 4.13 (dd, \( J = 10.1, 4.8 \) Hz, 1H), 3.70-3.63 (m, 2H), 3.53 (t, \( J = 10.3 \) Hz, 1H), 3.41 (s, 3H), 3.26 (t, \( J = 9.3 \) Hz, 1H), 2.76 (dd, \( J = 9.6 \) Hz, 3.6, 1H), 1.73-1.63 (m, 2H), 1.48-1.38 (m, 2H), 1.36-1.27 (m, 4H), 0.91 (t, \( J = 6.9 \) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 109.4, 108.7, 88.1, 81.5, 75.1, 70.2, 56.5, 56.2, 35.3, 32.8, 30.6, 25.0, 23.7, 15.1.

Synthesis of 4,6 heptyl protected deacetylated N-acetyl-D-glucosamine derivative 14:

750 mg of starting material, 9 was added to Chemglass tube for the microwave, along with 5 mL of 1M NaOH in ethanol solution. This reaction ramped to 150°C for 10 minutes then remained there for an additional 40 minutes. After the reaction was complete ethanol was removed and work up was done using DCM: Water (20 mL x 10 mL), the organic layer was dried and concentrated. The desired product was a white solid (596 mg, 91%), \( R_f = 0.44 \) in 5% DCM: MeOH. mp 186.1-187.5 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) 4.66 (d, \( J = 3.6 \) Hz, 1H), 4.58 (t, \( J = 5.1 \) Hz, 1H), 4.13 (dd, \( J = 10.1, 4.8 \) Hz, 1H), 3.70-3.63 (m, 2H), 3.53 (t, \( J = 10.3 \) Hz, 1H), 3.41 (s, 3H), 3.26 (t, \( J = 9.3 \) Hz, 1H), 2.76 (dd, \( J = 9.6 \) Hz, 3.6, 1H), 1.73-1.63 (m, 2H), 1.48-1.38 (m, 2H), 1.36-1.27 (m, 6H), 0.91 (t, \( J = 6.9 \) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 107.4, 106.7, 86.1, 79.5, 73.1, 68.2, 54.5, 54.2, 33.3, 28.9, 28.3, 23.0, 21.7, 20.9, 13.1.
Synthesis of 4,6 octyl protected deacetylated N-acetyl-D-glucosamine derivative 15:

750mg of starting material, 10 was added to Chemglass tube for the microwave, along with 5mL of 1M NaOH in ethanol solution. This reaction ramped to 150ºC for 10 minutes then remained there for an additional 40 minutes. After the reaction was complete ethanol was removed and work up was done using DCM: Water (20 mL x 10 mL), the organic layer was dried and concentrated. The desired product was a white solid (573 mg, 79%), Rf = 0.47 in 5% DCM: MeOH. mp 187.2-188.7 ºC. 1H NMR (400 MHz, CDCl3) 4.66 (d, J = 3.6 Hz, 1H), 4.58 (t, J = 5.1 Hz, 1H), 4.13 (dd, J = 10.1, 4.8 Hz, 1H), 3.70-3.63 (m, 2H), 3.53 (t, J = 10.3 Hz, 1H), 3.41 (s, 3H), 3.26 (t, J = 9.3 Hz, 1H), 2.76 (dd, J = 9.6, 3.6 Hz, 1H), 1.73-1.63 (m, 2H), 1.48-1.38 (m, 2H), 1.36-1.27 (m, 8H), 0.91 (t, J = 6.9 Hz, 3H). 13C NMR (100 MHz, CDCl3) 110.4, 109.4, 89.1, 82.5, 76.1, 71.2, 57.5, 57.2, 36.3, 33.9, 31.9, 31.6, 31.3, 26, 24.7, 16.1.

Synthesis of 4,6 nonyl protected deacetylated N-acetyl-D-glucosamine derivative 16:

750 mg of starting material, 11 was added to Chemglass tube for the microwave, along with 5mL of 1M NaOH in ethanol solution. This reaction ramped to 150 ºC for 10 minutes then remained there for an additional 40 minutes. After the reaction was complete ethanol was removed and work up was done using DCM: Water (20 mL x 10 mL), the organic layer was dried and concentrated. The desired product was a white solid (616 mg, 93%), Rf = 0.51 in 5% DCM: MeOH. mp 191.1-192.7 ºC. 1H NMR (400 MHz, CDCl3) 4.66 (d, J = 3.6 Hz, 1H), 4.58 (t, J = 5.1 Hz, 1H), 4.13 (dd, J = 10.1, 4.8 Hz, 1H), 3.70-3.63 (m, 2H), 3.53 (t, J = 10.3 Hz, 1H), 3.41 (s, 3H), 3.26 (t, J = 9.3 Hz, 1H), 2.76 (dd, J = 9.6 Hz, 3.6, 1H), 1.73-1.63 (m, 2H), 1.48-1.38 (m, 2H), 1.36-1.27 (m, 10H),
0.91 (t, $J = 6.9$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) 106.4, 105.4, 85.1, 78.5, 72.1, 67.2, 53.2, 32.3, 28.9, 27.9, 27.6, 27.3, 22, 20.7, 12.1.

**Synthesis of 4,6 decyl protected deacetylated N-acetyl-D-glucosamine derivative 17:**

750 mg of starting material, 12 was added to Chemglass tube for the microwave, along with 5 mL of 1M NaOH in ethanol solution. This reaction ramped to 150 ºC for 10 minutes then remained there for an additional 40 minutes. After the reaction was complete ethanol was removed, and work up was done using DCM:Water (20 mL x 10 mL), the organic layer was dried and concentrated. The desired product was a white solid (670 mg, 85 %), R$_f$ = 0.48 in 5% DCM:MeOH. mp 193.7-195.1ºC. $^1$H NMR (400 MHz, CDCl$_3$) 4.66 (d, $J = 3.6$ Hz, 1H), 4.58 (t, $J = 5.1$ Hz, 1H), 4.13 (dd, $J = 10.1$, 4.8 Hz, 1H), 3.70-3.63 (m, 2H), 3.53 (t, $J = 10.3$ Hz, 1H), 3.41 (s, 3H), 3.26 (t, $J = 9.3$ Hz, 1H), 2.76 (dd, $J = 9.6$, 3.6 Hz, 1H), 1.73-1.63 (m, 2H), 1.48-1.38 (m, 2H), 1.36-1.27 (m, 12H), 0.91 (t, $J = 6.9$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) 102.7, 101.2, 81.5, 71.7, 68.6, 62.7, 56.7, 55.3, 34.3, 31.9, 29.5, 29.4, 29.3, 24.1, 22.6, 14.1.
CHAPTER 4. SYNTHESIS AND STUDIES OF LMWGS CONTAINING COVALENTLY LINKED DRUG MOLECULES

4.1 ABSTRACT
Low molecular weight gelators (LMWGs) have attracted increasing attention due to the potential broad applications in many fields spanning from biomedical research to advanced materials. Several D-glucose and D-glucosamine derived gelators have been used for the encapsulation of drug molecules and the drug release profiles have been studied. However, covalently attaching a drug molecule to the carbohydrate based gelator and using chemical reactions to release the drug has not been studied extensively. In order to further understand how these drugs and gelator conjugates will self-assemble in aqueous solution, a few derivatives incorporating drug molecules within the LMWGs were synthesized and characterized. These derivatives showed poor gelation properties in aqueous mixtures and pure water. However, the ester linked naproxen derivatives can be hydrolyzed under basic conditions and these may have some implications for controlled release drug delivery systems.

4.2 INTRODUCTION
In recent years the study of LMWGs as drug delivery systems has become a wide area of interest. LMWGs have a wide range of capabilities from medical applications to environmental remediation. Carbohydrate based LMWGs have intrinsic biocompatibility and degradability and they can form environment friendly new materials. The resulting gels are fully reversible due to the noncovalent driving forces for gelation. Previously we have found that 4,6-\(O\)-benzylidene acetal protected D-glucose and D-glucosamine derivatives form robust organogels and hydrogels.
Several gels were explored for their application in naproxen encapsulation and release study. These gels were able to form stable gels in the presence of naproxen sodium and naproxen was released slowed from the gel phase to solution phase. Figure 48 shows compounds which were able to effectively form co-gel systems with drug molecules. External stimuli were applied to these co-gel systems to study their drug delivery properties. Goyal et al. synthesized a series of pH labile gelators which showed under acidic conditions it can be used as an effective drug delivery system. If a pH labile functional group is introduced into the gelator structure, the drug will effectively release from the gel matrix at a faster rate. To further investigate the functional group effect on the drug delivery systems Chen et al. synthesized a series of triazole derivatives on the first position of the sugar ring. These derivatives formed gels in a variety of solvents majority of the solvents were aqueous mixtures. The drug delivery profile was studied with Naproxen which was fully released from the gel matrix at 24 hours. The final series was a series which studied the third position of the sugar ring. Also, Chen et al. synthesized a series of 3-O-esters of N-acetyl-D-glucosamine derivatives. The drug delivery profile was studied using naproxen as the drug molecule. This drug delivery system was able to release 75% of the drug at 48 hours. The systems studied in our lab could effectively prove to release drug molecules from the self-assembled matrix to solution. Encapsulation of the drug molecules in the gel itself using some form of external stimuli as the source for release has been studied extensively in our lab, but covalently attaching a drug molecule to the gelator and using chemical reactions to release the drug has not been investigated in detail.
There are examples from the literature converting a drug molecule into a low molecular weight gelator. The structures of a few examples are shown in Figure 49. The first example was studied by Huang et. al. The combination of two drugs chlorambucil and gemcitabine for the multi-therapeutic effect on cancers. Which was found to show steady and long-term release for cancer therapy.\(^{67,104}\) There were a variety of examples using peptides as the backbone for the various gelators. Wang et. al. synthesized a naproxen based tetrapeptide. These self-assembling tetrapeptides were used as vaccine adjuvants which would ultimately assist in cancer therapy by simulating T cell responses and reducing inflammation associated with tumors.\(^{105}\) Similarly Xu et. al. was able to synthesize an NDP labeled hydrogelators that effectively created a molecular probe for anti-cancer therapy. Also, Xu et. al. synthesized a phosphatase induced supramolecular hydrogel, which self-assembles under the protein phosphatase since the will dephosphorylate the compound to the corresponding hydrogelators. These molecules may effectively form minimally invasive hydrogel drug delivery for anti-cancer therapy. The final example that will be discussed is using DNA-drug conjugates. Zhang et. al. developed a light-triggered nucleic acid-drug amphiphiles which was found to be carrier free drug delivery platforms. It was found that covalently attaching a drug moiety can achieve many applications for cancer therapy.\(^{106}\) These
drug delivery systems are carrier free and effectively showed that the variation in structure can obtain the anti-cancer therapy in many ways.

![Structures of NSAID derived gelators.](image)

Fig. 49 Structures of NSAID derived gelators.

In previous studies the use of non-steroidal anti-inflammatory drugs (NSAIDs) was of popularity due to their anti-inflammatory properties. Majumder *et. al.* has synthesized a series of naproxen derived salts which are shown in Figure 50. These molecules use secondary ammonium
monocarboxylates (SAM) and primary ammonium monocarboxylates (PAM) as synthons in order to produce effective salt based gelators with NSAID derived portions. Figure 1 below shows salts derived from the NSAID, naproxen. These salts form simple organic molecular topical gels which are capable of *in vivo* self-delivery of drugs.\(^{28}\)

![Salts derived from the NSAID – naproxen.](image)

**4.3 RESULTS AND DISCUSSIONS**

The syntheses for these compounds are shown in Scheme 1. The incorporation of drug molecules into O-alkylidene protected N-acetal-D-glucosamine were carried out by acylation of the amino headgroup 2 with bromoalkanoyl chlorides first and followed by S\(_2\) reactions. Compounds 6-10 were obtained. Examples of the characterization for one the compounds are shown in Figures 51-53- the proton and carbon NMR spectra for compound 8.
Scheme 4: Synthesis of drug-gelator conjugates by alkylation reactions.
Fig. 51 $^1$H NMR of compound 8 in CDCl$_3$
After these compounds were synthesized, their gelation properties were then screened in several different solvents. Their gelation abilities were tested in various aqueous mixtures and water to determine their gelation ability for biological drug delivery studies. From Table 8, we can determine that these gelators are not effective gelators at low concentrations, however at 30 mg/mL there were a few effective gels synthesized. Also, there were a few gels that formed if the sample at 20 mg/mL were cooled to 0°C. From previous study, we effectively made an effective hydrogelators with compound 1, therefore we decided to test a 1:1 mole ratio of compound 1:8, which was not effective and precipitated in all solvents. Figure 53 shows the IR spectrum of the

Fig. 52 $^{13}$C NMR of compound 8 in CDCl$_3$
solid material of 10 along with the gel made by 10 in EtOH: H2O 1:2 30mg/mL. We can conclude from this spectrum that the gel and solid have very similar properties at this higher concentration. Figure 54 shows the gel made by 10 in EtOH: H2O 1:2, along with their optical images which show the gel has a small vesicle morphology at 20x.

Table 8. Gelation test table of compounds 6-10.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>H2O 1:1</th>
<th>EtOH:H2O 1:1</th>
<th>EtOH:H2O 1:2</th>
<th>EtOH 1:1</th>
<th>DMSO 1:1</th>
<th>DMSO:H2O 1:1</th>
<th>DMSO:H2O 1:2</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>PG</td>
<td>G*</td>
<td>G*</td>
<td>S</td>
<td>S</td>
<td>G 30.0</td>
<td>G 30.0</td>
</tr>
<tr>
<td>7</td>
<td>I</td>
<td>G 30.0</td>
<td>G*</td>
<td>S</td>
<td>S</td>
<td>G*</td>
<td>G 30.0</td>
</tr>
<tr>
<td>8</td>
<td>I</td>
<td>I</td>
<td>G*</td>
<td>S</td>
<td>S</td>
<td>G*</td>
<td>I</td>
</tr>
<tr>
<td>9</td>
<td>PG</td>
<td>I</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>P</td>
<td>G*</td>
</tr>
<tr>
<td>10</td>
<td>I</td>
<td>I</td>
<td>G 30.0</td>
<td>S</td>
<td>S</td>
<td>P</td>
<td>I</td>
</tr>
<tr>
<td>8+1a</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
</tr>
</tbody>
</table>

For compounds forming gels, their MGCs are given in mg of gelator/mL of solvent, I-insoluble, P-precipitate, and S-soluble at 20 mg/mL, Cr-crystallizes. G*-Forms gel at 20 mg/mL when cooled to 0°C

a 1:1 mol ratio of Compound 8 (20mg): Compound 1 (10.5mg)
Fig. 53 – IR Spectra of compound 10 solid (blue) and gel (orange). The gel concentration was 30 mg/mL in EtOH:H₂O (v/v 1:2).
Fig. 54 a) Gel Photo of compound 10, 30 mg/mL EtOH: H2O 1:2 b) and c) OM images of compound 10, 30mg/mL EtOH: H2O 1:2 20X
These compounds did not form gels typically at up to 20 mg/mL. But conditions of cleavage of the esters were studied next to obtain the triggered release profile for naproxen. A time course experiment was done in basic conditions (pH 10 and pH 13) to determine if these could be an effective base triggered drug delivery system. For both experiments 2mg of compound 6 was dissolved in 1 mL of DMSO:H\textsubscript{2}O 1:2. 2 mL of pH 10 solution (Fig. 55) or pH 13 solution (Fig 56) was added to the solution. The Naproxen standard was composed of 0.8 mg of naproxen sodium with 1 mL of DMSO:H\textsubscript{2}O 1:2 and 2 mL of pH 10 (Fig. 55) or pH 13 (Fig. 56) solution. A time point was taken every 2 hours until the naproxen had reached full release. From Figure 55, the pH 10 study, we concluded that at 10 hours the covalent linkage had been cleaved. However, the pH 13 study had complete cleavage after 6 hours. Therefore, the stronger the base the less time it takes for a covalent linkage to cleave completely.
Fig. 55 2 mg of compound 6 was dissolved in 1 mL of DMSO:H₂O 1:2 and 2 mL of pH 10 solution. The naproxen standard was composed of 0.8 mg of naproxen sodium with 1 mL of DMSO: H₂O 1:2 and 2 mL of pH 10 solution. A time point was taken every hour for 10 hours.
Fig. 56 2 mg of compound 6 was dissolved in 1mL of DMSO:H₂O 1:2 and 2 mL of pH 13 solution. The naproxen standard was composed of 0.8 mg of naproxen sodium with 1 mL of DMSO: H₂O 1:2 and 2 mL of pH 13 solution. A time point was taken every hour for 6 hours.

Base on the UV-Vis absorption studies for naproxen-drug conjugate that the ester linkages can be hydrolyzed under basic conditions. The cleavage products will be fully characterized and studied in the future (with collaboration with other graduate students in the group). Although these compounds were not gelators on their own at room temperature, these compounds may be useful in forming two component systems using these compounds as the probe for the local environment.
4.4 CONCLUSIONS

In summary, several naproxen and acetaminophen derivatives have been synthesized and characterized. The drug-gelator conjugates were not effective gelators, however they may be useful in forming two-component gelators and as molecule probes. The naproxen derivatives can be hydrolyzed under basic conditions to release the free naproxen. The response towards base treatment at different time intervals were studied by UV-Vis absorption spectroscopy. Further studies are needed to characterize the base cleaved diols and the use of these compounds as fluorescent probes for carbohydrate based LMWGs with similar structures. Additional modifications may also include different 4,6-functional groups and derivatives with different spacers between naproxen and the sugar amide functions.

4.5 EXPERIMENTAL SECTIONS

General methods and materials. The solvents and reagents were used straight as they were received from the merchants. Purification was done by flash chromatography on a conventional column using 230-400 mesh silica gel. The solvent systems used for chromatography are all in a volume ratio. The solvent mixtures for all gelation tests are also in volume ratios. NMR analysis was conducted using a 400 MHz Bruker NMR spectrometer. Melting point measurements were carried out using a Stuart SMP40 automatic melting-point apparatus.
**Gelation testing:** On average, about 2 mg of a previously dried compound was placed in a vial, 1 dram in size. A series of solvents was then added until a concentration of 20 mg/mL was obtained. Once the vial is capped, heat the solution until the dried compound is completely dissolved. During certain cases the mixture should be sonicated in order to ensure a homogenous solution is formed. Once the compound is dissolved, let the mixture cool to room temperature. After fifteen minutes, if there is a clear solution still present in the vial it is said to be soluble. If the vial can be inverted without flow of solvent, the sample is said to be a stable gel, otherwise it is said to be unstable. In order to determine the minimum gelation concentration (MGC), a serial dilution was performed on the stable gels. The minimum gelation concentration is defined as the concentration prior to unstable gelation.

**Synthesis of 4-bromobutanoyl chloride.**

4-bromobutanoic acid (480 mg, 2.46 mmol, 1 eq) and oxalyl chloride (0.24 mL, 2.70 mmol, 1.1 eq) was added to a round bottom flask with 1 drop DMF and 6 mL DCM anhydrous as solvent. The reaction stirred from 0 °C to room temperature to 40 °C for 2 hours and then concentrated and used directly for the next step.

**Synthesis of 6-bromohexanoyl chloride**

Starting material (480 mg, 2.46 mmol, 1 eq) and oxalyl chloride (0.24 mL, 2.70 mmol, 1.1 eq) was added to a round bottom flask with 1 drop DMF and 6 mL DCM anhydrous as solvent. The reaction stirred from 0 degrees to room temperature to 40 C for 2 hours and then used directly for the next step.
General synthesis of 4,6-O-hexyl protected N-acetal-D-glucosamine halide derivatives.

Compound 2 (50 mg, 0.181 mmol, 1 eq.) was added to a round bottom flask with 75 mg of potassium carbonate (0.543 mmol, 3 eq.) was added to the flask with 3 mL of THF, this mixture stirred at 0°C for 1 hour, then 42 mg (0.199 mmol, 1.1 eq) of the acid chloride was added dropwise over the course of 1 hr. The mixture went from 0°C to RT over the course of 4 hours the reaction showed completion. The reaction mixture was quenched with solid sodium bicarbonate (0.05 eq). The mixture was filter. Phase-phase extraction was done using DCM: Water (20 mL, 3 times), the organic layer was dried. Flash chromatography was run to purify the reaction to afford the pure product.

Synthesis of 4,6-O-hexyl protected N-acetal-D-glucosamine ethyl bromide derivative 3:

Compound 2 (450 mg, 1.56 mmol, 1 eq), 678 mg K₂CO₃ (4.92 mmol, 3 eq) and 0.293 mL DIEA (1.638 mmol, 1 eq) were added to a 100 mL round bottom flask with 20 mL anhydrous DCM. The solution was placed in the ice both and allowed to stir for 0.5 h. Then, 346 mg bromoacetyl bromide (1.72 mmol, 1.1 eq.) was added to mixture dropwise and the reaction was kept for 1 hr. at 0°C. The reaction mixture was raised from 0°C to RT. The reaction was stirred for an additional 3 hrs. at RT. The mixture was washed by water (3 mL×2) to give white solid crude which was purified by column chromatography using eluent of pure DCM and 3 % MeOH/DCM to afford the product (464 mg, 75 %).

Synthesis of 4,6-O-hexyl protected N-acetal-D-glucosamine butyl bromide derivative 4:

Compound 2 (450 mg, 1.56 mmol, 1eq), 678 mg K₂CO₃ (4.92 mmol, 3 eq) and 0.293 mL DIEA (1.638 mmol, 1eq) were added to a 100mL flask with 20 mL anhydrous DCM. The solution was
placed in an ice both for 0.5h of stirring. Then, 319 mg of 4-bromobutanoyl chloride (1.72 mmol, 1.1 eq.) was added to mixture dropwise and the reaction was kept for 1 hr. at 0°C. The reaction mixture was raised from 0°C to RT. The reaction was stirred for an additional 3 hr. at RT. The mixture was washed by water (3 mL×2) to give white solid crude which was purified by column chromatography using eluent of pure DCM and 3% MeOH/DCM to afford the pure white product (494 mg, 1.16 mmol, 74.6%).

**Synthesis of 4,6-O-hexyl protected N-acetal-D-glucosamine hexyl bromide derivative 5:**
Compound 2 (450 mg, 1.56 mmol, 1 eq), 678 mg K₂CO₃ (4.92 mmol, 3 eq) and 0.293 mL DIEA (1.638 mmol, 1eq) were added to a 100 mL flask with 20 mL anhydrous DCM. The solution was place in the ice both for 0.5h of stirring. Then 525 mg of 6-bromohexanoyl chloride (2.46 mmol, 1.5 eq) was added to mixture dropwise and the reaction was kept for 1h under ice both conditions. Then the ice bath was removed. The reaction was kept for another 3hr at RT. The mixture was washed by water (3 mL×2) to give the crude white solid which was purified by column chromatography using eluent of pure DCM and 3% MeOH/DCM. The desired product, white solid (525 mg, 74.6%).

**General synthesis of ester linked 4, 6-O-alkylidene protected N-acetal-D-glucosamine derivatives with naproxen and acetaminophen:** Compound 3-5 (1 eq) was added to a scintillation vial with Naproxen sodium or paracetamol (2 eq) and 3 mL anhydrous DMF. The reaction stirred at 60°C for 20 hours. The solvent was removed under reduced pressure. The mixture was purified by column chromatography using eluent from 1% to 3% MeOH: DCM to afford desired product.
**Synthesis of compound 6:**

Compound 3 (75 mg, 0.189 mmol, 1 eq) was added to a scintillation vial with 95 mg Naproxen sodium (0.379 mmol, 2 eq) and 3 mL anhydrous DMF. The reaction stirred at 60 ºC for 20 hours. The solvent was removed under reduced pressure. The mixture was purified by column chromatography using eluent from 1% to 3% MeOH: DCM to afford desired product (89 mg, 82 %). Rf = 0.57 in solvent 3% MeOH: DCM. mp 152.3-154.2 ºC. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.75-7.70 (m, 3H), 7.42 (dd, $J = 8.5$ Hz, 1.8, 1H), 7.29 (s, 1H), 7.20 (dd, $J = 8.9$, 2.5 Hz, 1H), 7.15 (d, $J = 2.4$ Hz, 1H), 5.80 (d, $J = 9.2$ Hz, 1H), 4.81 (d, $J = 15.7$ Hz, 1H), 4.51 (t, $J = 5.1$ Hz, 2H), 4.47 (d, $J = 4.5$ Hz, 1H), 4.02-3.96 (m, 2H), 3.95 (s, 3H), 3.49-3.43 (m, 1H), 3.40-3.30 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.9, 167.9, 158.1, 134.8, 133.9, 129.2, 127.7, 126.1, 125.7, 119.5, 105.5, 102.7, 98.4, 81.1, 69.7, 68.3, 62.7, 62.4, 55.4, 55.0, 53.1, 45.3, 34.2, 31.7, 23.8, 22.5, 17.9, 14.0.

**Synthesis of compound 7:**

75 mg Compound 4 (0.178 mmol, 1 eq) was added to a scintillation vial with 90 mg of Naproxen sodium (.356 mmol, 2 eq) and 3 mL anhydrous DMF. The reaction stirred at 60ºC for 20 hr. The solvent was removed under reduced pressure. The mixture was purified by column chromatography using eluent from 1% to 3% MeOH: DCM to afford desired product (74mg, 72 %). Rf = 0.47 in solvent. 3% MeOH: DCM. mp 156.4-158.2 ºC. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.74-7.68 (m, 3H), 7.44 (d, $J = 8.5$ Hz, 1H), 7.18-7.11 (m, 2H), 4.69 (d, $J = 3.2$ Hz, 1H), 4.55 (t, $J = 5.1$ Hz, 1H), 4.11 (dd, $J = 10.1$, 4.8 Hz, 1H), 3.93 (s, 3H), 3.70 (t, $J = 9.5$ Hz, 1H), 3.67-3.59 (m, 1H), 3.55-3.49 (m, 2H), 3.36 (s, 3H), 3.23 (t, $J = 9.3$ Hz, 1H), 1.70-1.62 (m, 2H), 1.60 (d, $J = 7.1$ Hz, 3H), 1.47-1.37 (m, 2H), 1.36-1.25 (m, 4H) 0.91 (t, $J = 6.9$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 175.2, 168.6, 158.0, 134.8, 133.9, 129.2, 127.7, 126.1, 125.7, 119.5, 105.5, 102.7, 98.4, 81.1, 69.7, 68.3, 62.7, 62.4, 55.4, 55.0, 53.1, 45.3, 34.2, 31.7, 23.8, 22.5, 17.9, 14.0.
CDCl₃) δ 156.7, 134.6, 132.7, 128.3, 127.9, 126.2, 125.3, 125.0, 117.9, 104.6, 101.7, 99.3, 80.2, 70.1, 67.5, 61.7, 54.3, 33.2, 30.6, 22.7, 21.5, 17.3, 13.0.

Synthesis of compound 8:

75 mg Compound 5 (0.165 mmol, 1 eq) was added to a scintillation vial with 83 mg of Naproxen sodium (0.33 mmol, 2 eq) and 3 mL anhydrous DMF. The reaction stirred at 60ºC for 20 hr. The solvent was removed under reduced pressure. The mixture was purified by column chromatography using eluent from 1% to 3% MeOH: DCM to afford desired product (71 mg, 72%). Rf = 0.42 in solvent. 3% MeOH: DCM. mp 159.1 -160.9 ºC. ¹H NMR (400 MHz, CDCl₃) δ 7.74-7.67 (m, 3H), 7.42 (dd, J = 8.5, 1.8 Hz, 1H), 7.20-7.11 (m, 2H), 5.75 (d, J = 8.6 Hz, 1H), 4.66 (d, J = 3.8 Hz, 1H), 4.59 (t, J = 5.0 Hz, 1H), 4.18-4.03 (m, 3H), 3.94 (s, 2H), 3.89-3.83 (m, 1H), 3.83-3.76 (m, 1H), 3.66-3.59 (m, 1H), 3.58-3.51 (m, 1H), 3.37 (s, 3H), 2.16-2.07 (m, 2H), 1.48-1.37 (m, 2H), 1.35-1.20 (m, 6H), 1.48-1.38 (m, 2H), 1.35-1.20 (m, 6H), 0.90 (t, J = 6.9 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 174.2, 102.8, 98.7, 81.6, 71.0, 68.4, 62.5, 55.2, 54.1, 36.3, 34.2, 33.5, 32.4, 31.6, 27.6, 27.6, 24.6, 23.7, 22.5, 14.0.

Synthesis of compound 9.

Compound 3 (75 mg, 0.189 mmol, 1 equivalent) was dissolved in 3 mL of anhydrous DMF, then add 43 mg (0.284 mmol, 1.5 eq) of acetaminophen, and 52 mg (0.378 mmol, 2.0 eq) of K₂CO₃. The mixture was stirred at room temperature for 12 h. Phase-phase extraction was done using DCM: Water (20mL, 3 times). The organic layer was concentrated under pressure. Column chromatography was done with a final solvent eluent of 3% MeOH: DCM. 81% yield, 72 mg. Rf = 0.48 in solvent. 3% MeOH: DCM. mp 185.2 – 187.1 ºC. ¹H NMR (400 MHz, CDCl₃) δ 7.46 (d, J = 9.0 Hz, 2H), 6.91 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.1 Hz, 1H), 4.66 (d, J = 3.8 Hz, 1H), 4.59
(t, J = 5.0 Hz, 1H), 4.54 (t, J = 6.6 Hz, 1H), 4.25 (ddd, J = 19.2, 3.8, 3.7 Hz, 1H), 4.14 (dd, J = 10.0, 4.7 Hz, 1H), 3.87 (t, J = 9.6 Hz, 1H), 3.68-3.62 (m, 1H), 3.58-3.52 (m, 1H), 3.34 (s, 3H), 2.18 (s, 2H), 1.78-1.60 (m, 2H), 1.47-1.36 (m, 2H), 1.35-1.25 (m, 4H), 0.90 (t, J = 6.9 Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 169.0, 162.5, 142.7, 130.5, 125.9, 118.7, 109.5, 109.1, 86.9, 80.1, 73.4, 69.1, 64.9, 60.7, 55.8, 34.7, 31.9, 24.2, 23.9, 23.1, 14.3.

**Synthesis of compound 10.**

Compound 5 (75 mg, 0.165 mmol, 1 eq) was added to a scintillation vial was dissolved in 3 mL of anhydrous DMF, then add 37 mg (0.248 mmol, 1.5 eq) of acetaminophen, and 46 mg (0.33 mmol, 2.0 eq) of K$_2$CO$_3$. The mixture was stirred at room temperature for 12 h. Phase-phase extraction was done using DCM: Water (20mL, 3 times). The organic layer was concentrated under pressure. Column chromatography was done with a final solvent eluent of 3% MeOH: DCM. 57% yield, 48mg. R$_f$ = 0.42 in solvent. 3% MeOH: DCM. mp 185.2 – 187.1 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.39 (d, J = 8.9 Hz, 2H), 6.85 (d, J = 8.9 Hz, 2H), 5.86 (d, J = 8.3 Hz, 1H), 4.69 (d, J = 3.8 Hz, 1H), 4.60 (t, J = 5.0 Hz, 1H), 4.23-4.10 (m, 2H), 4.0 (t, J = 6.3 Hz, 2H), 3.82 (t, J = 9.6 Hz, 1H), 3.67-3.60 (m, 1H), 3.58-3.51 (m, 1H), 3.39 (s, 3H), 2.30 (t, J = 12.8 Hz, 2H), 2.17 (s, 3H), 1.85-1.63 (m, 4H), 1.58-1.47 (m, 2H), 1.44-1.40 (m, 2H), 1.33-1.25 (m, 2H), 0.94-0.87 (m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 173.8, 169.1, 166.1, 142.8, 130.1, 125.5, 118.2, 109.2, 87.3, 81.0, 72.9, 69.1, 64.8, 60.4, 55.5, 36.8, 34.3, 32.1, 28.2, 25.1, 24.8, 24.1, 23.7, 22.9, 14.2.
CHAPTER 5. CONCLUSIONS AND FUTURE STUDIES

This dissertation aims to study a series of carbohydrate based low molecular weight gelators in detail as emerging materials for a variety of applications. These carbohydrates are structurally diverse with the ability to functionalize the structure to assist with these various applications. The detailed literature background was reviewed in Chapter 1. Several classes of LMWGs were synthesized and characterized in chapters 2, 3, and 4.

In chapter 2, we have designed and synthesized a series of 4,6-O-acetal protected α-D-methyl glucosides and analyzed their gelation properties. We concluded that the inclusion of aromatic groups enhances the self-assembly properties while using glucose as building blocks. However, the aliphatic molecules did not perform as expected. The results indicated that stronger intermolecular forces are necessary for them to perform as LMWGs. Based on these results, further functionality of the 4,6 position with other functional groups should be further investigated in the future. Also changing the nature of the sugar moiety from glucose to other monosaccharides such as N-acetyl-D-glucosamine need to be investigated next.

In chapter 3, we have synthesized and characterized a series of 4,6-O-alkylidene protected N-acetyl-D-glucosamine and obtained several effective low molecular weight hydrogelators. This series of compounds had an overall good performance in a variety of solvents, especially for aqueous solutions. These gelators were studied for the formation of co-gels with naproxen and dyes. The gelation mechanism and gel stability etc were studied in details using rheology, NMR spectroscopy, etc. We conclude that various gelators could be used as drug delivery systems as well as assisting with dye removal.
In chapter 4, several naproxen and acetaminophen derivatives have been synthesized and characterized. The drug-gelator conjugates were not effective gelators, however they may be useful in forming two-component gelators and as molecule probes. The naproxen derivatives were hydrolyzed under basic conditions to release the free naproxen. The response towards base treatment at different time intervals were studied by UV-Vis absorption spectroscopy.

Due to the positive findings of the gelators synthesized we can now study their applications in the field of biomedicine and environmental applications. Also, the chain length effect on the 4,6 position of both glucose and glucosamine should be studied in further detail to find a trend. Based on the studies done in this dissertation, we can further investigate the biological properties of the synthesized gelators along with further studies to characterize the base cleaved diols and the use of these compounds as fluorescent probes for carbohydrate based LMWGs with similar structures. Additional modifications may also include different 4,6-functional groups and derivatives with different spacers between naproxen and the sugar amide functions.
REFERENCES


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# APPENDIX

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