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Synthesis and Characterization of Sugar Derivatives as Functional Gelators

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Synthesis and Exploration of Sugar Derivatives as Functional Gelators

A Dissertation

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

Doctor of Philosophy
In
Chemistry

By

Michael St. Martin

B.S. University of New Orleans, 2004
M.S. University of New Orleans, 2010

August 2012

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Dedicated to:

My Son, Emmanuel St Martin

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Abstract

Systems formed by the supramolecular assemblages of organic molecules known as organogelators and hydrogelators are currently, and only recently, a subject of great attention and promise. In this context, low molecular weight gelators (LMWGs) are of particular interest because they provide a bottom-up approach to the formation of supramolecular architectures through self-assembly. Gelator molecules do so via the initial formation of a one-dimensional array of individual molecules bound non-covalently through forces such as: hydrogen bonds, electrostatic forces, Van der Waals interactions, and other weak forces such as π - π interactions. These interactions then lead to secondary structure formation through a similar assembly mechanism. Understanding the gelation process through characterization techniques is critical to the development of a design rationale for gelator molecules. Past and current research performed by the Wang group indicates that analogues of various 4,6-benzylidene acetals form stable gels in organic, aqueous, and organic/aqueous solvents at varying concentrations. The basis of varying the 4,6-protecting groups on glucose and glucosamine derivatives is to discern the relative structure activity relationships of these systems, and as well to fabricate functional systems which respond to external stimulus. Stimuli responsive or trigger release gel systems formed by sugar based low molecular weight gelators (LMWGs) have applications as smart biocompatible materials, and such responsiveness in various media was explored and developed to determine the feasibility of such applications using monosaccharide derivatives.

Keywords: Low Molecular Weight Gelators, Organogelator, Hydrogelator, Self-Assembly, Soft Material, Carbohydrates, Sugars

Chapter I. Introduction

1. Gelators

Gelators are organic molecules which form soft materials known as “gels,” when incorporated into a solvent system. The molecular architecture of gels is constituted primarily of the gelling agent and a fluid which can be of an organic or aqueous nature. This 3-dimensional viscoelastic material is essentially a scaffold or matrix of gel molecules networked and entangled in such a way that solvent molecules become trapped in pockets or chambers within the matrix formation. The two main types of gels are known as polymer gels which may as well be referred to as chemical gels, or low molecular weight gelators which may as well be referred to as physical gels. One of these two primary types of gels known as polymer or chemical gels will not be extensively described in this thesis, although they are of great importance in the field of gel materials. Polymer gels are made up, as the moniker suggests, of a polymer network which forms a scaffold or gel ‘mesh,’ which entraps solvent molecules within pockets formed by the polymeric material (Figure 1.1). To date, there are already extensive uses of *polymer* gels in a

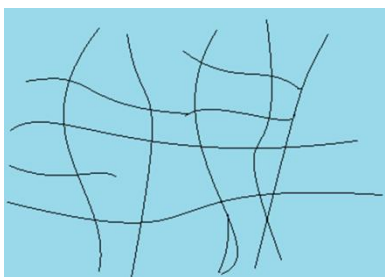


Figure 1.1 Depiction of a gel mesh created by a polymeric material

variety of applications. Bhosale et al used polymer hydrogels for particle dispersion¹, and as scaffolds to grow size-controlled particles. The electroacoustics of these systems were then analyzed to profile particle dynamic electrophoretic mobility within the gel mesh, which was found to be directly related to the cross-link density of the polymer matrix. Tejraj Aminabhavi et al employed a blend of microspheres of gelatin and hydroxyethyl cellulose to investigate the controlled release of theophylline (THP), an antiasthmatic drug, using a water-in-oil emulsion technique². Other important applications of polymer gels include but are not limited to: gel electrophoresis, as thickening agents, for topical drug delivery therapy, scaffolds for controlled drug release, tissue engineering, wound dressings, anti-adhesion materials, candles, diapers, fire retardants, hot & cold therapy packs, waste stabilization and environmental remediation, etc. Polymeric gels are indeed important in the applications to which they pertain, but are largely restricted to uses typically unique to non-thermoreversible superstructures.

Supramolecular or physical gels, in particular the assemblages of small molecules which form gels via non-covalent intermolecular interactions, are soft novel materials which have several current and potential utilities. Such molecules are known as “**Low Molecular Weight Gelators**,” or **LMWGs**. Materials such as LMWGs are capable of being thermoreversibly formed due to the types of intermolecular bonds associated with the matrix formation, and their applications extend to some of the aforementioned polymer gel applications in addition to having some exclusive uses^{4,5}. Such non-covalent interactions include: hydrogen bonding, π - π stacking, and Van Der Waals interactions. An example of a tetrathiofulvalene (TTF) species’ stacking array which is principally held together by such forces is illustrated below in Figure 1.2.

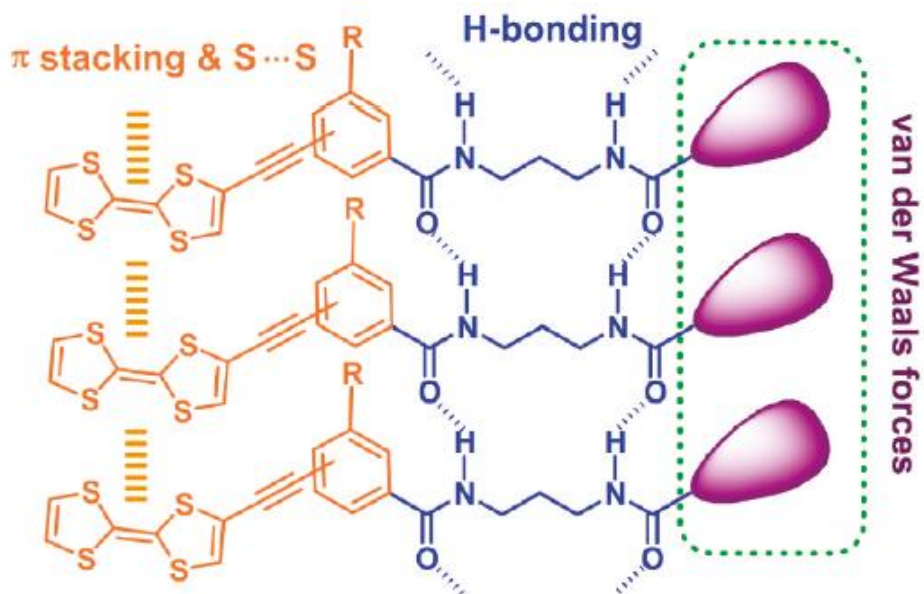


Figure 1.2 An intermolecular bonding array of TTF gelators depicting the various non-covalent interactions associated with LMWGs. Reprinted with permission from: Wang, X.; Xing, L.; Cao, W.; Li, X.; Chen, B.; Tung, C.; Wu, L.; *Langmuir*. Copyright 2011 American Chemical Society

The well established and yet still rapidly expanding field of LMWGs currently delivers a variety of useful materials, which will perhaps one day be considered indispensable as critical materials for everyday utilities from industrial, pharmaceutical, and common consumer applications. The characteristic property of thermoreversibility exhibited by LMWGs, entitles them to some niche applications, which include but are not limited to the advanced materials applications such as: pharmaceuticals, food, drug-delivery, biomimetics, enzyme-immobilization matrices, liquid crystalline materials, as templates for preparing other novel compounds, mechanical actuators, and in catalysis⁶. For example, trimethoxysilane bis urea **1** (Figure 1.3), which was synthesized in a one-pot reaction, was tested in a variety of organic/aqueous solvents, where the content of each of the gels formed is only 1% gelator molecule by weight³:

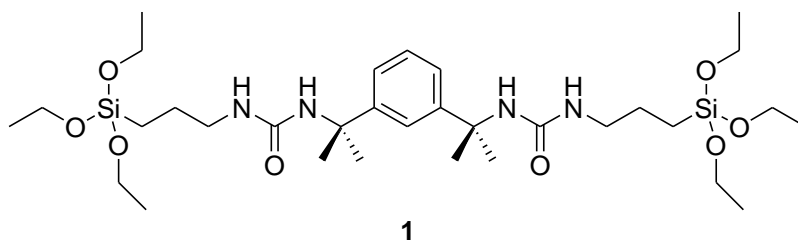


Figure 1.3 Trimethoxysilane bis urea 1

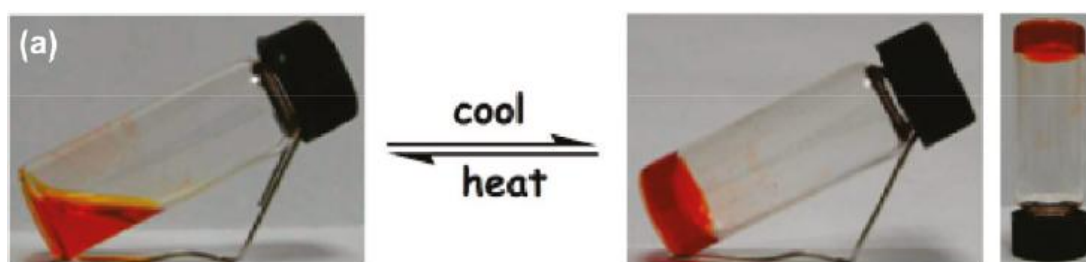


Figure 1.4 An illustration of the thermoreversibility of TTF LMWGs. The gel to sol transition can take place several times over before this functional property is exhausted. Reprinted with permission from: Wang, X.; Xing, L.; Cao, W.; Li, X.; Chen, B.; Tung, C.; Wu, L.; *Langmuir*. Copyright 2011 American Chemical Society

The determination of what exactly constitutes a gel is essentially a crude measurement of the human eye. The aforementioned “crude measurement” can be performed simply by observing a gelatinous material as being suspended for a short duration, such as in the upside down vial to the right in Figure 4.1. A gel is characterized by its flow property, which is solid-like under rheological considerations, yet has a composition which is predominantly liquid, with proportions which are commonly 99% liquid and about 1% gelator molecule. A more technical proposition was introduced by Flory, who defined a gel as: 1)“... a continuous structure with macroscopic dimensions that is permanent on the time scale of an analytical experiment and 2)

is solidlike in its rheological behavior.”⁴ This measurement can as well be made by subjecting a gelatinous material to the “dropping ball method,” which determines the gel integrity under temperature variances. This experiment is carried out by introducing a metal ball to the gel at a particular temperature, usually initially room temperature, and then heating the gel material until the metal ball begins to descend into the gel medium, thus breaching the integrity of the gel. Other rheological studies are carried out in a rheometer, which studies the flow properties of solid-like materials while under an applied force.

1.1 Gel Structure

The gel matrix, an entangled network of fibrous, sheet-like, or rod-like strands, which are secondary structures or cables formed from an anisotropic one-dimensional growth of the non-covalently bound gel molecules, trap solvent molecules within the pores or pockets that result from such entanglements. Images generated by a scanning electron microscopes (SEM image) or transmission electron microscopes (TEM image) are generally used to study the morphology of such materials. Scanning electron microscopes magnify surface structures in the micrometer range and provide a topographical image for secondary structure analysis.

1.2 Gelator Design Rationale

The discovery of gelator molecules has predominantly been a circumstance of fortune. That is to say, that the *design* of novel gelator molecules is limited. Such limitations are set by the confines of the understanding of the gelation phenomenon. Once a gelator molecule has been discovered, however, the rational design of analogues with minor tweaks and modifications, and a comprehensive understanding of the properties which support gelation are quickly grasped. It would appear as though an amphiphilic molecular balance must be struck in order for a compound to develop gelator properties. This hydrophobic/hydrophilic duality is illustrated in the 2-substituted anthriquinone structures **3-6** (Figure 1.5) synthesized by Chuan-Feng Chen et al for gel studies¹⁵:

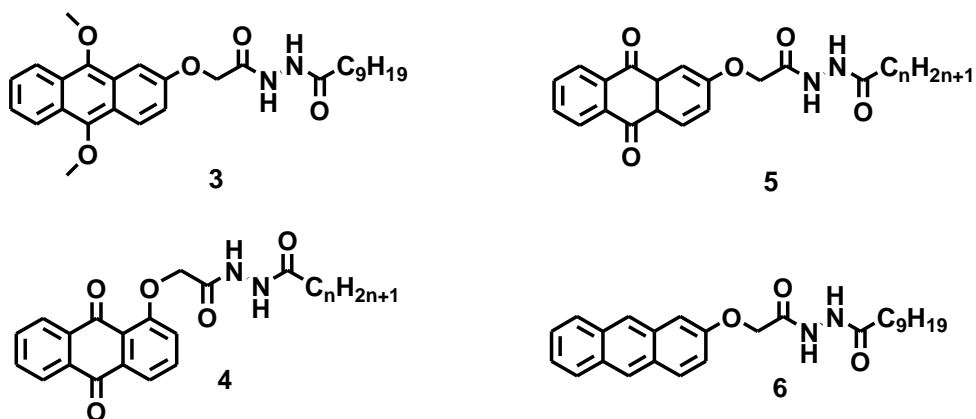


Figure 1.5 2-substituted anthriquinone structures **3-6**

This balance is inherently related to a composition of factors which include molecule-molecule interactions as well as solvent-molecule interactions. Molecule-molecule interactions are such that the forces involved pertain only to gelator molecule to gelator molecule interactions,

which are necessary for one-dimensional fibrillar assembly. The solvent-molecule interactions assist in a similar fashion, directing the molecular orientations critical for gel formation via hydrophobic and/or hydrophilic forces as well as surface tension forces. The sheer multitude of factors which must coalesce for gelation to be possible makes it relatively difficult for *ab initio* gelator design. Through the advancement of gelator research of the past few decades, although, the discovery of several classes of gelator compounds provides a platform of rationale for molecular design. Some known classes include: Amino acids (peptides), surfactants, amides, ureas, carbohydrates, fatty acids, porphyrin derivatives, nucleobases, tripodal compounds, quinolines, etc.

1.3 Gel Characterization

The characterization and study of these gels via the use of instrumental analysis is quite critical to understanding the gel superstructures. The advancement of gel instrumental analytical techniques, such as in instrumentation methods like NMR, scanning electron microscopy, X-ray crystallography, and fluorescence study techniques have greatly progressed the understanding of gelators and their physical properties as well as the assembly process associated with their creation⁵. The study of the gel suprastructure as distinguished from the gelator in solution has proven very revealing to the gelation process, or the gel-sol transition process, using the aforementioned instrumental techniques.

1.4 UV and Fluorescence Analysis

Yu Fang et al analyzed the gel-sol transition of structures **7-11** (Figure 1.6) through fluorescence spectroscopy, by attaching the fluorophore naphthalene to an open-chain glucose moiety with a hydrazine or extended diamine spacers²⁸.

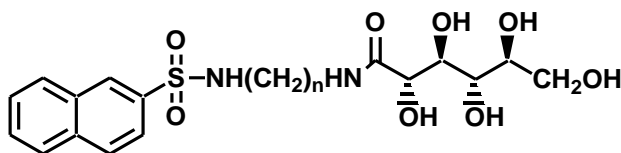
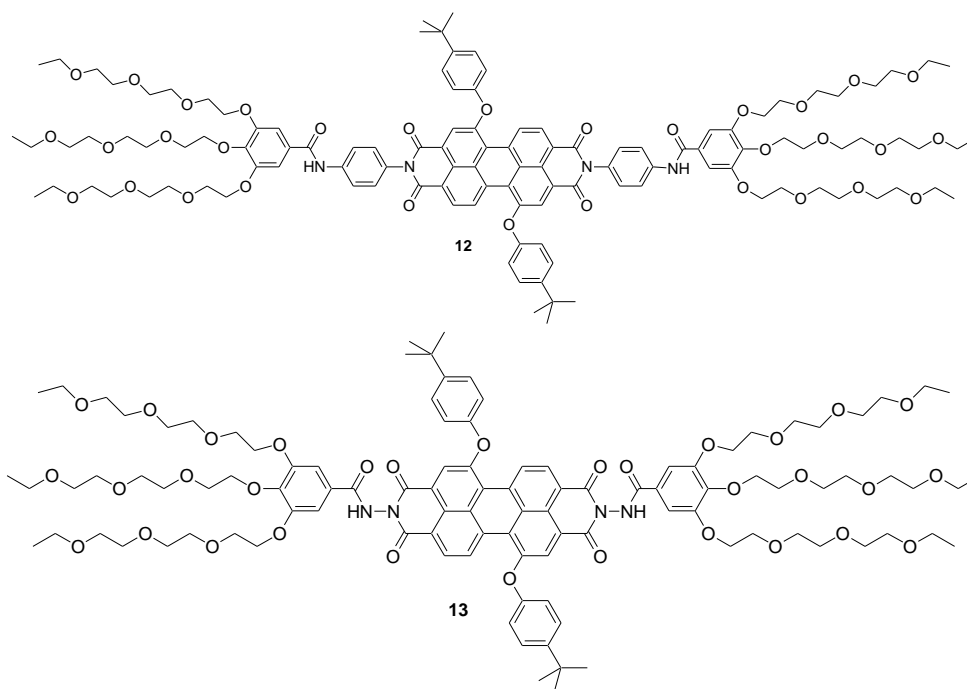


Figure 1.6 Glucose based fluorescent gelators **7-11** ($n = 0-5$)

The fluorescence study revealed an enhanced emission from the gel structure versus the emission of the gelator in solution. This distinction allowed for the group to interrogate the processes involved in gel-sol transition. Such a transition and its reverse glean very illustratively the physical processes involved on the molecular level, which can thoroughly be studied by examining the emission changes from the fluorophore moiety. The gelator molecule involved in the transition process may have incorporated into it a fluorophore which is essential to inducing the gelation process or the fluorophore may simply be appended to an existing gel molecule, meaning it is not critical to gelation and perhaps effects gelation only slightly. If, when subjected to UV and other fluorescence related frequencies, a gelator does not fluoresce significantly or even at all in solution, yet does so when aggregated in the gel matrix form, a process dubbed Aggregation Induced Enhanced Emission (AIEE) occurs. Xiyu Li et al observed such varying emissions from gel-sol transitions whilst studying morphologies and gel properties

of perylenetetracarboxylic diimides (PDIs)²⁶. The perylene functionality, the fluorophore, exhibits photoconductive properties which not only assist in structural analysis of gel morphologies, but as well may lend applicability in areas such as photoconductive nanostructure technology. As a functionalized gelator, the perylene rings provide the weak bonding contribution necessary for intermolecular aggregation in the form of $\pi - \pi$ stacking. This, in conjunction with appended hydrophilic polyoxyethylene or long chain hydrophobic tails, gave the PDIs the typical amphiphilicity necessary for gelation, as seen in compounds **12**, **13**, and **14** in Figure 1.7:



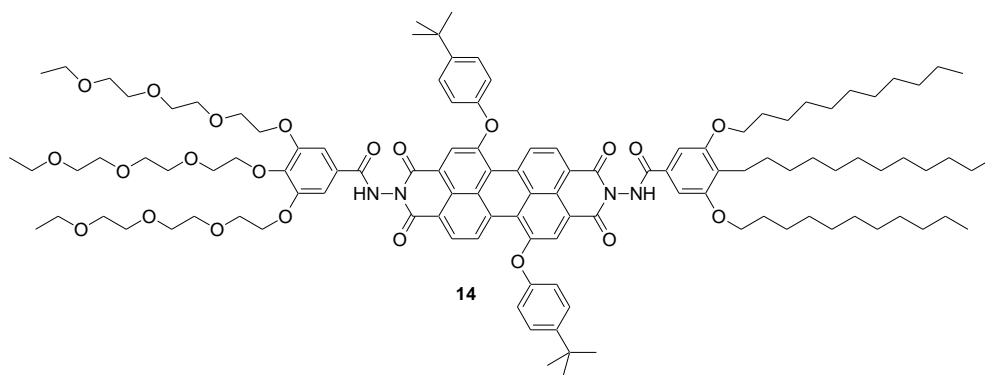


Figure 1.7 Molecular structures of compounds **12-14**.

The computed optimized molecular structures **12-14 (A-C)** are shown below in Figure 1.8²⁷:

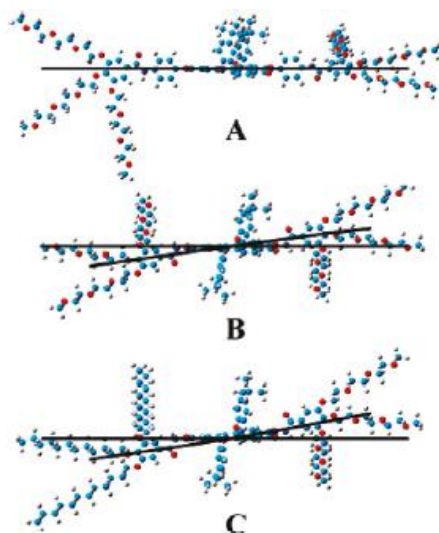


Figure 1.8 Reprinted with permission from Wu, H.; Xue, L.; Shi, Y.; Chen, Y.; Li, X.; *Langmuir*, **2011** Copyright 2011 American Chemical Society

The absorption/emission data was obtained from **12** and **14** in various organic solvents, the details of which are tabulated below. Compound **13** did not form a gel in any solvent tested.

Table 1.1 Gels of compounds **12** and **13**²⁶.

Compound	Gel I	Gel II	Gel III
12	Ethanol:Hexane 3.2 mM	Toluene:Methanol 7.8 mM	
14			Hexane 5.0 mM

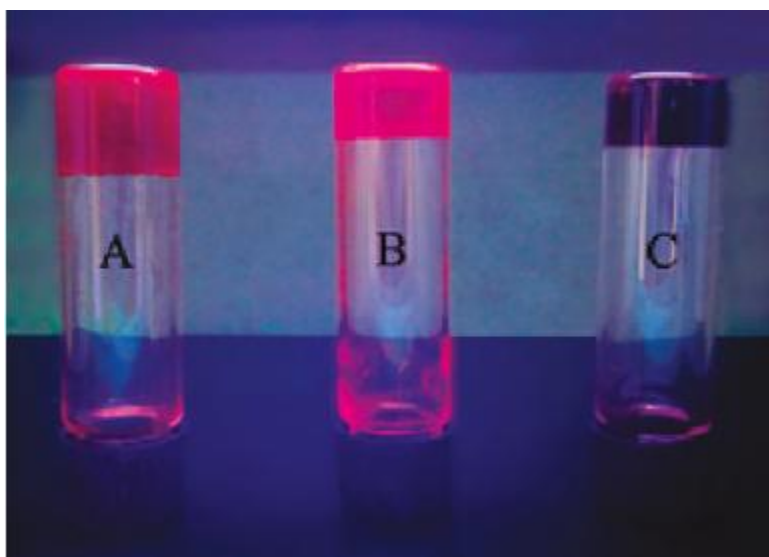


Figure 1.9 Irradiated with 365nm UV, the fluorescence of gels **I**, **II**, and **III** (with concentrations of 3.2, 7.8, and 5.0 mM respectively) is displayed. Reprinted with permission from Wu, H.; Xue, L.; Shi, Y.; Chen, Y.; Li, X.; *Langmuir*, **2011** Copyright 2011 American Chemical Society

From image **A** in Figure 1.8, one can note that the polyoxyethylene tails are coplanar with the PDI ring. This is because, in compound **12**, the phenyl linker between the tail groups and the PDI ring allows for this conformation to be possible which, in-turn, likely allows for the proper orientational stacking necessary for one dimensional growth—a typical critical criterion for gelation to occur. The absence of this linker in compound **13** likely attributes to its inability to gel any of the solvents tested. Compound **14** as well adopts a non-planar form, but it has

incorporated within it an aliphatic side-chain, which allows for hydrophobic interactions to cooperate with the π - π interactions and form gels. Even the most minute interchromophore distance variations are detectable by the very much sensitive techniques of UV-vis and fluorescence instrumentation. For instance, it was inferred by Xiyou Li et al that a significant blue shift of 35nm in the absorption spectra obtained²⁶ (Figure 1.10), comparing the PDI monomer and a concentrated PDI gel, that a relatively small interplanar distance separated face to face stacked PDI molecules. This led to the conclusion that such intermolecular distances of π - π stacked units in the H-aggregates form strong interactions in the ground state and therefore absorb at these higher energies. Fluorescence studies revealed that face-to-face stacking occurs in the aggregates formed in gel I. In consideration of the fact that, in the fluorescence spectrum of compound **11** in Figure 1.11, a red shift to 624 nm was observed from gel I relative to the monomer in CHCl_3 , it was inferred by Xiyou Li's group that an excimer like state must be adopted, and there must be interchromophore interactions even in the excited state. A defining feature of Li's PDIs is that the blue shifts are significantly greater than those observed in previously reported literature. They reasoned that this could be due to minimal slippage along the transverse and longitudinal axes, which if larger could perhaps cause a red shift. Their reasoning extended, and they noted that it has been observed that in-plane torsion between adjacent PDI molecules causes significant blue shift. Their reasoning therefore culminated in the belief that this particular PDI system exhibited minimal slippages along the transverse and longitudinal axes and this must be occurring along with strong in-plane torsion and small interplanar distance.

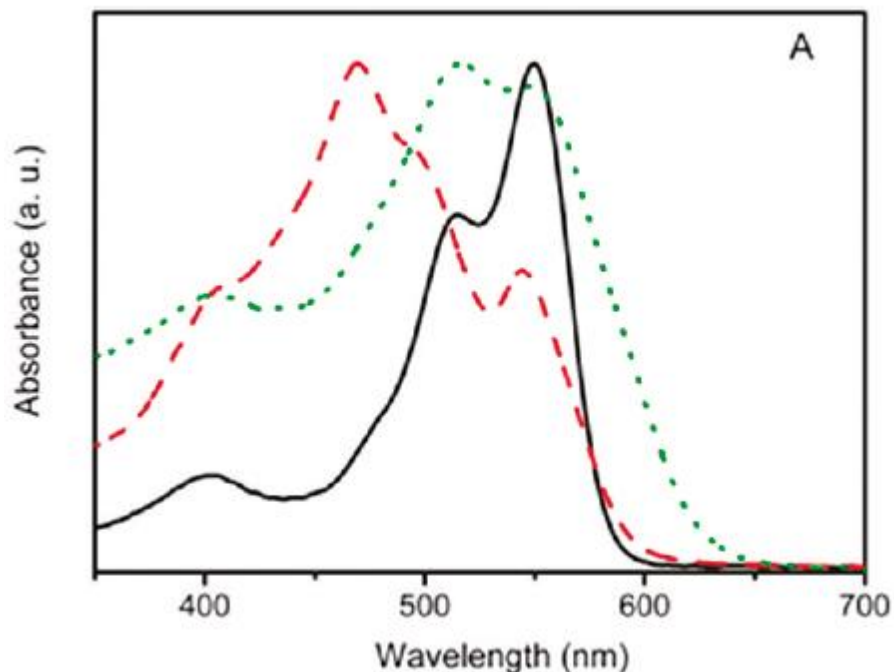


Figure 1.10 UV-vis absorption spectra of compound **12** in CHCl_3 (Solid), as a dilute gel (Dashed), and as a concentrated gel (Dotted). Reprinted with permission from Wu, H.; Xue, L.; Shi, Y.; Chen, Y.; Li, X.; *Langmuir*, **2011** Copyright 2011 American Chemical Society

A discrepancy in the microstructures of gels **I** and **II** is present, although as seen in Figure 1.10, similar shifts are observed due to face to face stacking assembly adopted by both gels. This difference, as mentioned, is in the microstructures and Li et al describe the change from opaque gel **I** to the transparent gel **II** as being attributed to differences in solubility. Gel **I**, which is in hexane/ethanol 1:1 v/v, forms large aggregates which induce opacity. The greater solubility of **1** in gel **II**, which is in toluene /methanol, causes the gel to be transparent.

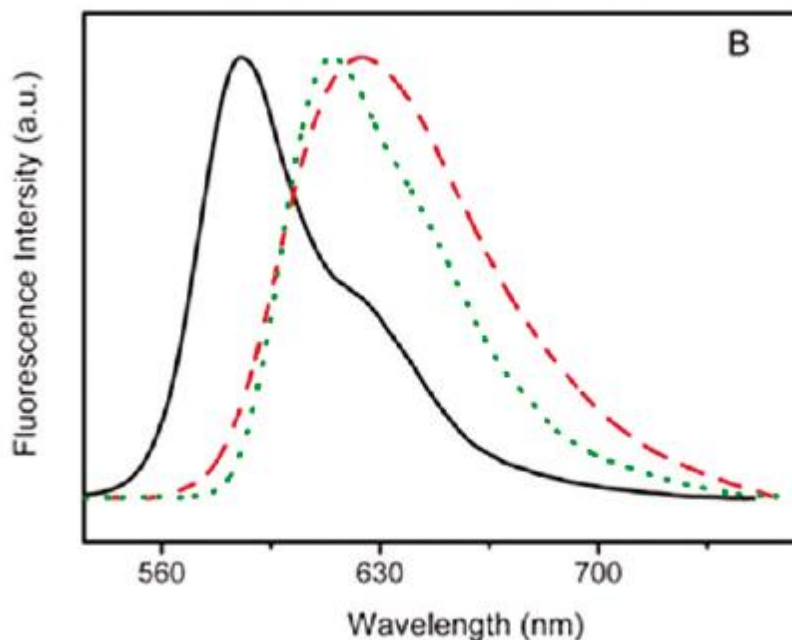


Figure 1.11 Fluorescence emission spectra of compound **12** in CHCl_3 (Solid), as a dilute gel (Dashed), and as a concentrated gel (Dotted). Reprinted with permission from Wu, H.; Xue, L.; Shi, Y.; Chen, Y.; Li, X.; *Langmuir*, **2011** Copyright 2011 American Chemical Society

As seen in Figure 1.12, face to face stacking is observed for compound **14** in gel form as well. This inference is based on the observed blue shift of 47 nm relative to the monomer in CHCl_3 . Further experimentation to assess compound **14**'s capacity to maintain a similar shift was performed, and it did indeed maintain such a shift down to 10^{-7} mol/L in a hexane solution. This suggests that face-to-face stacking occurs at least down to this concentration level. Compound **14** in gel form seems to form J-aggregates. The maximum at 540 nm and the new one forming at 644 are characteristic peaks for PDIs in a coplanar configuration and that have $\pi - \pi$ interactions.

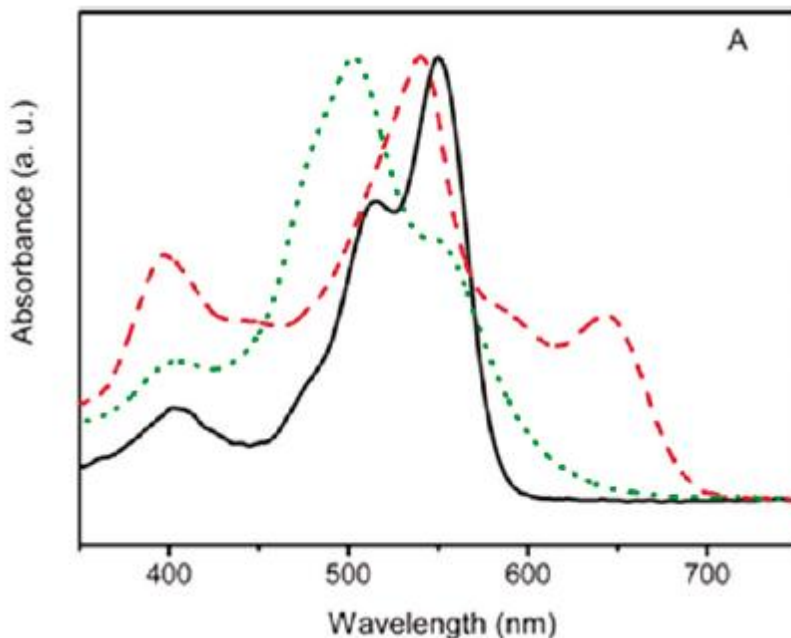


Figure 1.12 UV-vis spectra of compound **14** in CHCl_3 (Solid), Hexane (Dotted), and a dilute gel in hexane as a gelling solvent to form gel **III** (Dashed). Reprinted with permission from Wu, H.; Xue, L.; Shi, Y.; Chen, Y.; Li, X.; *Langmuir*, **2011** Copyright 2011 American Chemical Society

The absorption spectra, as mentioned above, are significantly different from each other. To the group's surprise, the emission spectra were not so different for compound **14** in the hexane solution versus as a gel in gel **III**, as seen in Figure 1.13. This was attributed to a different mode of assembly for each. In the hexane solution, an H-type aggregate formation is occurring because excimer-like emissions are observed. This solution, as observed by the naked eye, is red in color. The fluorescence of gel **III** shows an emissions signature characteristic to that of a J-aggregate assembly. This solution is black.

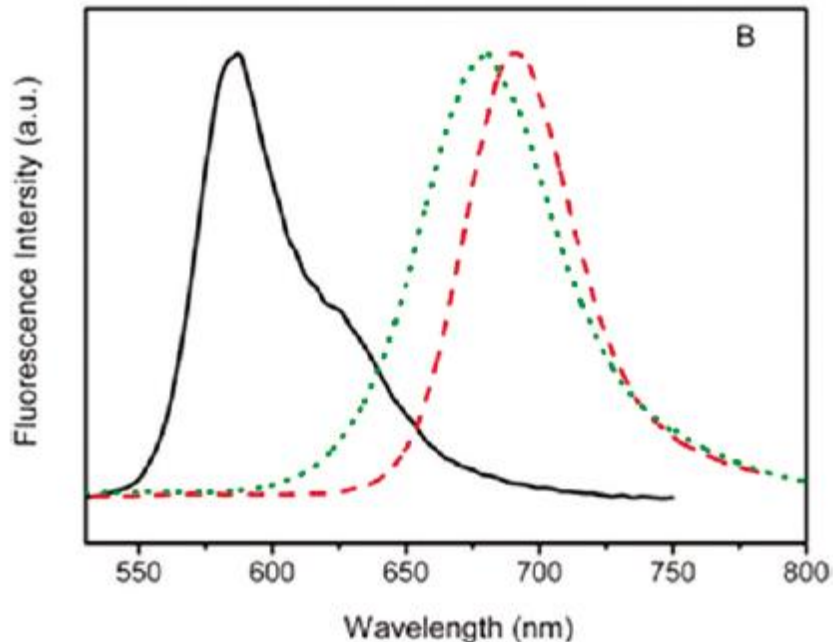


Figure 1.13 Fluorescence spectra of compound **14** in CHCl_3 (Solid), Hexane (Dotted), and a dilute gel in hexane as a gelling solvent to form gel **III** (Dashed). Reprinted with permission from Wu, H.; Xue, L.; Shi, Y.; Chen, Y.; Li, X.; *Langmuir*, **2011** Copyright 2011 American Chemical Society

Li et al developed a “speculated” microstructure for each of the gels **I**, **II**, and **III**. These structures were determined in-large part due to the fluorescence emission and UV-vis obtained. Additional characterizations were performed, including X-ray diffraction (XRD) and atomic force microscopy (AFM) measurements. For compound **12** gel **1**, the intermolecular orientations are face to face stacked. It was speculated that the primary contributing source for intermolecular non-covalent bonding was the $\pi - \pi$ interactions from the PDI moiety. The hydrophobic side-chains did not pack with high order due to bending and tangling, and small in-plane torsion was also attributed to gel **I**.

The “speculated” microstructures are presented below in Figure 1.14:

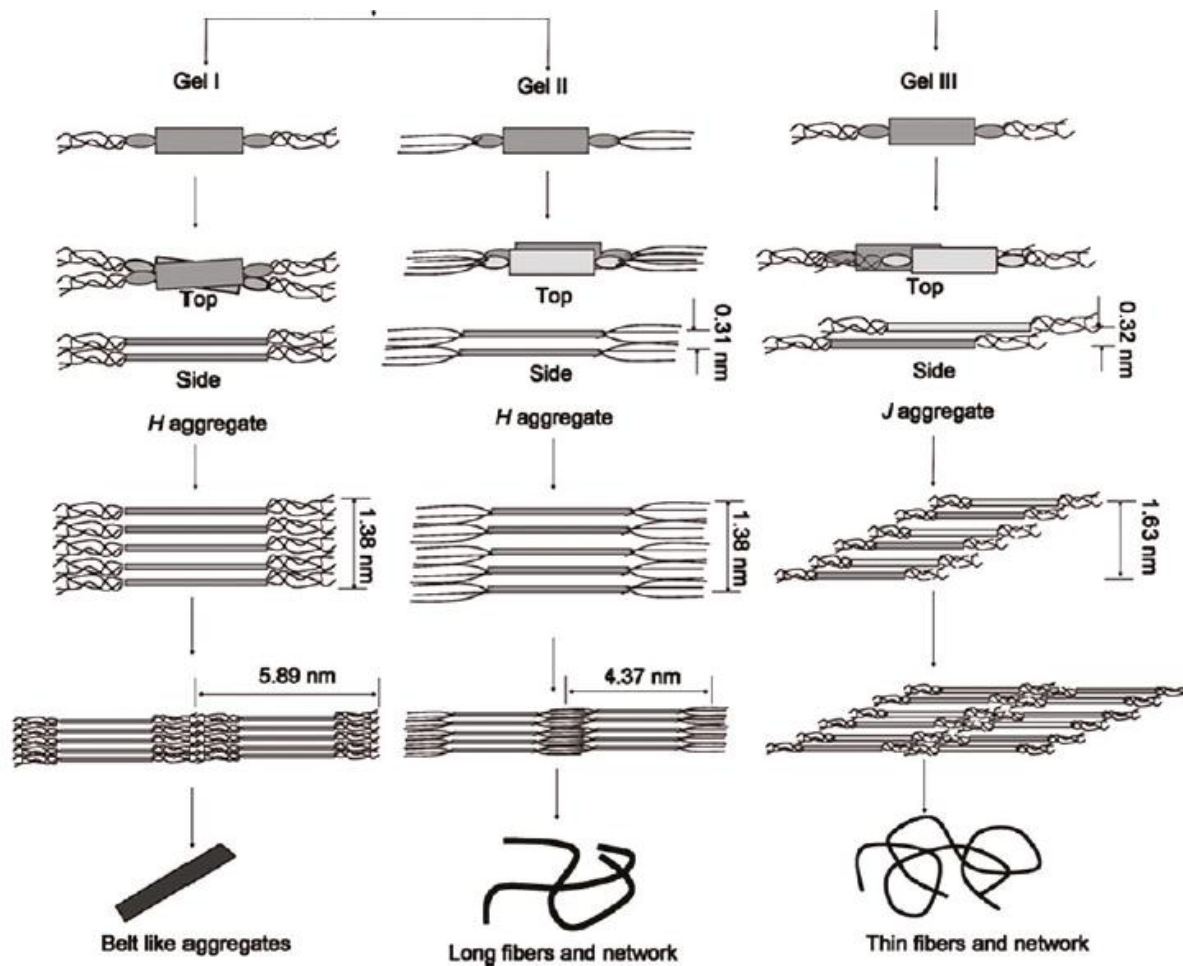


Figure 1.14 Speculated microstructures of gels formed by compounds **12** and **14**. Reprinted with permission from Wu, H.; Xue, L.; Shi, Y.; Chen, Y.; Li, X.; *Langmuir*, **2011** Copyright 2011 American Chemical Society

1.5 Probing the Mode of Gelator Assembly

The mode of assembly/disassembly which is involved in the aggregative formation or disruption of fibrils of gels may parallel the self-association of β -Amyloid plaque formation or

potential disruption, respectively, in the brain of Alzheimer afflicted persons. β -Amyloid plaque formation and brain deposition, which in-turn leads to brain lesions, is a major hallmark of Alzheimer's disease, and perhaps the primary culprit for the onset of this degenerative disease. Santiago V. Luis et al set out to probe a gel systems self-assembly pathways and load capacity under the effects of naproxen (**NPX**)²⁷, a non-steroidal anti-inflammatory drug (NSAID), in an effort to simulate how such a drug may affect β -Amyloid aggregate formation. Research has suggested that such an NSAID may interact with the amyloid plaques or at least the precursors thereof and inhibit their formation. The analysis of such aggregative action was performed by Luis and his group using peptidomimetic cyclophane compound **16**, with naproxen embedded within its gel matrix:

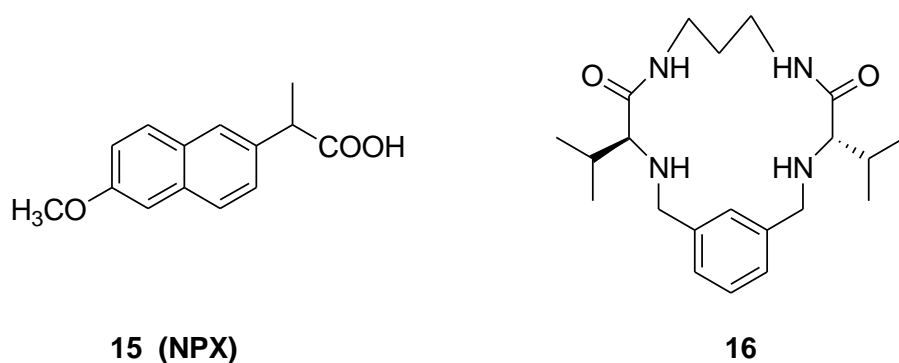


Figure 1.15 Chemical structures of Naproxen (**NPX**) and cyclophane compound **16**

With an NSAID such as naproxen embedded within the gel matrix, from a biomedical context regarding, for instance β -amyloid fibril disruption, time resolved fluorescence spectroscopy could be used effectively to elucidate the interactions the chromophore has with the gel assembly, as described by Luis et al. The integrity of the gels formed by **16**, which had varying concentrations of NPX incorporated within, was assessed by measuring the gel melting

temperatures (T_g). The observed melting trends indicated that the higher the NPX load was, the weaker the gel assembly (Lower T_g). In table 1.2, R represents the degree of linear correlation.

Table 1.2 The gradient melting temperature of gelator compound **16** loaded with **NPX**²⁷

16 (mg/mL)	NPX (M)	T_g (°C)	R
4	0.0	50.9 ± 0.7	0.9988
4	4.0 × 10 ⁻⁴	49.1 ± 0.4	0.9991
4	2.5 × 10 ⁻³	47.7 ± 0.7	0.9983

At this juncture it was clear that an effect, specifically a weakening one, had occurred from the addition of NPX, yet when absorption and steady-state fluorescence spectroscopy were performed, no notable spectroscopic changes had taken place from the NPX monomer in solution and in the gels. This compelled the group to explore other fluorescence techniques which would help in the interrogation of system integrity differences. Therefore, time correlated single photon counting (TCSPC), a time resolved fluorescence technique which correlates minute distinctions of fluorescent species in different environments. Absorption, excitation, and emission results were fit into the model below, which was calculated by using the following multiexponential equation (eq. 1.1) of individual decays (i):

equation 1.1:
$$F(t) = \sum \alpha_i e^{-t/\tau_i}$$

The following (Figure 1.16) illustrates the normalized spectra of NPX in toluene and in the gel state.

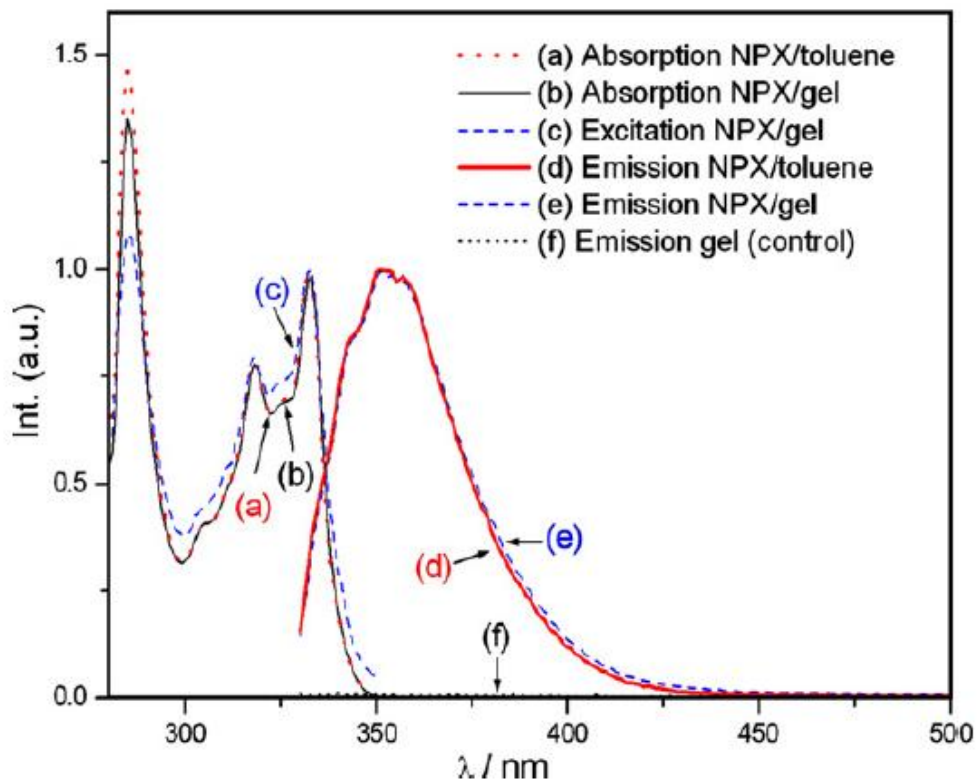


Figure 1.16 Normalized spectra of NPX in toluene and in the gel state. Permission license No. 2864890165106

The i components, which represent the various fluorescence lifetimes, are summated in the variable τ_i which represents the individual fluorescence lifetime, and α_i which is a representation of its contribution to the total signal. The degree to which the fluorescence decay times fit the multiexponential results properly is designated χ^2 . In accordance with previous data concerning NPX in various organic solvents, the monoexponential fit for its fluorescence decay time in toluene was $\chi^2 = 1.07$ where $\tau = 7.38\text{ns}$ [26]. The monoexponential decay for **16** in the gel state did not exhibit a good fit, although. When the biexponential,

however, was applied to the decay function, a more precise fit was observed. The observed lifetimes of the two contributors τ_1 and τ_2 were 7.89ns and 1.46ns, respectively. The variable τ_1 contributed to 97.3% of the signal, whereas τ_2 contributed to 2.7%. It was hypothesized by Luis et al that the larger component of the fluorescence lifetime can be attributed to the decay of NPX that is not interacting with the gel matrix, and that the smaller lifetime may correspond to NPX which is in the vicinity of gel fibers, and thus interacting with the architectural assemblage composed of **16**. To support this theory, gradient increase of the gelator molecule concentration was applied, which revealed that the smaller lifetime component gradually increased with increasing concentration. The logic was such that if the gelator molecule concentration increased, the interactions between NPX and **16** would increase proportionately due to its greater prevalence, thusly increasing the lifetime of τ_2 . This in fact was observed, as tabulated in the following table:

Table 1.3 Gels of gelator **16** at various concentrations irradiated with 350 nm UV with recorded fluorescence lifetimes²⁷

16 (mg/mL)	τ_1 (ns)	α_1 (%)	τ_2 (ns)	α_2 (%)	χ^2
0	7.38	100	-	-	1.07
4.0	7.89	97.3	1.46	2.7	1.11
7.3	8.27	95.1	1.34	4.9	1.24
10.3	8.30	93.0	1.16	7.0	1.17

The UV-vis absorption and fluorescence analyses performed by Luis et al did not show any significant distinctions in spectral results when steady state and conventional spectroscopic techniques were applied, yet when time resolved fluorescence spectroscopy was applied, distinctions between emission and excitation spectra were observed in normalized models.

Fluorescent probing, as past research has shown, can assist in elucidating the mechanism of action which is involved in gel formation, but there are sometimes external or internal stimuli that assist in architectural assembly. The mode of aggregation involved in these cases is sometimes not fully understood, yet our comprehension of how it occurs is rapidly growing. It has been known for some time now that impregnating a potential gel system with metal salts may either buttress or rigidify a gel, but may also lead to gel formation, where such formation would have otherwise not occurred. Additionally, thermal treatment or ultrasound irradiation may assist in gelation by providing the necessary energy to overcome certain barriers associated with the intermolecular orientations needed for one dimensional growth. Masamichi Yamanaka and Hiromitsu Fujii explored these effects²¹ with a gel system which uses tris-urea LMWG **17** in Figure 1.17.

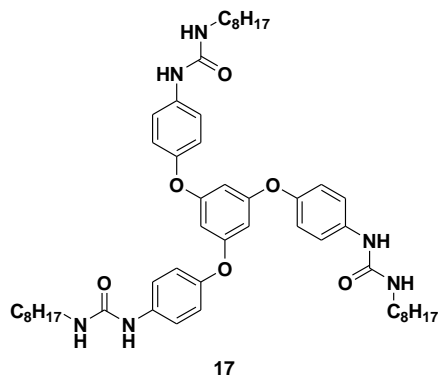
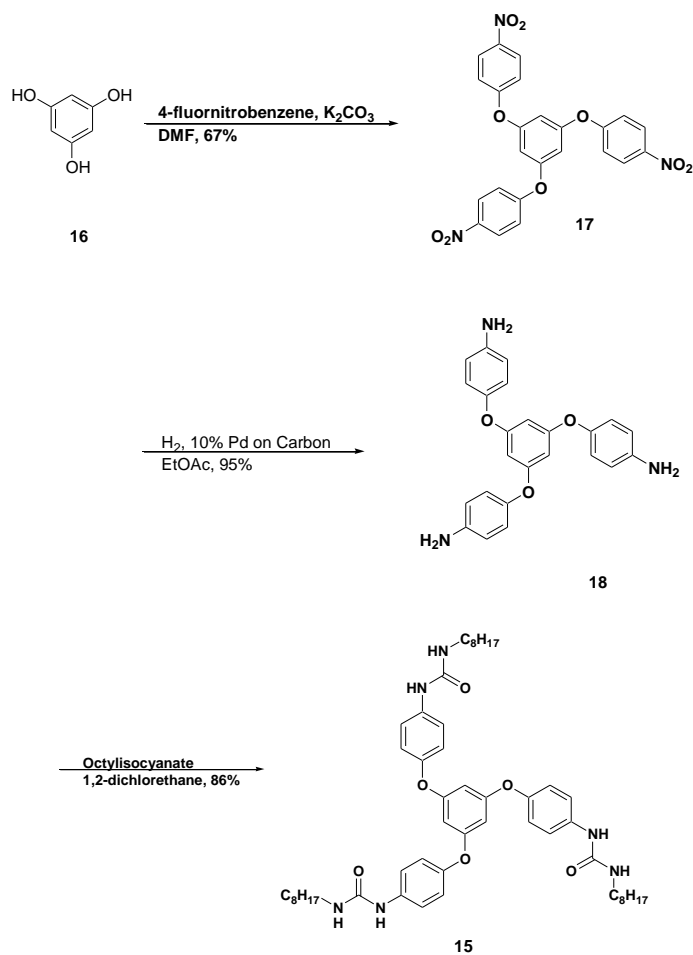


Figure 1.17 Tris-urea LMWG **17**.

Compound **17** has the property of C_3 symmetry, which is derived from functionalizing phloroglucinol. Initially, 4-fluoronitrobenzene was reacted with phloroglucinol via nucleophilic aromatic substitution to give a tris-nitro compound. The nitro groups were subsequently

reduced using hydrogen with palladium on carbon, and then this compound was reacted excess octylisocyanate, which afforded the white solid product of **17**, as illustrated in Figure 1.17. It should be noted that this is a highly versatile synthetic route, and alterations can easily be made to explore the use of other substituents on phloroglucinol and on the substituted aromatic ring.



Scheme 1.1 Synthesis of tris-urea **15**.

Four chloroalkane solvents were tested for the gel properties of **15** in each under various conditions. These solvents were: dichloromethane, chloroform, 1,1,2-trichloroethane, and 1,1,2,2-tetrachloroethane. The aforementioned treatments, which include thermal treatment

via heating and cooling to either room temperature or flash cooling using an ice bath, ultrasound irradiation using a sonicator, and/or metal salt doping were then applied using each of these solvents. Comparisons were made and system properties inferred from the gel responses to the internal and external stimuli applied. Compound **17** only formed a full gel in 1,1,2-trichloroethane with thermal treatment, and a partial gel in 1,1,2,2-tetrachloroethane. To test how a metal salt, namely CuBr_2 , would affect gelation, a stoichiometric equivalent was added to each the 1,1,2-trichloroethane and the 1,1,2,2-tetrachloroethane, as seen in Figure 1.19. Not only did this addition transform the partial gel of tetrachloroethane into a full gelator with an MGC of 5mM, but it as well decreased the MGC of the trichloroethane gel from 10mM to 5mM when thermally treated (Table 1.4).



Figure 1.18 Gel experimental results depicted in which mixtures of of the four previously mentioned chloroalkanes, (a) CH_2Cl_2 , (b) CHCl_3 , (c) 1,1,2-trichloroethane, and (d) 1,1,2,2-tetrachloroethane and tris-urea gel compound **17**. Reprinted with permission from Yamanaka, M.; Fujii, H.; *J. Org. Chem.*, **2009**, *74*, 5390–5394. Copyright 2009 American Chemical Society



Figure 1.19 Photographs acquired by Fujii et al of CuBr_2 doped gels of **17** along with the standard chloroalkanes (a) CH_2Cl_2 , (b) CHCl_3 , (c) 1,1,2-trichloroethane, and (d) 1,1,2,2-tetrachloroethane. Reprinted with permission from Yamanaka, M.; Fujii, H.; *J. Org. Chem.*, **2009**, *74*, 5390–5394. Copyright 2009 American Chemical Society

Table 1.4 Resultant properties of gels formed with **15** under thermal treatment conditions.²¹

additive	CH_2Cl_2	CHCl_3	1,1,2-trichloroethane	1,1,2,2-tetrachloroethane
none	I	I	G (10)	PG
CuBr_2	I	I	G (5)	G (5)

Key: Gel results with Tris-urea gelator **17** having concentrations of up to 25 mM, where: G = gel; PG = partial gel; I = insoluble suspension. The critical gelation concentrations are denoted as (mM)

Morphological transformations were as well observed in the SEM images of 1,1,2-trichloroethane gels (Figure 1.20), which exhibited a fibrous entanglement in the absence of CuBr_2 , and spherical particles in the presence of the metal salt. This suggests that the modes of assembly for each system are different. An SEM image was as well acquired for the partial gel of **17** formed in 1,1,2,2-tetrachloroethane in the presence and absence of CuBr_2 . Notably thinner fibrous aggregates formed in the metal salt loaded medium.

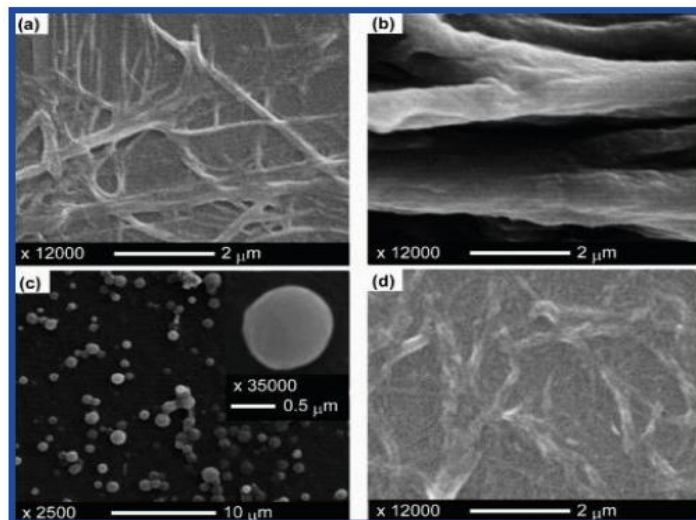


Figure 1.20 Xerogel images of (a) 1,1,2-trichloroethane gel with **17**; (b) 1,1,2,2-tetrachloroethane partial gel of **17**; (c) 1,1,2-trichloroethane gel with **17** and CuBr_2 ; and (d) 1,1,2,2-tetrachloroethane gel of **17** and CuBr_2 . Reprinted with permission from Yamanaka, M.; Fujii, H.; *J. Org. Chem.*, **2009**, *74*, 5390–5394. Copyright 2009 American Chemical Society

Under the influence of ultrasound irradiation gelation may be induced where it would otherwise have not occurred, as was the case with thermal treatment of compound **17**. The

Table 1.5 Resultant properties of gels formed with **17** under ultrasound irradiation treatment conditions²¹

additive	CH_2Cl_2	CHCl_3	1,1,2-trichloroethane	1,1,2,2-tetrachloroethane
none	I	G (15)	I	G (5)
CuBr_2	I	G (5)	I	G (5)
BiCl_3	G (15)	PG	I	G (20)
$\text{Y}(\text{NO}_3)_3$	PG	G (10)	I	I

Key: Gel results with Tris-urea gelator **17** having concentrations of up to 25 mM, where: G = gel; PG = partial gel; I = insoluble suspension. The critical gelation concentrations are denoted as (mM)

following table summarizes the results where sonication only and sonication plus metal salt incorporation were done.

1.6 Tuning Gel Morphology and Rheological Properties With Internal and External Stimuli

This study performed by Yamanaka and Fujii demonstrates how the tweaking of external and internal stimuli can affect gelation, particularly through thermal heating and cooling, ultrasound sonication, and metal salt/ligand doping. Cheng Wang et al have experimented with tuning techniques which trigger reversible gel-sol transitions under the influence of photo induced isomerization and redox chemistry using organogelators based on tetrathiofulvalene and azobenzene groups. Photoreactive groups such as azobenzene and stilbene have been incorporated into LMWGs with the intent for such groups to trigger gel-sol transitions^{11,12}. It is specifically the tetrathiofulvalene moiety which is electroactive and responds to redox conditions whether they are chemical or electrochemical. The multistimuli responsive gelator **18** has incorporated within it such functionalities by rationale design to exploit the aforementioned properties.

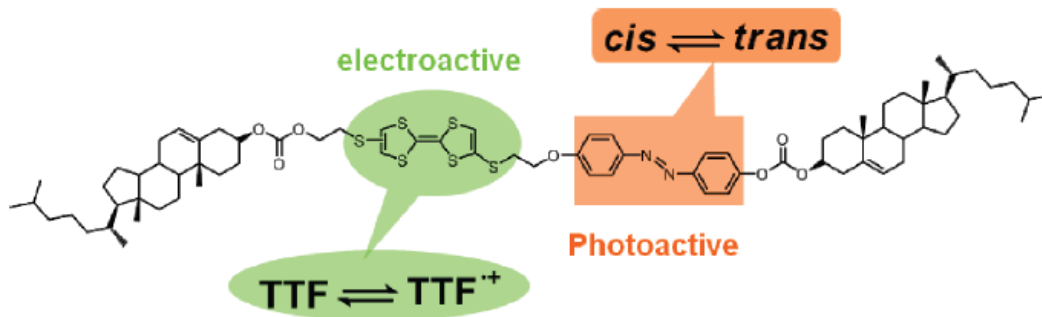


Figure 1.21 Tetrathiofulvalene (TTF) compound **18**. Reprinted with permission from: Wang, X.; Xing, L.; Cao, W.; Li, X.; Chen, B.; Tung, C.; Wu, L.; *Langmuir*. Copyright 2011 American Chemical Society

The oxidation state of the TTF moiety can reversibly change to $\text{TTF}^{\cdot+}$ radical cations or TTF^{2+} dications when redox conditions are applied. A conformational change is triggered by irradiating compound **18** with the proper wavelength of electromagnetic energy, which causes cis-trans isomerization. Simply incorporating the stimuli responsive functionalities into the gel molecule, however, will not necessarily provide the crucial balance that must be achieved in

Table 1.6. Gelation results for compound **18**.¹¹

solvent	gelation examination
$\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ (3/1, v/v)	G (4.0 mg/mL)
$\text{CHCl}_3/\text{CH}_3\text{OH}$ (3/1, v/v)	G (4.0 mg/mL)
$\text{CH}_2\text{Cl}_2/n\text{-hexane}$ (1/1, v/v)	G (4.0 mg/mL)
$\text{CHCl}_3/n\text{-hexane}$ (1/1, v/v)	G (4.0 mg/mL)
THF	G (4.0 mg/mL)
toluene	G (4.0 mg/mL)
$\text{CH}_2\text{Cl}_2/\text{CHCl}_3$	S
1,2-dichloroethane, CCl_4	P
<i>n</i> -hexane, cyclohexane, methanol, ethanol, DMF, DMSO, Acetone, CH_3CN , ethyl acetate	I

Key: G = gel, where MGCs are presented in mg/mL; S = soluble; P = precipitate; I = insoluble

order to construct a functional gelator molecule. This balance can be manipulated by attaching functional groups which will either decrease or increase the overall LogP value of the molecule, or in other words, the overall polarity. This was accomplished by tacking cholesterol to each end of the gel molecule. The gelation results are summarized in table 1.6. When analyzed in the gel form, compound **18** has a broad absorption band in the vicinity of 360nm, and it was observed that this broad band had diminished over time as another band had intensified in the range of 450nm. The band at 360nm can be assigned to the trans form of the azobenzene portion of **18**, and the emerging one at 450nm is assigned to the cis form. Wang et al reported that HPLC results indicated that the composition of the solution at t_0 was 81.6% trans and 18.4% cis. As seen in the below fluorescence spectrum, a photostationary state

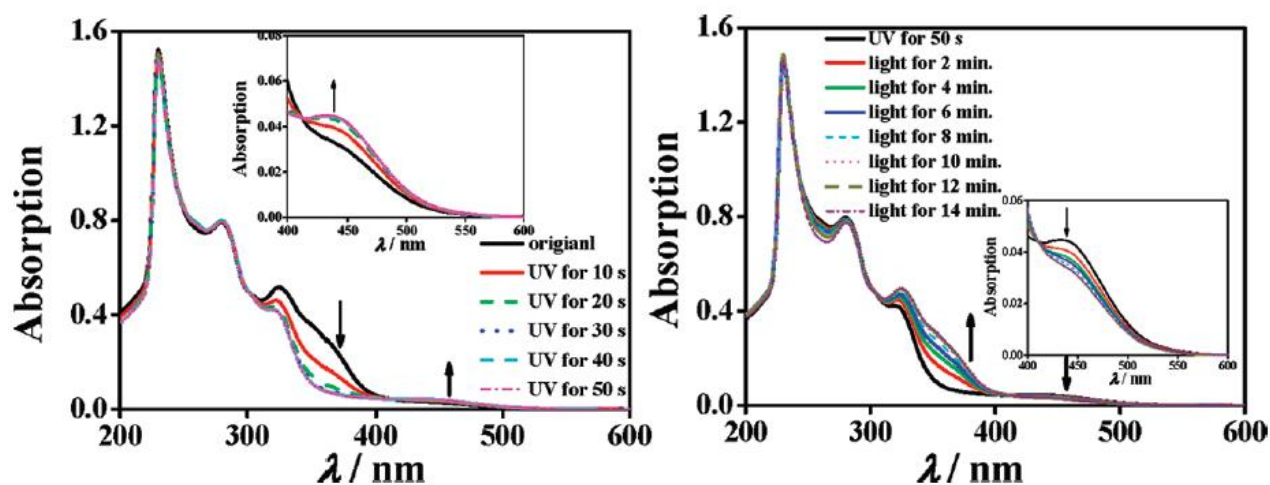


Figure 1.22 Left: The absorption spectra of TTF gelator **18** irradiated at 365nm for varying durations. Right: The absorption spectra for gelator **18** when irradiated with UV light, initially for 50 s, and then subsequently at varying times. The concentrations of each were 1.0×10^{-5} M in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ (3:1). The insets emphasize the 400–600 nm range. Reprinted with permission from: Wang, X.; Xing, L.; Cao, W.; Li, X.; Chen, B.; Tung, C.; Wu, L.; *Langmuir*. Copyright 2011 American Chemical Society

spectrum was acquired for 50s under UV irradiation conditions, and the resultant composition at this time was 96.8% cis and 3.2% trans. It was reported that continued irradiation of the sample with visible light energy reverted the samples composition to a predominating trans isomer presence. Interestingly, the cholesterol moiety not only made a hydrophobic contribution to the gel molecule, thusly helping to balance the overall polarity, but it also likely imparted chiral growth of the thin fiber formations. This is suggested by analysis of the CD spectra obtained by the group, which showed positive CD signals at 368 and 384nm. These signals gradually disappeared as the gel approached its solution phase through the application of heat.

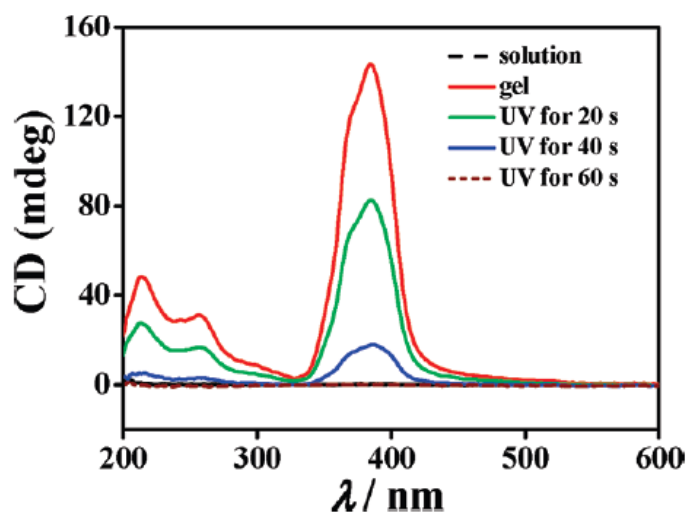


Figure 1.23 The CD spectra gelator **18** with a concentration of 8.0 mg/mL in CH_2Cl_2 (3/1, v/v) in: 1) Solution; and 2) the resultant gel and subsequent UV spectra thereof at 20, 40, and 60 s respectively. Reprinted with permission from: Wang, X.; Xing, L.; Cao, W.; Li, X.; Chen, B.; Tung, C.; Wu, L.; *Langmuir*. Copyright 2011 American Chemical Society

1.7 Hydrogelators as drug-delivery devices

Hydrogelator disassembly or the reverse under the influence of chemical stimuli such as enzymes for the purpose of drug delivery has been explored by George John et al⁶¹. Within the developing technology of hydrogelator drug delivery, LMWGs provide some distinct advantages to the currently more prevalent mode which uses polymer hydrogels. These include: possible lower toxicity, increased biodegradability, and also the property of thermoreversibility which is a more prominent LMWG feature. A variety of delivery platforms have been experimented with. One process simply entraps a hydrophobic drug within the gel matrix as seen in mechanism of action **A** in Figure 1.24 below. Another more rare condition is when the gel molecule is itself is the active therapeutic agent, in which case its capacity to gelate water is coincidence and not by design. And perhaps the most rational process, at least from the design standpoint, is to simply attach a therapeutic agent covalently to a known gelator using an enzyme-sensitive spacer.

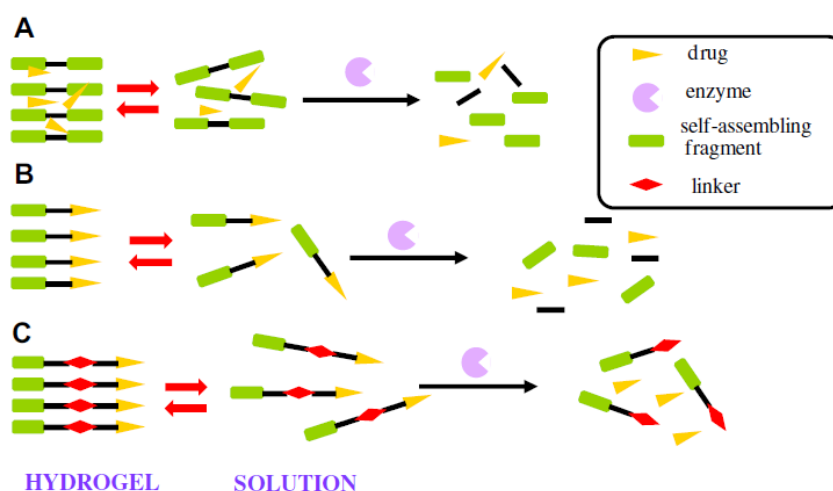
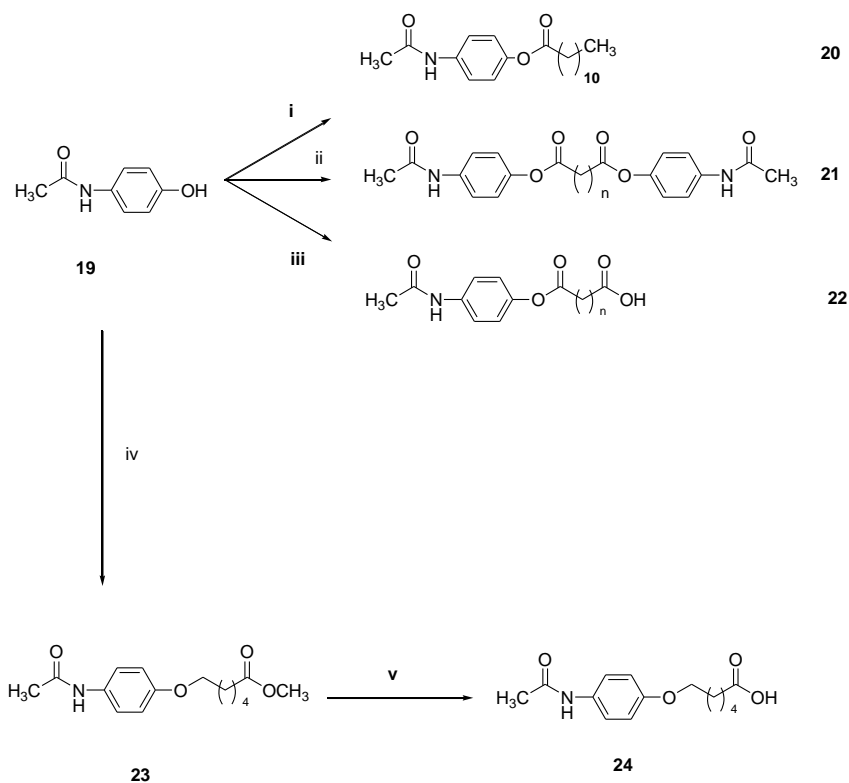


Figure 1.24 Various hydrogelator drug delivery models **A-C**.⁴² Permission license No. 2864891090877

One of the most alluring aspects of this form of enzymatically triggered drug delivery is that specific locations in the body can be triggered for such release. George John et al prepared a prodrug amphiphilic gel assembly which used the antipyretic acetaminophen. Studies were as well conducted to demonstrate this gelator's ability to host yet another therapeutic agent, namely curcumin, which is a known chemopreventative drug and is as well used as an anti-inflammatory agent. The synthesis of these hydrogelator amphiphiles is shown below starting from acetaminophen in Scheme 1.2:

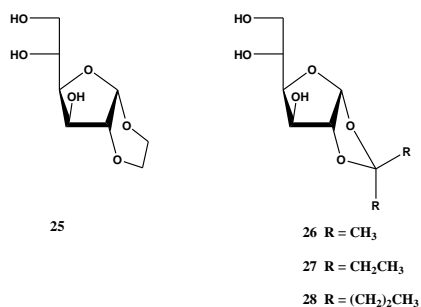


Scheme 1.2 Conditions for amphiphiles and bolaamphiphiles **19-24** from precursor acetaminophen: (i) dodecanoic acid, dicyclohexylcarbodiimide (DCC), dimethylaminopyridine (DMAP), anhydrous tetrahydrofuran (THF), rt, 24 h. (ii) ω -dicarboxylic acid (0.5 equiv.), DCC, DMAP, dry THF, rt, 48 h. (iii) ω -dicarboxylic acid (1.2 equiv.), DCC, DMAP, dry THF, rt, 24 h. (iv) 6-bromomethylhexanoate, K_2CO_3 , dry THF, reflux, 12 h. (v) NaOH, MeOH, rt, 12 h

The above design is based not only on the synthesis of amphiphiles, but also bolaamphiphiles which have hydrophilic polar groups attached at each end of a hydrophobic chain linker. By design, upon degradation, the gel does not produce toxic fragments or byproducts which could be considered harmful. This and several other factors must be evaluated as potential health hazards. As the acetaminophen is released, only a long-chain fatty acid accompanies the disintegration, an extremely important consideration for any such system.

1.8 Monosaccharide Based Gelators

Carbohydrate based gelators, namely monosaccharide based gel molecules, are of great importance to efforts in understanding gel systems¹⁰²⁻¹⁰⁴. Predictable hydrogen bond based networks, which can be formed by the many free –OH groups in monosaccharides are potential frameworks which could lead to gelation of various solvents. Accessibility to these hydrogen bond donors, abundance of them, and hydrophobic balance are three factors which are more easily controlled when dealing with monosaccharide systems, making them ideal candidates for designing gelators. For instance, Luboradzki et al performed analytical experiments on a tunable gelator system comprised of two different monosaccharides **25** and **26-28** (Figure 1.25), exploiting the three free –OH groups as hydrogen bond donors/acceptors for gel matrix assembly¹⁰⁵⁻¹⁰⁹.



Scheme 1.25 Glucofuranose monosaccharide gelators **25-28**. Varying amounts of **26**, **27**, or **28** added to **25** to 'tune' the gel assembly

The **R** groups projecting off of the dioxolane groups in compounds **26-28** help to modulate the hydrophobic chain length, thus helping establish the proper amphiphilicity necessary for gelation. In the case of a two component system such as this, adding a second molecule to the system may be critical for molecular assembly in an anisotropic fashion. In the case of Luboradzki et al, this addition only modified the gel structure, albeit in a fashion which in some cases enhanced the gel structure

Conclusion

The *design* of novel gelator molecules is limited currently, although, the discovery of the previously mentioned classes of gelator compounds does provides a platform of rationale for molecular design. Understanding the assembly process through the use of instrumentation and molecular probes gains the necessary insight to work toward such a goal. With every new gelator molecule synthesized, a step toward gelator *design* is taken. Various LMWG molecules were explored to illustrate the capacity of these systems to be used in applications such as drug delivery and other various stimuli responsive uses.

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Chapter II. A Glucose Based 4,6-O-Protected Diphenyl Ketal System

Abstract

Within the field of supramolecular chemistry, low molecular weight gelators are an important new class of compounds which are of special interest because of their wide scope of significant applications as advanced materials. Past and current research performed by the Wang group indicates that analogues of various 4,6-acetals of either 1-deoxy or 1-methoxy glucopyranosides form stable gels in organic, aqueous, and organic/aqueous solvents at various concentrations. To understand the structural requirements of such analogous sugar-headgroups, a series of 4,6-diphenyl acetal derivatives of glucose were synthesized, and their respective gel properties were analyzed in order to understand the structural influence of these novel molecules toward supramolecular gelation. The synthesis and characterization of these new compounds are presented in this chapter, as well as a detailed analysis of how such a series with an abundance of aromatic moieties promotes π - π stacking, and thus obstructs or contributes to gel matrix formation.

Introduction

Glucose based low molecular weight gelator (LMWG) systems have previously been explored by few to reveal that such molecules are indeed efficient and promising gelators¹. This class of carbohydrate based molecules is profoundly versatile, resulting from their structures^{2,3}. The key non-covalent forces which are involved in the formation of the supramolecular assemblies are: π - π interactions, Van der Waals interactions, and hydrogen donor/acceptor interactions⁴. Sugar based LMWGs may easily be incorporated with π systems, long aliphatic chains, and various other functional groups which serve to achieve a specifically desired amphiphilic equilibrium. Additionally, exploitation of pre-existing hydroxyl groups for the potential formation of hydrogen bonding arrays makes these systems attractive as ideal candidates for having inherent or at least potential gel properties. Carbohydrate based low molecular weight gelators not only exemplify a great capacity to form gels efficiently, but as well show great promise as biocompatible molecules. One such factor which is sometimes significantly important is the chirality which is inherent to glucose derived molecules⁵. The assemblies of gelators, which have inherent chirality, often form with helical winding. This inherent molecular chirality confers the observed helices in some of the macrostructures of the systems there-of. Saccharide molecules are functional heterocycles with free hydroxyl sites ready for selective functionalization as well. Sugars are a class of compounds which are versatile when it comes to functionalization, and the established platform of having a thorough understanding of selective functionalization provides pre-established routes to afford gel molecules. Das et al performed the synthesis of 4,6-*O*-protected *N*-glycosylamines **1-3** starting from simple D-

glucose (Figure 2.1) and subsequently anomerically appended with either iodine treated 2-aminopyridine **4** or 3-amino-2-chloropyridine **5** as seen in Figure 2.1^{13,14}. Multiple spectral analysis techniques were employed to explore interactions which were taking place that contributed to gel formation, which included π - π stacking and hydrogen bonding. It was also

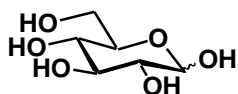
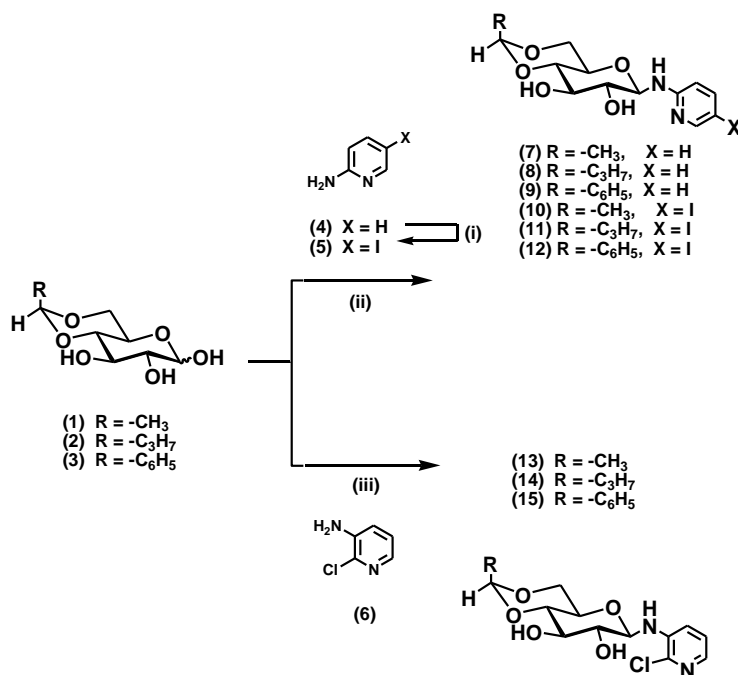


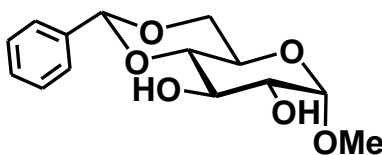
Figure 2.1 D-glucose



Scheme 2.1 Synthesis of *N*-glycolysalmines **1-3**: (i) 2-aminopyridine **4**, I₂, DMF, rt, 50%; (ii) 2-aminopyridine, 5-iodo-2-aminopyridine **5**, ethanol, rt, 23-69%; (iii) 3-amino-2-chloropyridine **6**, ethanol, rt, 60-71%. These reagents produced compounds **7-15** when reacted with the respective glucose derivative

noted by Das's group that dipole dipole interactions were as well responsible for holding together the gel structure, along with other 'modes of interaction' as revealed by computational methods^{15,16}. Utilizing simple monosaccharide molecules such as **glucose** as starting materials, the Wang group synthesizes gelator molecules and performs thorough analyses which prove instrumental to our understanding of such systems.

Past and current research performed by the Wang group reveals that analogues of various 4,6-acetals of either 1-deoxy or 1-methoxy glucopyranosides, such as those derived from headgroup **16**, form stable gels in organic, aqueous, and organic/aqueous solvents at varying concentrations. The derivatization of **16** entails either the selective functionalization of one of two free -OH groups to produce a "C2" or "C3" monomer, or the dual functionalization of each available -OH producing the **dimeric** form of analogue. The functional groups are typically esters, ureas, carbamates, or amides and they are usually terminated with a moderate to long hydrophobic tail. In the case of the monomers, either the C2 or C3 -OH remains unfunctionalized and may therefore be available for hydrogen bond donation.



16

Figure 2.2 A previously synthesized headgroup from which several analogues were synthesized that have proven to be effective gelators

The hydrogen bond stacking array is depicted Figure 2.3, where in the instance of this particular illustration, the C2 -OH is functionalized. Additionally, the 4,6-protecting group is aligned in

such a way that π - π stacking is permitted and thus as well contributes to the 1-dimensional, anisotropic growth.

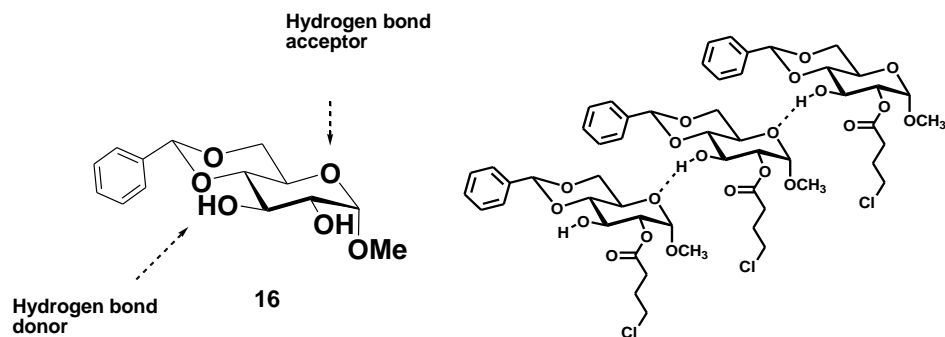
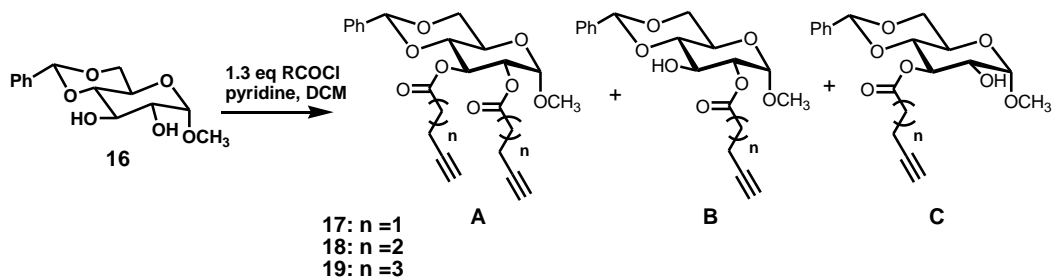


Figure 2.3 Representative hydrogen bonding array of glucose derived gelators from **16**

Previous research revealed that analogues **17-19** (A-C), which are derivatives of **16** that housed terminal alkynyl esters, were found to be good gelators in a variety of organic, aqueous, and organic/aqueous solvent mixtures (Scheme 14). The Wang group set out to understand the structural requirements which instilled these terminal acetylene containing glucose derivatives with gelation abilities. It was reasoned, regarding the structural requirements of the hydrophobic tails, that high packing order which may accompany analogues containing long aliphatic chains sometimes causes crystallization rather than a loosely held gel matrix structure. It was conjectured that the terminal acetylene functionalities of **17-19** disrupted the packing order of the gelator molecules, which hindered precipitation and allowed for the architectural assemblage needed to form the observed stable gels.



Scheme 2.2 The terminal alkynyl esters **17-19** (5-7 carbon length A-C) which were found to be good gelators various organic and organic/aqueous solutions

Results and Discussions

Compounds **16** and **20** are precursors to several known gelators which include esters, amides, carbamates, and ureas. A new series was analyzed for its gelator properties and probed to reveal any disparities in structural requirements regarding the 4,6-*O* position of the glucose and glucosamine analogues. Assessment of trends correlated with minor structural modifications of

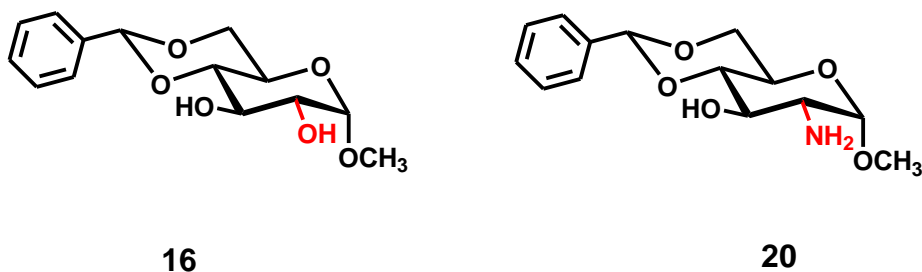


Figure 2.4 Juxtaposition of compounds **16** and **20**, differing structurally at the C2 position

the sugar headgroups or functionalities thereof, especially the 4,6-protecting group or anomeric appendage, has provided great insight into the structural requirements of multiple series of glucose-based gelators based on the general structure of **16** and **20**. To further investigate the structural requirements of such analogous sugar-headgroups and their derivatives, a series of 4,6-diphenyl acetal derivatives of glucose were synthesized from **38** in hopes of understanding the structural influence of these novel molecules toward supramolecular gelation. The structural requirements regarding the hydrophilic tails and anomeric functionalities had been thoroughly explored and, as seen in Figure 2.5, the diphenyl acetal as compared to a benzylidene acetal was predicted to have interesting and sustained gelation properties, due to its having an extra π system for building π stacking arrays which could provide more non-covalent bonding opportunities for building the gel matrix to exploit.

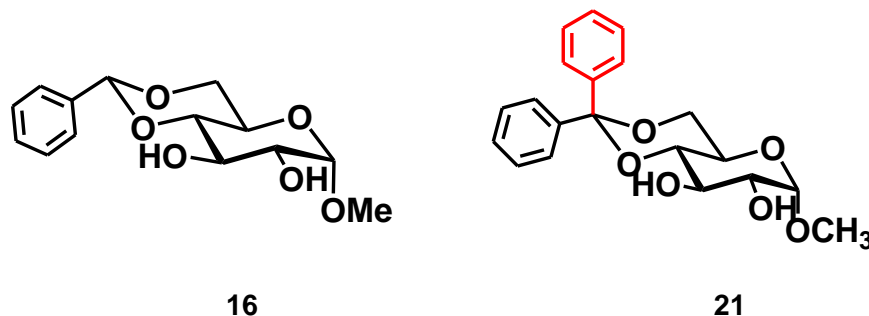
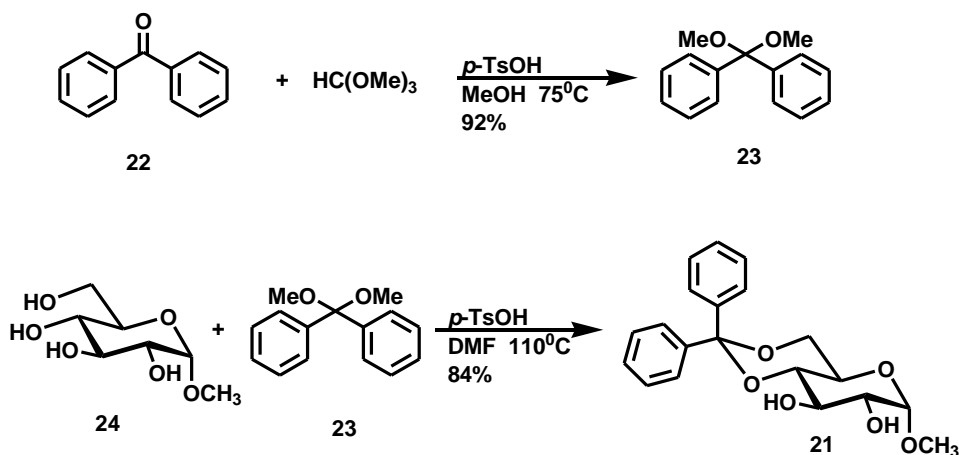


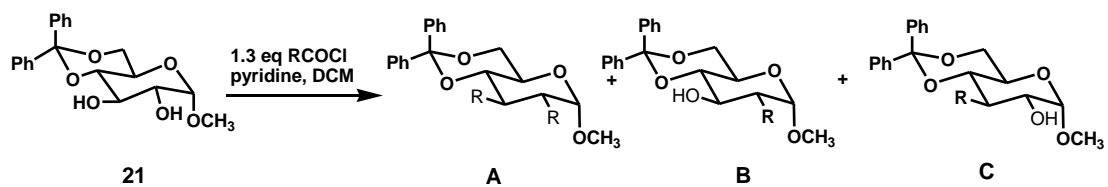
Figure 2.5 Headgroups **16** and **21**, with a 4,6-acetal modification on molecule **21**

The synthesis of **21** begins with the starting material benzophenone **22**, as seen in Scheme 2.3.

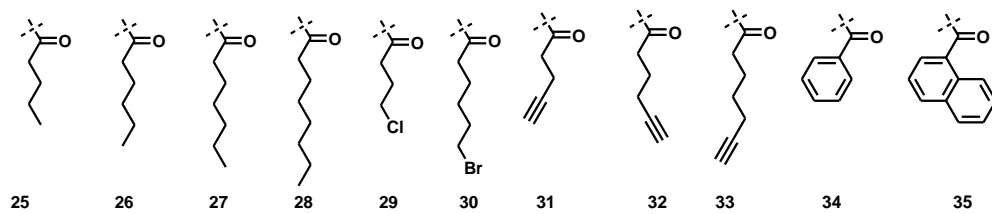


Scheme 2.3 Synthesis of diphenyl gelator headgroup **21**

Literature reports for the synthesis of **23** included various conditions using organometallic salts¹⁷, yet a simpler approach was desired, whilst maintaining a relatively high yield. The synthesis that was employed uses 3 equivalents of trimethylorthoformate in the presence of 10 mol% *p*-TsOH dissolved within methanol. A simple work-up using powdered sodium bicarbonate to quench the reaction, followed by filtration using cold dichloromethane provides pure product. This scheme is continued by subsequently 4,6-*O*-protecting methyl- α -D-glucopyranoside with dimethoxy acetal **23** to afford 4,6-diphenyl acetal glucopyranoside **21**. The esterifications performed on headgroup **21** (Scheme 19) typically yielded three products: the **C2** and **C3** monomers (analogues of type **B** and **C**, respectively), and **diester** form (analogues of type **A**) which has both –OHs functionalized. For the purpose of gelation studies, only the **C2** and **Diester** forms are reported (Table 2.1) because the **C3** formation wasn't consistently sufficient in producing enough material for analysis and testing, or was perhaps not even isolated at all.

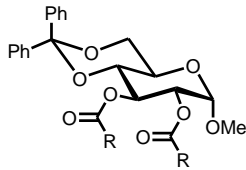
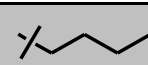
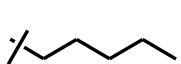
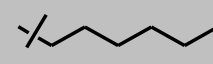
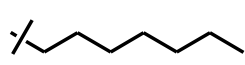
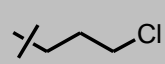
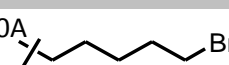
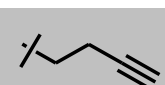
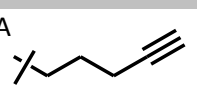
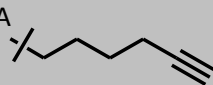
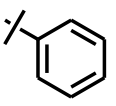
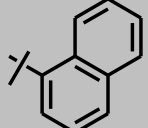


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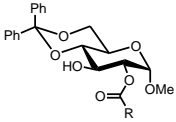
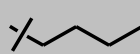
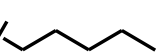
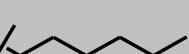







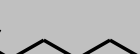
Scheme 2.4 Synthesis of ester analogues of monomeric forms **B** and **C**, and dimeric form **A**

Table 2.1 Gelation Results of the Diester Series

	Yield	Water	Hexane	EtOH	Water: EtOH	Water: DMSO
25A 	31 %	I	S	S	P	P
26A 	8 %	I	I	P	P	P
27A 	13 %	I	S	P	P	P
28A 	17 %	I	S	S	P	P
29A 	20 %	I	S	I	I	I
30A 	11 %	I	S	I	P	P
31A 	5 %	I	I	P	P	P
32A 	14 %	I	I	S	P	P
33A 	10 %	I	I	S	P	P
34A 	10 %	I	I	S	P	P
35A 	N/A	-	-	-	-	-

U, unstable gel; G, gel at room temperature; I, insoluble; Cr, crystallizes; S, soluble; P, precipitates

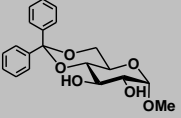
Table 2.2 Gelation Results of the C2 Monoester Series

	Yield	Water	Hexane	EtOH	Water:EtOH	Water:DMSO
					2:1	2:1
25B 	13 %	I	I	S	P	P
26B 	29 %	I	P	P	P	U (20)
27B 	42 %	I	S	P	P	P
28B 	43 %	I	I	S	P	P
29B 	40 %	I	I	S	P	P
30B 	38 %	I	I	P	P	P
31B 	30 %	I	S	I	P	U (20)
32B 	19 %	I	I	S	P	P
33B 	11 %	I	I	S	P	P
34B 	55 %	I	I	S	P	P
35B 	64 %	I	I	S	I	S

U, unstable gel; G, gel at room temperature; I, insoluble; Cr, crystallizes; S, soluble; P, precipitates

Considering that none of the esters from the diester or monoester series were able to form gels, the headgroup was tested to see if the additional –OH group would assist in gelation. At this point, it was evident that the absence of a hydrophobic tail, and with the introduction of yet another H-bond donor, the necessary amphiphilic equilibrium for gelation may be reestablished.

Table 2.3 Gelation results of glucose derived headgroup

Compound	Yield	Water	Hexane	EtOH	Water: EtOH	Water: DMSO
	84 %	P	I	S	G (10.5)	G (23)

U, unstable gel; **G**, gel at room temperature; **I**, insoluble; **Cr**, crystallizes; **S**, soluble; **P**, precipitates

The 4,6-diphenyl ester series did not prove to effectively gelate solvents of either aqueous or organic composition. It was conjectured that too high of a packing order was occurring due to oversaturation of the molecule with aromatic and aliphatic substituents which lead to strong intermolecular interactions. These groups either likely led to a packing order which was too high due to all of the π - π bonding contributions or perhaps was due to a packing order which was too low, due to disruption from the bulky 4,6 protecting group. An X-ray crystal structure was obtained for compound **35B**, which in addition to the aromatic moieties at the 4,6 position

has a naphthyl appendage at the C2 position. The molecular stacking array seen below (Figure 2.6) in the crystal lattice firmly suggests a packing order which was too high to form the necessary weaker bond interactions for gel matrix formation.

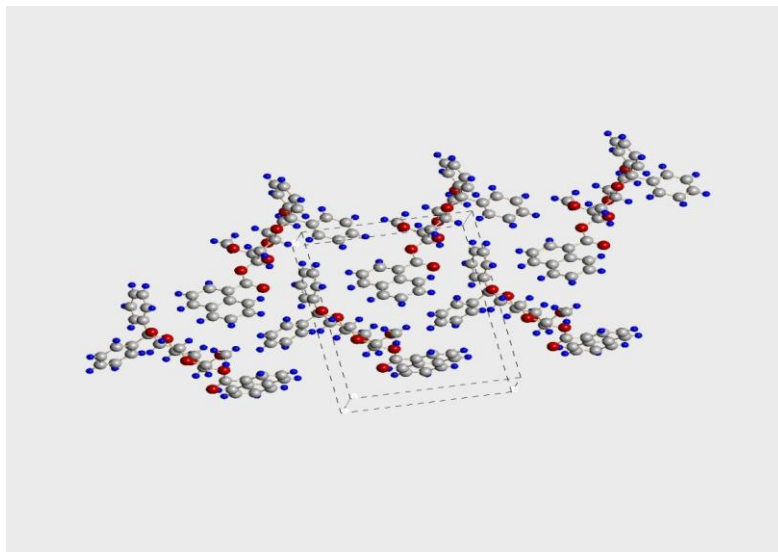
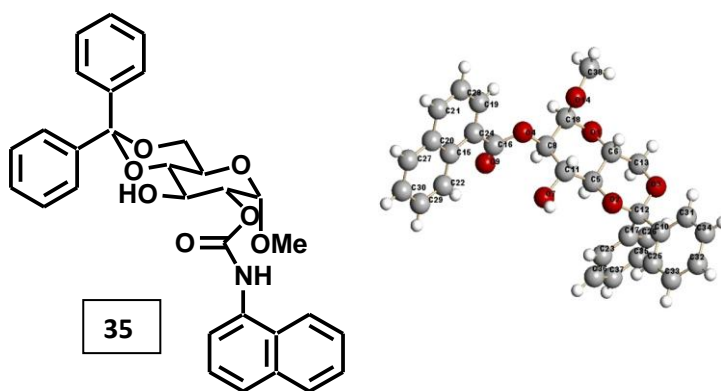
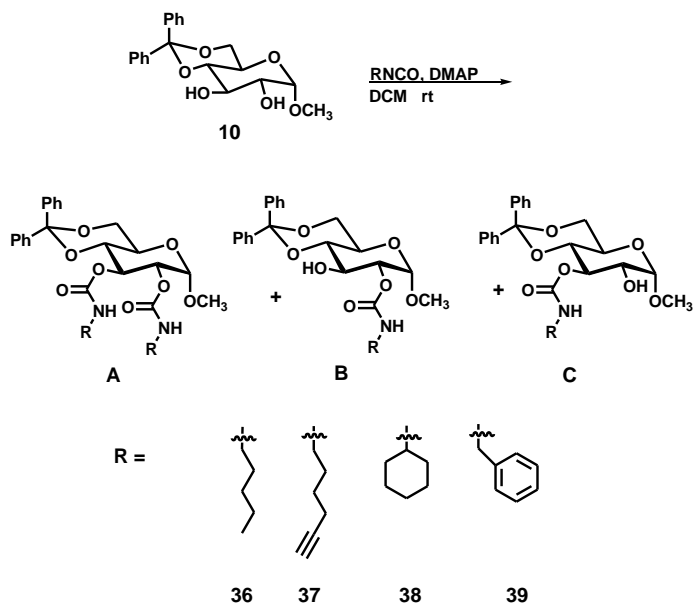


Figure 2.6 Rendered crystal structure for compound **35B**
Unit Cell of Compound **35B**

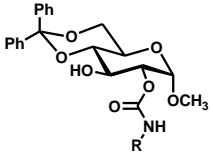
From headgroup **21**, carbamate analogues were synthesized. The provision of yet another hydrogen bond donor was expected to have desirable effects regarding such a series' ability to form gels. The synthesis follows in Scheme 20:



Scheme 2.5 Synthesis of carbamates analogues

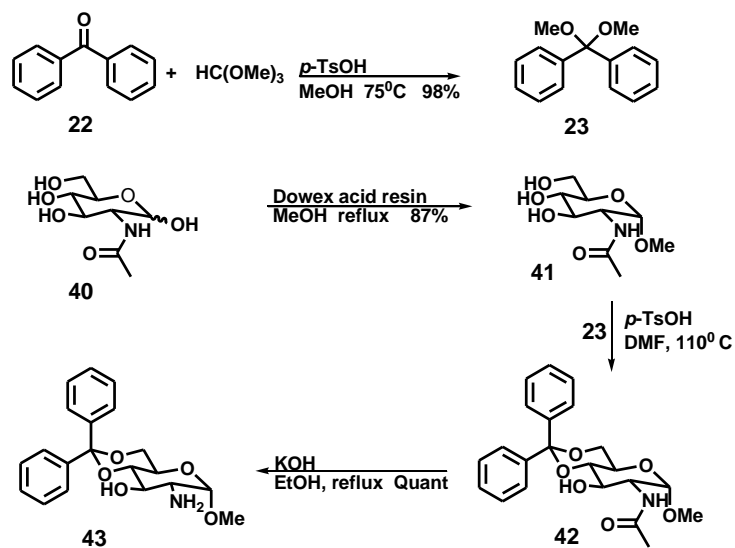
this series was not producing efficient gelators based on glucose. To more thoroughly probe the gelling capacity for the various analogues of the 4,6-diphenyl series, amide based LMWGs were synthesized. Although the esters did not prove to be efficient gelators, it was predicted

Table 2.3 Carbamate gel results

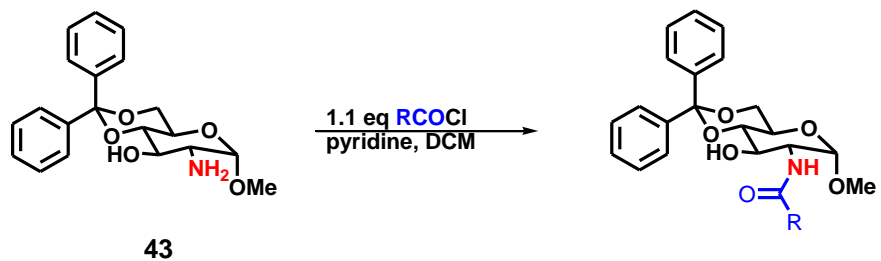
	Yield	Water	Hexane	EtOH	Water: EtOH	Water: DMSO
36	43 %	I	I	S	P	P
37	15 %	I	I	S	I	I
38	13 %	I	I	S	P	P
39	13 %	I	I	S	P	P

U, unstable gel; **G**, gel at room temperature; **I**, insoluble; **Cr**, crystallizes; **S**, soluble; **P**, precipitates
As the synthesis of these various carbamates analogues progressed, it was becoming clear that

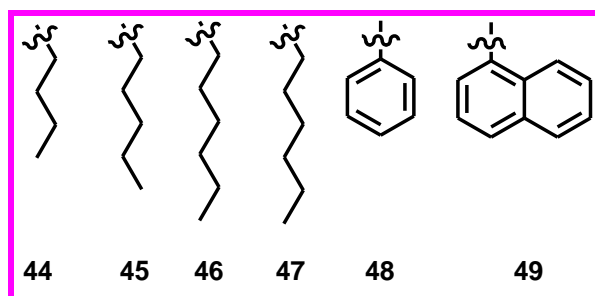
that the additional hydrogen bonding sites afforded by amides and carbamates may provide a packing order suited for gel matrix formation. The general synthesis for each gelator type is presented below in Scheme 2.6:



Scheme 2.6 Synthesis of N-acetyl glucosamine derived amides and ureas

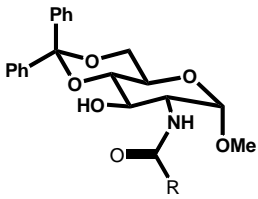


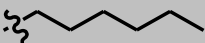
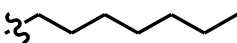
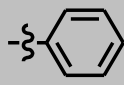
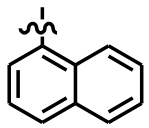


R =



Scheme 2.7 Synthesis of amide analogues

Table 2.4 Amide Gelator Results

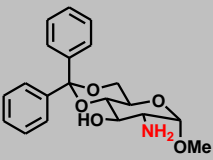
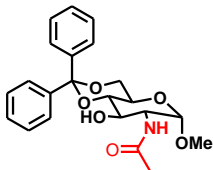
	Yield	Water	Hexane	EtOH	Water: EtOH	Water: DMSO
44 	88 %	I	I	S	P	U (20)
45 	73 %	I	I	S	G (6.3)	G (13.5)
46 	40 %	I	I	S	U (20)	G (5)
47 	37 %	I	I	S	P	G (10)
48 	85 %	I	I	U (21)	I	P
49 	77 %	I	I	S	P	P

U, unstable gel; G, gel at room temperature; I, insoluble; Cr, crystallizes; S, soluble; P, precipitates

As predicted, the additional –H bond donor site from the –NH bestowed some gelation properties to this system, although not as much as was observed with previous systems. This would suggest that even though some gel properties are restored when adding an –NH bond donor from amide derivatives, but that the diphenyl group was still somehow disrupting gelation. To further investigate the effects of having an amide or amino group directly attached

to the C2 of the glucosamine derivative, headgroup **43** and its precursor, -*N*-acetyl glucosamine derivative **42**, were tested for their gelation capabilities. Both were able to form stable gels in 2:1 water:DMSO, indicating that a shift toward hydrophilicity imparts a greater gelling capacity to this system.

Table 2.5 Glucosamine Headgroup Gel Results

Compound	Yield	Water	Hexane	EtOH	Water: EtOH	Water: DMSO
	72 %	I	I	S	P	G (23)
	-	I	I	S	P	G (8.7)

U, unstable gel; G, gel at room temperature; I, insoluble; Cr, crystallizes; S, soluble; P, precipitates

Conclusions

From investigation of the gelation results of the glucosamine derived headgroup, it is apparent that the additional phenyl ring makes this series too hydrophobic to gelate solvents effectively. As revealed by both the free amine and *N*-acetyl form of the headgroup, a shift toward greater

hydrophilicity restores gelling capacity. In the ester series, aromatic substituents, in addition to the extra phenyl group of the diphenyl ketal, likely led to oversaturation of π interactions, disallowing gel matrix formation, favoring precipitation. The carbamate analogues were expected to form gels in some solvents because of the additional –NH present for hydrogen bonding, yet did not. This as well leads to the conclusion that the additional aromatic ring disrupted, rather than encouraged gel formation. For the amides, short length hydrophobic tails were tolerated; this is due to the enhanced hydrogen bonding from the amide functional group.

Experimental section

*Synthesis of benzophenone dimethyl acetal **23***: To a 500 mL round bottomed flask, 16.12 g (88.5 mmol) of benzophenone was added and dissolved within 125 mL of MeOH and stirred at room temperature. To this stirred solution, 29 mL (3 equivalents) of trimethyl orthoformate was added along with 10 mol% (1.68 g) of *p*-toluene sulfonic acid. Another 3 equivalents of trimethyl orthoformate was additionally added 5 hours after the initial starting time. This reaction mixture was subsequently brought to 70°C and refluxed for 46 hrs, the reaction was neutralized with powdered sodium bicarbonate and then filtered and washed with DCM. The reaction solvent was evaporated affording the pure solid product. Yield: 92%; ¹H NMR (400 MHz, Chloroform-d) δ 7.50 (s, 3H), 7.29 (dd, 5H), 7.27 – 7.12 (m, 1H), 3.13 (d, *J* = 0.9 Hz, 5H).

Synthesis of 4,6-O-diphenyl-methyl- α -glucopyranoside 21: To a 500 mL round bottomed flask, 5.13 g (26.4 mmol) of methyl- α -glucopyranoside **24** was added and dissolved within 60 mL of DMF and stirred at room temperature. To this solution, 10.67 (2.25 equivalents) of benzophenone dimethyl acetal **23** and the reaction mixture was brought to 100⁰C. To this hot solution, 20 mol% of *p*-toluene sulfonic acid was added and the reaction mixture stirred for 21 hours, after which time stirring was discontinued. The flask was then adapted to a rotary evaporator and the methanol byproduct was removed to push the reaction toward completion. Added powdered sodium bicarbonate to this solution to neutralize acid, and then subsequently filtered. The solvent was then dried down overnight under nitrogen. The resulting solid, crude mixture was then subjected to an aqueous workup using chloroform, water, and brine. After separating the organic phase, it was dried using sodium sulfate and then filtered, and evaporated. A flash column using a hexane:EtOAc gradient was used, which ranged from 7:1 to 1:1. Yield: 84% ¹H NMR (400 MHz, Chloroform-d) δ 7.61 – 7.51 (m, 25H), 7.51 – 7.39 (m, 15H), 7.38 – 7.17 (m, 16H), 4.71 (d, *J* = 3.9 Hz, 4H), 4.12 (dd, *J* = 10.1, 4.9 Hz, 4H), 3.98 (td, *J* = 9.1, 1.8 Hz, 13H), 3.92 (dd, 1H), 3.78 (t, *J* = 10.3 Hz, 4H), 3.61 (t, *J* = 9.5 Hz, 26H), 3.51 (td, *J* = 4.0 Hz, 2H), 2.74 (d, *J* = 2.3 Hz, 4H), 2.24 (d, *J* = 9.6 Hz, 5H).

General method for the synthesis of esters for headgroup 21: These syntheses were performed typically using about 120 mg (0.33 mmol) of headgroup **21**, which was dissolved within 2mL of anhydrous DCM and stirred at 0⁰C. Then, about 5eq of pyridine is added, after which 1.3 equivalents of the appropriate acid chloride was added. The reaction mixture was

then allowed to warm to room temperature spontaneously within the ice bath used. After about 24hrs of reaction progression, the reaction was discontinued and a flash column was performed using a hexane:EtOAc gradient. If the acid chloride was not available, it was synthesized using 1.2-1.4 eq of the corresponding carboxylic acid, which was dissolved within 1.8 mL of DCM and stirred at room temperature. To this solution, 1eq of oxalyl chloride and one drop of DMF were added. After the acid chloride is maximally formed, this solution is added directly to the headgroup. Typically, the products isolated include a 2 and 3 monoesters, as well as the diester.

Synthesis of pentanoyl ester 25: The acid chloride was synthesized from pentanoic acid, oxalyl chloride, and DMF in dichloromethane at temperatures ranging from 0⁰C to room temperature. Added headgroup directly to acid chloride solution after about 1.5hrs. After about 24hrs, the reaction was discontinued and a flash column was performed using a hexane:EtOAc gradient which gave the pure 2-isomer and dimer with yields of 13% and 31.% respectively. 2-isomer ¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, *J* = 7.2 Hz, 2H), 7.46 (d, *J* = 7.7 Hz, 4H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.36 – 7.31 (m, 1H), 7.30 – 7.20 (m, 6H), 4.84 (d, *J* = 3.7 Hz, 1H), 4.72 (dd, *J* = 9.7, 3.8 Hz, 1H), 4.22 (td, *J* = 9.4, 3.4 Hz, 1H), 4.12 (dd, *J* = 10.1, 4.9 Hz, 1H), 3.96 (td, 1H), 3.80 (t, *J* = 10.3 Hz, 1H), 3.69 (t, *J* = 9.5 Hz, 1H), 3.37 (s, 3H), 2.45 – 2.38 (m, 3H), 1.63 (dt, *J* = 15.3, 7.5 Hz, 3H), 1.35 (dt, *J* = 14.6, 7.4 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (101 MHz, Chloroform-d) δ 173.8, 143.5, 138.5, 129.3, 128.6, 128.2, 127.8, 125.8, 102.7, 97.9, 75.6, 73.4, 69.3, 64.1, 63.0, 55.5, 34.0, 27.2, 22.3, 13.9. Diester: ¹H NMR (400 MHz, Chloroform-d) δ 7.53 – 7.15 (m, 11H), 5.67

(t, $J = 9.7$ Hz, 1H), 4.87 – 4.76 (m, 2H), 4.19 – 3.98 (m, 2H), 3.78 (dt, $J = 34.2, 10.0$ Hz, 2H), 3.37 (d, $J = 0.7$ Hz, 3H), 2.53 – 2.24 (m, 4H), 1.80 – 1.51 (m, 6H), 1.50 – 1.19 (m, 4H), 0.99 – 0.82 (m, 5H), 0.07 (d, $J = 0.7$ Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ 173.4 , 172.7 , 143.4 , 139.1 , 129.3 , 128.57, 128.1 , 127.3 , 125.4 , 102.3 , 97.9 , 73.4 , 71.5 , 69.1 , 64.3 , 63.3 , 55.5 , 34.4 , 34.0 , 29.9 , 27.5 , 27.1 , 22.4 , 13.9.

Synthesis of hexanoyl ester 26: Standard reaction conditions were performed for this reaction, which was discontinued after 26.5 hours. A flash column was performed using a hexane:EtOAc gradient, which afforded pure 2-isomer, 3-isomer, and dimer with 29%, 11%, and 8% yields respectively. 2 isomer ^1H NMR (400 MHz, CDCl_3) δ 7.55 (t, $J = 10.2$ Hz, 1H), 7.50 – 7.38 (m, 2H), 7.36 – 7.31 (m, 1H), 7.30 – 7.19 (m, 2H), 4.84 (d, $J = 3.7$ Hz, 1H), 4.72 (dd, $J = 9.7, 3.8$ Hz, 1H), 4.22 (td, $J = 9.5, 3.4$ Hz, 1H), 4.12 (dd, $J = 10.0, 5.0$ Hz, 1H), 3.96 (td, $J = 10.1, 4.8$ Hz, 1H), 3.80 (t, $J = 10.3$ Hz, 1H), 3.69 (t, $J = 9.5$ Hz, 1H), 3.38 (s, 1H), 2.45 (d, $J = 3.4$ Hz, 1H), 2.43 – 2.37 (m, 1H), 1.70 – 1.59 (m, 1H), 1.37 – 1.23 (m, $J = 22.3, 10.8, 5.6$ Hz, 2H), 0.89 (t, $J = 6.8$ Hz, 2H). ^{13}C NMR (101 MHz, Chloroform-d) δ 173.5 , 138.3 , 132.4 , 130.0 , 129.1 , 128.4, 127.9, 127.5 , 125.6 , 97.6 , 97.1 , 76.6 , 75.3 , 73.1 , 71.63 , 70.75 , 70.41 , 69.07 , 63.90 , 62.83 , 61.69 , 55.25 , 34.0 , 31.1, 24.5 , 22.2 , 13.8 . Dimer ^1H NMR (400 MHz, CDCl_3) δ 7.49 (d, $J = 7.3$ Hz, 2H), 7.47 – 7.41 (m, 2H), 7.39 (d, $J = 7.6$ Hz, 1H), 7.35 – 7.28 (m, 1H), 7.25 – 7.17 (m, 1H), 5.67 (t, $J = 9.8$ Hz, 1H), 4.84 (d, $J = 3.6$ Hz, 2H), 4.79 (dd, $J = 9.8, 3.7$ Hz, 1H), 4.14 (dd, $J = 10.1, 4.9$ Hz, 1H), 4.04 (td, $J = 10.1, 5.0$ Hz, 1H), 3.83 (t, $J = 10.3$ Hz, 1H), 3.74 (t, $J = 9.7$ Hz, 1H), 3.37 (s, 3H), 2.48 – 2.38 (m, 1H), 2.31 (td, $J = 7.5, 3.7$ Hz, 1H), 1.80 – 1.68 (m, 2H), 1.60 (dd, $J = 14.5, 7.4$ Hz, 2H), 1.36 (d, $J = 3.5$ Hz, 2H), 1.33 – 1.26 (m, 3H), 1.25 (s, 1H), 0.88 (td, $J = 6.7, 3.2$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 173.4 , 172.9 , 143.3 , 139.3 , 135.4 , 129.3 , 128.3 , 127.3 , 125.4 , 97.9 , 77.5 ,

76.9 , 73.4 , 71.5 , 69.1 , 64.2 , 63.2 , 55.4 , 36.0 , 34.6 , 34.2 , 31.5 , 31.3 , 29.9 , 25.1 , 24.7 , 22.5 , 14.1 , 1.2 .

Synthesis of heptanoyl ester 27: Standard reaction conditions were applied to this reaction, which was discontinued after 24hrs. ^1H NMR indicated that only the two isomer and dimer were formed. Performed workup with 5% sodium bicarbonate, and then ran a flash column using a hexane:EtOAc gradient which afforded the pure 2 isomer and diester giving yields of 42% and 13% respectively. 2 isomer ^1H NMR (400 MHz, CDCl_3) δ 7.57 (d, $J = 7.3$ Hz, 1H), 7.44 (dd, $J = 15.7, 7.3$ Hz, 2H), 7.34 (t, $J = 7.3$ Hz, 1H), 7.31 – 7.21 (m, 2H), 4.84 (d, $J = 3.7$ Hz, 1H), 4.72 (dd, $J = 9.7, 3.7$ Hz, 1H), 4.22 (td, $J = 9.5, 3.3$ Hz, 1H), 4.12 (dd, $J = 10.1, 4.9$ Hz, 1H), 3.96 (td, $J = 10.1, 4.9$ Hz, 1H), 3.80 (t, $J = 10.3$ Hz, 1H), 3.69 (t, $J = 9.5$ Hz, 1H), 3.37 (s, 1H), 2.46 (d, $J = 3.4$ Hz, 1H), 2.40 (t, $J = 7.5$ Hz, 1H), 1.69 – 1.59 (m, 1H), 1.37 – 1.24 (m, 3H), 0.88 (t, $J = 6.6$ Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ 173.8 , 143.5 , 138.5 , 129.3 , 128.4 , 127.8 , 125.8 , 102.7 , 97.9 , 75.6 , 73.4 , 69.3 , 64.1 , 63.1 , 55.5 , 34.3 , 31.6 , 28.8 , 25.1 , 22.7 , 14.2 . Dimer ^1H NMR (400 MHz, CDCl_3) δ 7.48 (t, $J = 7.0$ Hz, 2H), 7.44 (dd, $J = 9.0, 4.5$ Hz, 4H), 7.40 (d, $J = 7.1$ Hz, 2H), 7.35 – 7.29 (m, 4H), 7.28 – 7.22 (m, 2H), 7.22 – 7.17 (m, 2H), 5.67 (t, $J = 9.7$ Hz, 1H), 4.84 (d, $J = 3.6$ Hz, 1H), 4.82 – 4.77 (m, 1H), 4.15 (dd, $J = 10.0, 4.9$ Hz, 1H), 4.04 (td, $J = 10.0, 4.9$ Hz, 1H), 3.83 (t, $J = 10.2$ Hz, 1H), 3.74 (t, $J = 9.7$ Hz, 1H), 3.38 (s, 3H), 2.50 – 2.38 (m, 2H), 2.37 – 2.27 (m, 2H), 1.79 – 1.66 (m, 2H), 1.64 – 1.54 (m, 3H), 1.45 – 1.35 (m, 10H), 1.35 – 1.23 (m, 6H), 0.88 (q, $J = 6.1$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 173.4 , 172.7 , 143.3 , 139.1 , 129.3 , 128.3 ,

127.3 , 125.4 , 97.9 , 73.4 , 71.5 , 69.1 , 64.3 , 63.2 , 55.4 , 34.6 , 34.3 , 31.6 , 29.9 , 29.0 , 25.4 ,
25.0 , 22.6 , 14.2 , 1.2 .

Synthesis of octanoyl ester 28: Standard reaction conditions were applied, under which the 2 isomer and dimer formed primarily. The reaction was discontinued after about 24hrs, and a flash column was performed using a hexane:EtOAc gradient which afforded pure 2-isomer and dimer with yields of 43% and 17% respectively. 2 isomer ^1H NMR (400 MHz, CDCl_3) δ 7.57 (d, $J = 7.3$ Hz, 2H), 7.44 (dd, $J = 15.6, 7.6$ Hz, 4H), 7.34 (t, $J = 7.3$ Hz, 1H), 7.30 – 7.18 (m, 6H), 4.84 (d, $J = 3.7$ Hz, 1H), 4.72 (dd, $J = 9.7, 3.8$ Hz, 1H), 4.22 (t, $J = 9.5$ Hz, 1H), 4.12 (dd, $J = 10.1, 4.9$ Hz, 1H), 3.96 (td, $J = 10.2, 4.8$ Hz, 1H), 3.80 (t, $J = 10.3$ Hz, 1H), 3.69 (t, $J = 9.5$ Hz, 1H), 3.37 (s, 3H), 2.40 (t, $J = 7.5$ Hz, 2H), 1.63 (dd, $J = 14.4, 7.0$ Hz, 3H), 1.36 – 1.23 (m, 9H), 0.88 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 173.7 , 143.5 , 138.5 , 129.3 , 128.4 , 127.8 , 125.8 , 97.9 , 75.2 , 73.6 , 69.3 , 64.1 , 63.0 , 55.5 , 34.3 , 31.8 , 29.1 , 25.0 , 22.3 , 14.30 . Dimer ^1H NMR (400 MHz, CDCl_3) δ 7.47 (dd, $J = 13.2, 4.4$ Hz, 4H), 7.41 (dd, $J = 13.9, 6.5$ Hz, 13H), 7.31 (t, $J = 7.0$ Hz, 2H), 7.27 – 7.22 (m, 4H), 7.21 – 7.17 (m, 1H), 5.67 (t, $J = 9.8$ Hz, 1H), 4.84 (d, $J = 3.7$ Hz, 1H), 4.80 (dd, $J = 9.8, 3.7$ Hz, 1H), 4.14 (dd, $J = 10.1, 4.9$ Hz, 1H), 4.04 (td, $J = 10.1, 4.9$ Hz, 1H), 3.83 (t, $J = 10.3$ Hz, 1H), 3.74 (t, $J = 9.7$ Hz, 1H), 3.37 (s, 3H), 2.49 – 2.37 (m, 3H), 2.37 – 2.27 (m, 2H), 1.79 – 1.68 (m, 2H), 1.64 – 1.54 (m, 3H), 1.43 – 1.22 (m, 16H), 0.87 (dt, $J = 9.2, 6.8$ Hz, 7H). ^{13}C NMR (101 MHz, Chloroform-d) δ 173.4 , 172.7 , 143.3 , 139.1 , 129.3 , 128.3 , 127.3 , 125.4 , 102.3 , 97.9 , 73.4 , 71.5 , 69.1 , 64.3 , 63.2 , 55.4 , 34.7 , 34.3 , 31.8 , 29.2 , 25.4 , 25.1 , 22.8 , 14.2 , 1.2 .

Synthesis of 4-chlorobutyl ester 29: Standard reaction conditions were applied, under which the 2-isomer and dimer were formed primarily. After about 24hrs, discontinued reaction and worked up with 5% a sodium bicarbonate aqueous solution, and then performed a flash column using a hexane:EtOAc gradient. This afforded pure 2-isomer and dimer giving 40% and 20% yields respectively. 2 isomer ^1H NMR (400 MHz, CDCl_3) δ 7.60 – 7.55 (m, 2H), 7.45 (q, 2H), 7.34 (t, $J = 7.3$ Hz, 1H), 7.31 – 7.20 (m, 2H), 4.84 (d, $J = 3.7$ Hz, 1H), 4.74 (dd, $J = 9.7, 3.8$ Hz, 1H), 4.23 (td, $J = 9.5, 3.4$ Hz, 1H), 4.13 (dd, $J = 10.1, 4.9$ Hz, 1H), 3.96 (td, $J = 10.1, 4.9$ Hz, 1H), 3.80 (t, $J = 10.3$ Hz, 1H), 3.69 (t, $J = 9.6$ Hz, 1H), 3.60 (t, 1H), 3.38 (s, 3H), 2.61 (t, $J = 6.9$ Hz, 2H), 2.52 (dd, $J = 3.4, 0.9$ Hz, 1H), 2.16 – 2.07 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.6 , 143.4 , 138.51 , 129.1 , 128.4 , 127.8 , 125.8 , 102.7 , 97.8 , 76.5 , 75.6 , 73.6 , 69.3 , 64.1 , 63.1 , 55.5 , 44.0 , 31.3 , 27.8 . Dimer ^1H NMR (400 MHz, CDCl_3) δ 7.48 (t, $J = 7.2$ Hz, 3H), 7.46 – 7.40 (m, 4H), 7.33 (t, $J = 7.2$ Hz, 2H), 7.28 – 7.17 (m, 2H), 5.67 (t, $J = 9.8$ Hz, 1H), 4.86 (d, $J = 3.7$ Hz, 1H), 4.82 (dd, $J = 9.8, 3.7$ Hz, 1H), 4.15 (dd, $J = 10.1, 4.9$ Hz, 1H), 4.04 (td, $J = 10.1, 4.9$ Hz, 1H), 3.84 (t, $J = 10.3$ Hz, 1H), 3.76 (t, $J = 9.7$ Hz, 1H), 3.66 (t, $J = 6.3$ Hz, 2H), 3.59 (t, $J = 6.3$ Hz, 2H), 3.39 (s, 1H), 2.74 – 2.59 (s, 3H), 2.54 (t, $J = 7.2$ Hz, 3H), 2.18 (dtd, $J = 13.6, 6.9, 2.3$ Hz, 2H), 2.07 (tt, $J = 13.7, 6.7$ Hz, 2H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.2 , 171.7 , 143.2 , 138.9 , 129.4 , 128.5 , 128.2 , 127.3 , 125.4 , 102.4 , 97.7 , 76.9 , 73.3 , 71.8 , 69.6 , 64.2 , 63.2 , 55.5 , 44.0 , 31.2 , 27.8 , 27.6 .

Synthesis of 6-bromohexanoyl ester 30: Standard reaction conditions were applied, and after a duration of 48hrs, the reaction was discontinued and worked-up using 5% sodium bicarbonate in aqueous solution. The 2-isomer and dimer were isolated after performing

column chromatography, affording yields of 38% and 11% respectively. 2-Isomer ^1H NMR (400 MHz, CDCl_3) δ 7.57 (d, $J = 7.3$ Hz, 2H), 7.45 (q, 2H), 7.34 (t, $J = 7.3$ Hz, 2H), 7.30 – 7.21 (m, 2H), 4.84 (d, $J = 3.7$ Hz, 1H), 4.73 (dd, $J = 9.7, 3.8$ Hz, 1H), 4.22 (td, $J = 9.5, 3.4$ Hz, 1H), 4.13 (dd, $J = 10.1, 4.9$ Hz, 1H), 3.96 (td, $J = 10.1, 4.9$ Hz, 1H), 3.80 (t, $J = 10.3$ Hz, 1H), 3.69 (t, $J = 9.5$ Hz, 1H), 3.53 (t, $J = 6.6$ Hz, 1H), 3.40 (dd, $J = 10.8, 4.0$ Hz, 1H), 3.38 (s, 3H), 2.48 (d, $J = 3.5$ Hz, 1H), 2.43 (t, $J = 7.3$ Hz, 1H), 1.92 – 1.84 (m, 2H), 1.84 – 1.75 (m, 1H), 1.73 – 1.63 (m, 2H), 1.50 (ddd, $J = 18.5, 8.9, 6.0$ Hz, 2H). ^{13}C NMR (101 MHz, Chloroform-d) δ 167.4, 143.5, 138.5, 134.0, 130.9, 129.4, 128.9, 128.2, 128.1, 127.9, 126.5, 125.96, 124.7, 98.0, 75.7, 74.2, 69.5, 64.2, 63.1, 55.71. Diester: ^1H NMR (400 MHz, Chloroform-d) δ 7.56 – 7.39 (m, 3H), 7.39 – 7.16 (m, 5H), 4.85 (d, $J = 3.8$ Hz, 1H), 4.80 (dt, $J = 10.0, 2.4$ Hz, 0H), 4.21 – 3.98 (m, 1H), 3.78 (dt, $J = 32.9, 10.0$ Hz, 1H), 3.57 – 3.27 (m, 3H), 2.55 – 2.26 (m, 2H), 1.88 (h, $J = 7.0$ Hz, 6H), 1.67 – 1.57 (m, 1H), 1.54 – 1.41 (m, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.7, 172.1, 143.0, 138.6, 132.4, 130.0, 129.1, 128.2, 128.0, 127.1, 125.2, 102.2, 97.6, 76.6, 73.1, 71.4, 69.1, 64.0, 63.0, 55.2, 44.7, 34.1, 33.7, 33.3, 32.2, 29.6, 27.5, 26.2, 24.3, 24.0, 22.6.

Synthesis of 4-pentynoyl ester 31: The acid chloride was not available, therefore it was prepared using the aforementioned procedure. The yields obtained for the 2-isomer, 3-isomer, and dimer were: 30%, 9%, and 5% respectively. 2 isomer ^1H NMR (400 MHz, CDCl_3) δ 7.58 (d, 2H), 7.45 (q, 2H), 7.34 (t, $J = 7.3$ Hz, 1H), 7.30 – 7.20 (m, 2H), 4.85 (d, $J = 3.7$ Hz, 1H), 4.74 (dd, $J = 9.7, 3.8$ Hz, 1H), 4.24 (td, $J = 9.5, 2.5$ Hz, 1H), 4.13 (dd, $J = 10.1, 4.9$ Hz, 1H), 3.97 (td, $J = 10.2, 4.9$ Hz, 1H), 3.80 (t, $J = 10.3$ Hz, 1H), 3.70 (t, $J = 9.5$ Hz, 1H), 3.38 (s, 3H), 2.69 – 2.62 (m, 2H), 2.60 –

2.50 (m, 3H), 2.01 (t, $J = 2.6$ Hz, 1H). 3 isomer ^1H NMR (400 MHz, CDCl_3) δ 7.52 (d, $J = 7.8$ Hz, 1H), 7.43 (dd, $J = 13.0, 7.3$ Hz, 2H), 7.32 (t, $J = 7.3$ Hz, 1H), 7.28 – 7.17 (m, 2H), 5.41 (t, $J = 9.6$ Hz, 1H), 4.72 (d, $J = 3.8$ Hz, 1H), 4.14 (dd, $J = 10.1, 4.9$ Hz, 1H), 3.98 (td, $J = 10.1, 4.8$ Hz, 1H), 3.81 (t, $J = 10.3$ Hz, 1H), 3.67 (t, $J = 9.7$ Hz, 1H), 3.55 (td, 1H), 3.43 (s, 1H), 2.77 (t, $J = 7.2$ Hz, 1H), 2.64 (ddd, $J = 14.9, 7.3, 2.5$ Hz, 1H), 2.20 (d, $J = 11.4$ Hz, 1H), 1.95 (t, $J = 2.6$ Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ 169.1 , 141.0 , 136.0 , 126.9 , 125.9 , 125.3 , 123.4 , 100.2 , 95.3 , 80.1 , 75.0 , 74.7 , 74.4 , 73.0 , 71.5 , 66.9 , 66.7 , 61.6 , 60.6 , 53.0 , 30.9 , 12.1 . Dimer ^1H NMR (400 MHz, CDCl_3) δ 7.53 – 7.36 (m, 2H), 7.31 (dd, $J = 14.2, 6.9$ Hz, 1H), 7.26 – 7.17 (m, 2H), 5.68 (t, $J = 9.5$ Hz, 1H), 4.85 (t, $J = 4.4$ Hz, 1H), 4.82 (d, $J = 3.7$ Hz, 1H), 4.15 (dd, $J = 10.1, 5.0$ Hz, 1H), 4.04 (td, $J = 10.1, 4.9$ Hz, 1H), 3.84 (t, $J = 10.3$ Hz, 1H), 3.75 (t, $J = 9.7$ Hz, 1H), 3.38 (s, 3H), 2.73 – 2.67 (m, 2H), 2.64 – 2.56 (m, 2H), 2.52 – 2.45 (m, 1H), 1.98 (t, $J = 2.6$ Hz, 1H), 1.95 (t, $J = 2.6$ Hz, 1H).

Synthesis of 5-hexynoyl ester 32: C2 Yield: 19%; Diester Yield: 14% ^1H NMR (400 MHz, Chloroform-d) δ 7.56 (d, 4H), 7.50 – 7.36 (m, 16H), 7.31 – 7.15 (m, 7H), 4.90 – 4.80 (m, 5H), 4.73 (dd, $J = 9.7, 3.7, 0.9$ Hz, 2H), 4.23 (t, 5H), 4.13 (q, 2H), 3.96 (td, $J = 10.1, 4.9$ Hz, 4H), 3.80 (t, $J = 10.3$ Hz, 2H), 3.69 (t, 2H), 3.39 (s, 7H), 2.63 – 2.36 (m, 8H), 2.27 (td, $J = 12.5, 9.3, 6.1, 2.8$ Hz, 7H), 2.02 – 1.72 (m, 10H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.6 , 172.0 , 143.3 , 139.0 , 129.3 , 128.3 , 127.3 , 125.4 , 102.3 , 97.8 , 83.3 , 77.5 , 73.2 , 71.7 , 69.5 , 64.2 , 63.2 , 55.5 , 32.8 , 23.9 , 23.6 , 17.9 (d, $J = 6.2$ Hz). Diester: ^1H NMR (400 MHz, Chloroform-d) δ 7.44 (s, 6H), 7.36 – 7.15 (m, 7H), 5.67 (t, $J = 9.8$ Hz, 1H), 4.84 (d, 2H), 4.80 (dd, 1H), 4.15 (q, $J = 10.1, 4.9$ Hz, 1H), 4.04 (td, $J = 10.1, 5.0$ Hz, 1H), 3.83 (t, $J = 10.3$ Hz, 2H), 3.73 (t, $J = 9.7$ Hz, 1H), 3.38 (d, $J = 0.7$ Hz,

3H), 2.71 – 2.44 (m, 4H), 2.29 (dtd, $J = 34.5, 7.0, 2.7$ Hz, 4H), 2.02 – 1.77 (m, 5H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.3 , 171.8 , 143.0 , 138.7 , 129.1 , 128.0 , 127.1 , 125.2 , 102.1 , 97.5 , 82.9 , 76.6 , 73.8 , 71.4 , 69.8 , 64.0 , 63.0 , 55.2 , 32.6 , 29.6 , 23.6 , 23.4 , 17.6.

Synthesis of 6-heptynoyl ester 33: C2 Yield: 11%; Diester Yield: 10% ^1H NMR (400 MHz, Chloroform-d) δ 7.57 (dd, 2H), 7.50 – 7.39 (m, 4H), 7.38 – 7.18 (m, 5H), 4.84 (d, $J = 3.8$ Hz, 1H), 4.72 (dd, 1H), 4.22 (td, $J = 9.4, 3.4$ Hz, 1H), 4.17 – 4.08 (m, 1H), 3.96 (td, $J = 10.2, 4.8$ Hz, 1H), 3.80 (t, $J = 10.3$ Hz, 1H), 3.69 (t, $J = 9.4$ Hz, 1H), 3.38 (s, 3H), 2.49 – 2.39 (m, 3H), 2.22 (td, $J = 7.1, 2.7$ Hz, 2H), 1.99 – 1.92 (m, 1H), 1.78 (p, $J = 7.3$ Hz, 2H), 1.64 – 1.56 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-d) δ 173.3 , 143.5 , 138.2 , 129.4 , 128.4 , 127.8 , 125.8 , 97.8 , 75.8 , 75.6 , 73.5 , 69.3 , 68.8 , 64.1 , 63.0 , 55.5 , 33.7 , 27.8 , 24.1 , 18.3 . Diester: ^1H NMR (400 MHz, Chloroform-d) δ 7.52 – 7.37 (m, 6H), 7.36 – 7.15 (m, 4H), 5.66 (t, $J = 9.8, 1.0$ Hz, 1H), 4.85 (d, $J = 3.7$ Hz, 2H), 4.80 (dd, $J = 9.8, 3.7, 1.0$ Hz, 1H), 4.25 – 4.10 (m, 1H), 4.03 (td, $J = 10.0, 4.9$ Hz, 1H), 3.84 (t, $J = 10.3, 9.2$ Hz, 2H), 3.74 (t, 1H), 3.38 (s, 3H), 2.56 – 2.41 (m, 9H), 2.39 – 2.32 (m, 1H), 2.21 (ddd, $J = 10.8, 6.9, 2.6$ Hz, 4H), 1.99 – 1.89 (m, 12H), 1.76 – 1.63 (m, 1H), 1.65 – 1.50 (m, 5H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.9 , 172.3 , 143.3 , 139.0 , 129.3 , 128.3 , 127.3 , 125.4 , 102.3 , 97.8 , 83.9 , 76.9 , 73.2 , 71.6 , 69.3 , 69.0 , 64.2 , 63.2 , 55.5 , 34.1 , 33.7 , 27.9 , 24.4 , 24.1 , 18.3 .

Synthesis of benzoyl ester 34: C2 Yield: 55%; Diester: 10% C2: ^1H NMR (400 MHz, Chloroform-d) δ 8.09 (d, $J = 7.1, 1.1$ Hz, 2H), 7.65 – 7.54 (m, 3H), 7.52 – 7.40 (m, 6H), 7.41 – 7.31 (m, 4H), 7.33 – 7.17 (m, 3H), 4.96 (d, 2H), 4.39 (t, 1H), 4.16 (dd, $J = 10.0, 4.9$ Hz, 1H), 4.03 (td, $J = 10.1, 4.9$ Hz, 1H), 3.84 (t, $J = 10.3$ Hz, 2H), 3.77 (t, $J = 9.5$ Hz, 1H), 3.38 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 166.5, 143.6, 138.6, 133.6, 130.2, 129.7, 129.4, 128.5, 127.9, 125.9, 98.09, 77.6, 75.7, 74.2, 69.4, 64.2, 63.1, 55.6. Diester: ^1H NMR (400 MHz, Chloroform-d) δ 8.12 (d, $J = 7.1, 1.2$ Hz, 2H), 8.00 (d, $J = 8.4, 1.2$ Hz, 2H), 7.65 – 7.45 (m, 16H), 7.43 – 7.27 (m, 6H), 7.28 – 7.14 (m, 3H), 6.12 (t, $J = 9.6, 1.0$ Hz, 1H), 5.11 (d, $J = 12.6, 3.4, 1.0$ Hz, 2H), 5.08 (dd, $J = 0.9$ Hz, 0H), 4.28 – 4.13 (m, 2H), 3.96 (t, 2H), 3.41 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 166.2, 165.7, 143.3, 139.1, 133.5, 130.0, 129.3, 128.6, 128.2, 127.4, 125.5, 102.5, 98.0, 73.8, 72.7, 69.9, 64.6, 63.3, 55.6.

Synthesis of naphthoyl ester 35: Discontinued reaction after about 22hrs, at which time the reaction conversion was about 95%. After performing a flash column using a hexane:EtOAc gradient, the yield obtained was 64%. ^1H NMR (400 MHz, CDCl_3) δ 8.90 (d, $J = 8.6$ Hz, 1H), 8.25 (d, $J = 7.2$ Hz, 1H), 8.04 (d, $J = 8.0$ Hz, 1H), 7.89 (d, $J = 8.0$ Hz, 1H), 7.61 (dd, $J = 8.1, 2.0$ Hz, 4H), 7.50 (ddd, $J = 23.7, 15.7, 7.9$ Hz, 7H), 7.39 – 7.32 (m, 2H), 7.31 – 7.22 (m, 4H), 5.07 (dt, $J = 9.3, 3.8$ Hz, 2H), 4.45 (td, $J = 9.3, 3.3$ Hz, 1H), 4.18 (dd, $J = 10.0, 4.9$ Hz, 1H), 4.12 – 4.00 (m, 1H), 3.86 (t, $J = 16.4, 5.7$ Hz, 1H), 3.80 (t, $J = 9.5$ Hz, 1H), 3.42 (s, 3H), 2.62 (d, $J = 3.3$ Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ 167.4, 143.5, 138.5, 134.0, 130.9, 129.4, 128.5, 128.1, 127.0, 126.5, 125.9, 124.7, 102.8, 98.0, 75.7, 74.2, 69.5, 64.2, 63.1, 55.7.

General method for the synthesis of the carbamates from headgroup 21: To a scintillation vial, 0.5mmol of compound **21** was dissolved in 2 mL of DCM or THF and stirred at rt-30 °C. Then, about 0.6mmol of the corresponding isocyanate and a drop of anhydrous triethyl amine were added to the solution. The mixture was left stirring for 12-18 hs, after which time the mixture was concentrated to dryness under nitrogen or rotavap (for larger scale). The crude residue was purified by flash chromatography using a hexane/EtOAc gradient(9:1 to 3:1). The purified compound was subjected to gelation screening.

Synthesis of pentyl carbamate 36: The crude product was diluted with hexane/EtOAc and filtered and then washed with hexane, and the product obtained is pure. Isolated pure product using this method, giving a yield of 65% of pure material. ¹H NMR (400 MHz, CDCl₃) δ 7.49 (dd, *J* = 6.6, 3.0 Hz, 1H), 7.38 (ddd, *J* = 7.0, 4.7, 1.4 Hz, 1H), 5.55 (s, 1H), 4.95 – 4.69 (m, 1H), 4.33 (dd, *J* = 10.4, 5.0 Hz, 1H), 4.16 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.86 (t, *J* = 9.1 Hz, 1H), 3.71 (t, *J* = 10.3 Hz, 1H), 3.54 (t, *J* = 9.3 Hz, 1H), 3.45 – 3.35 (m, 1H), 3.30 (t, *J* = 10.8 Hz, 1H), 3.15 (dt, *J* = 12.5, 6.3 Hz, 1H), 1.49 (dt, *J* = 14.3, 7.3 Hz, 2H), 1.41 – 1.23 (m, 8H), 0.89 (t, *J* = 7.0 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 156.0, 137.6, 128.8, 126.5, 102.2, 81.2, 73.3, 72.7, 71.4, 68.9, 41.6, 29.6, 29.2, 22.5, 14.1.

5-hexynyl carbamate 37: The isocyanate was formed via curtius rearrangement of 6-heptynoic acid using DPPA and TEA in THF at 60°C. The resulting product was then added directly to the sugar headgroup. Column purification employing a hexane:EtOAc gradient afforded a 15%

yield. ^1H NMR (400 MHz, Chloroform- d) δ 7.61 – 7.53 (m, 2H), 7.51 – 7.42 (m, 9H), 7.38 – 7.26 (m, 3H), 7.27 – 7.12 (m, 1H), 4.96 (t, J = 5.9 Hz, 1H), 4.85 (d, J = 3.7 Hz, 1H), 4.64 (dd, J = 9.7, 3.8, 1.0 Hz, 1H), 4.22 – 4.02 (m, 3H), 3.94 (td, J = 10.1, 4.8 Hz, 1H), 3.80 (t, 1H), 3.69 (t, J = 9.5 Hz, 1H), 3.39 (s, 3H), 3.22 (q, J = 6.7 Hz, 3H), 2.70 (d, J = 3.6 Hz, 1H), 2.21 (td, J = 6.9, 3.1 Hz, 3H), 1.99 – 1.91 (m, 1H), 1.69 – 1.51 (m, 10H), 1.26 (t, J = 7.1, 1.0 Hz, 2H). ^{13}C NMR (101 MHz, Chloroform- d) δ 156.1 , 143.5 , 138.5 , 135.4 , 129.3 , 128.6, 128.1, 127.8 , 125.8 , 102.7 , 98.4 , 84.1 , 77.5 , 75.7 , 74.0 , 69.6 , 68.9 , 64.1 , 63.1 , 55.4 , 40.8 , 29.9 , 29.0 , 25.6 , 18.2 , 1.2.

Synthesis of cyclohexyl carbamate 38: The crude was product was purified on a flash column using hexane:DCM:acetone, the purified product has trace amount of urea byproduct. Yield: 13%; ^1H NMR (400 MHz, Chloroform- d) δ 7.62 – 7.54 (m, 2H), 7.52 – 7.38 (m, 4H), 7.38 – 7.17 (m, 4H), 4.85 (d, 2H), 4.62 (dd, J = 9.7, 3.8 Hz, 1H), 4.22 – 4.13 (m, 2H), 4.15 – 4.10 (m, 1H), 3.95 (td, J = 10.1, 4.8 Hz, 1H), 3.80 (t, J = 10.3 Hz, 1H), 3.69 (t, J = 9.5 Hz, 1H), 3.53 – 3.41 (m, 1H), 3.40 (s, 3H), 2.65 (d, J = 3.5 Hz, 1H), 1.75 – 1.65 (m, 7H), 1.63 – 1.52 (m, 2H), 1.42 – 1.27 (m, 7H), 1.20 – 1.05 (m, 4H).

Benzyl carbamate 39: Yield: 13%; ^1H NMR (400 MHz, Chloroform- d) δ 7.62 – 7.54 (m, 2H), 7.51 – 7.39 (m, 4H), 7.38 – 7.18 (m, 11H), 5.24 (t, J = 6.0 Hz, 1H), 4.88 (d, J = 3.8 Hz, 1H), 4.69 (dd, J = 9.7, 3.7 Hz, 1H), 4.45 – 4.30 (m, 2H), 4.19 (td, J = 9.4, 3.3 Hz, 2H), 4.13 (dd, J = 10.1, 4.8 Hz, 1H), 3.95 (td, J = 10.1, 4.9 Hz, 1H), 3.80 (t, J = 10.3 Hz, 1H), 3.70 (t, J = 9.5 Hz, 1H), 3.40 (s, 3H), 2.62

(d, $J = 3.5$ Hz, 1H). ^{13}C NMR (101 MHz, Chloroform- d) δ 156.1 , 143.5 , 138.5 , 138.1 , 129.3 , 128.9 , 128.6, 128.1, 127.81, 125.8 , 98.4 , 75.6 , 74.3 , 69.6 , 64.1 , 63.1 , 55.5 , 45.4 , 29.9 .

Synthesis of N-acetyl-4,6-O-diphenyl-methyl- α -glucosamine 42: To a 500 mL round bottomed flask, 3.52 g (14.9 mmol) of α -methyl-D-glucosamine was added and dissolved within 40 mL of DMF and stirred at room temperature. To this solution, 6.11 g (2.25 equivalents) of benzophenone dimethyl acetal **23** was added and the solution was brought to 100 $^{\circ}\text{C}$. To this hot solution, 20 mol% of *p*-toluene sulfonic acid was added. Once the reaction peaked, stirring was discontinued and the flask was adapted to a rotary evaporator. After removing the methanol byproduct, the reaction proceeded further. At this point, the solvent was removed via a nitrogen stream overnight, and then a workup was performed using DCM/water. After isolation of the organic phase, it was dried with sodium sulfate, filtered, and evaporated. The crude mixture was subsequently purified via flash chromatography using a hexane:EtOAc gradient ranging from 7:1 to pure EtOAc. ^1H NMR (400 MHz, Chloroform- d) δ 7.59 (dd, $J = 8.2, 1.1$ Hz, 6H), 7.49 (dd, $J = 8.2, 1.2$ Hz, 6H), 7.42 (t, 12H), 7.34 – 7.30 (m, 2H), 7.29 – 7.16 (m, 13H), 5.86 (d, $J = 8.8$ Hz, 3H), 5.29 (d, $J = 1.1$ Hz, 1H), 4.60 (d, $J = 3.8$ Hz, 3H), 4.11 (dddd, $J = 9.7, 8.6, 4.1, 1.0$ Hz, 6H), 3.99 – 3.84 (m, 13H), 3.80 (t, 3H), 3.70 (t, 3H), 3.37 (s, 8H), 3.07 (d, $J = 3.9, 1.0$ Hz, 3H), 1.63 (s, 2H).

Pentyl amide 44: Yield: 88%; ^1H NMR (400 MHz, Chloroform- d) δ 7.85 – 7.77 (m, 2H), 7.64 – 7.55 (m, 5H), 7.54 – 7.38 (m, 10H), 7.37 – 7.16 (m, 7H), 5.82 (d, $J = 8.8$ Hz, 2H), 4.60 (d, $J = 3.8$ Hz, 2H), 4.12 (td, $J = 9.7, 4.3$ Hz, 4H), 3.98 – 3.83 (m, 8H), 3.78 (t, 2H), 3.69 (t, $J = 9.3$ Hz, 1H), 3.37 (s, 8H), 3.09 (d, $J = 3.7$ Hz, 2H), 2.25 (td, $J = 7.7, 1.3$ Hz, 4H), 1.73 – 1.55 (m, 9H), 1.45 – 1.28

(m, 4H), 1.25 (s, 1H), 0.92 (t, $J = 7.3$ Hz, 7H). ^{13}C NMR (101 MHz, Chloroform-d) δ 174.9 , 143.7 , 138.8 , 135.4 , 132.6 , 130.3 , 129.3 , 128.62, 128.1, 127.8 , 125.7 , 102.5 , 99.0 , 76.9 , 76.2 , 71.5 , 64.1 , 63.4 , 55.3 , 54.1 , 36.6 , 27.9 , 22.4 , 14.0 .

Hexyl amide 45: Yield: 73%; ^1H NMR (400 MHz, Chloroform-d) δ 7.60 (d, 2H), 7.58 (s, 5H), 7.53 – 7.38 (m, 9H), 7.37 – 7.28 (m, 10H), 7.30 – 7.07 (m, 7H), 5.82 (d, $J = 8.7$ Hz, 2H), 5.30 (d, $J = 0.7$ Hz, 1H), 4.60 (d, $J = 3.8$ Hz, 2H), 4.12 (td, $J = 9.7, 4.2$ Hz, 5H), 4.00 – 3.86 (m, 8H), 3.80 (t, $J = 10.2$ Hz, 2H), 3.70 (t, $J = 9.3$ Hz, 2H), 3.37 (d, $J = 0.7$ Hz, 6H), 2.24 (t, 5H), 1.73 – 1.60 (m, 6H), 1.40 – 1.23 (m, 11H), 0.90 (t, $J = 6.8, 5.8, 2.8$ Hz, 7H). ^{13}C NMR (101 MHz, Chloroform-d) δ 174.9 , 143.7 , 138.8 , 129.3 , 128.5, 128.1, 127.8 , 125.7 , 102.5 , 99.0 , 77.5 , 76.2 , 71.5 , 64.1 , 63.4 , 55.3 , 54.1 , 36.8 , 31.5 , 25.5 , 22.5 , 14.1 .

Heptyl amide 46: Yield: 40%; ^1H NMR (400 MHz, Chloroform-d) δ 7.63 – 7.55 (m, 2H), 7.53 – 7.38 (m, 4H), 7.37 – 7.26 (m, 3H), 7.29 – 7.05 (m, 1H), 5.82 (d, $J = 8.8$ Hz, 1H), 5.30 (s, 1H), 4.60 (d, $J = 3.8$ Hz, 1H), 4.12 (td, $J = 9.3, 4.1$ Hz, 2H), 3.91 (dtd, $J = 14.8, 9.7, 4.1$ Hz, 4H), 3.81 (t, $J = 10.2$ Hz, 1H), 3.71 (t, $J = 9.3$ Hz, 1H), 3.37 (s, 3H), 3.08 (d, $J = 4.0$ Hz, 1H), 2.24 (t, $J = 7.5$ Hz, 2H), 1.68 – 1.58 (m, 3H), 1.42 – 1.23 (m, 8H), 0.92 – 0.84 (m, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 174.40 (d, $J = 2.4$ Hz), 143.7 , 138.7 , 132.6 , 130.3 , 129.3 , 128.68, 128.1, 127.81 , 125.7 , 99.0 , 76.2 , 71.4 , 64.1 , 63.4 , 55.4 , 54.1 , 45.1 , 36.5, 33.9, 32.5 , 29.9 , 27.8 , 26.5 , 24.9 .

Octanoyl amide 47: Yield: 37%; ^1H NMR (400 MHz, Chloroform-d) δ 7.63 – 7.55 (m, 2H), 7.55 – 7.38 (m, 4H), 7.37 – 7.30 (m, 6H), 7.28 – 7.11 (m, 2H), 5.82 (d, $J = 8.7$ Hz, 1H), 4.60 (d, $J = 3.8$ Hz, 1H), 4.19 – 4.06 (m, 2H), 3.98 – 3.87 (m, 5H), 3.78 (t, 1H), 3.69 (t, $J = 9.3$ Hz, 1H), 3.37 (s, 3H), 3.11 (s, 1H), 2.24 (t, $J = 7.5$ Hz, 2H), 1.68 – 1.58 (m, 4H), 1.36 – 1.21 (m, 10H), 0.92 – 0.81 (m, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 174.9 , 143.7 , 138.8 , 129.3 , 128.56, 128.1, 127.8 , 125.7 , 102.5 , 99.0 , 76.2 , 71.6 , 64.1 , 63.4 , 55.3 , 54.1 , 36.8 , 31.8 , 29.9 , 29.2 , 25.8 , 22.8 , 14.2.

Benzoyl amide 48: Yield: 85%; ^1H NMR (400 MHz, Chloroform-d) δ 7.84 – 7.74 (m, 2H), 7.73 – 7.58 (m, 14H), 7.54 – 7.45 (m, 5H), 7.45 – 7.34 (m, 2H), 7.27 – 7.21 (m, 3H), 6.51 (d, $J = 8.9$ Hz, 1H), 4.72 (d, $J = 3.8$ Hz, 1H), 4.34 (td, $J = 9.9, 8.9, 3.8$ Hz, 1H), 4.14 (dd, $J = 10.0, 4.7$ Hz, 2H), 4.06 (t, $J = 10.0, 9.1$ Hz, 1H), 3.80 (q, 3H), 3.41 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 168.7 , 143.6 , 138.7 , 133.8 , 132.2 , 130.1 , 129.3 , 128.8 , 128.6, 128.1, 127.8 , 127.4 , 125.7 , 102.6 , 99.1 , 76.9 , 76.2 , 71.5 , 64.2 , 63.5 , 55.5 , 54.5 .

Naphthoyl amide 49: Yield: 77%; ^1H NMR (400 MHz, Chloroform-d) δ 8.65 – 8.58 (m, 1H), 8.40 – 8.29 (m, 1H), 7.95 (d, $J = 8.2$ Hz, 2H), 7.91 – 7.81 (m, 0H), 7.73 – 7.61 (m, 15H), 7.56 – 7.51 (m, 2H), 7.46 – 7.38 (m, 2H), 7.34 – 7.16 (m, 3H), 6.37 (d, $J = 9.0$ Hz, 1H), 4.82 (d, $J = 3.8$ Hz, 1H), 4.46 (td, $J = 10.2, 9.0, 3.8$ Hz, 1H), 4.15 (dd, $J = 9.9, 4.6$ Hz, 2H), 4.09 (t, 1H), 3.94 (dd, $J = 10.0, 4.6$ Hz, 3H), 3.89 – 3.77 (m, 2H), 3.39 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 170.9 , 143.6

, 138.7 , 133.9, 131.1 , 130.2 , 129.4 , 128.68, 128.18, 127.8 , 127.5, 126.7 , 125.7 , 125.4, 124.97
, 102.6 , 99.1 , 76.9 , 76.3 , 71.6 , 64.1 , 63.5 , 55.5 , 54.6.

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Chapter III. A 2,5-Dimethoxy-4,6-*O*-Protected Benzylidene Acetal System

Abstract

Low molecular weight gelators (LMWGs) are an important new class of compounds which are of special interest because of their wide scope of applications as advanced materials. The Wang group has been working on the discovery and the potential applications of sugar based LMWGs. We have found that 4,6-benzylidene acetals of glucopyranoside derivatives form stable gels in organic, aqueous, and organic/aqueous solvents. To understand the structural requirements and to design acid sensitive LMWGs, we synthesized and characterized a series of 2,5-dimethoxy benzylidene acetal derivatives of D-glucose and D-glucosamine. The acid lability of such a system is attributed to the electron releasing nature of the methoxy substituents on the phenyl ring of the acetal.

Introduction

Low molecular weight gelators (LMWGs) are important compounds within the fields of biomedical chemistry and advanced materials, which form supramolecular architectures. The architectures of LMWGs are comprised of a self-assembled, three-dimensional cross-linked network of non-covalently bound gelator molecules. These compounds (LMWGs) possess structural properties which allow them to immobilize solvent molecules within their assembly, which in-turn engenders a gelatinous material. The resulting material is principally held together by non-covalent attractive forces between the gelator molecules such as: hydrogen bonding, hydrophobic forces, π - π interactions, London forces, dipole-dipole interactions, etc. Gelators exhibit a variety of morphological properties which, in-turn, lend them to a wide scope of potential applications in: pharmaceuticals, food, drug-delivery Potential, biomimetics, enzyme-immobilization matrices, liquid crystalline materials, as templates for preparing other novel compounds, mechanical actuators, reaction catalysis, and many more such applications which are being explored. Sugar based systems can be both monomeric as in the case with LMWGs, and polymeric such as chitosan or polysaccharide systems. The transferability of gel properties from a parent polymeric to a monomeric LMWG system has been wondered. One such sugar based system was developed by Rajendran et al, employed chitosan as a gelation agent at various molecular weights: 150 KDa, 400 KDa, and 600 KDa (Figure 3.1). Gelator systems employing chitosan have been reported⁵, but the research performed by Rajendran thoroughly explores the different grades of chitosan, as well as the physiochemical characteristics to build a release profile of the embedded drug Acyclovir. Acyclovir is a therapy used to combat the Herpes simplex virus. Their focus was a treatment which released Acyclovir

nanoparticles to the ocular surface of the afflicted, using the chitosan gel matrix as the loading platform. To achieve gelation with the chitosan fragments, tri polyphosphate (TPP) anions were loaded into the system. The group concluded that varying the chitosan fragment sizes affected the physiochemical and release characteristics of the Acyclovir nanoparticles, and that tuning and scaling the size of these gelator molecules can provide a release profile that is specifically wanted.

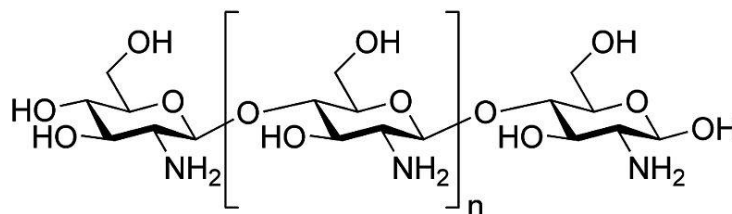


Figure 3.1 Chitosan subunit

Compounds **1** and **2** were used as headgroups for the synthesis of a series of effective low molecular weight gelators.

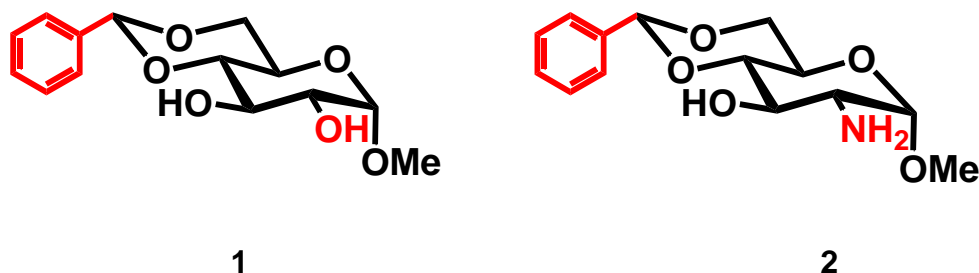


Figure 3.2 Glucose and glucosamine based headgroups **1** and **2**

In this research, we would like to prepare LMWGs with acid labile functional groups in their structures. Such compounds have applications for triggered release delivery systems. Using 2,5-dimethoxy-4,6-*O*-benzylidene- α -methyl glucopyranoside **3** or its glucosamine counterpart **4**, various analogues of esters, amides, and carbamates were synthesized and analyzed for their gelation properties:

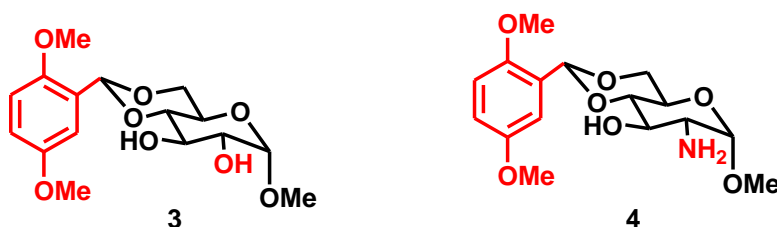
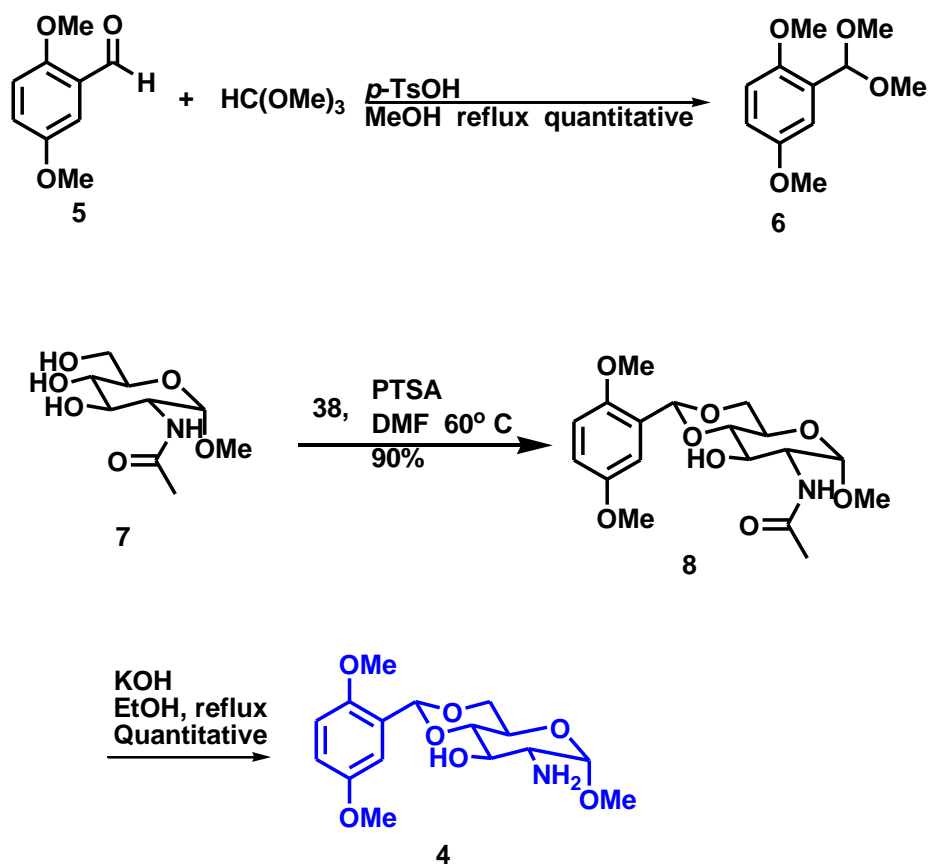


Figure 3.3 2,5 Dimethoxy 4,6-protected glucose and glucosamine headgroups **3** and **4**

Results and Discussion

The synthesis of the 2,5-dimethoxy headgroup began with readily available starting material 2,5-dimethoxy benzaldehyde, which was transformed to the dimethyl acetal **6** employing trimethyl orthoformate along with a catalytic quantity of sulfuric acid in methanol under refluxing conditions. The primary substrate, glucosamine **4**, was synthesized starting from N-acetal-D-glucosamine, which was transformed to the 1-MeO N-acetyl-D-glucosamine derivative using Amberlite IR 120 acid resin in methanol under refluxing conditions. The 1-MeO derivative was then reacted with dimethyl acetal **6** in DMF in the presence of catalytic *p*-toluenesulfonic

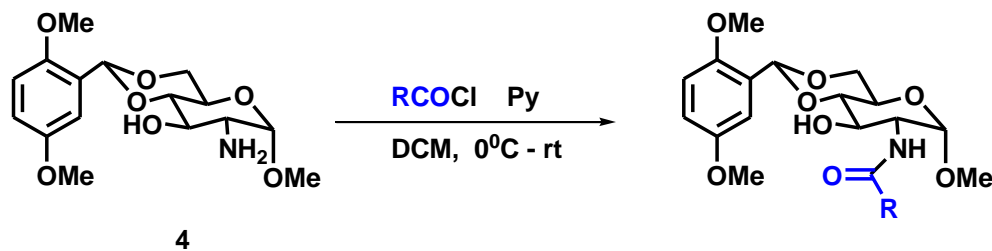
acid at 60°C. To finalize product formation, deacetylation is performed using potassium hydroxide in methanol at reflux temperature to produce glucosamine compound **4**.



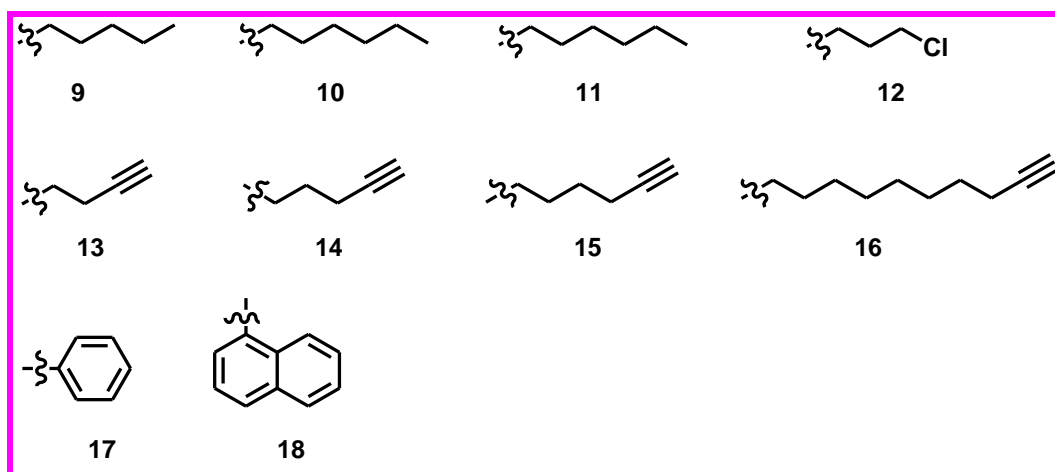
Scheme 3.1 Synthesis of 2,5-dimethoxy glucosamine headgroup

From this 2,5-dimethoxy headgroup, the following amides were synthesized using the acid chlorides corresponding to the appended amide tails. If the acid chloride was not readily available it was synthesized from its corresponding carboxylic acid. These reactions were performed under basic conditions using pyridine and the solvent used was almost always

dichloromethane. The temperatures used were typically room temperature, although at the addition of the acid chloride starting at 0⁰ C was desired to control the reactivity of the system.



R =

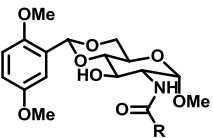


Scheme 3.2 Synthesis of various amide analogues of the 2,5-dimethoxybenzaldehyde-4,6-glucosamine system

This is a concern when the competing reaction, which may take place at the C3 -OH of the headgroup, is more feasible due to certain reaction conditions or reactants involved. The amide syntheses are illustrated in Scheme 3.2.

As gelators, the amides were very efficient. The solvent mixtures of either water:ethanol and water:DMSO gave the best results. Compound **9** was even a good hydrogelator with a minimum gelation concentration (MGC) of 2.5 mg/mL. This was likely due to the reaching of the necessary equilibrium between hydrophobicity and hydrophilicity necessary for gelation. The gelling capacity was as well attributed to the critical bonding components such as hydrogen bond donors/acceptors and the π stacking system.

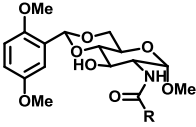
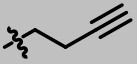
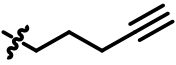
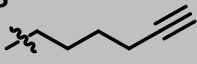
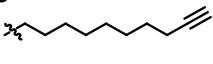
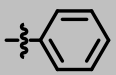
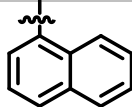
Table 3.1 Gelation results of amide analogues



	Yield	Water	Hexane	EtOH	Water: EtOH 2:1	Water: DMSO 2:1
8	Quant	P	I	S	S	S
9	17 %	G (2.5)	I	S	G (20)	G (6.7)
10	100 %	I	I	S	G (6.7)	G (6.7)
11	77 %	I	I	Cr	G (3.3)	G (3.7)
12	44 %	I	I	S	G (20)	P

U, unstable gel; **G**, gel at room temperature; **I**, insoluble; **Cr**, crystallizes; **S**, soluble; **P**, precipitates

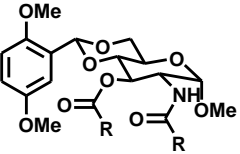
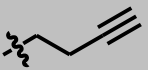
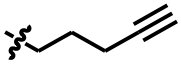
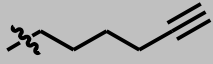
Table 3.2 Gelation results of amide analogues continued

	Yield	Water	Hexane	EtOH	Water: EtOH	Water: DMSO
					2:1	2:1
13 	26 %	I	I	S	G (5.7)	G _t (5)
14 	31 %	I	I	S	P	S
15 	19 %	G (8.3)	I	P	G (22)	G (17.5)
16 	45 %	I	I	P	G (3.3)	G (3)
17 	97 %	I	I	S	P	U (20)
18 	62 %	I	I	P	G (4)	G (4)

U, unstable gel; G, gel at room temperature; I, insoluble; Cr, crystallizes; S, soluble; P, precipitates

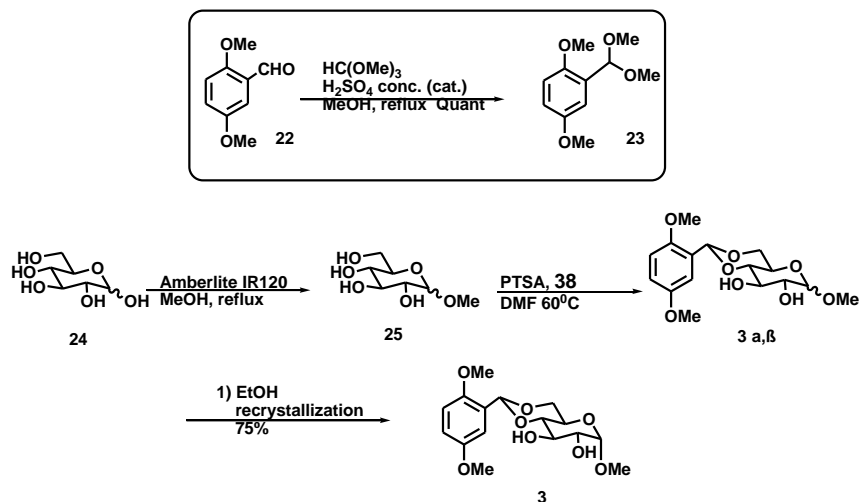
Some difunctionalized amides were as well isolated and tested for their gelation abilities. These were functionally amides at the C2 position, yet were esters at the C3 position. Table 3.3 has within it the tabulated results, which indicate that such systems may form unstable and even some stable gels, yet not as efficiently as the mono-substituted amides, where the C3 is in the free –OH form. This suggests that the Clog P should lean more towards water solubility relative to the C2 functionalized amides of this series.

Table 3.3 Gelation Results of Difunctionalized Amides

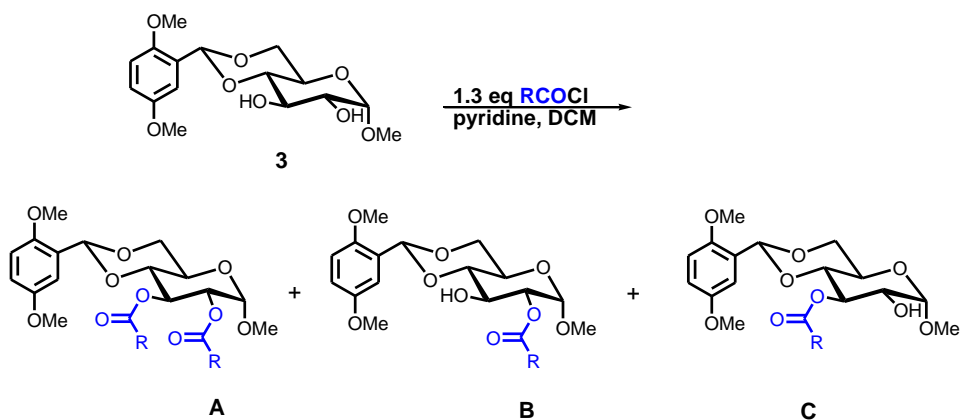
		Yield	Water	Hexane	EtOH	Water: EtOH	Water: DMSO
19		7%	I	I	S	U (20)	P
20		26%	I	P	S	I	U (20)
21		24%	I	I	S	P	G (20)

U, unstable gel; G, gel at room temperature; I, insoluble; Cr, crystallizes; S, soluble; P, precipitates

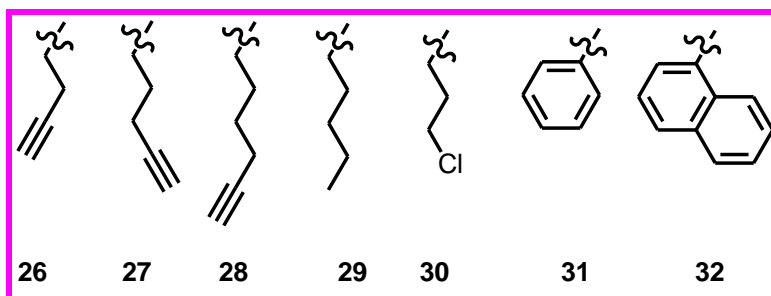
Depriving the gelator system of the hydrogen bond donor gained from the incorporation of the N-H from the amide series is one way in which the Wang group theoretically controls the Log P values of our gel molecules when designing analogues. The following series of esters were synthesized with this in mind (Scheme 3.4) from headgroup **3** (Scheme 3.3). The availability of two vicinal hydroxyl groups reduces the selectivity for the C2 position, which is indeed favored over the C3, yet not to the extent that the reactivity is exclusive to that region. This is exploited by controlling the reaction conditions using excess acid chloride, and usually the C2, C3, and dimer are isolated as products from the reactions. As with the glucosamine series, compound **23** is synthesized and appended to the glucose monomer derivative **25** at the 4,6-position.



Scheme 3.3 Synthesis of 4,6-protected 2,5-dimethoxy glucose headgroup **3**



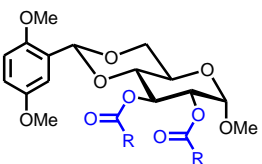
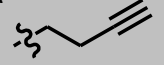
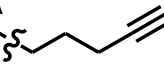
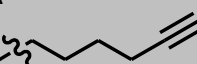
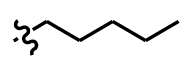
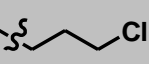
R =



Scheme 3.4 Synthesis of ester analogues for the 2,5-dimethoxybenzaldehyde-4,6-glucosamine system

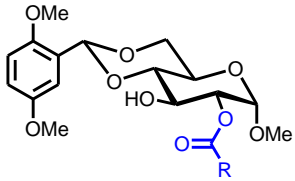
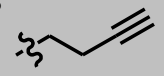
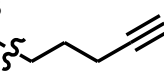
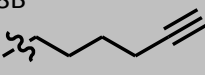
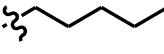
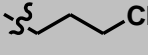
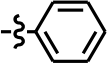
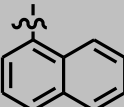
Of the esters synthesized, none formed gels. A wide variety of tails ranging from long/short chain aliphatic, terminal acetylene, and aromatic in nature were appended and tested for gelation, yet to no avail. A few of the results are listed below, and further exploration of this system was ceased due to the fact that it didn't yield good preliminary results.

Table 3.4 Gelation results of the ester analogues tested

		Yield	Water		Hexane	EtOH	Water: EtOH	Water: DMSO
26A		11 %	I	I		P	P	P
27A		40 %	I	P		S	P	P
28A		42 %	I	P		S	P	P
29A		13 %	I	S		S	P	P
30A		21 %	I	I		S	P	P

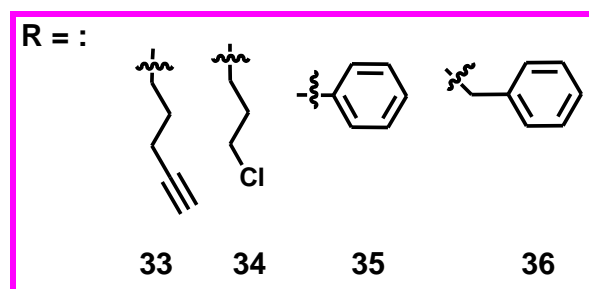
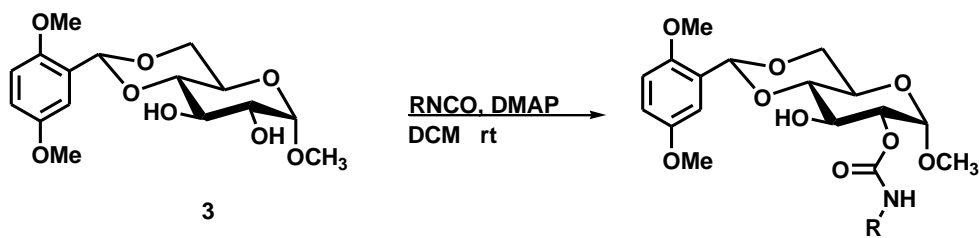
U, unstable gel; **G**, gel at room temperature; **I**, insoluble; **Cr**, crystallizes; **S**, soluble; **P**, precipitates

Table 3.5 Monoester Gelator Results

	Yield	Water	Hexane	EtOH	Water: EtOH	Water: DMSO
					2:1	2:1
26B 	17 %	I	I	P	P	P
27B 	14 %	P	I	S	P	S
28B 	18 %	I	I	S	P	P
29B 	33 %	I	I	S	P	P
30B 	24 %	I	I	P	P	P
31B 	41 %	I	I	S	P	P
32B 	74 %	I	I	S	P	P

U, unstable gel; **G**, gel at room temperature; **I**, insoluble; **Cr**, crystallizes; **S**, soluble; **P**, precipitates

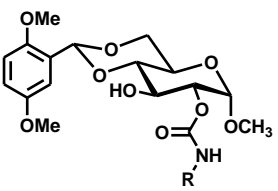
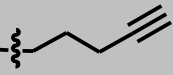
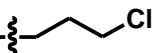
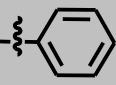
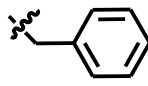
Having an additional hydrogen bond donor and acceptor for our gelator molecules is achieved by synthesizing carbamates analogues using the 2,3-dihydroxy glucose headgroup.



Scheme 3.5 Synthesis of carbamates LMWGs

The carbamate series proved rather promising, and several dimer molecules were isolated in addition to the C2 isomers. Of the dimers tested, none formed gels. The C2 isomers prove to be efficient gelators in water:ethanol, water:DMSO, and performed surprisingly well in Marvel oil. Marvel oil is very similar in composition to crude oil. Relative to the amide series, the carbamates series may have performed better in such a solvent due to the shift toward a more hydrophilic system, with stronger intermolecular interactions present.

Table 3.6 Carbamate Gelator Results

		Yield	Water	Hexane	EtOH	Water: EtOH 2:1	Water: DMSO 2:1
33		17 %	I	I	Cr	G (5)	G (20)
34		27 %	I	I	Cr	G (5)	G (20)
35		50 %	I	Cr	I	G (3.3)	G (2.9)
36		43 %	I	I	Cr	G (4.4)	G (2.2)

U, unstable gel; **G**, gel at room temperature; **I**, insoluble; **Cr**, crystallizes; **S**, soluble; **P**, precipitates

This series, incorporating a 2,5-dimethoxy acetal at the 4,6-position of glucose and glucosamine, includes: esters, carbamates, and amides, of which the carbamates and amides appear to be the more efficient gelators. Carbamates and amides house an additional hydrogen bonding center, and this in conjunction with the hydrophobic tails contributed to establishing the necessary hydrophobic/ hydrophilic equilibrium for supramolecular gel-matrix assembly. An acid stability test was performed on amide **11** to analyze the extent to which the 2,5-dimethoxy system would be labile in the presence of acid. A more elaborate study will be further explored in my fourth chapter. Gel systems which are responsive to external stimuli in an intended fashion, eliciting a desired response, may prove useful in a variety of applications

such as timed active ingredient release. The rudimentary experimental setup entails gel formation, preferably at a concentration greater than the MGC to ensure gel robustness. This gel is then subjected to an acid solution of known concentration, and the gel decay is recorded at intervals. The following Figure 3.4 illustrates these rudimentary results:

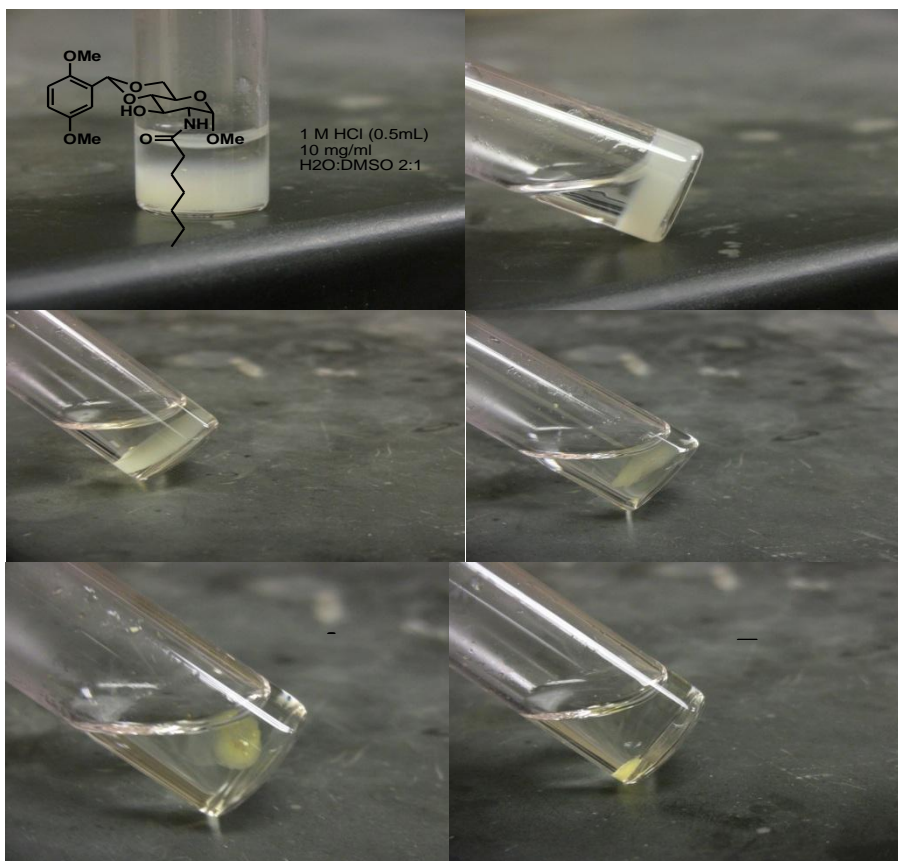


Figure 3.4 Acid stability test of amide **11**

At the terminal point of the experiment (5hrs), the gel had all but disappeared. Granted the hydrochloric acid concentration was 1M. A more subtle approach will be employed in future experiments, to further build the acid profile of a variety of hydro- and organogelators. Future studies will test the response of the gels to acid at different pHs, and attempt to quantify the acid triggered responses.

Conclusions

Several new gelator compounds were synthesized and characterized. This series, incorporating a 2,5-dimethoxy acetal at the 4,6-position of glucose and glucosamine, includes: amides, esters, and carbamates, of which the carbamates appear to be the more efficient gelators. Carbamates house an additional hydrogen bonding center, and this in conjunction with the hydrophobic tails perhaps contributed to establishing the necessary hydrophobicity/hydrophilicity equilibrium for supramolecular gel-matrix assembly.

Experimental

Synthesis of 2,5-dimethoxy benzaldehyde dimethyl acetal 6: To a 250ml round bottomed flask, 1 drop of concentrated sulfuric acid was added to 40ml of MeOH and this solution was brought to 70°C. To this warm solution was added ~7g of 2,5-dimethoxy benzaldehyde and 1.05 eq of trimethylorthoformate. An ¹H NMR was taken at 2hrs which indicated full conversion to the desired product. Discontinued reaction and began work-up at 4.25hrs. The work-up entailed quenching the reaction with saturated aqueous NaHCO₃, filtering, and then concentrating this solution on a roto-vap to yield 9.1g of pure brown liquid product. Yied: Quantitative ¹H NMR (400 MHz, Chloroform-d) δ 7.16 – 7.06 (m, 1H), 6.88 – 6.78 (m, 2H), 5.63 (d, *J* = 0.5 Hz, 1H), 3.79 (d, *J* = 10.0 Hz, 7H), 3.37 (d, *J* = 0.4 Hz, 7H).

Methylation of N-acetyl glucosamine 7: To a 250 round bottom flask, 3.04g of starting material was added and dissolved within 60ml of MeOH and brought to reflux (70°C). To this solution was added 3.09g of acid resin along w/ molecular sieves. According to ¹H NMR @ 22hrs, reaction conversion was quantitative. Discontinued reaction at 25hrs and concentrated on roto-vap. Filtered IR120 resin and washed thoroughly with MeOH, concentrated on roto-vap to afford compound **8**. Yield obtained was 84%.

4,6-(2,5-dimethoxy benzylidene) N-acetyl glucosamine headgroup 8: To a 250ml round bottom flask, 2.75g of α-methyl glucosamine **2** was dissolved within 17ml of DMF and stirred @ 60°C. To this solution was added 10mol% of *p*-TsOH, and then 2.73g (1.1eq) of 2,5-dimethoxy benzaldehyde dimethyl acetal. ¹H NMR spectra at 4.25hrs and 21.5hrs looked similar (70% conv.), therefore added another 0.2 eq of acetal. When the reaction reached 45hrs, observed 90% conversion, put rxn on roto-vap for 1/2hr, quenched w/ sodium bicarb, filtered, and blew away DMF under N₂ overnight. Performed a work-up which entailed dissolving the reaction mixture within 150ml of DCM, and then washing this organic phase with water and saturated aqueous sodium bicarbonate and drying the organic phase under sodium sulfate. After this mixture was filtered and concentrated, a recrystallization was attempted in EtOH which afforded mostly pure product with only DMF as a contaminant. ¹H NMR (400 MHz, Chloroform-d) δ 7.16 (d, *J* = 3.0 Hz, 1H), 6.90 – 6.77 (m, 3H), 5.91 (s, 1H), 5.85 (d, *J* = 8.8 Hz, 1H), 4.72 (d, *J* = 3.8 Hz, 1H), 4.31 – 4.17 (m, 2H), 3.95 – 3.73 (m, 11H), 3.64 – 3.50 (m, 1H), 3.41 (s, 4H), 2.96 (d, *J* = 4.6 Hz, 2H), 2.88 (d, *J* = 0.7 Hz, 1H), 2.06 (s, 3H). ¹³C NMR (101 MHz, Chloroform-d) δ 171.3 ,

153.6 , 150.8 , 126.0 , 115.9 , 112.3 , 98.8 , 97.1 , 82.2 , 77.3 , 70.7 , 69.0 , 62.4 , 56.3 , 55.7 , 55.2 , 53.9 , 23.3 .

2,5-dimethoxy-4,6-O-benzylidene- α -MeO-glucosamine 4: To a 250ml round bottom flask, 4.04g of the starting material was added and dissolved within 30ml of EtOH. To this solution was added 3.6g of NaOH (3N concentration). Another 20ml of EtOH was added later to fully dissolve reactants (thus diluting the conc. of NaOH). Quantitative conversion to the desired product was observed at 20hrs (as observed by ^1H NMR). Work-up: dissolve in DCM; wash w/ water, brine, and then dry using sodium sulfate, filter and concentrate. ^1H NMR (400 MHz, Chloroform-d) δ 7.16 (d, J = 3.0 Hz, 1H), 6.91 – 6.76 (m, 2H), 5.89 (s, 1H), 5.29 (d, J = 0.8 Hz, 1H), 4.67 (d, J = 3.5 Hz, 1H), 4.28 – 4.18 (m, 1H), 3.86 – 3.65 (m, 9H), 3.50 – 3.34 (m, 4H), 2.82 – 2.74 (m, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ 115.9 , 112.2, 100.8 , 96.9 , 82.0 , 77.0 , 76.6 , 71.5 , 69.1 , 62.6 , 56.3, 55.7 , 55.4 .

Amide Syntheses The common procedure by which the amides were synthesized entails the addition of about 50mg of starting material to a flame dried scintillation vial, and then dissolving it within 1ml of DCM. To this solution is added about three equivalents of pyridine and this solution is then stirred. To this, about 1 equivalent of the acid chloride is added. A work-up procedure using water and brine extraction may yield pure product, but if not column chromatography using a Hex:EtOAc gradient ranging from 6:1 to 1:1 is used.

Hexanoyl amide 9: Yield: 17%; ^1H NMR (300 MHz, Chloroform-d) δ 7.16 (d, J = 2.9 Hz, 1H), 6.91 – 6.76 (m, 2H), 5.92 (s, 1H), 5.81 (d, J = 8.7 Hz, 1H), 4.72 (d, J = 3.8 Hz, 1H), 4.34 – 4.16 (m, 3H), 3.97 – 3.72 (m, 11H), 3.59 (t, J = 8.7 Hz, 1H), 3.41 (s, 4H), 3.01 (d, J = 3.4 Hz, 1H), 2.25 (t, J = 7.6 Hz, 3H), 1.67 (q, J = 7.4 Hz, 3H), 1.38 – 1.20 (m, 4H), 0.95 – 0.84 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-d) δ 135.4 , 116.1 , 112.5 , 99.0 , 97.2 , 82.4 , 71.0 , 69.2 , 62.6 , 56.5 , 56.0 , 55.5 , 54.1 , 36.8 , 36.0 , 31.5 , 25.4 , 22.5 , 14.1 .

Heptanoyl amide 10: Yield: 100%; ^1H NMR (400 MHz, Chloroform-d) δ 7.15 (d, J = 3.0 Hz, 1H), 6.89 – 6.77 (m, 2H), 5.91 (s, 1H), 5.82 (d, J = 9.1 Hz, 1H), 4.72 (d, J = 3.8 Hz, 1H), 4.31 – 4.18 (m, 2H), 3.94 – 3.71 (m, 10H), 3.64 – 3.50 (m, 1H), 3.41 (s, 3H), 2.38 – 2.20 (m, 3H), 1.70 – 1.58 (m, 2H), 1.39 – 1.23 (m, 9H), 1.17 (s, 1H), 0.88 (h, J = 3.2, 2.4 Hz, 4H). ^{13}C NMR (101 MHz, Chloroform-d) δ 174.8 , 153.9 , 151.0 , 126.3 , 116.2 , 115.5 , 112.55, 99.1 , 97.3 , 82.4 , 70.8 , 69.2 , 62.6 , 56.5 , 56.0 , 55.5 , 54.2 , 36.8 , 33.9 , 31.7 , 29.0 , 25.7 , 24.9 , 22.7 , 14.2 .

Octanoyl amide 11: Yield: 77% ^1H NMR (400 MHz, Chloroform-d) δ 7.16 (d, J = 3.0 Hz, 1H), 6.89 – 6.77 (m, 2H), 5.91 (s, 1H), 5.82 (d, J = 8.9 Hz, 1H), 4.72 (d, J = 3.8 Hz, 1H), 4.31 – 4.17 (m, 2H), 3.94 – 3.71 (m, 10H), 3.64 – 3.48 (m, 1H), 3.41 (s, 3H), 2.25 (dd, J = 8.2, 6.9 Hz, 2H), 1.69 – 1.60 (m, 5H), 1.34 – 1.21 (m, 10H), 0.91 – 0.79 (m, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 174.8 , 153.9 , 151.0 , 126.3 , 116.3 , 112.5, 99.0 , 97.3 , 82.4 , 77.5 , 70.9 , 69.2 , 62.6 , 56.5 , 56.2 , 55.5 , 54.1 , 52.6 , 36.8 , 31.8 , 29.2, 25.8 , 22.8 , 14.1.

4-Chlorobutanamide 12: Yield: 44%; ^1H NMR (400 MHz, Chloroform-d) δ 7.15 (d, 2H), 6.90 – 6.83 (m, 4H), 6.80 (s, 1H), 5.91 (s, 4H), 5.86 (d, $J = 9.0$ Hz, 2H), 5.30 (d, $J = 0.9$ Hz, 1H), 4.72 (d, $J = 3.7$ Hz, 2H), 4.30 – 4.19 (m, 4H), 3.90 (t, $J = 9.6$ Hz, 2H), 3.79 (s, 16H), 3.77 (s, 5H), 3.68 – 3.54 (m, 5H), 3.42 (s, 5H), 2.80 (s, 2H), 2.45 (t, 4H), 2.19 – 2.07 (m, 4H), 1.30 – 1.23 (m, 7H), 0.92 – 0.81 (m, 5H).

4-Pentynyl amide 13: Yield: 26% ^1H NMR (400 MHz, Chloroform-d) δ 7.26 (s, 1H), 7.15 (d, $J = 3.0$ Hz, 2H), 6.89 – 6.77 (m, 4H), 6.01 (d, $J = 8.9$ Hz, 2H), 5.91 (s, 2H), 4.72 (d, $J = 3.8$ Hz, 2H), 4.31 – 4.19 (m, 4H), 3.97 – 3.72 (m, 19H), 3.66 – 3.53 (m, 2H), 3.41 (s, 6H), 2.97 – 2.85 (m, 3H), 2.60 – 2.35 (m, 8H), 2.02 (t, $J = 2.6$ Hz, 2H), 1.25 (t, $J = 5.7$ Hz, 1H), 0.94 – 0.82 (m, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.34 , 153.90 , 151.07 , 135.46 , 126.35 , 116.11 , 112.56 (d, $J = 9.5$ Hz), 99.11 , 97.30 , 83.04 , 82.29 , 75.81 , 70.71 , 69.73 , 69.23 , 62.72 , 56.56 , 56.02 , 55.57 , 54.22 , 35.53 , 15.14 . ^{13}C NMR (101 MHz, Chloroform-d) δ 172.3 , 153.9 , 151.0 , 135.6 , 126.3 , 116.11 , 112.5, 99.1 , 97.3 , 83.0 , 82.2 , 75.8 , 70.7 , 69.7 , 69.2 , 62.7 , 56.5 , 56.0 , 55.5 , 54.2 , 35.5 , 15.1 .

4-Pentynyl amido ester 19: Yield: 7%; ^1H NMR (400 MHz, Chloroform-d) δ 7.18 – 7.09 (m, 3H), 6.89 – 6.77 (m, 5H), 5.90 (d, $J = 9.5$ Hz, 3H), 5.83 (s, 3H), 5.30 (t, 9H), 4.72 (d, $J = 3.7$ Hz, 3H), 4.41 – 4.23 (m, 5H), 3.92 – 3.68 (m, 26H), 3.41 (s, 7H), 2.56 – 2.34 (m, 18H), 2.07 – 1.96 (m, 2H), 1.88 (t, $J = 2.6$ Hz, 2H), 1.26 (d, $J = 2.1$ Hz, 4H), 0.07 (s, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ

172.3 , 171.0 , 153.8 , 116.0 , 112.5 , 99.2 , 97.2 , 79.3 , 76.9 , 75.7 , 70.7 , 69.6, 69.1, 63.1 , 56.6 ,
56.0 , 55.6 , 52.6 , 35.3 , 33.6 , 33.4 , 14.7 , 14.4 .

5-Hexynyl amide 14: Yield: 31%; ^1H NMR (400 MHz, Chloroform-d) δ 7.15 (d, J = 3.0 Hz, 1H),
6.89 – 6.77 (m, 2H), 5.89 (s, 2H), 4.71 (d, J = 3.8 Hz, 1H), 4.32 – 4.18 (m, 2H), 3.94 – 3.73 (m,
10H), 3.63 – 3.52 (m, 1H), 3.41 (s, 3H), 2.40 (t, J = 7.3 Hz, 2H), 2.28 (tt, J = 6.6, 2.8 Hz, 2H), 2.02 –
1.96 (m, 1H), 1.97 – 1.78 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-d) δ 173.7 , 153.9 , 151.0 ,
126.4 , 123.7 , 116.1 , 112.5 , 110.6 , 99.1 , 97.3 , 95.6 , 82.4 , 76.9 , 70.8 , 69.5 , 69.2 , 62.6 ,
56.4, 56.0 , 55.5 , 54.0 , 35.1 , 24.1 , 17.8 .

5-Hexynyl amido ester 20: Yield: 26%; ^1H NMR (400 MHz, Chloroform-d) δ 7.11 (td, J = 3.0 Hz,
3H), 6.85 (d, J = 8.9 Hz, 6H), 6.81 (d, J = 9.0 Hz, 3H), 5.85 (t, J = 6.2 Hz, 6H), 5.82 (s, 4H), 5.30 (d,
3H), 5.28 (s, 4H), 4.71 (d, J = 3.6 Hz, 3H), 4.37 – 4.28 (m, 5H), 4.26 (dd, 2H), 3.95 – 3.84 (m, 25H),
3.79 (s, 8H), 3.76 (s, 8H), 3.42 (s, 8H), 2.41 (t, 20H), 2.33 – 2.26 (m, 5H), 2.23 (dt, J = 6.9, 3.5 Hz,
5H), 2.18 – 2.12 (m, 4H), 1.98 (t, J = 2.6 Hz, 2H), 1.94 – 1.84 (m, 11H), 1.85 – 1.62 (m, 7H), 0.06
(s, 1H).

6-Heptynyl amide 15: Yield: 19% ^1H NMR (400 MHz, Chloroform-d) δ 7.26 (s, 1H), 7.15 (d, J =
3.0 Hz, 1H), 6.90 – 6.77 (m, 2H), 5.91 (s, 1H), 5.82 (d, J = 8.7 Hz, 1H), 4.72 (d, J = 3.8 Hz, 1H), 4.32
– 4.18 (m, 2H), 3.78 (s, 10H), 3.59 (t, J = 8.8 Hz, 1H), 3.41 (s, 3H), 2.91 (s, 1H), 2.33 – 2.17 (m,
4H), 1.95 (t, J = 2.6 Hz, 1H), 1.85 – 1.72 (m, 2H), 1.63 – 1.52 (m, 7H). ^{13}C NMR (101 MHz,

Chloroform-d) δ 174.1 , 155.3 , 116.1 , 112.5 , 99.0 , 97.3 , 82.4 , 76.9 , 70.9 , 69.2 , 68.8 , 62.6 , 56.5 , 55.9 , 55.5 , 54.1 , 36.2 , 27.9 , 24.8 , 18.3 .

6-Heptynyl amido ester 21: Yield: 24%; ^1H NMR (400 MHz, Chloroform-d) δ 7.11 (t, 1H), 6.88 – 6.84 (m, 1H), 6.84 – 6.79 (m, 1H), 5.84 (s, 1H), 5.79 (d, $J = 9.4$ Hz, 1H), 5.30 (t, $J = 10.0$ Hz, 1H), 4.72 (d, $J = 3.7$ Hz, 1H), 4.32 (td, $J = 10.0, 3.7$ Hz, 1H), 4.26 (dd, $J = 9.9, 4.5$ Hz, 1H), 3.88 (dd, 1H), 3.80 (s, 3H), 3.76 (d, $J = 0.8$ Hz, 3H), 3.70 (t, $J = 9.4$ Hz, 1H), 3.41 (s, 3H), 2.29 (q, 2H), 2.23 – 2.14 (m, 4H), 2.06 (ddd, $J = 7.7, 6.7, 2.8$ Hz, 2H), 1.95 (td, $J = 2.7, 0.9$ Hz, 1H), 1.88 (td, $J = 2.7, 0.8$ Hz, 1H), 1.75 – 1.61 (m, 5H), 1.55 – 1.50 (m, 1H), 1.48 – 1.40 (m, 2H).

10-Undecanoyl amide 16: Yield: 45% ^{13}C NMR (101 MHz, Chloroform-d) δ 174.72 , 153.89 , 151.08 , 126.38 , 116.11 , 112.55 (d, $J = 8.1$ Hz), 99.08 , 97.30 , 84.96 , 82.45 , 70.89 , 69.23 , 68.36 , 62.67 , 56.56 , 56.01 , 55.52 , 54.13 , 36.84 , 29.47 – 29.02 (m), 28.85 , 28.60 , 25.76 , 18.57 .

Benzoyl amide 17: Yield: 97%; ^1H NMR (400 MHz, Chloroform-d) δ 7.85 – 7.77 (m, 2H), 7.58 – 7.41 (m, 3H), 7.17 (d, $J = 3.0$ Hz, 1H), 6.90 – 6.78 (m, 2H), 6.50 (d, $J = 8.8$ Hz, 1H), 5.94 (s, 1H), 4.84 (d, $J = 3.9$ Hz, 1H), 4.45 (ddd, $J = 10.3, 8.8, 3.9$ Hz, 1H), 4.35 – 4.22 (m, 1H), 4.02 (td, $J = 9.6, 3.3$ Hz, 1H), 3.80 (s, 8H), 3.73 – 3.60 (m, 1H), 3.45 (s, 3H), 3.04 (d, $J = 3.3$ Hz, 1H). ^{13}C NMR (101

MHz, Chloroform-d) δ 170.6 , 153.9 , 151.0 , 134.1 , 133.8 , 131.1 , 130.2 , 128.5 , 127.5 , 126.7 , 126.3 , 125.5, 124.9 , 116.1 , 112.5 , 99.2 , 97.3 , 82.5 , 70.9 , 69.2 , 62.2 , 56.6 , 56.0 , 55.6 , 54.6

Naphthoyl amide 18: Yield: 62% ^1H NMR (400 MHz, Chloroform-d) δ 8.39 – 8.30 (m, 1H), 7.97 – 7.81 (m, 2H), 7.66 (dd, J = 7.0, 1.3 Hz, 1H), 7.60 – 7.42 (m, 3H), 7.17 (d, J = 3.0 Hz, 1H), 6.91 – 6.78 (m, 2H), 6.37 (d, J = 8.9 Hz, 1H), 5.94 (s, 1H), 4.93 (d, J = 3.9 Hz, 1H), 4.60 – 4.49 (m, 1H), 4.36 – 4.21 (m, 1H), 4.02 (t, J = 9.7 Hz, 1H), 3.91 – 3.74 (m, 8H), 3.67 (t, J = 9.0 Hz, 1H), 3.42 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 170.6 , 153.9 , 151.0 , 135.4 , 134.1 , 133.8 , 131.1 , 130.2 , 128.5 , 127.5 , 126.7 , 126.3 , 125.5, 124.9 , 116.1 , 112.5, 99.2 , 97.3 , 82.5 , 70.9 , 69.2 , 62.8 , 56.6 , 56.0 , 55.6 , 54.6 , 1.2 .

Synthesis of 4,6-(2,5-dimethoxy benzylidene) glucose headgroup 3 To a 100ml round bottom flask, 3.01g of the starting material was added and dissolved within 20ml of DMF, and to this solution was added 10mol% *p*-TsOH and then it was stirred at 60 $^{\circ}$ C. To this solution, 1.1eq of 2,5-dimethoxy bezaldehyde dimethyl acetal was added (diss. w/in 1ml DCM). After ~4hrs, ^1H NMR indicated 90-95% conversion to product, and at 5.66 hrs put solution on a roto-vap to remove MeOH and further the reaction. Quenched rxn with sodium bicarbonate, filtered, and performed work-up: DCM/water/brine. Dried under sodium sulfate and then filtered and concentrated. Current Yield: 84%

Common procedure for ester synthesis: To a scintillation vial, about 100mg of the starting material headgroup is added to a flame dried scintillation vial and then dissolved with 1ml of DCM and stirred. To this solution, about five equivalents of pyridine is added and the solution is brought to 0°C. To this cold solution, about 1.3 equivalents of the acid chloride is added and the solution is stirred at 0°C for another hour and then allowed to approach room temperature. If the acid chloride is unavailable then the carboxylic acid is used to prepare it using oxalyl chloride and DMF (cat.). Upon reaction completion, column chromatography is performed using a Hex:EtOAc gradient ranging from 20:1 to 1:1 and then flushed. This typically yields at least the C2 and dimer, and sometimes the C3 functionalized esters.

4-Pentynyl ester 26: Yield 17%; ¹H NMR (400 MHz, Chloroform-d) δ 7.15 (d, *J* = 2.4 Hz, 1H), 6.88 – 6.83 (m, 1H), 6.80 (d, *J* = 1.8 Hz, 0H), 5.91 (s, 1H), 4.95 (d, *J* = 4.0, 1.7 Hz, 1H), 4.83 (dd, *J* = 9.6, 3.8, 1.1 Hz, 1H), 4.27 (dd, *J* = 9.8, 4.6, 1.8 Hz, 1H), 4.19 (t, *J* = 9.6 Hz, 1H), 3.91 – 3.80 (m, 1H), 3.79 (s, 1H), 3.78 (s, 2H), 3.58 (t, *J* = 9.4, 1.8 Hz, 1H), 3.41 (s, 3H), 2.66 (t, 2H), 2.58 – 2.51 (m, 2H), 1.99 (td, *J* = 2.6, 0.9 Hz, 1H). ¹³C NMR (101 MHz, Chloroform-d) δ 171.6 , 153.9 , 151.0 , 126.1 , 116.2 , 115.5 , 112.5 , 97.7 , 97.3 , 82.6 , 81.6 , 74.1 , 69.3 , 68.8 , 62.3 , 56.5 , 56.0 , 55.7 , 33.4 , 14.6 , 1.2 . Diester: Yield: 11%; ¹H NMR (400 MHz, Chloroform-d) δ 7.26 (d, *J* = 1.8 Hz, 1H), 7.13 (d, *J* = 3.1, 1.2 Hz, 2H), 6.89 – 6.83 (m, 4H), 6.84 – 6.70 (m, 2H), 5.80 (d, *J* = 1.2 Hz, 2H), 5.60 (t, *J* = 9.5, 1.3 Hz, 2H), 4.94 (s, 4H), 4.91 (d, *J* = 3.8, 1.3 Hz, 1H), 4.27 (dd, 2H), 3.94 (td, *J* = 9.6, 4.7 Hz, 2H), 3.78 (s, 18H), 3.76 (s, 4H), 3.66 (t, *J* = 9.7, 1.3 Hz, 2H), 3.41 (s, 6H), 2.66 – 2.54 (m, 14H), 2.57 – 2.46 (m, 7H), 2.46 – 2.35 (m, 2H), 2.01 – 1.94 (m, 2H), 1.92 – 1.83 (m, 2H). ¹³C

NMR (101 MHz, Chloroform-d) δ 171.3 , 170.7 , 153.9 , 151.0 , 126.2 , 116.3 , 112.4, 97.7 , 97.3 , 82.5 , 79.4 , 75.8 , 72.0 , 69.54, 69.1, 62.6 , 56.6 , 55.9, 55.6 , 33.4, 14.5, 1.2 .

5-Hexynyl ester 27: C2 Yield: 14% ^1H NMR (400 MHz, Chloroform-d) δ 7.16 (d, J = 3.0 Hz, 1H), 6.87 (ddd, J = 9.0, 3.0, 0.8 Hz, 1H), 6.83 – 6.76 (m, 0H), 5.91 (s, 1H), 4.95 (d, 1H), 4.82 (dd, J = 9.6, 3.8, 0.8 Hz, 1H), 4.27 (dd, J = 9.8, 4.4 Hz, 1H), 4.16 (t, J = 9.5 Hz, 1H), 3.84 (dd, J = 9.5, 4.5 Hz, 1H), 3.80 (s, 4H), 3.78 (s, 4H), 3.57 (t, J = 9.3 Hz, 1H), 3.41 (s, 3H), 2.57 (t, J = 7.4 Hz, 2H), 2.28 (td, 2H), 2.04 – 1.94 (m, 1H), 1.92 – 1.84 (m, 2H). Diester Yield: 40%; ^1H NMR (400 MHz, Chloroform-d) δ 7.13 (d, J = 3.0 Hz, 1H), 6.85 (dd, J = 9.0, 3.0 Hz, 2H), 6.80 (d, J = 9.0 Hz, 1H), 5.81 (s, 1H), 5.60 (t, J = 9.8 Hz, 1H), 4.95 (d, J = 3.8 Hz, 2H), 4.90 (dd, J = 9.9, 3.7 Hz, 1H), 4.28 (dd, J = 10.2, 4.9 Hz, 1H), 3.94 (td, J = 9.9, 4.8 Hz, 1H), 3.79 (s, 7H), 3.77 (s, 3H), 3.66 (t, J = 9.6 Hz, 1H), 3.42 (s, 3H), 2.49 (td, J = 7.3, 2.2 Hz, 2H), 2.40 (t, J = 7.4 Hz, 2H), 2.26 (td, J = 7.0, 2.7 Hz, 2H), 2.16 (td, J = 7.0, 2.6 Hz, 2H), 1.97 (t, J = 2.6 Hz, 1H), 1.83 (td, J = 7.2, 2.2 Hz, 1H), 1.79 – 1.69 (m, 2H), 0.07 (s, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.6, 172.0 , 153.9 , 151.0 , 126.2 , 116.3 , 112.5 , 112.2 , 97.8 , 97.3 , 97.0 , 83.2, 79.5 , 77.5 , 73.6 , 71.8 , 71.4 , 70.9 , 70.1 , 69.7, 68.9, 62.6 , 62.2 , 56.6 , 56.0 , 55.5, 32.9, 23.7, 17.8.

6-Heptynyl ester 28: Yield: 18%; ^1H NMR (400 MHz, Chloroform-d) δ 7.16 (d, J = 3.0 Hz, 1H), 6.91 – 6.84 (m, 1H), 6.83 (s, 1H), 5.91 (s, 1H), 4.95 (d, J = 3.8 Hz, 1H), 4.82 (dd, J = 9.7, 3.8 Hz, 1H), 4.28 (dd, J = 9.7, 4.4 Hz, 1H), 4.18 (t, J = 9.5 Hz, 1H), 3.84 (dd, J = 9.6, 4.4 Hz, 1H), 3.80 (s, 4H), 3.78 (s, 3H), 3.57 (t, J = 9.3 Hz, 1H), 3.41 (s, 3H), 2.45 (t, J = 7.2 Hz, 2H), 2.22 (td, J = 7.0, 2.7 Hz, 2H), 2.08 – 1.94 (m, 1H), 1.84 – 1.72 (m, 2H), 1.64 – 1.52 (m, 8H), 1.44 – 1.16 (m, 1H), 0.92 – 0.82 (m, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 173.4 , 153.5 , 126.1 , 116.2 , 112.5 , 97.8 , 97.3 , 84.1 , 81.7

, 77.5 , 73.6 , 71.9 , 71.2 , 70.8 , 69.2 , 68.9 , 62.3 , 56.5 , 56.0 , 55.5 , 33.7 , 27.8 , 24.1 , 18.3 .
Diester Yield: 42%; ^1H NMR (400 MHz, Chloroform-d) δ 7.13 (d, $J = 3.0$ Hz, 1H), 6.90 – 6.82 (m, 2H), 6.82 – 6.74 (m, 1H), 5.82 (s, 1H), 5.57 (t, $J = 15.4, 9.8$ Hz, 1H), 4.96 (d, 2H), 4.90 (dd, 1H), 4.28 (dd, $J = 10.3, 5.3$ Hz, 1H), 3.93 (td, $J = 9.8, 4.8$ Hz, 1H), 3.79 (s, 9H), 3.77 (s, 3H), 3.42 (s, 3H), 2.38 (td, $J = 7.9, 4.1$ Hz, 6H), 2.28 (td, $J = 7.2, 3.0$ Hz, 2H), 2.20 (td, 2H), 2.05 (td, 2H), 1.95 (td, $J = 2.6, 0.7$ Hz, 2H), 1.89 (td, $J = 2.7, 0.8$ Hz, 1H), 1.80 – 1.60 (m, 8H), 1.60 – 1.51 (m, 2H), 1.49 – 1.40 (m, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ 173.0 , 172.3 , 153.9 , 151.0 , 126.2 , 116.3 , 112.5 , 112.2 , 97.8 , 97.3 , 84.0 , 79.5 , 71.7 , 69.2 , 68.9 , 62.6 , 56.6 , 55.9 , 55.6 , 33.8 , 27.9 , 27.6 , 24.1 , 18.3 , 18.1 .

Hexanoyl ester 29: Yield: 33%; ^1H NMR (400 MHz, Chloroform-d) δ 7.16 (d, $J = 3.0$ Hz, 1H), 6.86 (dd, $J = 11.9, 8.9$ Hz, 2H), 6.81 (s, 0H), 5.91 (s, 1H), 4.95 (d, $J = 3.8$ Hz, 1H), 4.81 (dd, $J = 9.7, 3.8$ Hz, 1H), 4.27 (dd, $J = 9.8, 4.5$ Hz, 1H), 4.17 (td, $J = 9.5, 2.4$ Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.57 (t, $J = 9.3$ Hz, 1H), 3.41 (s, 3H), 2.56 – 2.39 (m, 2H), 2.39 (s, 0H), 1.74 – 1.61 (m, 1H), 1.43 – 1.28 (m, 4H), 0.90 (t, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 173.7 , 153.9 , 151.0 , 126.2 , 116.2 , 112.5 , 97.8 , 97.3 , 81.7 , 73.6 , 69.9 , 68.5 , 62.3 , 56.5 , 56.0 , 55.6 , 34.3 , 31.3 , 24.8 , 22.5 , 14.1 . Diester Yield: 13%; ^1H NMR (400 MHz, Chloroform-d) δ 7.14 (d, $J = 3.1$ Hz, 1H), 6.84 (d, $J = 3.1$ Hz, 1H), 6.80 (d, $J = 9.0$ Hz, 1H), 5.80 (s, 1H), 5.60 (t, $J = 9.8$ Hz, 1H), 4.94 (d, $J = 3.8$ Hz, 1H), 4.89 (dd, 0H), 4.27 (dd, $J = 10.2, 4.9$ Hz, 1H), 4.00 – 3.85 (m, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.65 (t, $J = 9.7$ Hz, 1H), 3.41 (s, 3H), 2.32 (q, $J = 5.6$ Hz, 1H), 2.23 (td, $J = 3.2$ Hz, 1H), 1.61 (q, $J = 7.4$ Hz, 1H), 1.34 – 1.25 (m, 3H), 1.24 – 1.16 (m, 3H), 0.89 (t, $J = 6.9$ Hz, 3H), 0.77 (t, 2H).

4-Chlorobutyryl ester 30: C2 Yield: 24%; ^1H NMR (400 MHz, Chloroform-d) δ 7.16 (d, $J = 3.0$ Hz, 1H), 6.86 (dd, $J = 12.1, 9.1$ Hz, 2H), 6.81 (s, 0H), 5.91 (s, 1H), 4.95 (d, $J = 3.8$ Hz, 1H), 4.83 (dd, $J = 9.7, 3.8$ Hz, 1H), 4.28 (dd, $J = 9.8, 4.5$ Hz, 1H), 4.18 (t, $J = 9.5$ Hz, 1H), 3.84 (s, 0H), 3.78 (s, 4H), 3.61 (t, 3H), 3.41 (s, 3H), 2.62 (t, $J = 7.2$ Hz, 2H), 2.24 – 2.06 (m, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 172.6 , 155.3 , 153.5 , 151.0 , 126.1 , 116.2 , 112.5 , 97.7 , 97.3 , 81.7 , 73.8 , 69.2 , 68.9 , 62.2 , 56.5 , 56.0 , 55.6 , 44.0 , 31.4 , 27.8 . Diester Yield: 21%; ^1H NMR (400 MHz, Chloroform-d) δ 7.13 (d, $J = 3.0$ Hz, 1H), 6.90 – 6.77 (m, 2H), 5.81 (s, 1H), 5.59 (t, $J = 9.8$ Hz, 1H), 5.30 (s, 1H), 4.96 (d, $J = 3.7$ Hz, 1H), 4.90 (d, 1H), 4.28 (dd, $J = 10.3, 4.8$ Hz, 1H), 3.94 (td, $J = 9.9, 4.8$ Hz, 1H), 3.81 (s, 7H), 3.77 (s, 3H), 3.66 (t, $J = 9.6$ Hz, 3H), 3.57 (t, 1H), 3.45 (s, 5H), 2.55 (td, $J = 7.1, 2.4$ Hz, 2H), 2.45 (t, $J = 7.1$ Hz, 2H), 2.14 – 2.04 (m, 4H), 2.06 – 1.96 (m, 2H), 4.99 – 4.96 (m, 0H).

Benzoyl ester 31: Yield: 41%; ^1H NMR (400 MHz, Chloroform-d) δ 8.16 – 8.04 (m, 1H), 7.65 – 7.51 (m, 1H), 7.50 – 7.42 (m, 1H), 7.18 (d, $J = 3.1$ Hz, 1H), 6.86 (dd, $J = 12.2, 9.1$ Hz, 1H), 6.82 (s, 0H), 5.94 (s, 0H), 5.07 (dd, $J = 3.6$ Hz, 1H), 5.03 (d, $J = 3.8$ Hz, 0H), 4.36 (t, $J = 9.3$ Hz, 0H), 4.30 (dd, 0H), 3.92 (td, $J = 9.9, 4.7$ Hz, 1H), 3.82 (s, 1H), 3.79 (s, 2H), 3.65 (t, $J = 9.4$ Hz, 1H), 3.41 (s, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ 166.4 , 153.9 , 151.0 , 133.5 , 130.1 , 129.7 , 128.6 , 126.2 , 116.2 , 112.5 , 98.0 , 97.3 , 81.8 , 74.2 , 69.2 , 62.3 , 56.5 , 56.0 , 55.7 .

Naphthoyl ester 32: Yield: 74%; ^1H NMR (400 MHz, Chloroform-d) δ 8.92 (d, 1H), 8.27 (d, $J = 7.3, 1.3$ Hz, 1H), 8.10 – 7.98 (m, 1H), 7.89 (d, $J = 8.1$ Hz, 1H), 7.75 – 7.60 (m, 1H), 7.58 – 7.39 (m, 2H), 7.19 (d, $J = 2.9$ Hz, 1H), 6.99 – 6.85 (m, 1H), 6.82 (d, $J = 1.0$ Hz, 0H), 5.97 (s, 1H), 5.38 – 5.24 (m,

0H), 5.18 – 5.12 (m, 1H), 4.42 (t, 1H), 4.32 (dd, 1H), 3.96 (td, $J = 9.8, 4.8$ Hz, 1H), 3.81 (s, 6H), 3.70 (t, 1H), 3.46 (s, 2H).

General method for carbamate synthesis The standard procedure by which carbamates are synthesized is dependent on the availability of the isocyanate. If the isocyanate needed is unavailable, then it must be prepared from the corresponding carboxylic acid via Curtius rearrangement. This is done by first dissolving the acid in 1-1.5 ml of THF (50mg scale), and then adding 1-2 equivalents of base, preferably dry triethylamine. To this solution, 2eq of DPPA is added and stirred at about 60°C for 2 hours under anhydrous conditions. Proceeding from here, the headgroup is simply added to the solvent mixture at 0°C and stirred overnight.

Phenyl carbamate 33: Yield: 50%; ^1H NMR (400 MHz, Chloroform-d) δ 7.39 – 7.34 (m, 1H), 7.31 – 7.27 (m, 1H), 7.26 – 7.18 (m, 1H), 7.19 – 7.08 (m, 1H), 6.87 (dd, $J = 9.0, 3.0$ Hz, 0H), 6.85 (d, $J = 3.2$ Hz, 0H), 5.93 (s, 0H), 5.91 (d, $J = 4.6$ Hz, 0H), 5.03 (d, $J = 5.0$ Hz, 1H), 4.84 (dd, 1H), 4.29 (dt, $J = 10.3, 5.2$ Hz, 1H), 4.19 (t, $J = 9.6$ Hz, 0H), 3.87 (dd, $J = 9.5, 4.5$ Hz, 0H), 3.79 (s, 2H), 3.77 (s, 1H), 3.60 (t, $J = 9.4$ Hz, 0H), 3.45 (s, 1H), 3.43 (d, $J = 4.7$ Hz, 0H), 2.56 (s, 1H). ^{13}C NMR (101 MHz, Chloroform-d) δ 153.9 , 152.9 , 151.0 , 137.7 , 129.2 , 126.1 , 123.8 , 118.9 , 116.1 , 112.6 , 98.2 , 97.3 , 81.7 , 74.3 , 69.2 , 69.0 , 62.4 , 56.5 , 56.0 , 55.6 .

Benzoyl Carbamate 34: Yield: 43%; ^1H NMR (400 MHz, Chloroform-d) δ 7.39 – 7.30 (m, 1H), 7.30 – 7.23 (m, 1H), 7.16 (d, $J = 3.0$ Hz, 0H), 6.86 (dd, $J = 9.0, 3.1$ Hz, 0H), 6.83 (s, 0H), 5.91 (s,

0H), 5.26 (t, $J = 5.9$ Hz, 0H), 5.00 (d, $J = 3.8$ Hz, 0H), 4.77 (dd, $J = 9.7, 3.8$ Hz, 0H), 4.37 (d, $J = 5.9$ Hz, 1H), 4.27 (dd, $J = 9.5, 4.1$ Hz, 0H), 4.14 – 4.11 (m, 0H), 3.83 (s, 1H), 3.79 (s, 2H), 3.59 (t, $J = 9.2$ Hz, 0H), 3.43 (s, 1H), 2.62 (s, 0H).

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Chapter IV. Studies of Stimuli Responsiveness and Trigger Release Applications for Advanced Gelator Systems

Abstract

Stimuli responsive or trigger release gel systems formed by low molecular weight gelators (LMWGs), from the standpoint of having applicable utility, are a testament to the great potential that hydrogels and organogels have in forming smart materials. Inherent to such systems are molecular moieties which are sensitive to an external stimulus such as a change in pH, irradiation with electromagnetic energy, temperature modifications, and chemical stimuli. Selectively incorporating such functionalities or molecules embedded within the gel matrix offers predisposed controllable abilities for gel molecules, but as well introduces new problems such as the loss of gel properties due to the novel integrations, which may inhibit gelation. Of the many applications for tentative use of supramolecular hydrogel systems, the “Holy Grail” of all such uses is said to be drug delivery. Exploring these new systems not only gives opportunity for new material discovery, but as well illustrates LMWG tolerances for functional group additions which may prove insightful to the continued effort to produce gelators by design.

Introduction

A comprehensive exploration of the potential applications of physical gels, which are soft novel materials formed by molecular aggregates of low molecular weight gelators (LMWGs), is bound to reveal valuable uses for such soft macromolecular assemblies. These assemblies are endowed with the property of thermoreversibility due to the aggregates being bound in a non-covalent fashion, which is to say they are bound by weak forces such as hydrogen bonds, Van der Waals interactions, π interactions, and ionic forces. The introduction of an external stimulus which either triggers sol-gel transitions, gel swelling, color changes, or gel degradation which could lead to the release of embedded molecules, is an approach which makes gelators a controllable system with versatile functionality. For instance, the release of the 'model' drugs 8-aminoquinoline (AQ) and 2-hydroxyquinoline (HQ) were studied and profiled by Jan van Esch et al as they were released from gels formed by the gelator molecule N,N'-dibenzoyl-L-cystine (DBC).

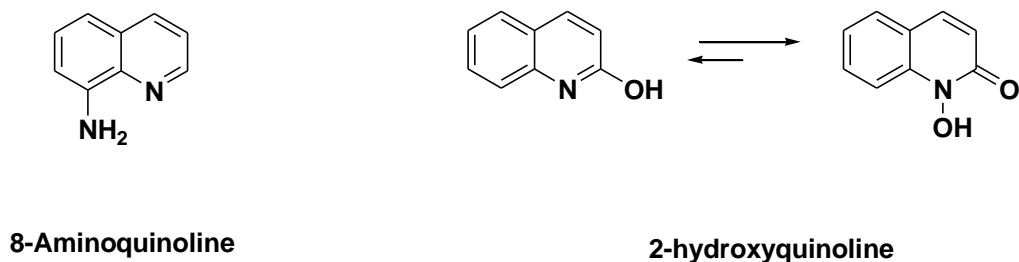


Figure 4.1. Model drugs 8-aminoquinoline (AQ) and 2-hydroxyquinoline (HQ) which are entrapped within the DBC gel matrix

The supramolecular assembly, being comprised of DBC molecules, allows for it to be responsive to pH stimulus, due to the carboxylic acid groups present within the molecule. Using 8-

aminoquinoline (AQ) and 2-hydroxyquinoline (HQ) is relevant because the derivatives of quinolines are known antimalarial and antileishmanial drugs. The group selected 8-aminoquinoline as a model drug because it could interact strongly with the DBC supramolecular assembly via not only Van der Waals and hydrogen bonding interactions, but as well through the amine interactions with the carboxylic acid groups, i.e. [DBC-COO⁻H₃N-AQ]. This particular

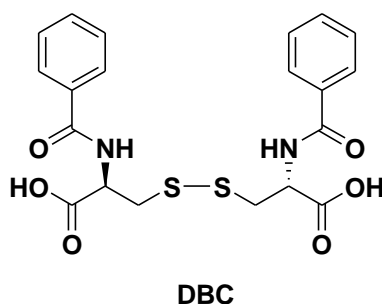


Figure 4.2 N,N'-dibenzoyl-L-cystine

selection represents a characteristic slow release of AQ coinciding with gel degradation. In contrast, a faster release was predicted and observed in the time release profile of HQ, which doesn't have the same strong interaction with the dicarboxylic acid groups. Gels were formed using varying DBC: AQ/HQ concentrations and their release profiles were analyzed using UV/vis spectroscopy. To instigate gel degradation, an NaOH solution was carefully introduced after gel formation. Jan van Esch et al collected the supernatant above each gel formed in DBC at varying times as it degraded. Assuming a degradation system which follows first order kinetics, the rate of AQ or HQ release was fit to the equation 1.

Equation 1. $Q = Q_0 (1 - e^{-kt})$

In this first order equation, Q represents either AQ or HQ at time t , and Q_0 represents the initial quantity of either model drug component (Figure 4.3).

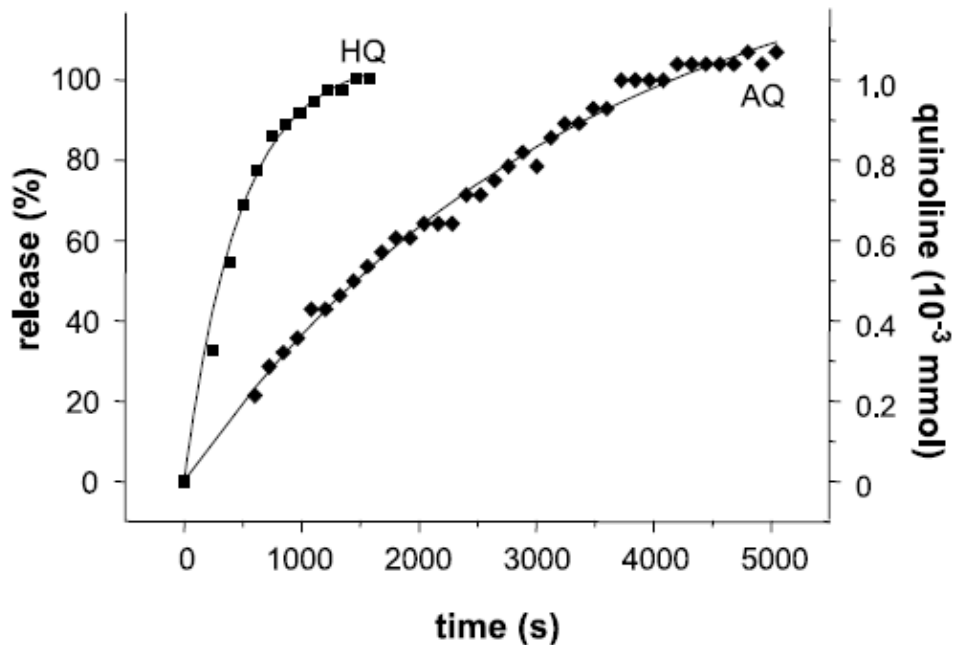
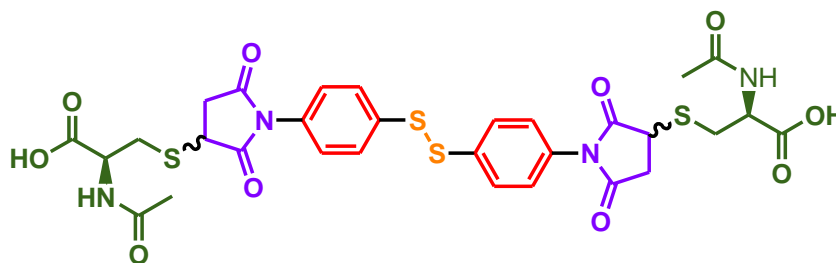


Figure 4.3 A first order kinetics fitting for the released percentages and concentrations of HQ and AQ. Each line fitting represents the release profiles from gels containing 0.2 wt.% DBC with 1.0mM of quinoline embedded within each. Permission liscence number: 2876830157358.

The above figure illustrates a the kinetics of a first order release profile, yet it was indicated that AQ interacts so strongly with the DBC gelator molecules that it follow a gel degradation release profile, and does not necessarily follow a first order release. The release of HQ was shown to be about 7 times faster than that of AQ and the differences of these two systems illustrates how similar systems may be developed for drug delivery.

Molecules which form supramolecular assemblies are found serendipitously on all occasions except when designed through analogy. A recurring theme of an amphiphilic hodgepodge of integrated functionalities, which is a sliding scale of properties ranging from hydrophilic to hydrophobic in nature, seems to be key to having such gelating abilities. Salvador Tomas et al studied a gel system which housed a hydrophobic, aromatic moiety linked via a disulfide bond, and a maleimide linker which could be further functionalized by appending the hydrophilic *N*-acetyl-L-cysteine (NAC) amino acid to it (Figure 4.4).



5

Figure 4.4 *N*-acetyl-L-cysteine (NAC) molecule featuring multi-stimuli responsive functionalities

This system is part of a rare type of gelators which are known as ‘multiresponsive low molecular weight gelators.’ Temperature stimulus which activates the sol-gel transitions and vice versa in most gelator systems is exploited with this series of gels, but there are additional stimuli responsive characteristics as well. Due to the presence of the *N*-acetyl-L-cysteine amino acid group, responsiveness to pH is as well inherent to this gel system. Yet another stimuli-

responsive feature incorporated within the gelator molecule is the disulfide bond which may be reduced. Although not in all circumstances may the resulting thiols be oxidized back to the disulfide linkage, some instances are reported as having reversibility in this regard. Amidst this slew of stimuli responsive groups, yet another gel-sol transition may be achieved by hydrolysis of the maleimide functionality. As one might expect, the requirements for incorporating multiple stimuli responsive functionalities may in itself disrupt a systems ability to gelate. None-the-less, compound **5** can gelate water at minimum gelation concentrations ranging from 0.1 (supergelator range) to 0.86 wt% at various pH readings. Tomas et al demonstrated this gelator as a potential system for drug delivery using vitamin B₁₂, which was released under the various gel-sol transition inducing mechanisms. The following Figure 4.5 illustrates how the release rates can be variably controlled by selection of the external stimulus.

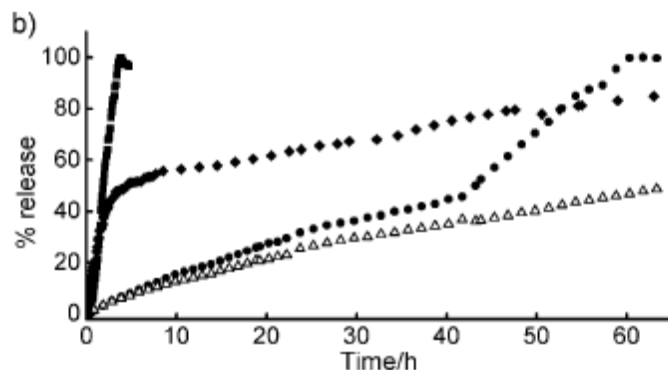
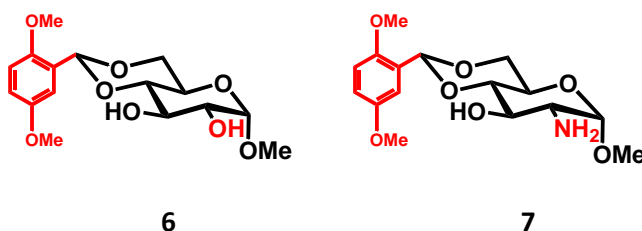


Figure 4.5 A release profile of vitamin B₁₂ under various gel-sol stimulus conditions. The square represents a reducing solution. The diamond represents the release under acidic pH (5.4 pH). The circle represents the spontaneous hydrolysis of the gelator. The empty triangle represents the release without external stimulus (pH 6.0/ control). Permission license number: 2877921284114

Tomas et al were able to maintain the critical balance of hydrophobicity versus hydrophilicity whilst as well introducing several stimuli responsive functionalities in this gel system. Furthermore, the use of such a system for drug delivery furthers the continued efforts of groups performing analysis of gelator systems for biomedical applications.

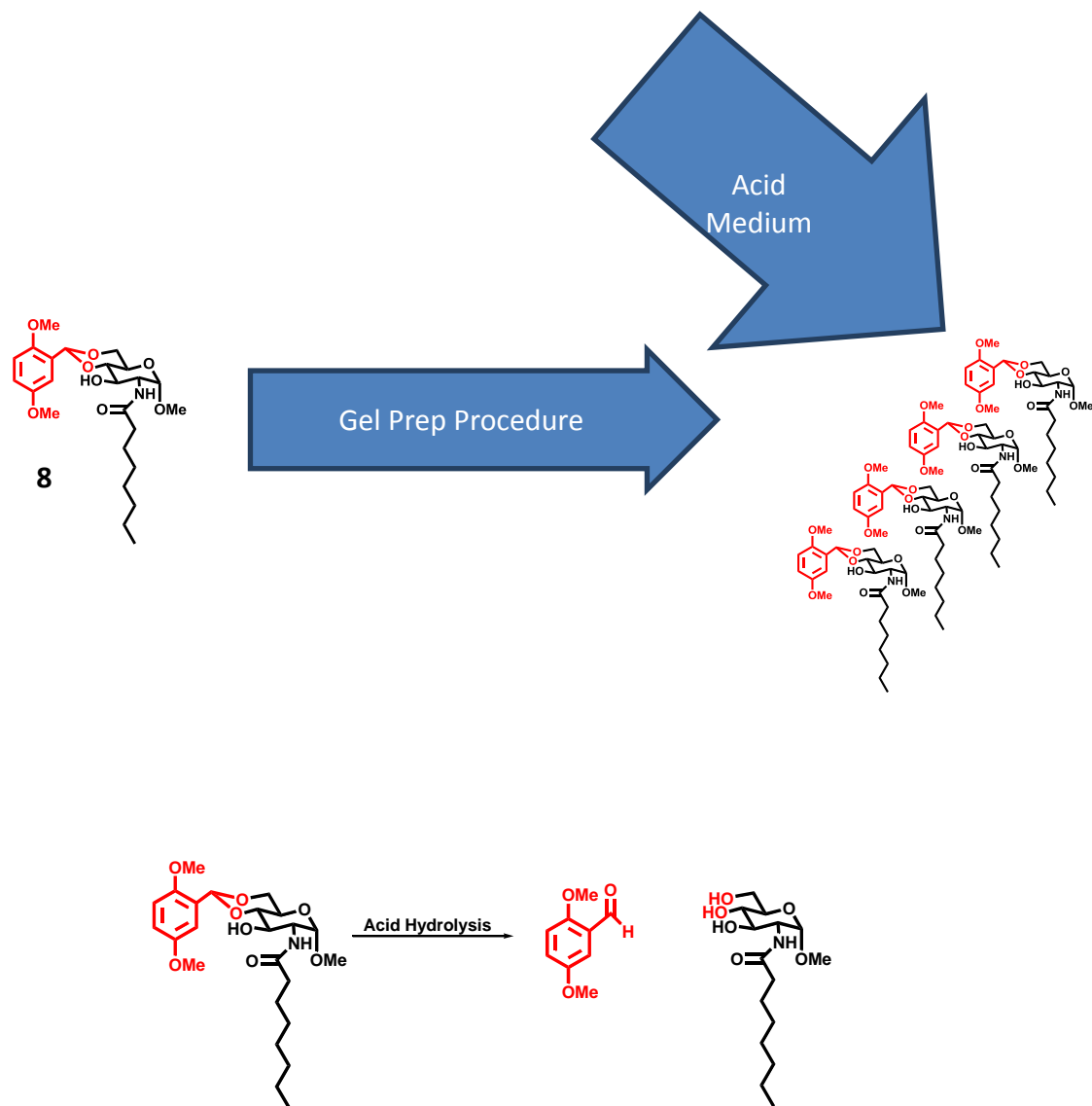
Results and Discussion

Trigger release studies were developed by affecting the gel-sol transitions for two types of triggered release gelators: 1) acid sensitive gelators, and 2) base sensitive gelators. Specifically, the acid sensitivity imparted to gelators of the 4,6-protected glucose and glucosamine series was done so by adding the electron releasing –OMe groups at the 2,5 position of the phenyl rings of glucose compounds **6** and **7**. Having such groups present on the phenyl ring made the acetal functionality more acid labile, and therefore acid as an external stimulus could effectively provide a gel-sol transition upon introduction to the gel system. The gelation capabilities of this series were well established, and therefore selection of the optimal gelator was simple.



Scheme 4.6 Glucose and glucosamine gelator headgroups with the acid labile acetals at the 4,6-position

The preliminary acid-sensitivity studies entailed performing the gel preparation procedure using octanoyl amide compound **8**. After gelation has taken hold, an acid medium of 1 M HCl was



Scheme 4.1 Gel-sol transition afforded by acid medium addition

introduced to cause cleavage of the acid labile acetal group, and in turn caused gel degradation as illustrated by Scheme 5. The degradation process was monitored via photography (Figure 4.7). The setup entailed making identical gel vials containing 10 mg of **8**, gelating 0.5 mL of a 2:1 water:DMSO solution.

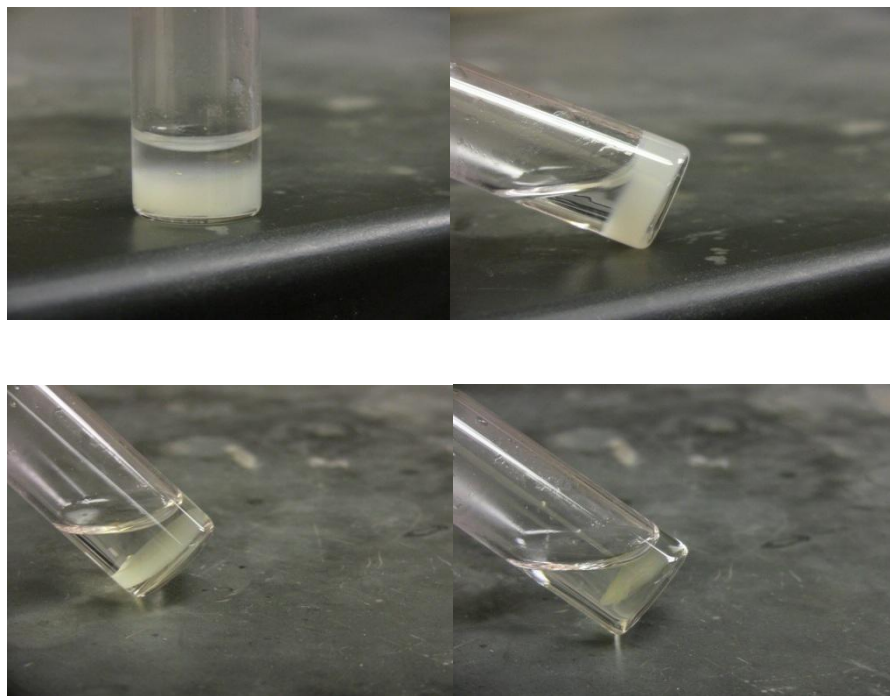
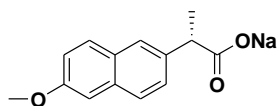


Figure 4.7. Gel degradation via acid hydrolysis. From left to right, top to bottom: T_0 ; 40 mins; 1 hr 20 mins; 3 Hrs

After developing the rudimentary procedure for initiating gel degradation through external stimulus, a study to illustrate the capacity of gelator systems to act as trigger release models for drug delivery was set up. Naproxen, a non-steroidal anti-inflammatory drug, or NSAID was incorporated into a gel formed by **8**, which was subsequently degraded in the presence of acid to release the naproxen (NPX). An illustration of the release profile can be seen in Figure 4.9, in which the release occurs over a period of time, and that rate is directly proportional to the gels



Naproxen Sodium (NPX)

9

Figure 4.8 Naproxen sodium, an NSAID

degradation in the presence of an acid medium.

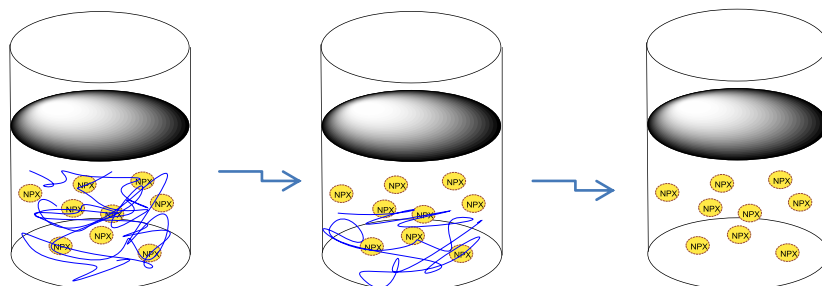


Figure 4.9 Predicted time-release mechanism for the release of NPX from a gel formed by **8**. 30 mg of NPX was dissolved within 0.5 mL of a 2:1 water:DMSO solution and 0.5 mL of a 1 M HCl solution was added to several identical gel vials.

Upon addition of the acid medium to the gels formed, contrary to expectations, the gel did not degrade over time. Several photographs at various time intervals were taken to reveal the formation of a white barrier, which disallowed gel degradation, as seen in Figure 4.10 This barrier

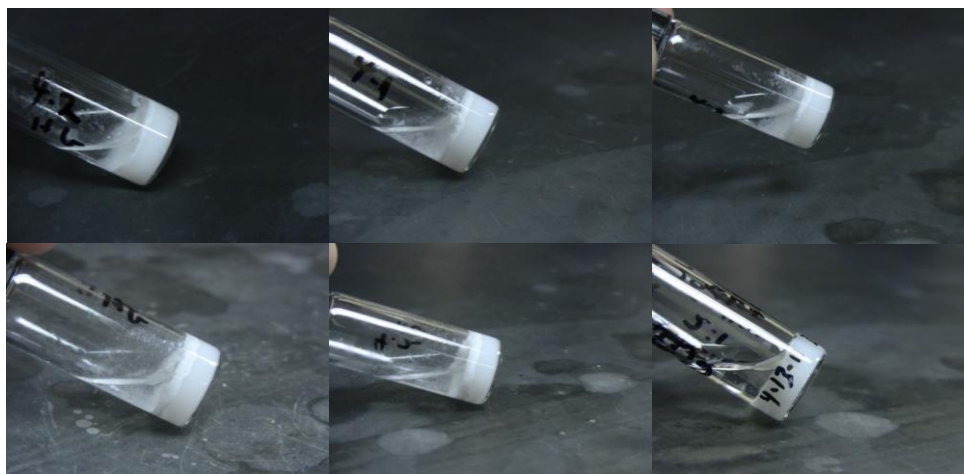
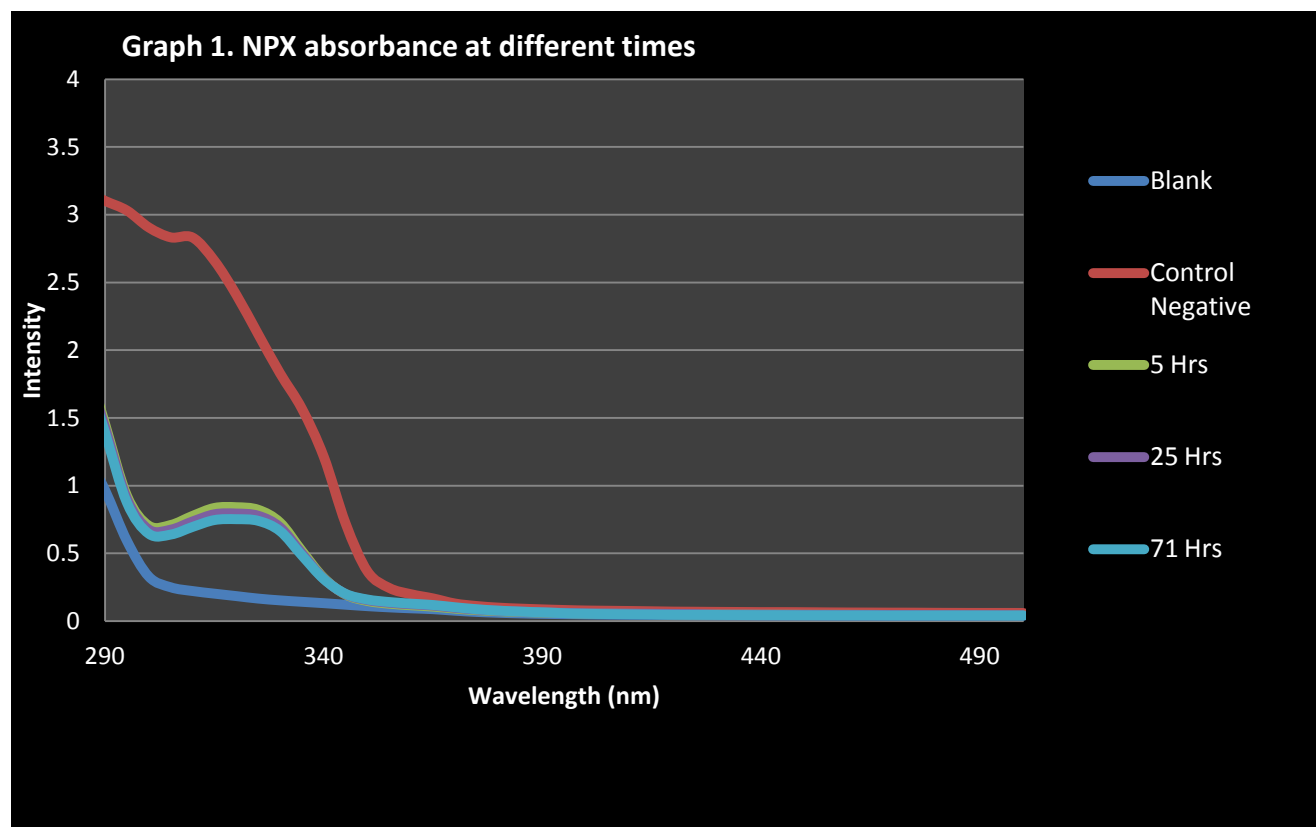


Figure 4.10 Gel state after introducing acid medium at: 0.5 hrs; 3 hrs; 4.5 hrs; 25 hrs; 71 hrs; Control

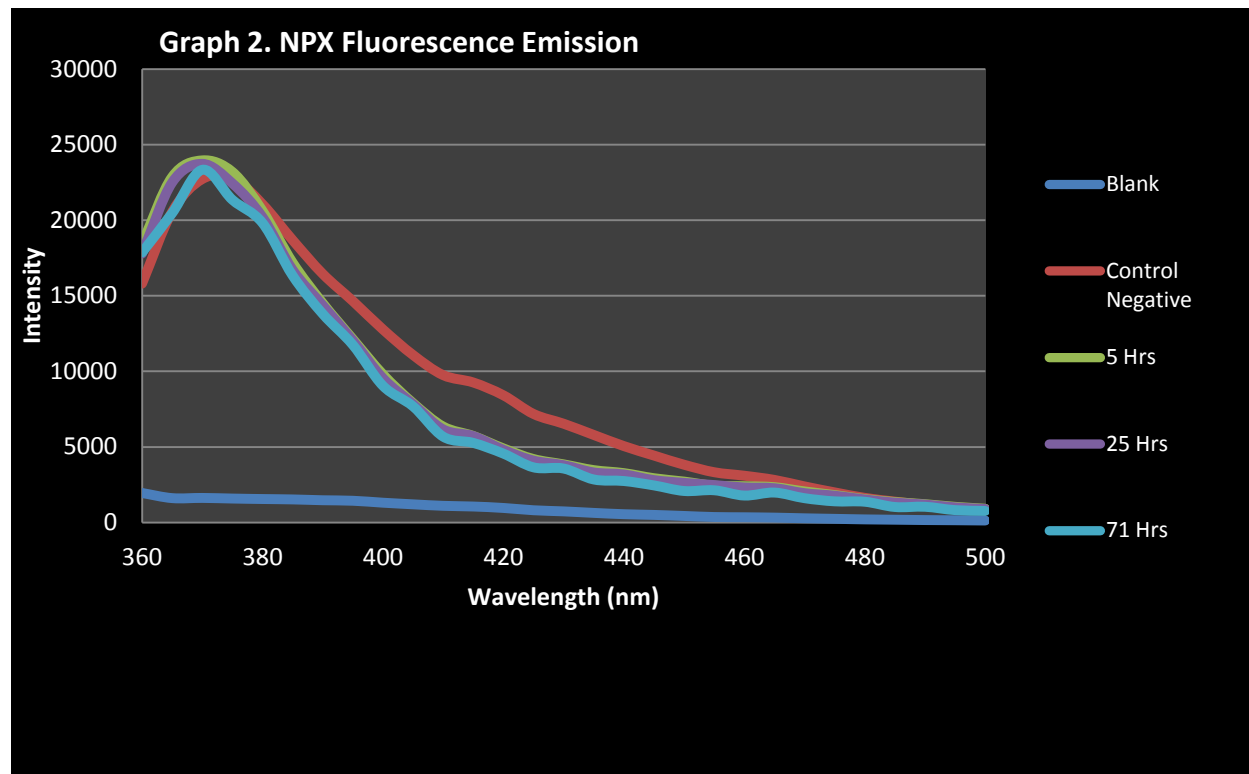
formed due to the formation of the acidified form of naproxen, which is insoluble in water. The insolubility of the acid form of naproxen caused a precipitate to form which disallowed gel degradation even after 71 hrs. To investigate the controlled-release profile, the contents of the vials were analyzed using spectrophotometric analytical techniques, the first of which is the



Graph 1. Absorbance of NPX at different time intervals. The absorbance for the negative control is greater than that for the sample aliquots due to a barrier formation which disallowed NPX release.

absorbance (Graph 1). The absorbance peaks for NPX of the aliquots taken are relatively steady, indicating that the release was in fact disallowed due to the barrier formation. The control negative, which employed only water, has a greater quantity of NPX simply through the

diffusion of the NPX through the gel without degradation. Fluorescence spectroscopy was as well performed to reveal similar trends, as seen in Graph 2.

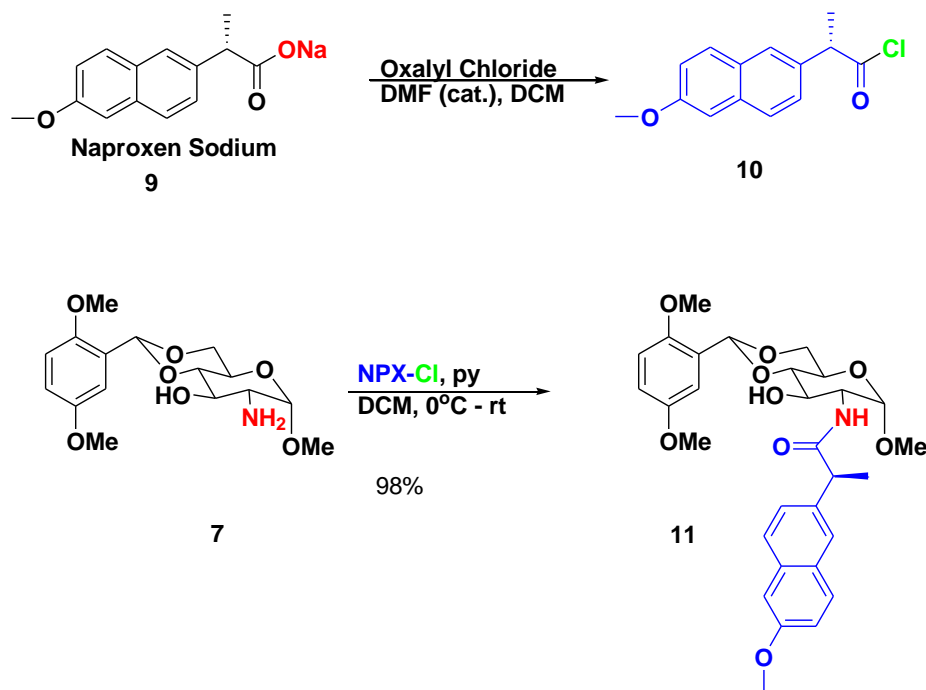


Graph 2. Fluorescence emission spectra of NPX

The unsuccessful attempt, at least at this juncture, to produce a gel system which acts as a model for a drug delivery system prompted me to seek another route in which solubility issues would be of no consequence regarding naproxen. To develop a system which still uses an acid medium, however, requires that the acidified form of naproxen not be present upon gel degradation. To achieve this, naproxyl chloride **10** was synthesized, and then subsequently

appended to the glucosamine derivative **7** to produce compound **11**, as seen in Scheme 4.2.

Taking this route could effectively lead to naproxyl prodrugs which, when exposed to certain



Scheme 4.2 Synthesis of naproxyl amide **11**

external stimuli, degrades or is metabolized to the therapeutic agent NPX, indirectly. Upon isolation of compound **11**, gel tests were performed to determine this systems' capacity to gelate various organic and aqueous solvents. As tabulated in Table 4.1, compound **11** forms a stable gel in 2:1 water:DMSO at an MGC of 5 mg/mL. With the introduction of an acid stimulus, the gel degrades to produce a glucosamine fragment with the naproxyl amide still in-tact, which

theoretically could be further degraded and released via enzymatic interactions. Several photographs were taken to monitor the gel degradation over time under exposure to the acid

Table 4.1 Gelation results for compound **11**

Compound	Yield	Water	Hexane	EtOH	Water: EtOH	Water: DMSO
11	98%	I	I	S	I	G (5)

U, unstable gel; **G**, gel at room temperature; **I**, insoluble; **Cr**, crystallizes; **S**, soluble; **P**, precipitates

medium. The gel almost completely degraded over the span of 24 hours.

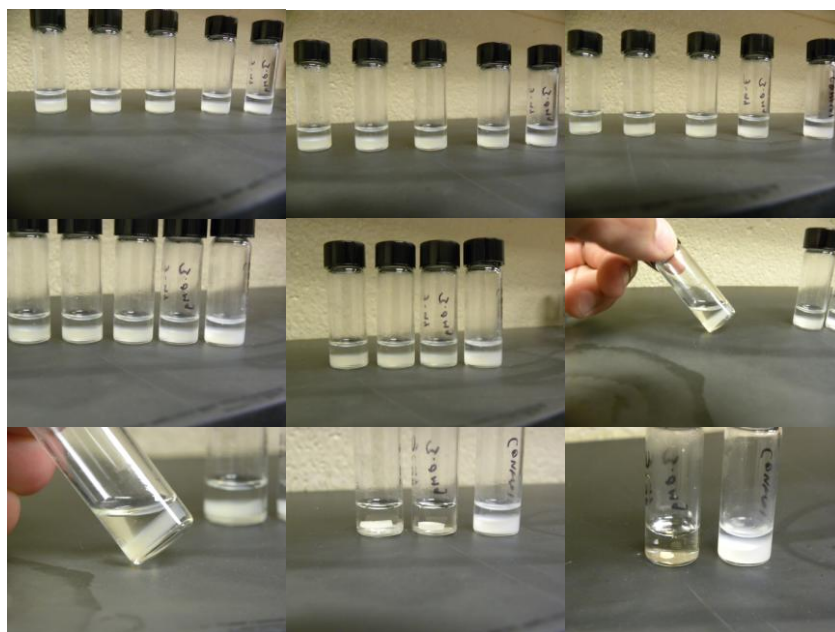
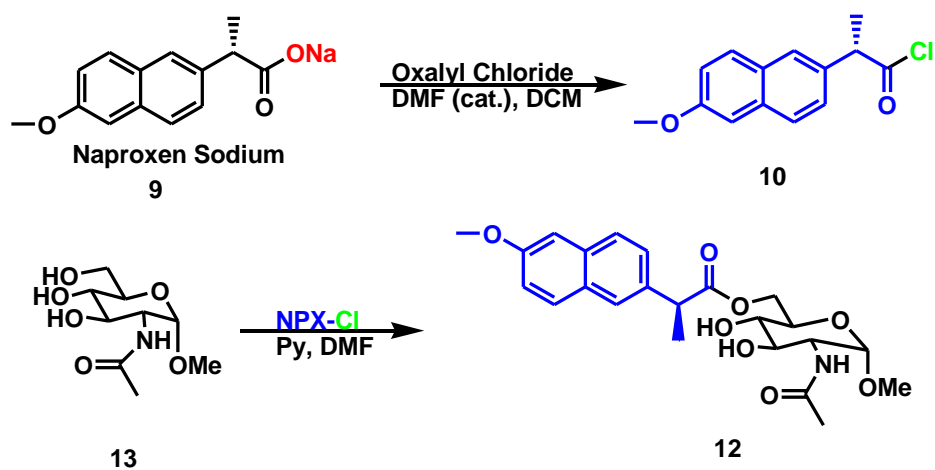


Figure 4.9 Photographic chronology of acid mediated gel degradation of compound **11**.

After development of a few acid based stimuli-responsive profiles of glucose and glucosamine based low molecular weight gelators, a base mediated system was desired. In consideration of the fact that these gelator systems house a 4,6-protecting group which is aromatic in nature, the naproxyl group was appended to the primary position of N-acetyl 1-MeO glucosamine to form compound **12** as seen in Scheme 1.3. With the trajectory of the aromatic NPX group being similar



Scheme 1.3. Synthesis of compound **12** via esterification at the C6 of 1-MeO *N*-acetyl glucosamine

to that of any 4,6-appended aromatic groups, it was conjectured that the gelation capabilities of such a system would be preserved. The gelation properties were tested in various solvents to reveal that compound **12** does not form a gel in any of the solvents tested (Table 4.2). At this juncture, it was determined that with the C4 –OH increasing the molecules overall cLogP was shifted towards a hydrophilic nature, and therefore some hydrophobicity must be restored

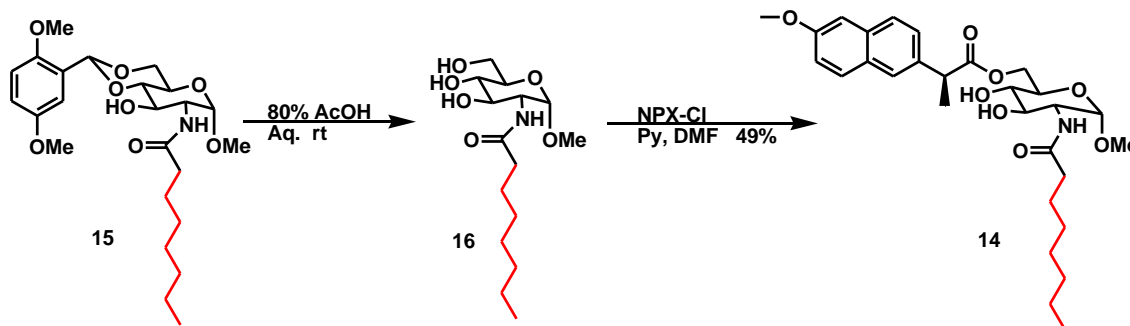
to the molecule to impart gel properties once again. This was achieved by introducing an octanoyl

Table 4.2. Gelation properties of compound **12**

Compound	Yield	Water	Hexane	EtOH	Water: EtOH	Water: DMSO
12	31%	I	I	S	C	P

U, unstable gel; **G**, gel at room temperature; **I**, insoluble; **Cr**, crystallizes; **S**, soluble; **P**, precipitates

group at the amide position, rather than the shorter acetyl group, which likely didn't contribute much to the necessary Van Der Waals interactions necessary for supramolecular assembly to form gels. Compound **14** was synthesized by deprotecting the 2,5-dimethoxy 4,6-benzylidene acetal protecting group of the N-octanoyl amide **15**, and then subsequently appending naproxyl chloride at the primary position to afford the potential pro-drug gelator molecule **14** (Scheme 4.4). As predicted, this compound which now has incorporated within it a long aliphatic chain



Scheme 4.4 Synthesis of octanoyl amide **14**

which shifts the aliphatic balance toward a more hydrophobic cLogP, now has the capacity to gelate organic/aqueous solvents as shown in Table 4.3. Compound **14** not only gellates water:EtOH and water:DMSO solvent mixtures (2:1), but it as well does so efficiently with MGCs lower than 3 mg/mL. Effectively, this gel system is representative of a gel scaffold

Table 4.3 Gelation results of octanoyl amide **14**

Compound	Yield	Water	Hexane	EtOH	Water: EtOH	Water: DMSO
14	49%	P	I	S	G (2.1)	G (2.8)

U, unstable gel; **G**, gel at room temperature; **I**, insoluble; **Cr**, crystallizes; **S**, soluble; **P**, precipitates

composed of not only a gelator, but a molecule which is responsive to an external stimulus, which upon degradation, releases naproxen from its prodrug parent in a basic medium. In this instance, the naproxen is soluble in aqueous medium because it is in its basic, salt form. The progression of the decay was again monitored by photography, which illustrates the gels decay over a period of 1 hour. The gels formed were at an MGC of 4 mg/mL, and the basic medium was a 1 M NaOH solution. The timed-release profile of the gel formed by compound **14** was much more rapid than that of the release profile observed in the case of acetal cleavage in acid mediums. As seen in Figure 4.10, shortly after addition of the basic medium, the gel began to

rise and degrade as predicted. Fluorescence and UV/vis data was obtained to monitor the decay

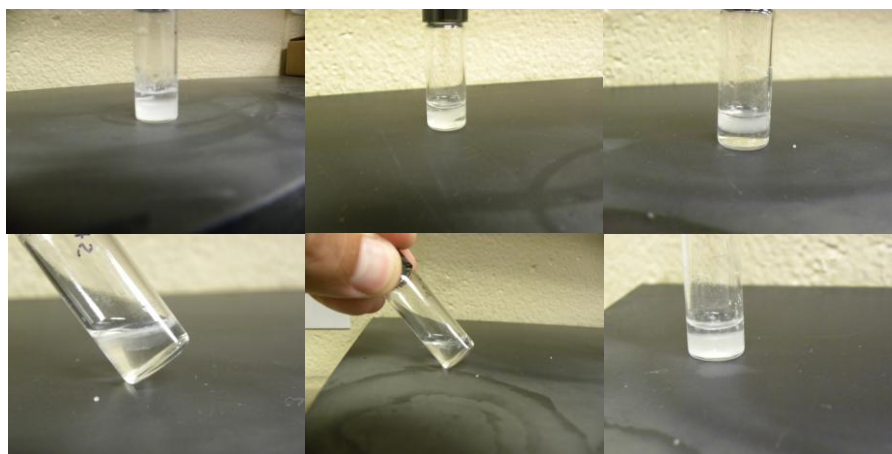
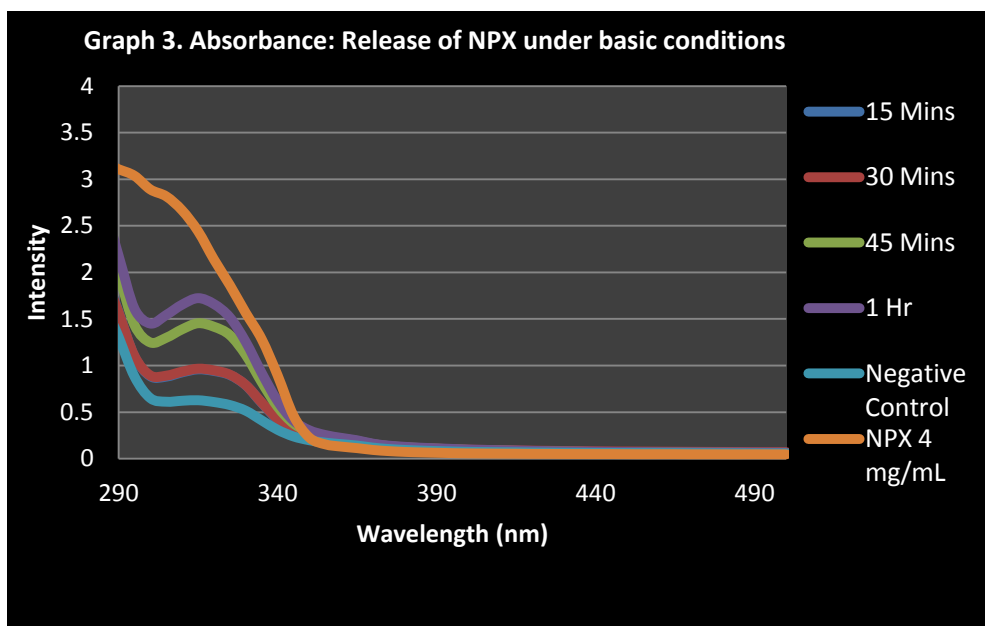
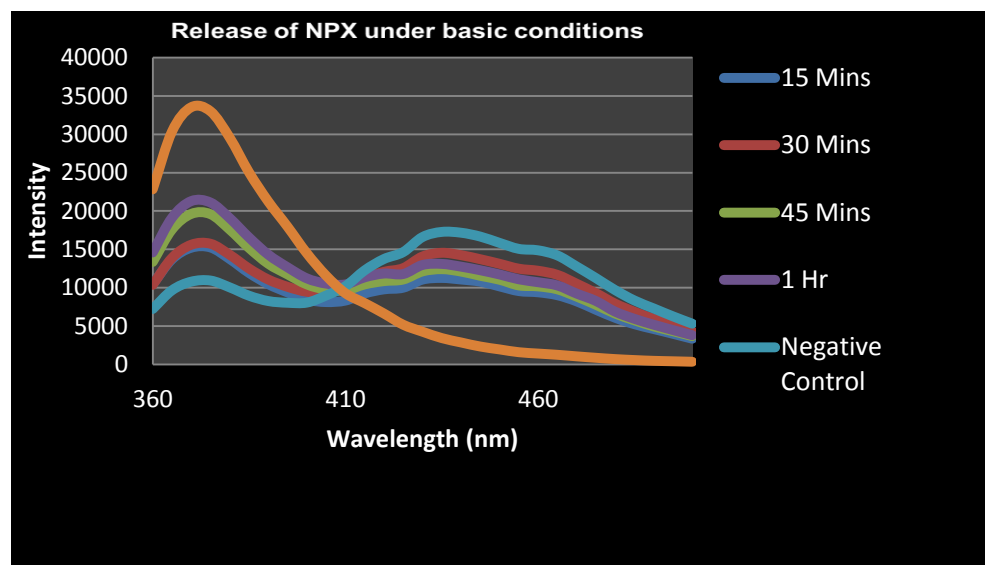


Figure 4.10 Gel degradation of compound **14** via basic medium

and subsequent release of NPX through basic cleavage at the C6 position of molecule **14**. As depicted in graphs **3** and **4**, the release profile of NPX increases proportionally with time, and the control shows a minor quantity of NPX present.



Graph 3. UV/vis absorption of NPX cleaved from gel molecule **14**



Graph 4. Fluorescence emission spectrum of NPX cleaved from compound **14**

Conclusions

Two gelator series containing several types of analogues were synthesized and analyzed for their gelation properties. In each series, the amide type gelators consistently performed better due to the addition of an –H bond donor center, and as well placement next to the C2 of the sugar ring. Studies of applications for advanced gelator systems led to the discovery of various –NPX appended gelator molecules, one of which served as a ‘proof of concept’ for a pro-drug gelator molecule.

Experimental

Synthesis of naproxyl chloride 10 To a 50 mL round bottomed flask, 0.303 g (1.2 mmol) was added and dissolved within 8 mL of dichloromethane and stirred at 0°C for a few minutes until all was dissolved. To this cold solution, 1.1 equivalents (0.15 mL) of oxalyl chloride was added drop-wise over 5 minutes. The solution turned a bright yellow initially, and at this juncture added DMF drop-wise until all starting materials were consumed and maintained 0°C for an hour and allowed reaction to spontaneously proceed to room temperature and stir for an additional two hours. After this total 3 hour time period, the reaction was complete as indicated by TLC. Purification simply entails blowing down all volatile contents under nitrogen, after which quantitative yield is obtained. ¹H NMR (400 MHz, Chloroform-d) δ 7.80 – 7.66 (m, 6H), 7.35 (dd, *J* = 8.5, 1.9 Hz, 2H), 7.22 – 7.11 (m, 4H), 4.26 (q, *J* = 7.0 Hz, 2H), 3.93 (d, *J* = 0.7 Hz, 5H), 1.68 (dd, *J* = 7.1, 0.7 Hz, 5H). ¹³C NMR (101 MHz, Chloroform-d) δ 175.9 , 158.3 , 134.4 ,

132.7 , 129.6 , 129.1 , 127.9 , 127.5 , 127.2 , 126.3 , 126.1 , 119.6 , 115.5 , 105.8 , 77.5 , 57.6 , 55.5 , 18.9 .

Synthesis of N-Naproxyl-4,6-O-Benzylidene-Methyl- α -D-Glucosamine 11 To a scintillation vial, 0.1069g (0.31 mmol) was added and dissolved within 1 mL of DCM. To this stirred solution, 1.1 equivalents (0.0857g) of naproxyl chloride was added along with 3 equivalents (0.08 mL) of pyridine. This reaction was allowed to proceed for 8 hours, after which time it was discontinued and an DCM/ aqueous work-up using a saturated ammonium chloride solution was performed. After drying with sodium sulfate and filtering, the organic phase was evaporated to provide an off-white powder. Yield: 98% ^1H NMR (400 MHz, Chloroform-d) δ 7.77 – 7.64 (m, 3H), 7.41 (dd, J = 8.5, 1.9 Hz, 1H), 7.18 – 7.07 (m, 2H), 6.06 (d, J = 8.5 Hz, 1H), 4.51 (d, J = 3.7 Hz, 1H), 4.43 (dd, J = 12.0, 5.6 Hz, 1H), 4.31 (dd, J = 12.0, 2.2 Hz, 1H), 3.90 (s, 5H), 3.67 – 3.50 (m, 2H), 3.20 (td, J = 10.0, 8.8 Hz, 1H), 3.04 (s, 3H), 2.01 (s, 3H), 1.59 (d, J = 7.1, 3.4 Hz, 3H).

Synthesis of N-acetyl-6-O-Naproxyl-Methyl- α -D-Glucosamine 12 To a scintillation vial, 0.1016g (0.432 mmol) was added and dissolved within 3 mL of DMF, stirred, and brought to 0 $^{\circ}$ C. To this cooled solution, 5 equivalents (0.2 mL) of pyridine were added, along with 1.1 equivalents (0.1289g) of naproxyl chloride and allowed reaction to proceed overnight. Upon reaction completion, the crude mixture was dried under nitrogen and subsequently purified via column chromatography using a hexane:EtOAc gradient ranging from 9:1 to 1:1. Yield: 31% ^1H NMR

(400 MHz, Chloroform-d) δ 7.77 – 7.64 (m, 3H), 7.41 (dd, J = 8.5, 1.9 Hz, 1H), 7.18 – 7.07 (m, 2H), 6.06 (d, J = 8.5 Hz, 1H), 4.51 (d, J = 3.7 Hz, 1H), 4.43 (dd, J = 12.0, 5.6 Hz, 1H), 4.31 (dd, J = 12.0, 2.2 Hz, 1H), 3.90 (s, 5H), 3.67 – 3.50 (m, 2H), 3.20 (td, J = 10.0, 8.8 Hz, 1H), 3.04 (s, 3H), 2.01 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 174.8 , 172.0 , 157.6 , 135.4 , 133.6 , 129.1 , 128.8 , 127.1 , 126.3 , 126.0 , 119.0 , 105.5 , 97.9 , 77.3 , 73.7 , 71.1 , 69.5 , 63.4 , 55.2 , 54.6 , 53.5 , 45.4 , 23.2 , 18.3 .

Synthesis of N-Octanoyl Methyl- α -D-Glucosamine 13 To a scintillation vial, 50.4 mg of *N*-Octanoyl-4,6-(2,5-dimethoxy) benzylidene Methyl- α -D-Glucosamine was added and dissolved within a 85% acetic acid solution and stirred at room temperature for 4.5 hours. Upon reaction completion, an aqueous workup was performed using water, brine, and DCM as the organic phase. After drying with sodium sulfate, filtering, and evaporating the crude mixture was purified using column chromatography. The solvent gradient used was DCM:MeOH ranging from 5-25% MeOH in DCM. Yield: 98% ^1H NMR (400 MHz, Chloroform-d) δ 6.39 (d, J = 8.8 Hz, 2H), 4.62 (d, J = 3.6 Hz, 2H), 3.94 – 3.85 (m, 1H), 3.74 (dd, J = 3.4, 1.7 Hz, 3H), 3.58 – 3.38 (m, 5H), 3.39 – 3.27 (m, 7H), 3.16 (s, 19H), 2.21 – 2.11 (m, 4H), 1.58 – 1.49 (m, 3H), 1.29 – 1.17 (m, 22H), 0.85 – 0.76 (m, 11H).

Synthesis of N-Octanoyl-6-O-Naproxyl-Methyl- α -D-Glucosamine 14 To a scintillation vial, 0.037g of triol **16** was added and dissolved within 1 mL of DMF along with 5 equivalents (0.05 mL) of pyridine and stirred at 0°C. To this cold solution, 1.1 equivalents of naproxyl chloride was

added and it was stirred for 12 hrs, after which time an aqueous extraction was performed ammonium chloride, brine, and DCM as the organic phase. After isolation of the DCM phase, it was subsequently dried using sodium sulfate, filtered, and evaporated. The crude mixture was then loaded onto a column and purified using a DCM:MeOH gradient, in which the product eluted at 2% DCM in MeOH. Yield: 49% ^1H NMR (400 MHz, Chloroform-d) δ 7.70 (d, 5H), 7.46 – 7.35 (m, 2H), 7.18 – 7.06 (m, 3H), 5.77 (d, J = 8.3 Hz, 1H), 4.55 – 4.42 (m, 2H), 4.33 – 4.24 (m, 1H), 3.91 (s, 8H), 3.62 (ddd, J = 11.6, 5.6, 2.8 Hz, 1H), 3.52 (td, J = 10.2, 9.1 Hz, 1H), 3.38 – 3.28 (m, 1H), 3.16 (t, J = 9.3 Hz, 1H), 3.08 (s, 3H), 2.20 (t, J = 7.6 Hz, 2H), 1.65 – 1.47 (m, 7H), 1.33 – 1.17 (m, 11H), 0.91 – 0.82 (m, 4H). ^{13}C NMR (101 MHz, Chloroform-d) δ 175.6 , 175.1 , 157.8 , 135.7 , 135.3 , 133.9 , 129.4 , 129.11 , 127.4 , 126.67, 126.1 , 119.2 , 115.5 , 105.7 , 98.20 , 76.9 , 74.6 , 71.3 , 69.6 , 63.5 , 55.5 , 54.9 , 53.7 , 45.6 , 36.7 , 31.8 , 29.9 , 29.2 , 25.7 , 22.8 , 18.4 , 14.2 .

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