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**CHARACTERIZATION OF 3-ESTER AND 3-CARBAMATE DERIVATIVES OF N-
ACETYL-D-GLUCOSAMINE AND THEIR USE IN CONTROLLED DRUG DELIVERY**

by

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August 2017

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ABSTRACT

SYNTHESIS AND CHARACTERIZATION OF 3-ESTER AND 3-CARBAMATE DERIVATIVES OF N-ACETYL D-GLUCOSAMINE AND THEIR USE IN CONTROLLED DRUG DELIVERY

Consuelo Garcia
Old Dominion University, 2017
Director: Dr. Guijun Wang

Low molecular weight gelators (LMWGs) are a class of compounds which reversibly form a network that traps solvents to form gels. Gelation by LMWGs is driven solely by non-covalent interactions such as hydrogen bonding, π - π stacking, and hydrophobic interactions. LMWGs can be designed such that the gel-sol and sol-gel transitions happen as a response to a specific stimulus. These stimulus responsive gels or “smart” gels can be used in a wide variety of applications including tissue regeneration, biosensing, and controlled drug delivery.

Among the different types of compounds that are LMWGs, carbohydrate based systems are especially interesting. Carbohydrates are abundant, renewable, biocompatible, and have numerous hydroxyl groups which can be readily functionalized. Our group has previously found that organogelators and hydrogelators can be obtained from *D*-glucose and *D*-glucosamine by selectively functionalization of the hydroxyl groups. Various C-2 acyl derivatives including esters and carbamates are found to be effective LMWGs for both water and organic solvents. In this study, the functionalization at the C-3 position of glucosamine derivative was carried out. Two types of C-3 derivatives including esters and carbamates were synthesized and characterized by ^1H and ^{13}C NMR spectroscopy and LCMS. These compounds were then analyzed for gelation properties in a series of selected solvents. Several compounds were found to be effective organogelators, the resulting gels were characterized using IR, rheology, optical microscopy, etc.

The use of these gelators for controlled drug delivery was tested and it was found that the gels loaded with naproxen sodium or chloramphenicol released the drug in an acidic environment.

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This thesis is dedicated to my parents, my brother, and my fiancé. Thanks for being my biggest cheerleaders.

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I would like to thank the many people who have contributed to the completion of this thesis. To the past and present graduate students and postdocs from Dr. Guijun Wang's research group, thank you for answering my questions and teaching me how to do synthesis and analysis. To my committee members, thank you for guidance on the editing of this manuscript. And to my advisor, Dr. Guijun Wang, thank you for all your guidance during my time as a graduate student at Old Dominion University.

NOMENCLATURE

Armoc	aryl-methoxycarbonyl
ATP	adenosine triphosphate
C ₁₂ DMAO	dodecyldimethylamine oxide
CAB	3- β -cholesteryl-4-(2-anthryloxy) butanoate
DI	deionized
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
EG	ethylene glycol
EtOH	ethanol
FT-IR	Fourier transform infrared
GalNac	<i>N</i> -acetylgalactosamine
H ₂ O	water
H ₂ SO ₄	sulfuric acid
HCl	hydrochloric acid
IR	infrared
LCA	lithocholic acid
LCMS	liquid chromatography mass spectrometry
MGC	minimum gelation concentration
Pa	Pascals
NaOH	sodium hydroxide
TEA	trimethylamine
TTF	tetrathiafulvalene
UV-Vis	ultraviolet visible

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1. INTRODUCTION TO GELS

Gels are semi-solid substances formed when the gelator molecules form a 3-D network which immobilizes solvent molecules.¹ When the network is formed from new chemical bonds between gelator molecules, the gel is called a chemical gel or a macromolecular gel. These bonds are formed irreversibly. Therefore, the gel cannot return to the solution phase after being formed. The compounds used to form chemical gels are typically large polymers. Chemical gels have been studied for centuries and are used in a diverse array of applications including cosmetics, food, and medicine.¹⁻²

Compared to macromolecular gels, supramolecular gels are a relatively new field of study. Supramolecular gels typically have a much lower molecular weight than macromolecular gels, and thus are often called low molecular weight gelators (LMWGs). Gel formation is driven by non-covalent interactions between gelator molecules and solvent; therefore, gelation is thermally reversible. The most common interactions seen in the formation of reversible gels are hydrogen bonding, Van der Waals forces, dipole-dipole interactions, π - π stacking, and hydrophobic interactions.³⁻⁴ Supramolecular gels are often weaker than their macromolecular counterparts. However, their smaller size makes the easier to synthesize and purify; and the reversibility of the gel-sol transitions can be taken advantage of for a variety of uses.^{1,3}

Supramolecular gels were first reported in the 1930s. These gels were discovered by serendipity.^{1-2,5} These first LMWGs were used in lubricants, inks, and napalm. After the initial discovery, almost no further research was done on supramolecular gels due to a lack of understanding on how LMWGs could be intelligently designed. Then, in the mid-90s, there was a

rapid resurgence in LMWG-related research because of the many potential applications of LMWGs and a desire to better understand the mechanism of molecular self-assembly.⁵

Usually, when gelation is discovered by serendipity, similar molecules are synthesized to determine which parts of the molecule were essential for gel formation. One such example is 3- β -cholesteryl-4-(2-anthryloxy)butanoate (CAB) depicted in **Fig. 1**. Weis and Lin discovered by chance that CAB can form stable organogels.⁶ They tested different modifications of CAB to determine which interactions were essential for gelation. They found that replacing the anthryl moiety with a naphthyl or phenyl group resulted in non-gelation, most likely due to the decrease in π - π stacking. Esters, amides, ureas, ethers, and carbamates were the best linker groups, most likely due to hydrogen bonding interactions. The secondary structure of the molecule was also important. Molecules with a more rod like secondary structure formed more stable gels than molecules with a bent structure.⁷

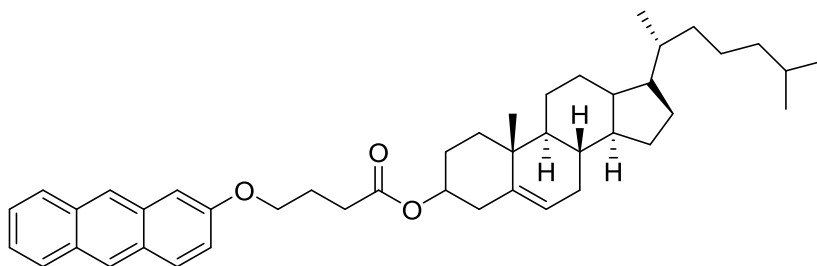


Fig. 1: Structure of CAB

Although it is still impossible to say from simply looking at a compound's structure whether or not it would be able to form a supramolecular gel, the discovery of LMWGs is no

longer left to serendipity. Research done by multiple groups during the resurgence of interest in LMWGs led to the following rules for the design of supramolecular gelators: (i) the presence of intermolecular interactions needed for self-assembly, (ii) control of interactions with the solvent to prevent crystallization (i.e., heating) and (iii) a factor to induce fiber cross-linking (i.e. sonication).⁴⁻⁵

In recent years, several new approaches for finding LMWGs have emerged. Many of these approaches are similar to the library based approaches seen in drug discovery. As is often the case with drug delivery, most of these studies are based on modified structures of known gelator compounds. A known gelator or a portion of a known gelator serves as a scaffold which is modified to improve solvent compatibility or to introduce additional functional groups. The resulting compounds are tested for their ability to form gels.^{1,5} More recently, some groups have reported a combinatorial approach to finding new gelators.⁸⁻⁹ These rational approaches to the design of supramolecular gelators will allow researchers to design and discover LMWGs for a wide variety of applications.

1.1 Stimulus responsive gels

The use of stimulus responsive LMWGs for a wide variety of biological and medical applications is an area of increasing interest. This would require the rational design of a molecule which not only forms a stable gel but which also contains a functional group which undergoes a gel-sol transition as a response to an external stimulus. Most LMWGs are thermally responsive, meaning they typically go into the solution phase when heated and return to the gel phase when

cooled. In addition to temperature, many gels can respond to other stimuli such as pH, redox, and light.¹⁰⁻²¹

Responsive to changes in pH is one of the most common methods for controlling gel-sol transition. These types of gelators contain moieties which are sensitive to acids or bases. For example, many carbohydrate derived gelators contain acetal protecting groups which can be cleaved under acidic conditions^{14, 21} (**Fig. 2a**). When supramolecular hydrogelators containing carboxylic acid moieties (**Fig. 2b**) are placed under basic conditions, the carboxylic acids are deprotonated and the resulting electrostatic interactions destabilize the gel.^{11, 22}

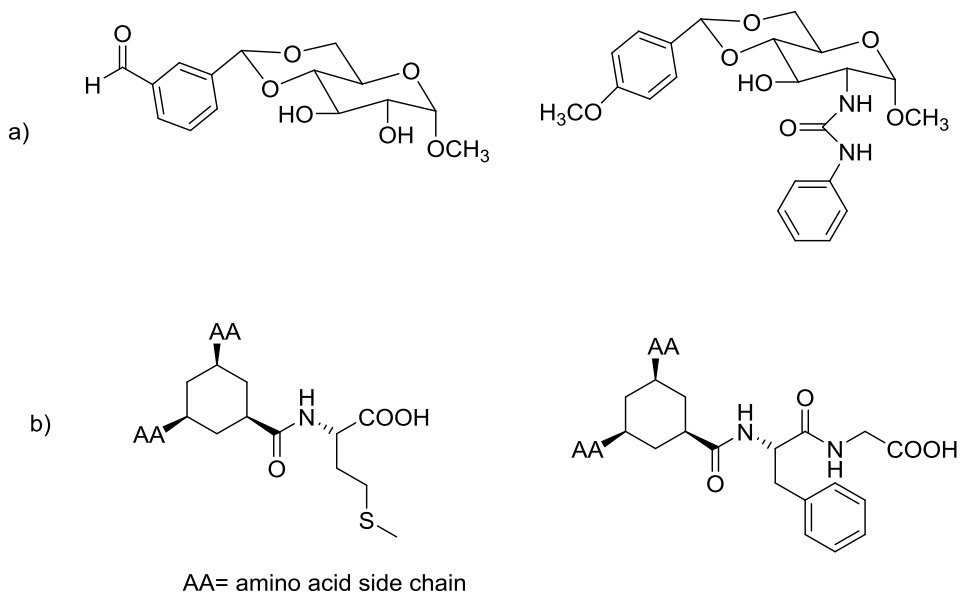


Fig 2: a) Acid responsive LMWGs containing acetal protecting groups, and b) Base responsive LMWGs containing carboxylic acid moieties.

Redox responsiveness is another common method for controlling gel-sol transitions. Redox responsive LMWGs contain moieties which respond to oxidizing or reducing agents. For example, the dipeptide based hydrogelators in **Fig. 3** contain redox responsive aryl-methoxycarbonyl (Armoc) groups at the N terminus. The groups are cleaved under oxidative (**Fig. 3a**) or reductive (**Fig. 3b**) conditions. Cleavage of the Armoc group induces the gel-sol transition.

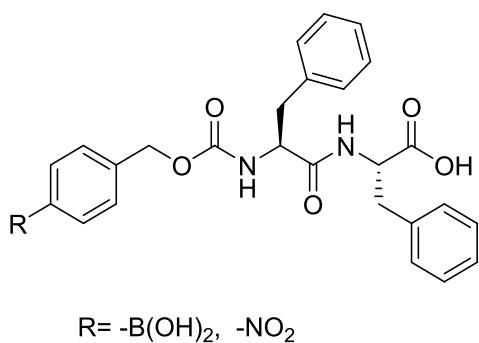


Fig. 3: Redox responsive dipeptide hydrogelators

Tetrathiafulvalene (TTF) can be transformed into its cationic or dicationic forms through redox chemistry (**Fig. 4**). A TTF derivative was first reported as an organic conductor in 1973.²³ Since then, numerous groups have found that TTF derived gelators formed gels which reversibly respond to redox reactions. Oxidation of the TTF group results in a gel-sol transition. It is believed that the positive charge disrupts the intermolecular interactions needed to form the gel.^{16, 24-25}

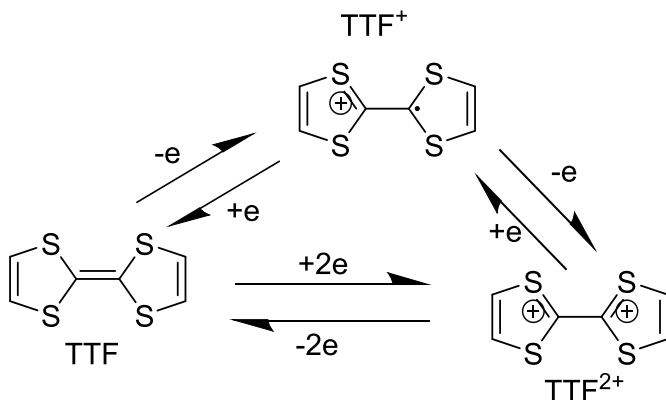


Fig. 4: Oxidized and reduced species of tetrathiafulvalene (TTF)

Enzyme responsive supramolecular gels are very useful for biomedical applications. They can be designed to respond to enzymes associated with particular tissues, organs, or medical conditions. Kinases and phosphatases are complementary classes of enzymes which can be used to reversibly control the formation of hydrogels (**Fig. 5**). Phosphatases cleave phosphate moieties from proteins, leaving a free hydroxyl group. Kinases transfer phosphate groups from adenosine triphosphate (ATP) to substrates containing free OH groups. When peptide based gelators are dephosphorylated by phosphatases, a sol-gel transition is observed.^{18, 26-27} It is believed that the hydroxyls provides hydrogen bonding interactions needed for supramolecular self-assembly. The gelation can be reversed when the gel is incubated with protein kinases in the presence of ATP.¹⁸

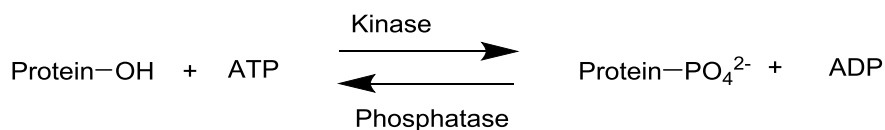


Fig. 5: Complementary kinase/phosphatase reactions

Photosensitive supramolecular gels contain chromophores which absorb light of a certain wavelength. Absorption of the light triggers reactions which change the physical structure of the gelator. This induces or disrupts the interactions needed for the supramolecular network. Photoresponsive gels can be used for sensors, drug delivery, and electronics.²⁸ Since conjugated systems are best for absorbing light, most chromophores contain multiple double bonds. Absorption of light can trigger *cis-trans* isomerization. Typically, *trans* isomers can form gels and *cis* isomers cannot.²⁸⁻²⁹

Some ring opening and closing reactions can be induced by light. The gelator in **Fig. 6** can undergo ring opening and closing upon exposure to different wavelengths of light. When the ring is closed, the molecule is unable to form gels due to its non-planar conformation. When irradiated with UV light, the ring opens and the resulting isomer is able to form stable hydrogels through π stacking.

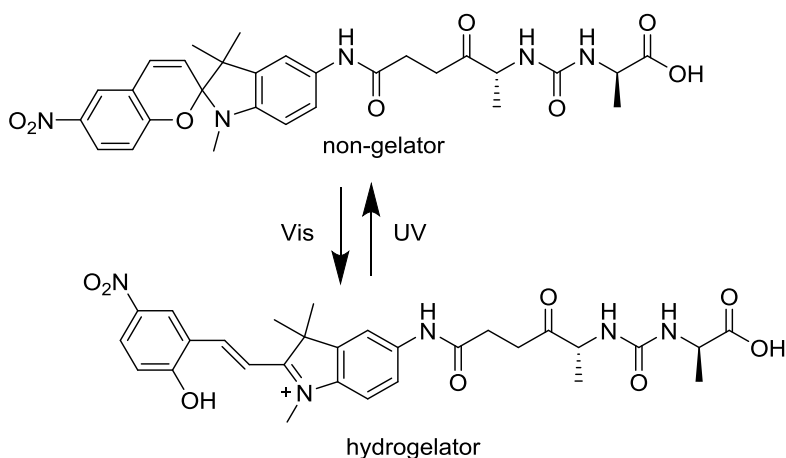


Fig. 6: Photoresponsive hydrogelator undergoing photo-induced ring opening and closing reactions

Knowledge of how reversible gel-sol transitions can be controlled has helped researchers find diverse uses for LMWGs. This, along with recently developed rational approaches to LMWG discovery, allows for a much more purposeful approach in the design of LMWGs as “smart” materials. It is now easier to predict whether a compound can form a gel and if that gel will respond to environmental stimuli. However, it is still impossible to say with complete certainty whether the desired gelation properties will be observed until the testing is done.

1.2 Sugar based gelators

Carbohydrate based LMWGs are an expanding area of research. Carbohydrates are naturally abundant, cheap, renewable, and biocompatible. The chiral hydroxy groups can be selectively functionalized with groups which facilitate gelation and respond to external stimuli.³ The sugar alcohol *D*-sorbitol (**Fig. 7**) is one of the simplest examples. A solution of *D*-sorbitol in ethanol can be cooled and sonicated to form a supramolecular gel.³⁰ Many groups have modified *D*-sorbitol and reported the gelation properties of *D*-sorbitol derivatives in a large variety of solvents. The amphiphilic *D*-sorbitol derivative 1,3:2,4-di-*O*-benzylidene sorbitol can dissolve in numerous solvents because it contains both hydrophobic and hydrophilic groups.³¹ Because of this, they are able to form robust gels in organic solvents and polar solvents such as polyethylene glycol and polypropylene glycol.³¹⁻³²

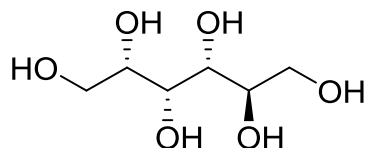


Fig. 7: Structure of *D*-sorbitol

Cyclodextrins are cyclic oligosaccharides consisting of six to eight glucose units joined by 1,4 α -linkages (**Fig. 8**).³ They are able to form gels in many organic solvents and in mixtures of water and organic solvents. Early studies of β -cyclodextrin organogels show that solvent molecules are located both inside and outside of the cavity when the supramolecular network is formed.³³ Host-guest interactions between cyclodextrins and guest molecules can be manipulated to affect gelation properties.³⁴⁻³⁵

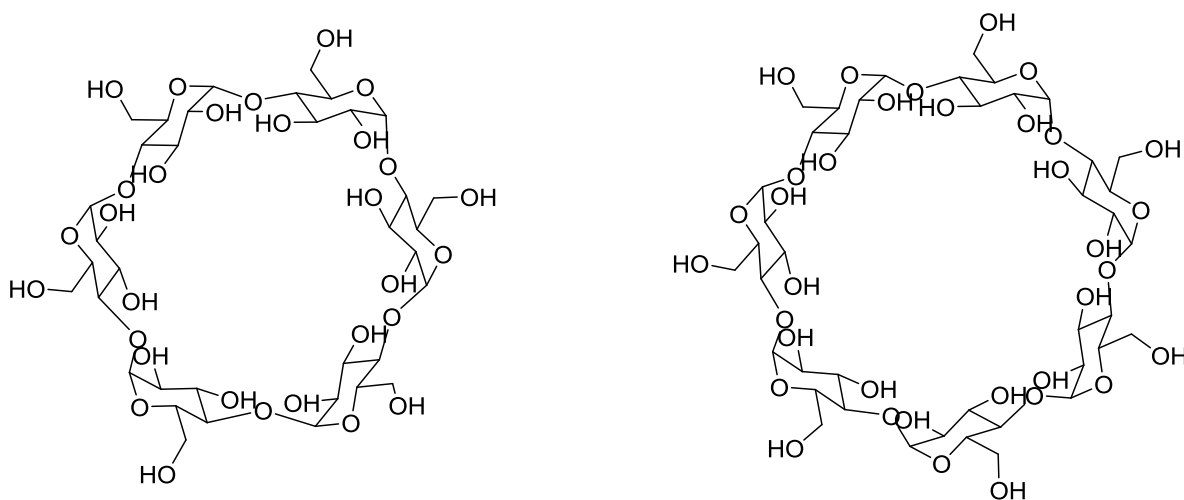


Fig. 8: Examples of cyclodextrins

Gluconamide type amphiphiles are carbohydrate based gelators attached to a long hydrocarbon chain through an amide bond. **Fig. 9** shows some of the first gluconamide type hydrogelators reported in 1985. Hydrogels formed at lower temperatures with decreasing lengths of alkyl chains. Gelators containing 10 or 12 carbon alkyl chains crystallized out of solution at room temperature. Gelators containing more amide bonds tended to form gels at lower

temperatures. It is believed that hydrogelation with gluconamides is favored by strong hydrogen bonds. Therefore, gelators containing more hydrogen bonding groups can be expected to be more efficient.³⁶

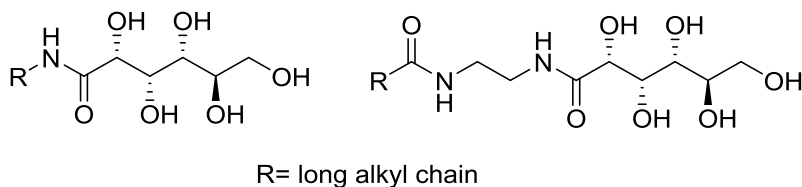


Fig. 9: Structures of early gluconamide type gelators

Monosaccharides common building block for low molecular weight gelators. Our group recently synthesized a series of peracetylated *N*-acetyl glucosamine based triazole derivatives.³⁷ Peracetylated glucosamine azide was reacted with a series of alkynes to make a library of triazole compounds with the structure shown in **Fig. 10**. Almost all the compounds were able to form at least one gel in the solvents tested. Four analogues formed toluene gels at 20 mg/mL and one long alkyl chain derivative was able to form a gel in ethanol. Increasing the number of methylene groups was shown to improve the efficiency of a gelator.

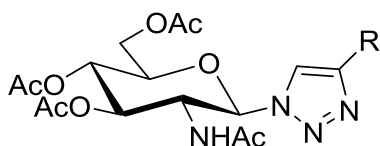


Fig. 10: Structure of glucosamine based triazole derivatives

Methyl 4,6,*O*-benzylidene derivatives of monosaccharides, such as the glucose derivative in **Fig. 11**, are a useful building block for synthesizing LMWGs. These compounds are characterized by unprotected OH groups at the 2 and 3 positions; protection of the anomeric OH with a methyl group; and protection of the 4-OH and 6-OH with benzylidene acetal.³

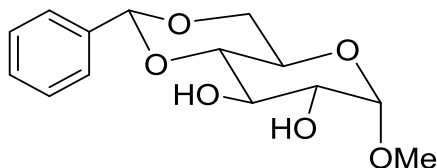


Fig. 11: Structure of methyl 4,6,*O*- benzylidene glucose

Investigation of the gelation properties of methyl 4,6,*O*-benzylidene derivatives of monosaccharides showed that gelation is primarily driven by intermolecular hydrogen bonding between the OH groups.³⁸ Gelation ability was highest when the spatial arrangement of gelator molecules allowed both 2-OH and 3-OH groups to participate in intramolecular interactions. Many groups have synthesized LMWGs based on these benzylidene protected monosaccharide building blocks.

Our group synthesized a series of 4,6,*O*-benzylidene-methyl- α -D-glucopyranose derivatives with modifications at the 2 position (**Fig. 12**).³⁹ Many of these compounds formed robust organogelators and hydrogelators. Esters with the general structure **12a** form stable gels in polar solvents when the R group is a short alkyl chain. Carbamates with the structures **12b** and **12c** formed gels with lower minimum gelation concentrations due to the additional hydrogen bonding from the carbamate NH. Amides and ureas with structures **12d** and **12e** also showed enhanced gelation compared to esters **12a**. Amides and ureas containing alkyl chains formed robust gels in

mixtures of water with DMSO or ethanol and the aryl derivatives were also able to form some gels in polar solvents.

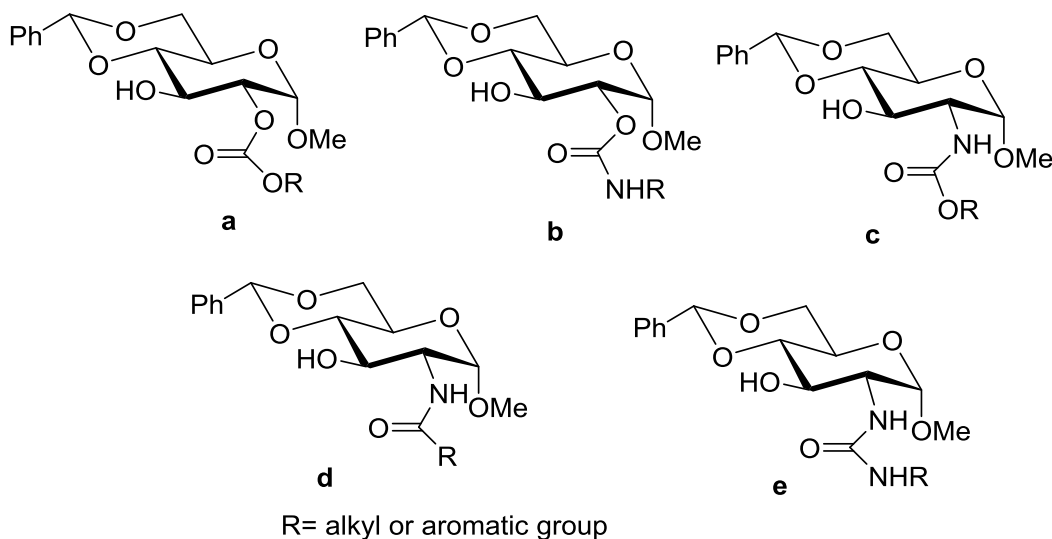


Fig. 12: Structures of 4,6-*O*-benzylidene- α -methyl-*D*-glucopyranose derivatives modified at the 2 position

A later paper examined the gelation properties of the 1-deoxyglucose analogues (**Fig. 13**). These analogues did not contain the *o*-methoxy group in the anomeric position. The hydroxyl groups in the 2 and 3 positions were derivatized to create a series of monoesters and diesters. Most of the diesters were able to form gels in ethanol and in mixtures of water and DMSO. The most effective gelators were diesters containing aromatic groups or diacetylenes. The 2- and 3-monoesters did not perform as well in the gel test.⁴⁰

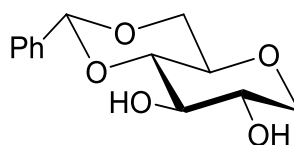


Fig. 13: Structure of 4,6-*O*-benzylidene-1-deoxy-glucose

1.3 The use of supramolecular gels in environmental applications

Knowledge of how the gelation properties of LMWGs can be altered allows researchers to design them with a specific purpose in mind. When designing a low molecular weight gelator for a particular application, the compound must (i) be able to efficiently form a gel in an appropriate solvent system and (ii) if appropriate, should be able to undergo a gel-sol or sol-gel transition in response to some external stimulus. In some cases, some LMWGs need to be able to only form gels with certain liquids when added to a mixture.

One situation in which LMWGs need to exhibit very specific gelation properties is when they are used in oil spill cleanup. Supramolecular gels are materials of interest for oil spill cleanup because they do not harm the environment and can immobilize large volumes of liquid. The reversibility of the formation of gels means that the gelator can be recovered and reused. A low molecular weight gelator used in oil spill cleanup should preferentially form gels with hydrocarbons in the presence of water. The resulting gel should be stable and easily separable from water.⁴¹

The first report of a phase selective LMWG was published in 2001. The gelator was a simple amino acid derivative called *N*-lauroyl L-alanine (**Fig. 14**). The compound was added to a 1:1 mixture of commercial oil and water. The mixture was heated to dissolve the solid. As soon as the liquids returned to room temperature, the oil phase was completely immobilized while the aqueous phase was left undisturbed. The selective gelation was made possible by *N*-lauroyl L-alanine's unique structure. The long alkyl chain excluded water while the polar COOH and CONH groups formed the supramolecular network through intermolecular hydrogen bonding.

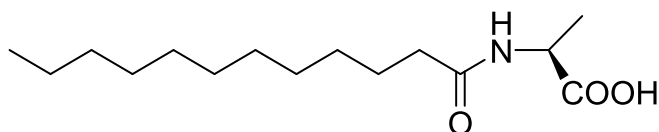


Fig. 14: Structure of *N*-lauroyl *L*-alanine

Since that report, many other phase selective organogelators have been designed. Like *N*-lauroyl *L*-alanine, most of these compounds had a long hydrocarbon chain and hydrogen bonding groups such as esters and amides. However, their practical application was limited by the fact that almost all of them had to undergo a heating and cooling cycle before forming a gel with oil.⁴²⁻⁴³ The first reported LMWG which quickly (< 90 s) and selectively formed gels with oils at room temperature was a simple phenylglycine derivative (**Fig. 15**). A few years later, a glucosamine derived LMWG which could instantly (< 45s) gelate oil from an oil/water mixture was reported.⁴⁴

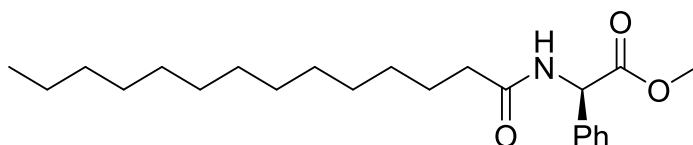


Fig. 15: Structure of phenylglycine derivative which selectively gelates oil at room temperature

The discovery of LMWGs which exhibited phase selective gelation without a heating-cooling cycle was important development. However, all of these gelators had to be introduced into oil/water mixtures in water miscible carrier solvents such as ethanol. Most of these carrier solvents are toxic and remain in the water after the oil gels are separated from the aqueous phase. This

concern was addressed by developing a phase selective organogelator which could be delivered to the oil/water mixture in a non-polar carrier solvent which co-congealed with the oil (**Fig. 16**).

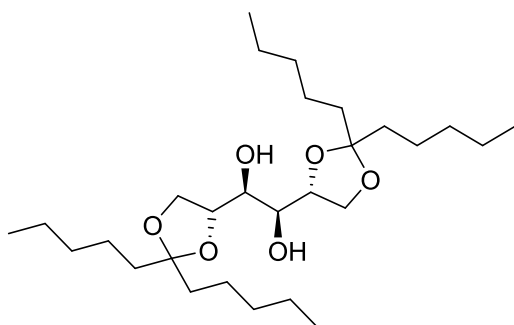


Fig. 16: Structure of phase selective organogelator which can be delivered to an oil/water mixture in a non-polar carrier solvent

Removal of dyes and other pollutants from water is another practical environmental application of LMWGs. This is conventionally done with activated charcoal or clay. There has been recent interest in the development of other materials for this purpose including polymeric organogels and organic-inorganic hybrid LMWGs. An ideal gelator for this purpose should have both hydrophobic and hydrophilic domains to efficiently bind with many different types of dye. It should also form a network with porous structure.⁴⁵

Lithocholic acid (LCA) possesses many of the characteristics of a gelator which can be used for dye adsorption. It is a biocompatible cholesterol derivative which has been found to participate in many different supramolecular systems.⁴⁶ When combined with an organic amine

such as dodecylmethylamine oxide (C₁₂DMAO), the resulting ion pairs (**Fig. 17**) form hydrogen bonding networks which drives hydrogelation.⁴⁷.

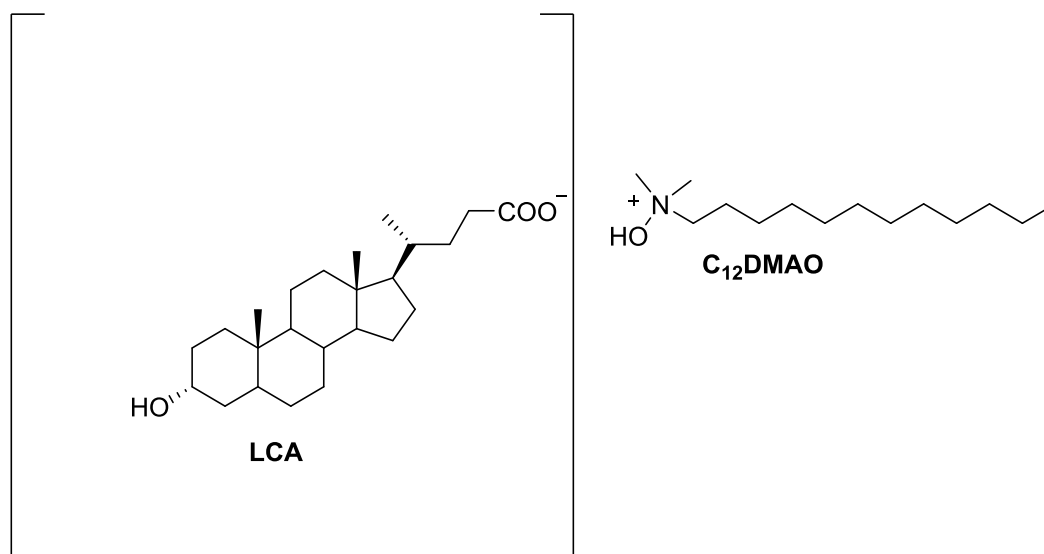


Fig. 17: Ion-pairing between LCA and C₁₂DMAO

The xerogel formed from LCA and C₁₂DMAO was tested for its ability to adsorb dye molecules out of water. The dyes tested were amido black 10B, methyl orange, rhodamine 6G, and chrome azurol S (**Fig. 18**). Adsorption efficiency was much higher for amido black 10B than it was for the other three dyes. Since FT-IR studies showed no obvious changes in the stretching and bending vibrations of hydrogen bonding groups, it is believed that dye adsorption is primarily driven by hydrophobic interactions. It can be concluded that amido black 10B is able to participate in more hydrophobic interactions with the gelators.⁴⁷

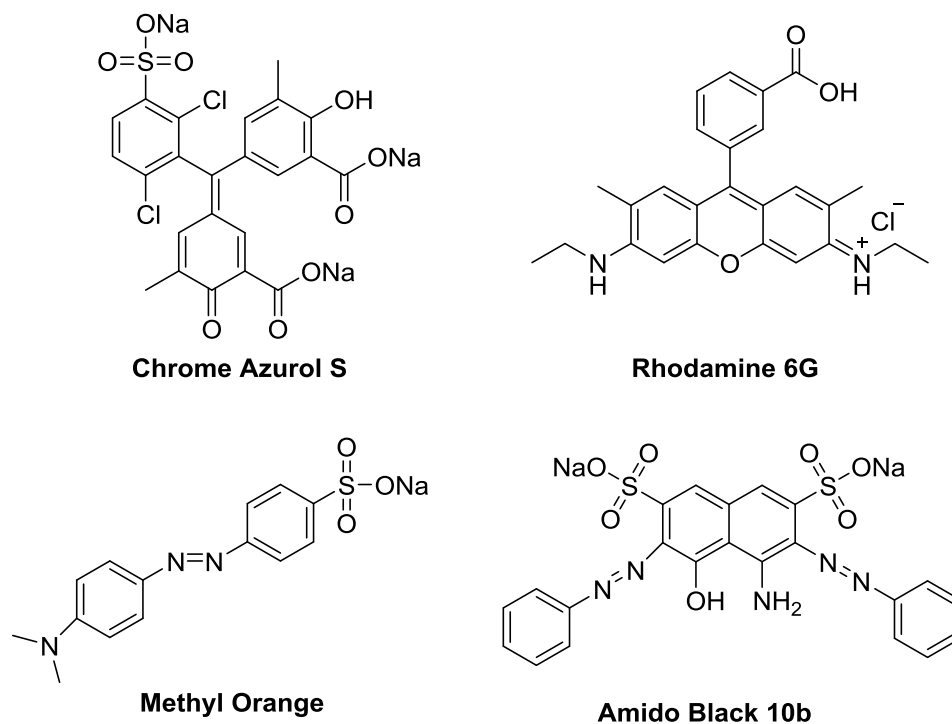


Fig. 18: Structures of dyes used in adsorption studies with LCA/C₁₂DMAO xerogels

Some gelators can be designed to adsorb different dyes in different environments. This creates a highly versatile material which can be used to adsorb and separate a wide variety of dyes. The first reported molecule which can be used in this way is dibenzylidene sorbitol hydrazide (**Fig. 19**).⁴⁸ Unlike many other LMWGs used for dye adsorption, the gels formed from this compound remain stable over a wide pH range.

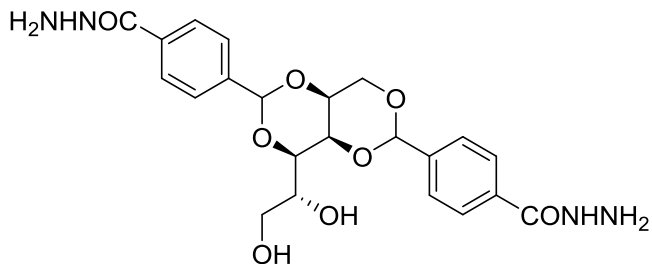


Fig. 19: Structure of dibenzylidene sorbitol hydrazone

Dye adsorption studies with hydrogels formed by dibenzylidene sorbitol hydrazone found that adsorption efficiency for methylene blue, acid blue 25, and naphthol blue black (**Fig. 20**) changed as a function of environmental pH. In basic media, methylene blue was selectively adsorbed from a mixture of all three dyes. In acidic media, only acid blue 25 and naphthol blue black were adsorbed. This phenomenon can be explained by examining the structures of the dyes. Since the dye adsorption is primarily dependent on hydrophobic interactions, maximum adsorption is achieved when the dye molecule's charge is lowest. For methylene blue, this occurs at high pH's when the amines are not protonated. For the other two dyes, this occurs at lower pH's because protonating the amine groups counteracts the negative charge from the sulfonate groups.⁴⁸

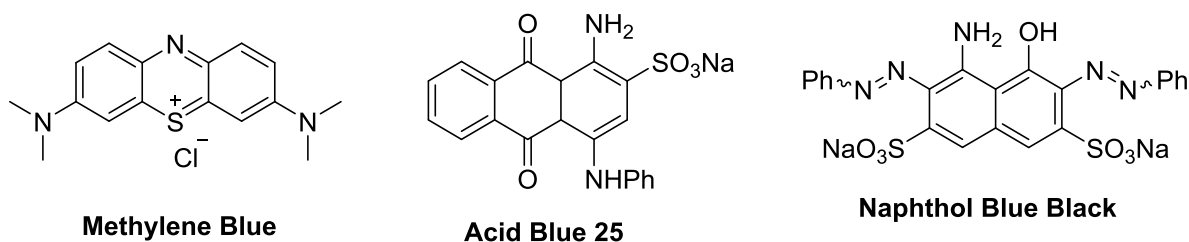


Fig. 20: Structures of dyes used in adsorption studies with dibenzylidene sorbitol hydrazone hydrogels

Charged LMWGs can adsorb select dyes through an ion exchange mechanism. The compound in **Fig. 21** is a ligand for divalent metal cations. It is a precursor to low molecular weight metallogelators which have negatively charged carboxylate groups balanced by free sodium ions. When the gelator comes into contact with positively charged dyes, the free sodium ions are replaced by dye molecules. When the gelator is added to a mixture of differently charged dyes, only the positively charged dyes are adsorbed.⁴⁹

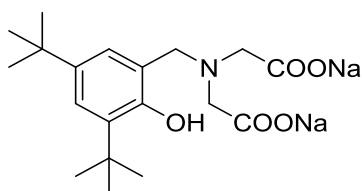


Fig. 21: Structure of the precursor to negatively charged metallogelator

1.4 The use of pH responsive LMWGS for Controlled Drug Delivery

pH responsive supramolecular gels are ideal for controlled drug delivery. The drug is encapsulated in the gel as long as the gel is stable. When the gel becomes unstable in response to a change in pH, the drug is released. Different tissues and organ systems usually have different environments. A pH responsive delivery system would ensure that the drug is only released at the intended site. This would increase the potency of the drug at the intended target while minimizing any side effects.

Usually, pH sensitivity is introduced by incorporating ionizable groups.^{11, 50} These groups are ionized after protonation or deprotonation. The resulting electrostatic interactions destabilize the gel. In some situations, it is preferable to use a neutral delivery system. The first neutral delivery system was reported in 2002. A bisacrylamide acetal cross-linker with a *p*-methoxy

substituent (**Fig. 22**) was synthesized and used to prepare an acid sensitive copolymerizing acrylamide gel. The *para*-substituted acetal ensures that the cross-linker is hydrolysed under acidic conditions (pH 5). All hydrolysis byproducts are neutral, making this the first uncharged pH sensitive gelator.⁵¹

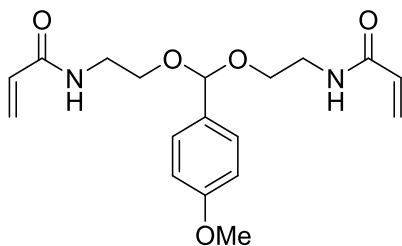


Fig. 22: Structure of acid labile bisacrylamide acetal cross-linker

Many pH responsive hydrogels used for drug release are peptide based. However, peptide gelators are not the only ones which can be used for controlled release. There is increasing interest in the synthesis and applications of stimulus responsive DNA based hydrogels.⁵²⁻⁵³ The anticancer drug doxorubin can be loaded onto a DNA hydrogel microcapsule. pH dependent drug release studies show no doxorubin release at pH 7.2 or pH 9.0. At pH 5.0, doxorubin is steadily released in forty minutes. Circular dichroism experiments show that i-motif structures are formed at acidic pH's. Therefore, it is concluded that destabilization of the gel is driven by the pH induced change in secondary structure.⁵⁴

Sugar based LMWGs can also be used for controlled drug delivery. In 2005, a novel pH responsive two-component hydrogel was reported. The two components of the hydrogel were an *N*-acetylgalactosamine (GalNac) appended glutamate ester (**Fig. 23a**) and an amphiphilic carboxylic acid derivative (**Fig. 23b**). On their own, neither compound could form pH responsive

hydrogels. The hydrogels of **23a** were not pH sensitive and **23b** could not form hydrogels. Hydrogels composed of a near equimolar mixture of **23a** and **23b** showed acid triggered gel-shrinkage. The shrinkage was reversed by neutralization. FT-IR studies before and after hydrogel shrinkage elucidated the mechanism of swelling and shrinking. After shrinkage, a peak corresponding to COOH stretching appeared whereas a peak corresponding to COO⁻ disappeared. It was proposed that the presence of the negative charge in a neutral environment led to electrostatic repulsion between gel fibers, which caused hydrogel swelling. By contrast, acid induced neutralization of the carboxylate groups removed the electrostatic repulsion and triggered hydrogel shrinkage. Vitamin B12 was successfully encapsulated in this two component hydrogel and quantitatively released in an acidic environment.⁵⁵

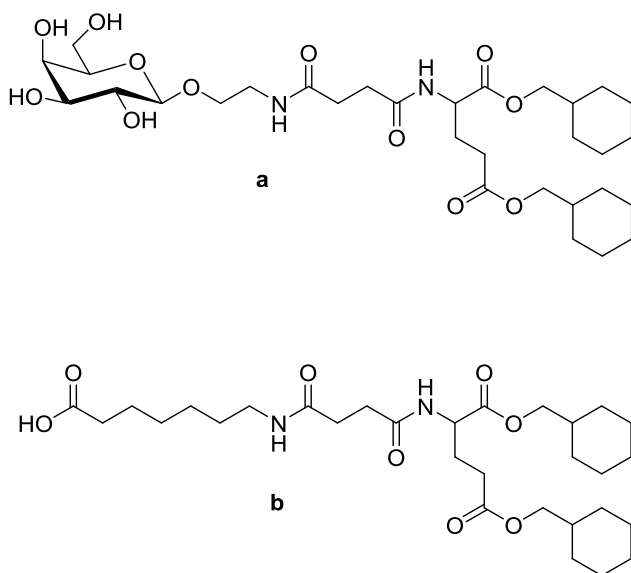


Fig. 23: Structures of components of mixed hydrogel system, a) GalNAc appended glutamate ester and b) amphilic carboxylic acid derivative

Our group synthesized a series of 2-amides and 2-ureas derived from 4,6-*O*-*p*-methoxybenzylidene- α -methyl-D-glucosamine (**Fig. 24**).²¹ Nearly all of the compounds were able to form stable gels in 1:2 DMSO:H₂O. Many of the urea derivatives formed gels in ethanol and in 1:2 EtOH:H₂O; and many of the amide derivatives formed stable hydrogels. Comparison of the gel test data to previous work shows that the addition of the *p*-methoxy group enhances gelation. Addition of diluted H₂SO₄ to these gels and their non-substituted analogues showed that the *p*-methoxy substituent made the compounds more acid labile. This is because the *p*-methoxy benzylidene acetal can be more easily cleaved by acid. Our group then tested the gels' capacity for pH-responsive controlled drug release.

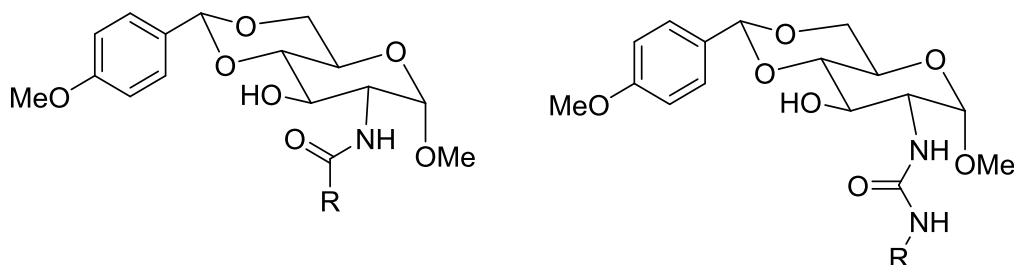


Fig. 24: Structures of amide and urea derivatives of 4,6-*O*-*p*-methoxy- α -methyl-N-acetyl-D-glucosamine

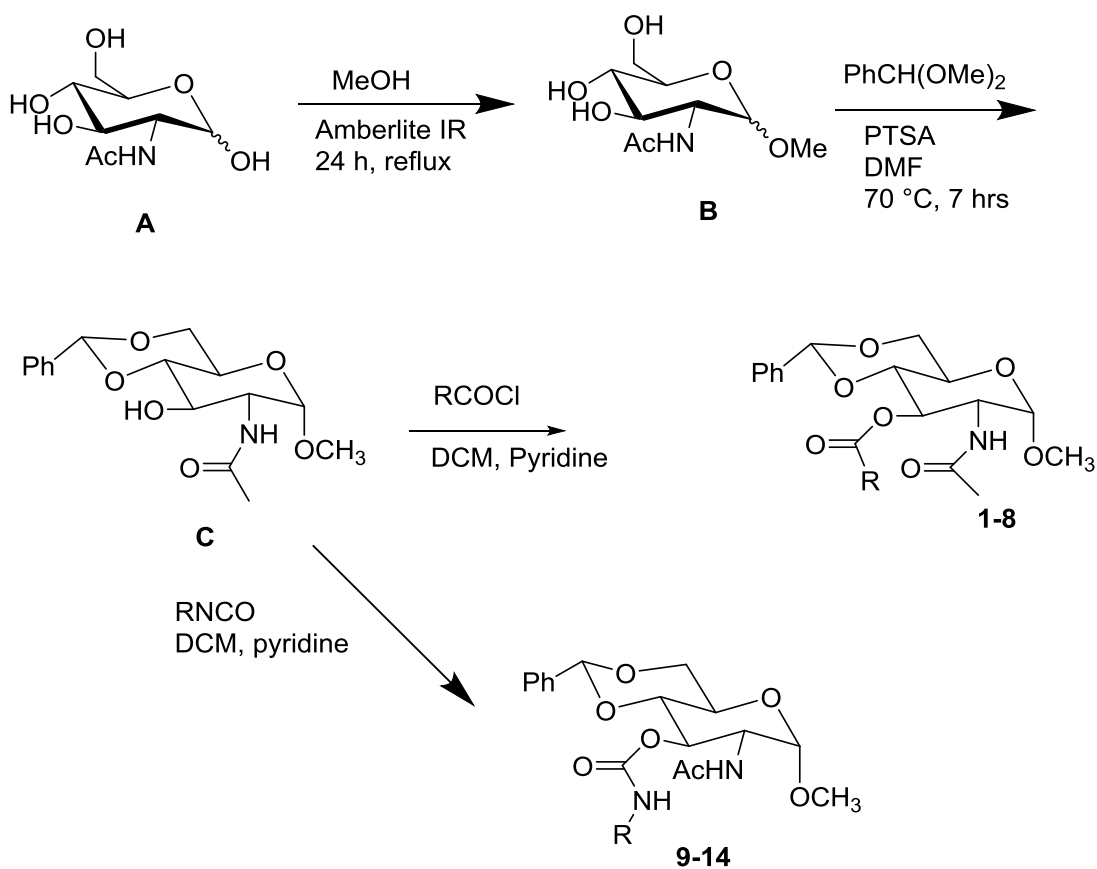
Naproxen sodium was incorporated into the gels. The release of naproxen sodium at different pH's was measured by UV/Vis spectrometry. The naproxen was released very slowly under neutral conditions and about half of the total naproxen was released after 9 hours. When 0.1 M HCl was added to the gel, the naproxen was released much more rapidly. About half of the naproxen was released after 1 hour and it was almost all of it was released after 6 hours.

Much of the previous work by our group focuses on 2-derivatives of the benzylidene acetal protected monosaccharides. In this work, we synthesized and characterized 3-ester and 3-carbamate derivatives of 4,6,*O*- α -methyl-*N*-acetyl-*D*-glucosamine. Since these compounds possess groups which have been shown to participate in interactions crucial to the formation of supramolecular networks, we hypothesized that these compounds would be efficient gelators. After synthesizing the library of compounds, we tested their ability to form gels. We analyzed the gels with rheology, optical microscopy, temperature dependent ^1H NMR and FT-IR to further understand the composition of the supramolecular networks and the driving forces behind their formation.

We also hypothesized that these gels would exhibit pH responsive behavior. The ester and carbamate moieties at the 3 position can be hydrolyzed under basic conditions. Drug release studies with naproxen sodium and chloramphenicol showed that the gels became unstable under basic conditions; therefore, drugs were released much faster in a basic environment.

2. RESULTS AND DISCUSSION

A series of 3-carbamate and 3-ester derivatives of 4,6,-*O*-benzylidene- α -methyl-*N*-acetyl-*D*-glucosamine were synthesized. The benzylidene protected glucosamine building block **C** was made via a two-step process starting with *N*-acetyl-*D*-glucosamine. The *o*-methoxy group was attached to the anomeric position by Fischer esterification. The product of this reaction was immediately protected with dimethyl benzaldehyde. After compound **C** was purified, the 3 position was derivatized with acid chlorides and isocyanates to yield compounds **1-14** (Scheme 1).³⁹



Scheme 1: Synthesis of 3-ester and 3-carbamate derivatives

The abilities of the compounds to form gels were tested with the inverted vial method. 2 mg of pure, dry compound was dissolved in 0.2 mL of solvent. The solid gelator was dissolved in the solvent with heating and sonication and allowed to cool on the benchtop for up to 30 minutes. A stable gel formed a semi solid on the bottom of the vial which did not run down the sides of the vial when inverted (**Fig. 23**). If a stable gel was observed more solvent was added until the minimum gelation concentration was reached.

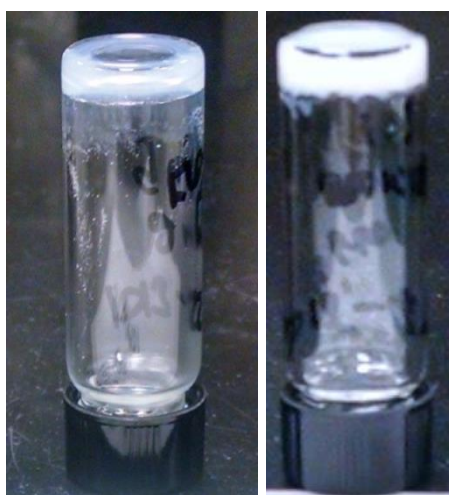
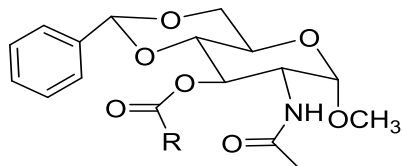


Fig. 25: Gel pictures of compound **6** in glycerol (left) and compound **10** in EtOH:H₂O (1:2) (right)

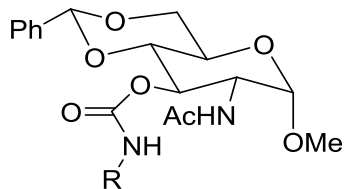
Results of the gel test for the 3-ester series are shown in **Table 1**. Almost all of the gels were able to form stable gels in mixtures of water with either DMSO or ethanol. The p-bromo ester **7** formed gels toluene and ethanol. Overall, this series formed gels with relatively high MGCs. The majority of gels had a MGC of 10 or 20 mg/mL. The lowest MGC seen in this series was 6.7 mg/mL for the phenyl ester **6** in 1:2 DMSO:H₂O.

Table 1: Gel test results of ester derivatives

	1	2	3	4	5	6	7	8
R								
Pump oil	G20	S	G10	G10	G10	G6.7	I	S
Engine oil	I	S	S	S	S	I	P	P
Mineral oil	I	I	P	I	I	I	I	P
Toluene	S	S	S	S	S	UG	G 20	S
IPA	S	S	S	S	S	S	P	P
EtOH	S	S	S	S	S	S	G 20	S
H ₂ O	I	I	P	P	I	I	I	I
EtOH:H ₂ O (1:1)	S	S	P	G 10	P	P	I	P
EtOH:H ₂ O (1:2)	S	G 10	G 10	UG	P	P	I	I
DMSO:H ₂ O (1:1)	S	G 20	G 10	UG	G 10	G20	P	UG
DMSO:H ₂ O (1:2)	P	P	G 10	P	G 10	G 6.7	I	G 20
EG	S	S	S	P	S	P	UG	P
Glycerol	P	P	P	P	P	G 20	P	P

S= soluble; P= precipitate; I = insoluble; UG = unstable gel; G = gel followed by MGC in mg/mL, EG= ethylene glycol

The gel test results for the 3-carbamate series are shown in **Table 2**. Like the 3-ester derivatives, almost all of these compounds formed gels in water mixed with either ethanol or DMSO. The phenyl carbamate **13** and benzyl carbamate **14** were formed gels in toluene. The hexyl carbamate **11** formed a gel in ethylene glycol. The pentyl carbamate **10** and phenyl carbamate **13** formed gels in glycerol. Overall, the carbamate compounds proved to be more efficient gelators than the ester derivatives. They were able to form gels in a larger variety of solvents and the gels formed by the carbamate compounds had lower MGCs.

Table 2: Gel test results of carbamate derivatives

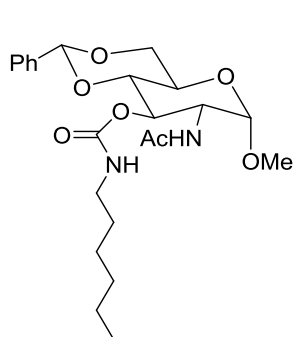
Compound	9	10	11	12	13	14
R						
Pump oil	I	G20	UG	I	UG	I
Engine oil	I	I	I	I	P	S
Mineral oil	I	I	I	I	I	I
Toluene	UG	S	S	S	G 10	G 20
IPA	S	S	S	S	UG	P
EtOH	S	S	S	S	S	UG
H ₂ O	I	I	I	I	I	I
EtOH:H ₂ O (1:1)	P	P	G 10	G 5	G 20	G 2.5
EtOH:H ₂ O (1:2)	G 20	G 10	G 5	G 3.3	I	P
DMSO:H ₂ O(1:1)	P	G 20	G 10	G 6.7	P	S
DMSO:H ₂ O(1:2)	I	G 20	S	I	G 10	G 10
Ethylene glycol	UG	P	G 10	I	I	S
Glycerol	I	G 20	I	S	G 20	P

S= soluble; P= precipitate; I = insoluble; UG = unstable gel; G = gel followed by MGC

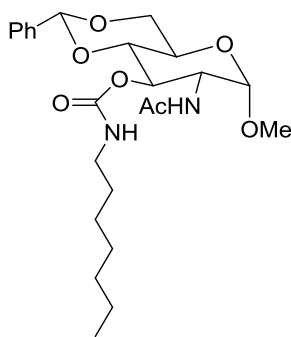
The melting point ranges of some of the gels formed by hexyl carbamate **10**, heptyl carbamate **11**, and cyclohexyl carbamate **12** in 1:1 DMSO:H₂O were measured (**Table 3**). The three temperatures recorded were the temperature at which liquid was first seen, the temperature at which the gel was halfway melted, and the temperature at which the gel was completely at the liquid phase. The gels started melting at 41.5-50.8 °C and completely melted at 77.2- 122.2 °C. The melting point range for the gels increased as gel concentration decreased. All of the gels measured in this experiment showed a large melting point range, which suggests that the gels are relatively stable to heat.

Table 3: The melting point range for some of the gels in 1:1 DMSO:H₂O

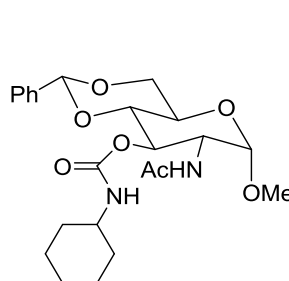
Compound	Gel conc. in 1:1 DMSO:H ₂ O (mM; mg/mL)	T1 (°C)	T2 (°C)	T3 (°C)
10	44.4; 20	48.0	71.3	77.2
11	21.5; 10	50.8	85.1	95.6
12	14.9; 6.7	41.5	91.3	122.2



Compound 10



Compound 11



Compound 12

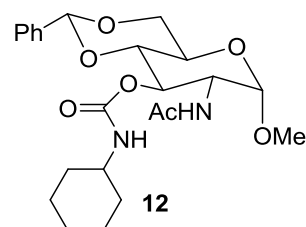
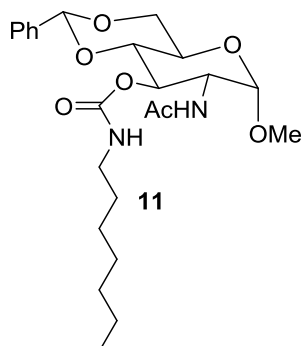
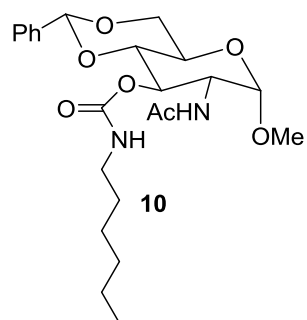
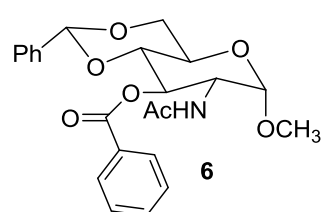
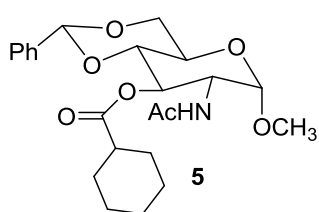
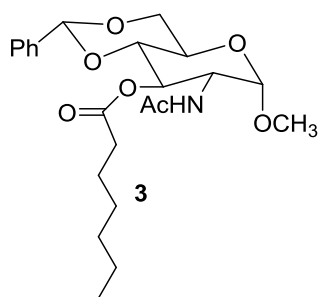
The hexyl ester **3**, cyclohexyl ester **5**, phenyl ester **6**, hexyl carbamate **10**, heptyl carbamate **11**, and cyclohexyl carbamate **12** were all tested for their water tolerability. Gels formed with water as the solvent are often best for biological or medical applications because water is non-toxic. If a compound is not able to gelate pure water, a compound which can form a stable gel with a high ratio of water to another solvent is best for this type of application.

None of the compounds in this series were able to form gels in pure water. They were not polar enough to dissolve in water, even when heated. However, many of them were able to form gels in mixtures of water and DMSO. The limits of these compounds' abilities to form gels in aqueous DMSO was tested by dissolving the compounds in DMSO. Water was added incrementally. After each addition of water, the solution was heated with a heat gun and sonicated to bring the gelator into solution and the vial was left on the benchtop to cool to room temperature. The observations after each incremental addition of water were recorded until the compound could no longer form a stable gel (**Table 4**).

Table 4: Water Tolerability Study

Compound	+0.1 mL	+ 0.2 mL	+0.1 mL	+0.1 mL	+0.1 mL	DMSO:H ₂ O
	DMSO	H ₂ O	H ₂ O	H ₂ O	H ₂ O	ratio
3	S	G	UG	N/A	N/A	1:2
5	S	G	G*	G*	UG	1:4
6	S	G	P	N/A	N/A	1:2
10	S	G	P	N/A	N/A	1:2
11	S	G	P	N/A	N/A	1:2
12	S	G	P	N/A	N/A	1:2

S= soluble; I = insoluble; G= spontaneous gelation; UG= unstable gel; G*= gel formed after heating and sonicating



The morphology of the gels was studied by optical microscopy. All of the supramolecular networks observed this way showed a uniform assembly of fibers. The benzyl carbamate **14** in 1:2 DMSO:H₂O formed a network of long, thin fibers layered on top of each other (**Fig. 24a**). The cyclohexyl ester **5** in 1:2 DMSO:H₂O formed long, slightly thicker fibers (**Fig. 24b**). The p-bromo ester **7** in toluene formed a network of very slender fibers (**Fig. 24c**). The hexyl ester **3** in 1:1 DMSO:H₂O formed a dense network of thick fibers.

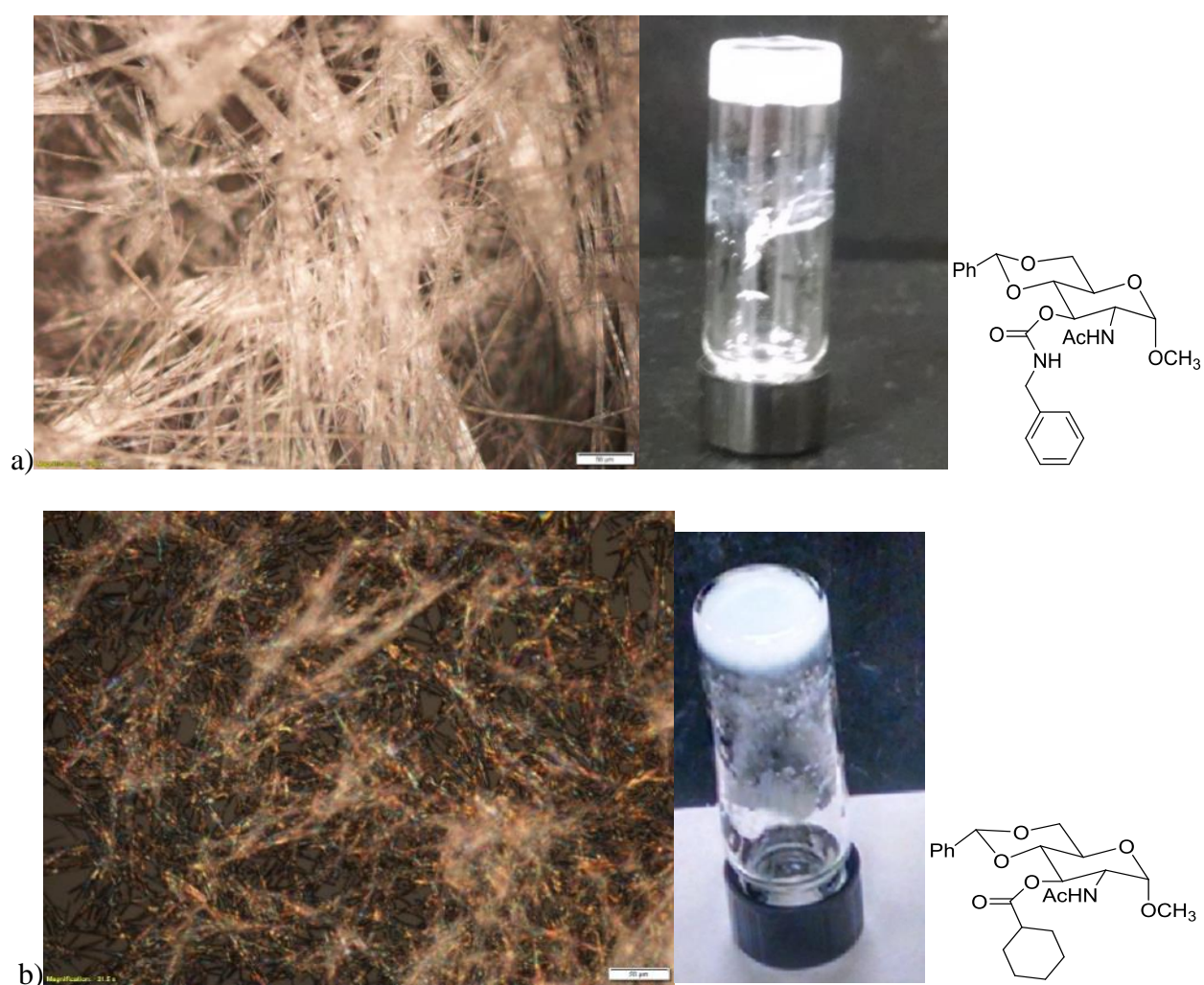


Fig. 26: Optical micrographs of a) compound **14** in 1:2 DMSO:H₂O (21.9 mM; 10 mg/mL) and b) compound **5** in 1:2 DMSO:H₂O (23.1 mM; 10 mg/mL)

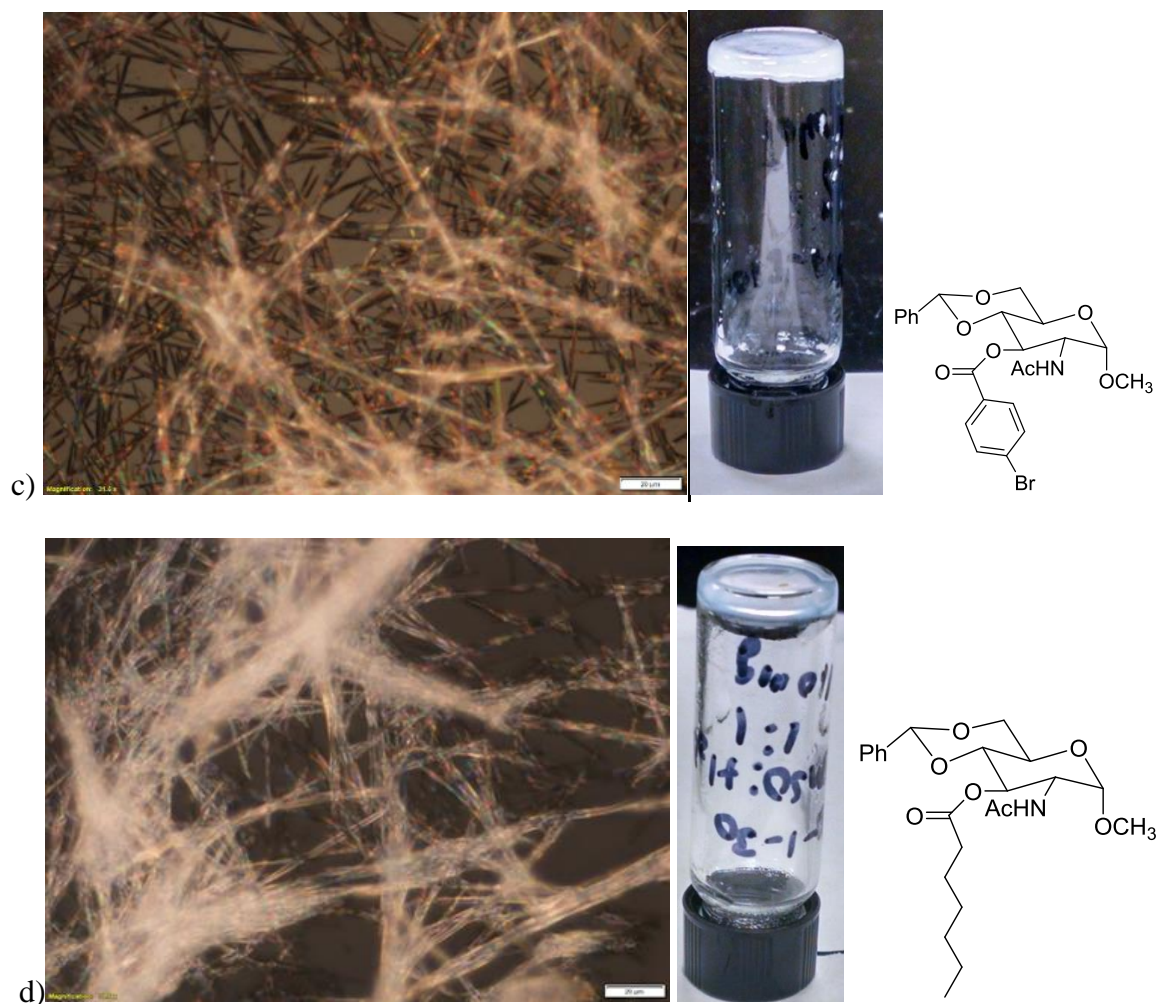


Fig. 26: Optical micrographs of c) compound **7** in toluene (39.6 mM; 20 mg/mL) and d) compound **3** in 1:1 DMSO:H₂O (23.0 mM; 10 mg/mL)

The heptyl carbamate **11** in 1:1 DMSO:H₂O formed a network of short, branched fibers (**Fig. 27a**). The phenyl carbamate **13** in 1:1 EtOH:H₂O formed a dense fibrous network (**Fig. 27b**). The *p*-methoxy ester **8** in 1:1 DMSO:H₂O formed a network of short, flat fibers (**Fig. 27c**). The pentyl carbamate **9** in 1:1 DMSO:H₂O formed long, thin fibers (**Fig. 27d**).

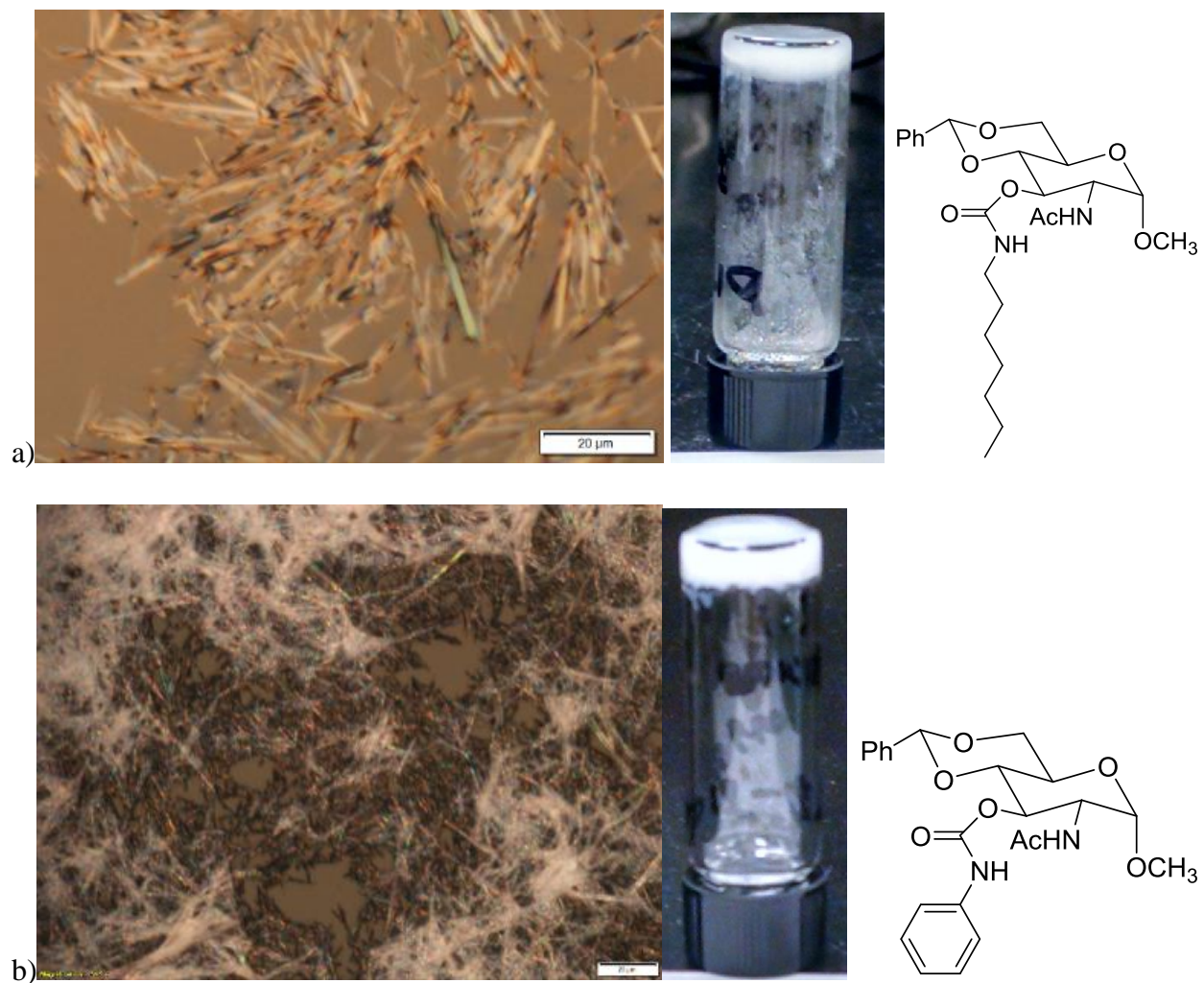


Fig. 27: a) compound **11** in 1:1 DMSO:H₂O (21.5 mM; 10 mg/mL) and b) compound **13** in 1:1 EtOH:H₂O (45.2 mM; 20 mg/mL)

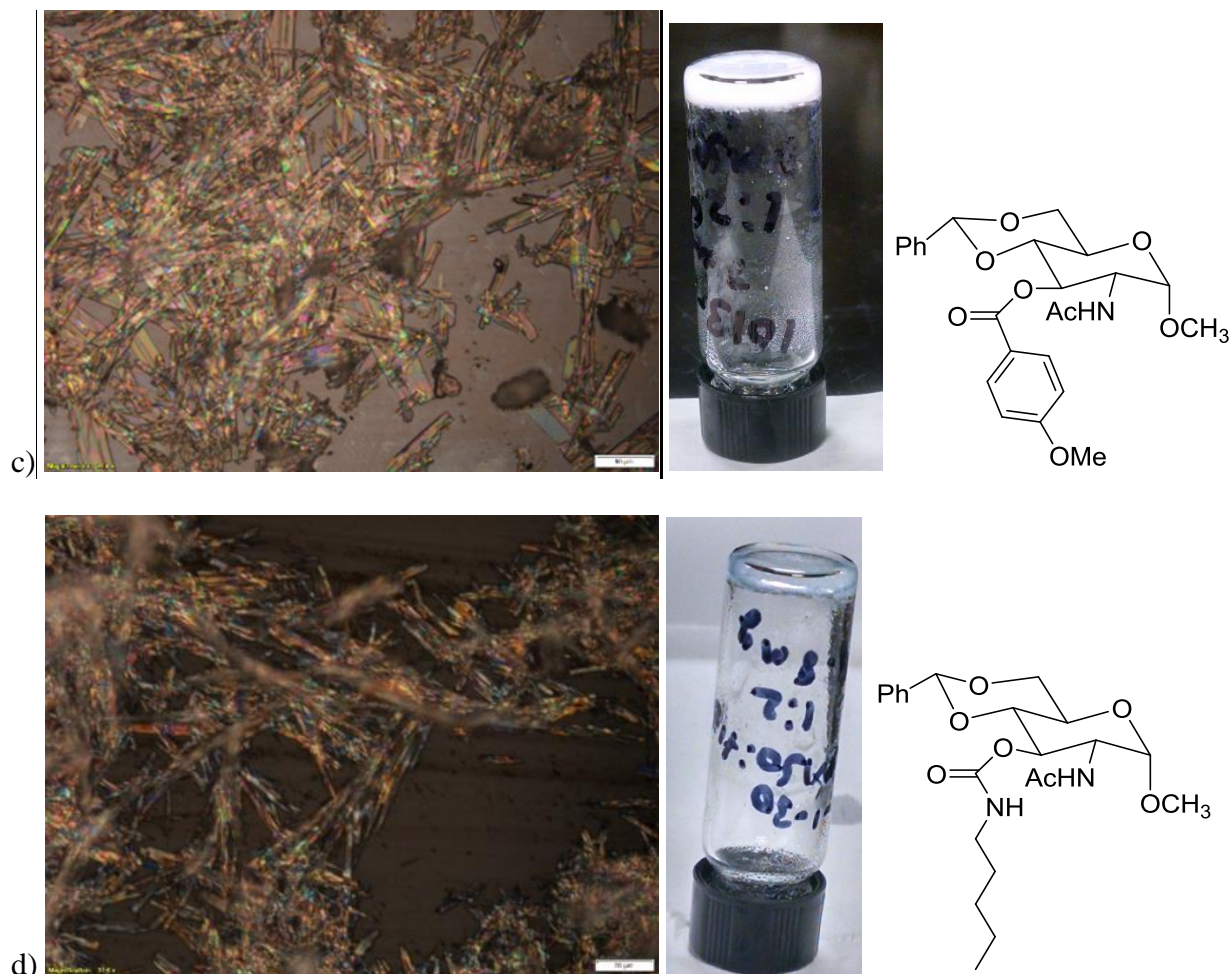


Fig. 27: c) compound **8** in 1:2 DMSO:H₂O (43.7 mM; 20 mg/mL) and d) compound **9** in 1:2 EtOH:H₂O (45.8 mM; 20 mg/mL)

The IR spectra of the gels were measured to further elucidate the types of interactions which drive the gelation process. **Fig. 28** shows the IR spectra of the *p*-bromo ester compound **7**, the 39.6 mM gel formed by compound **7** in ethanol, and ethanol by itself. Comparison of the spectra of the solid gelator **7** and the gel formed with EtOH show a change in intensity in the peaks at 1589 cm⁻¹ and 843 cm⁻¹. These correspond to the aromatic C=C stretch and aromatic C-H bend,

respectively. This observation suggests that π - π stacking is one of the driving forces behind the supramolecular self-assembly.

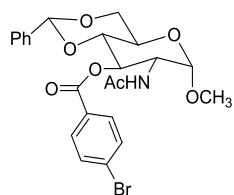
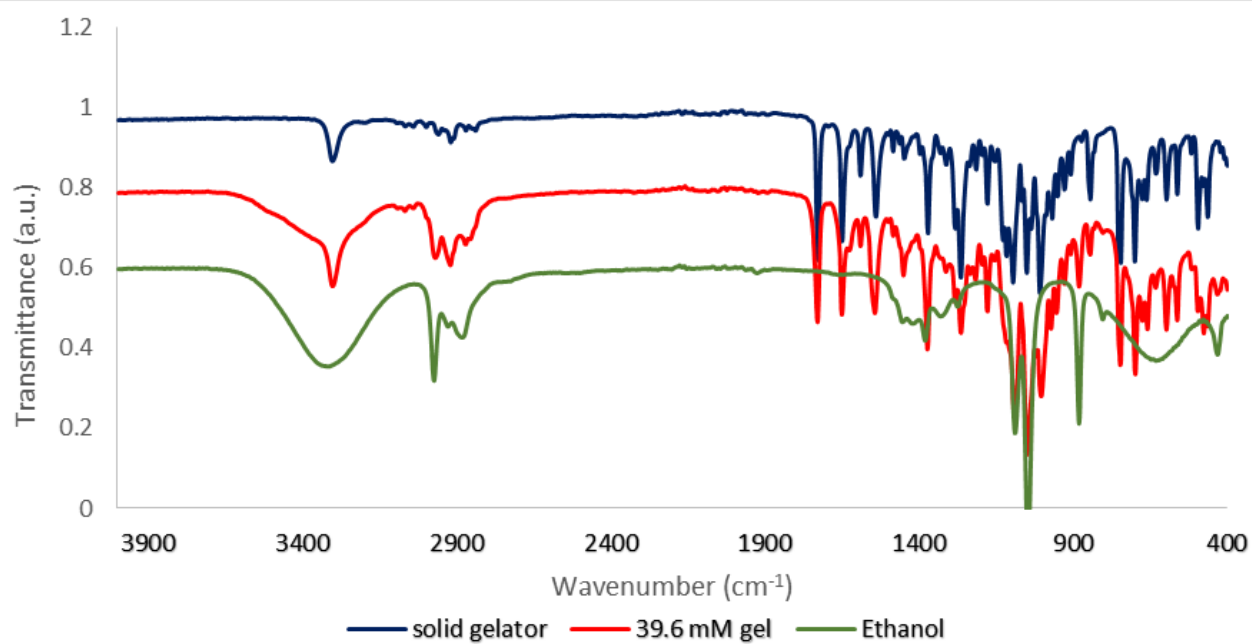
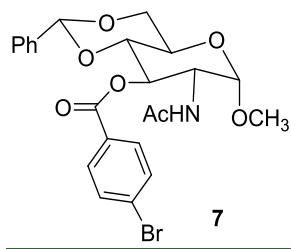


Fig. 28: IR spectrum of compound **7** (blue), gel of compound **7** (39.6 mM mg/mL; 20 mg/mL) in EtOH (red), and EtOH (green). The y axis are arbitrary relative values.

A similar observation is found when comparing the spectra of the cyclohexyl carbamate **12** and the 7.36 mM gel formed by compound **12** in 1:2 EtOH:H₂O (**Fig. 29**). There were notable changes in peak intensity at 1540 cm⁻¹ and 700 cm⁻¹. These peaks respectively correspond to the aromatic C=C stretch and the aromatic C-H bend. Like the previous IR study, this confirms that intermolecular π - π stacking is important in the formation of gels.

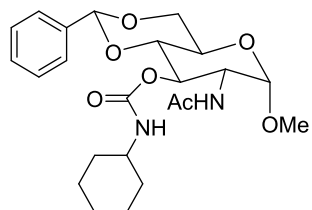
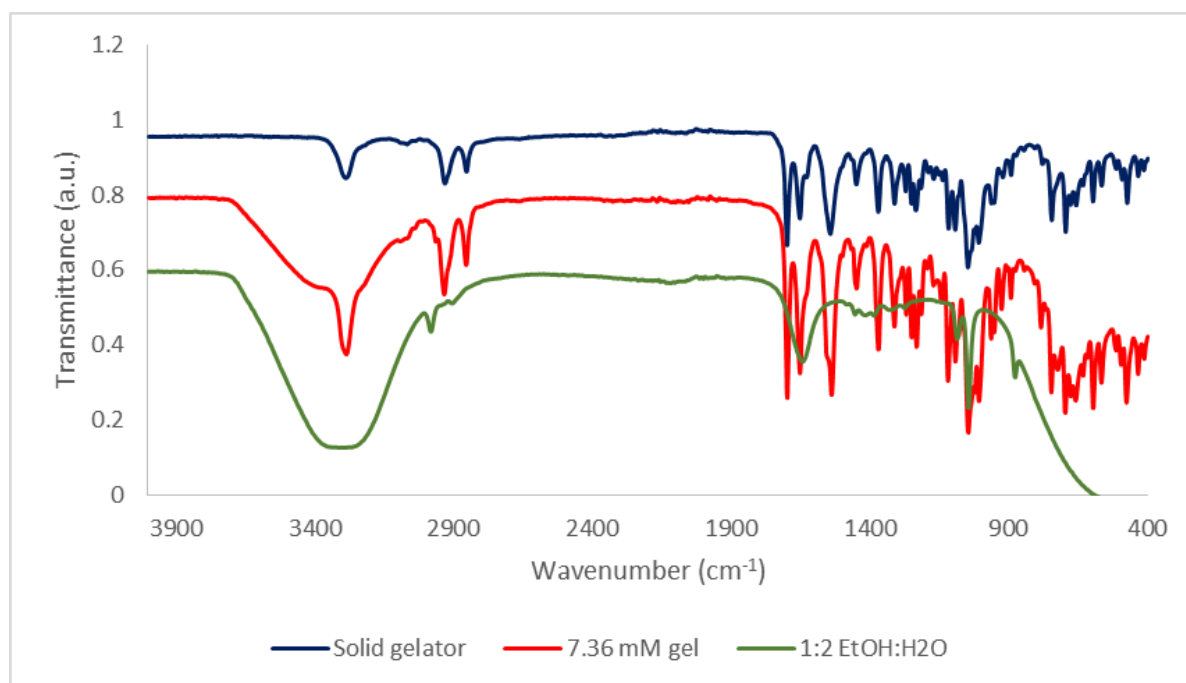
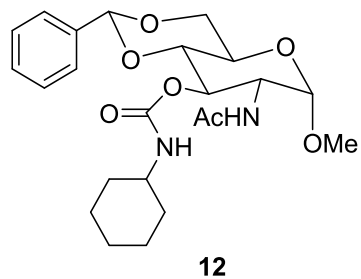


Fig. 29: IR spectrum of compound **12** solid (blue), gel of compound **12** (7.36 mM; 3.3 mg/mL) in 1:2 EtOH:H₂O (red), and control 1:2 EtOH:H₂O solvent.

3D modeling with compound **14** confirmed the importance of intermolecular π - π stacking interactions for self-assembly. Optimized structures of two-molecule models showed the phenyl rings from the benzylidene protecting group arranged parallel to each other, which would allow π - π stacking interactions to occur. The model also showed oxygen and nitrogen atoms from each molecule in close proximity to each other, which suggests the presence of dipole-dipole interactions (**Fig. 30**).

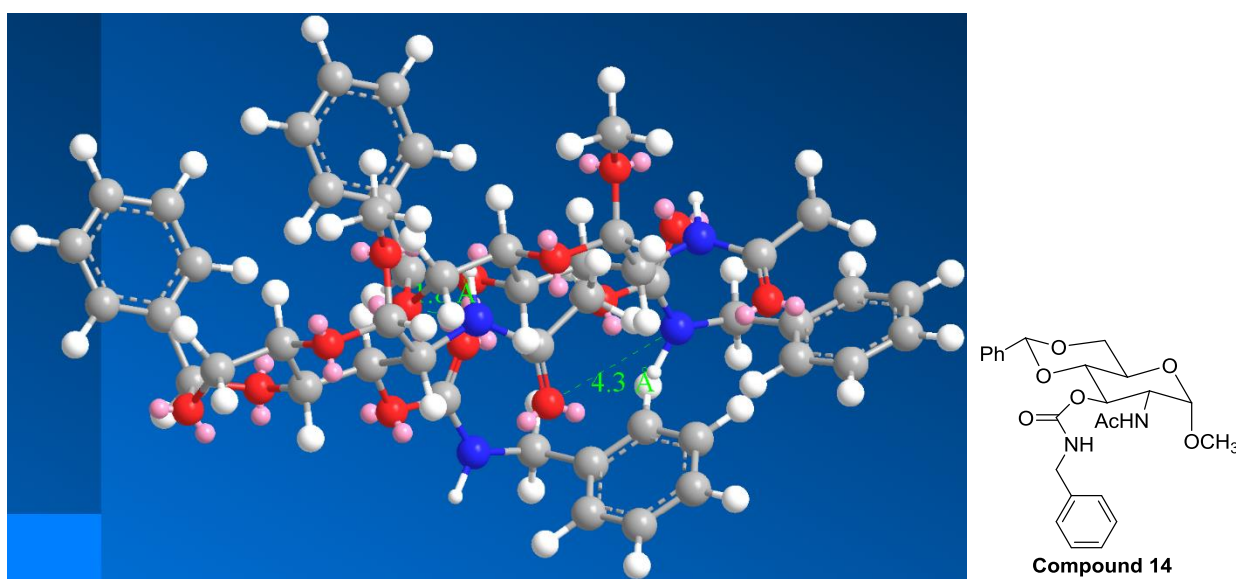


Fig. 30: Optimized structure of two-molecule model of Compound **14**, in which the green dashed lines show intermolecular dipole-dipole interactions between oxygen and nitrogen atoms

¹H NMR spectroscopy studies at different temperatures for compounds **7** and **14** showed shifts in some of the signals as the temperature was increased. These results suggest that these protons participate in hydrogen bonding interactions which contribute to the molecular packing

necessary for gelation. **Fig. 31** shows the structures and ^1H NMR spectra of compounds **7** and **14**. The acetyl NH signal of compound **7** shifts from 5.84 to 5.80 ppm and the anomeric signal shifts from 4.77 to 4.78 ppm. There are also small shifts observed in the acetal (5.57 to 5.55 ppm) and acetyl CH_3 (3.44 to 3.45 ppm) signals (**Fig. 32**). The acetyl NH signal from compound **14** shows a shift from 6.01 to 5.98 ppm and its anomeric signal shifts from 4.74 to 4.76 ppm. No change is observed in the acetal signal and a small shift from 3.40 to 3.41 ppm was observed in the acetyl CH_3 signal (**Fig. 33**).

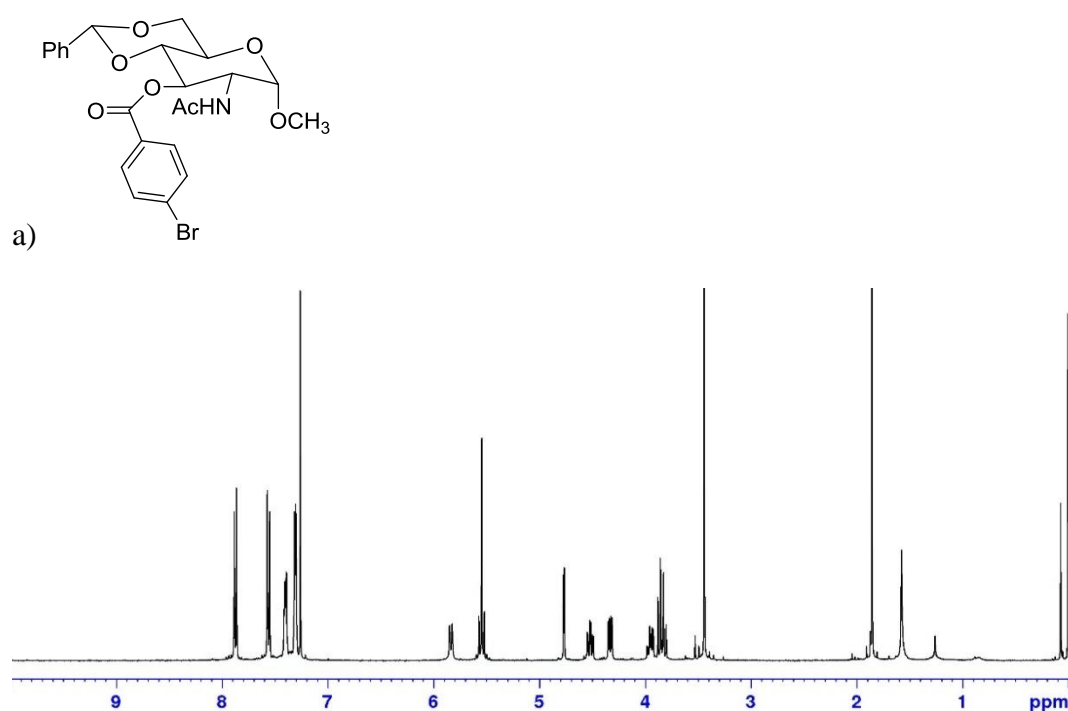


Fig. 31a: ^1H NMR spectrum of compound **7**.

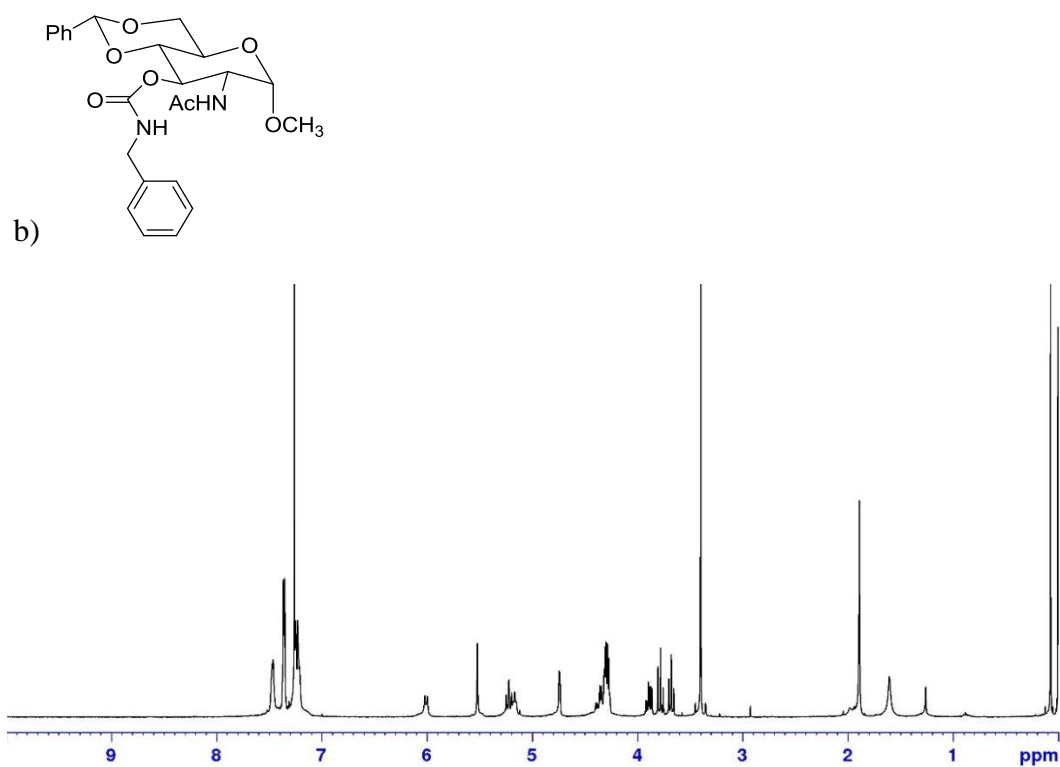
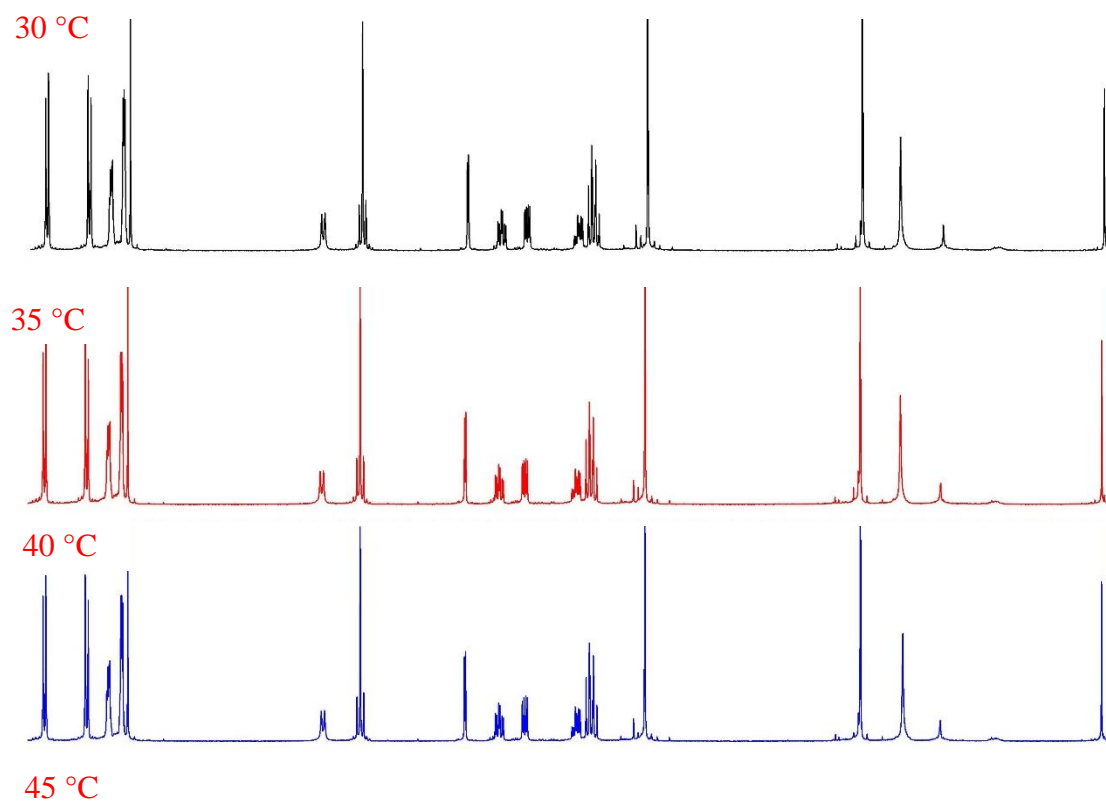


Fig. 31b: ^1H NMR spectra of compound **14**.



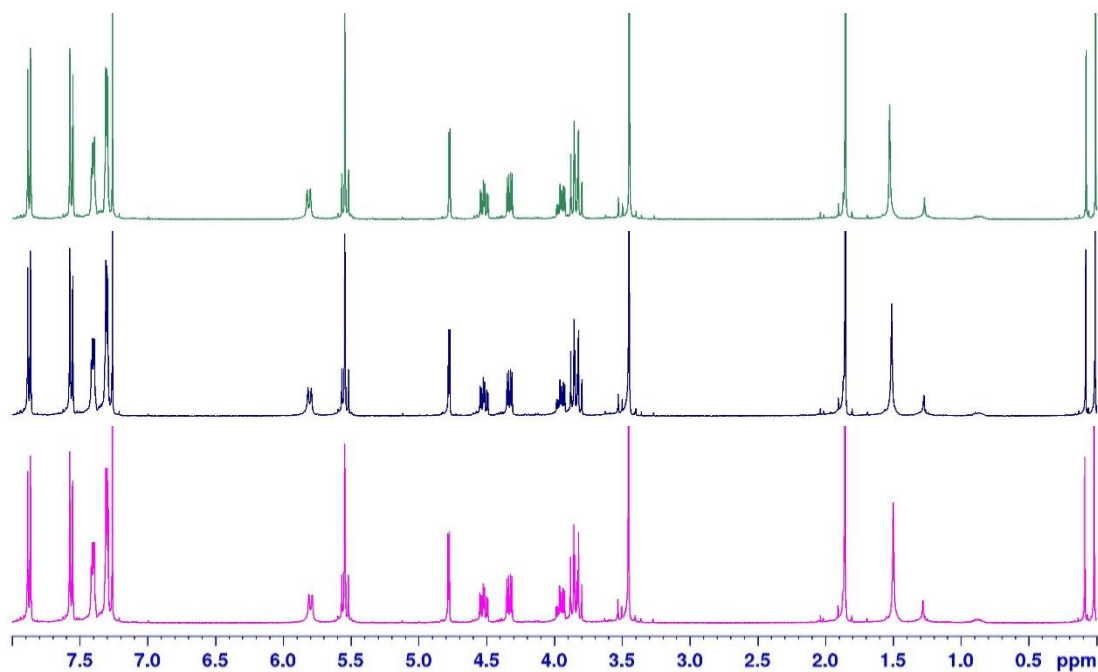
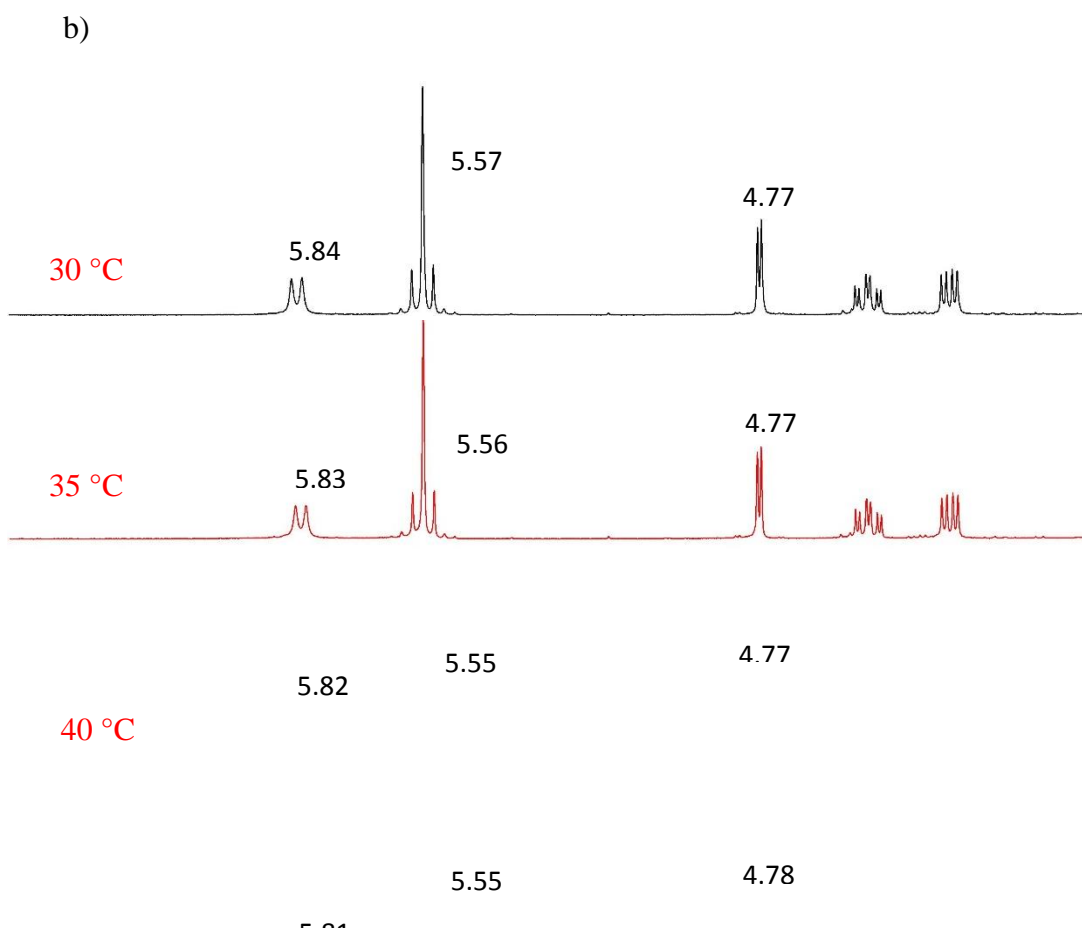


Fig. 32 a) Variable temperature ¹H NMR (CDCl₃, 400 MHz) study of compound 7 expansion from 0 to 8 ppm.



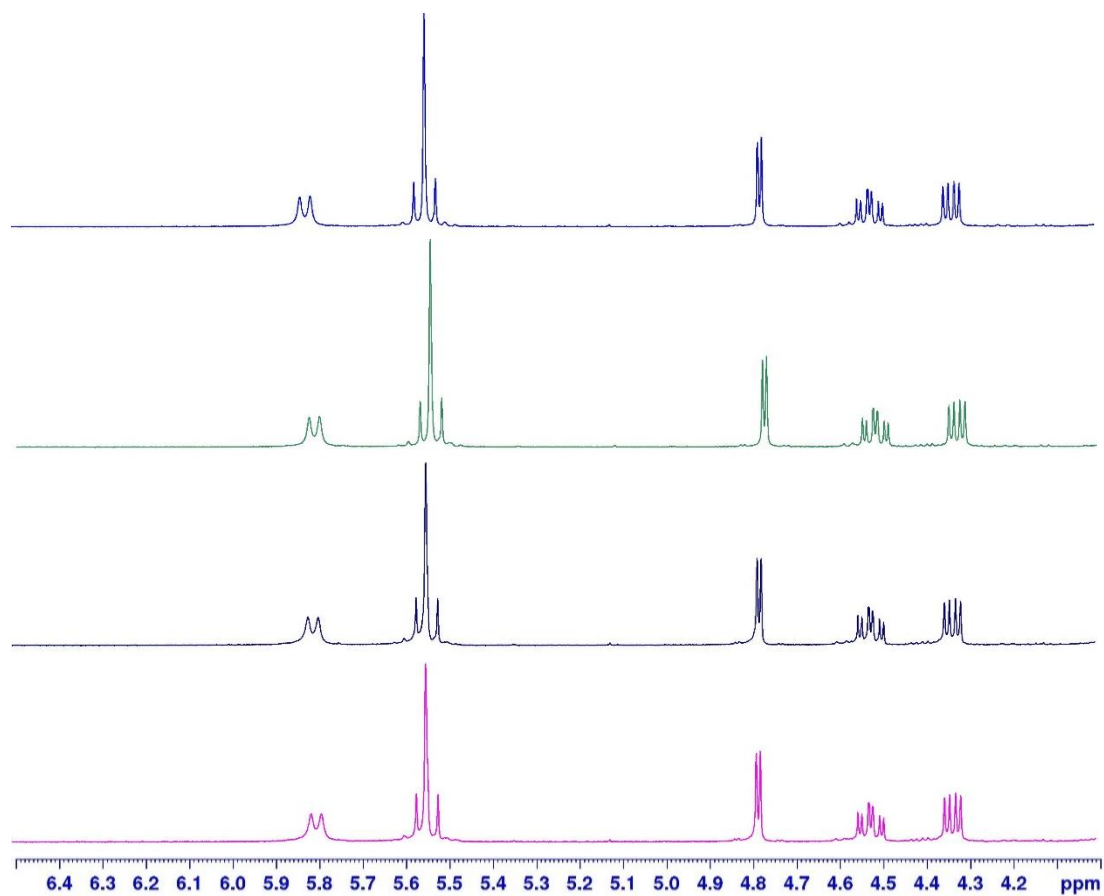
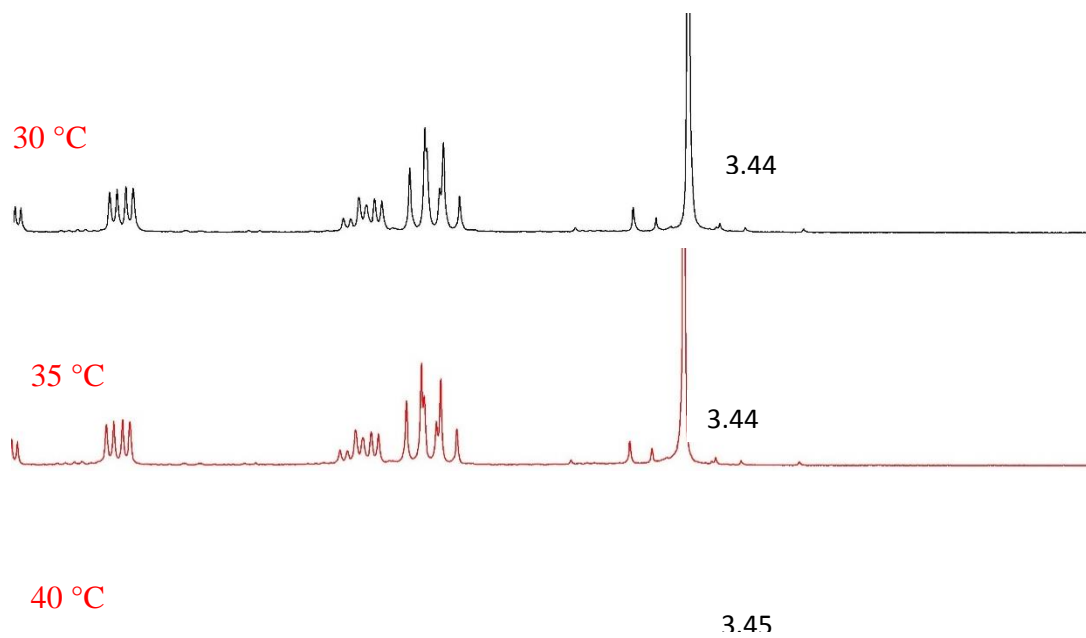


Fig. 32 b) Variable temperature ^1H NMR (CDCl_3 , 400 MHz) study of compound **7** expansion from 4.0 to 6.5 ppm

c)



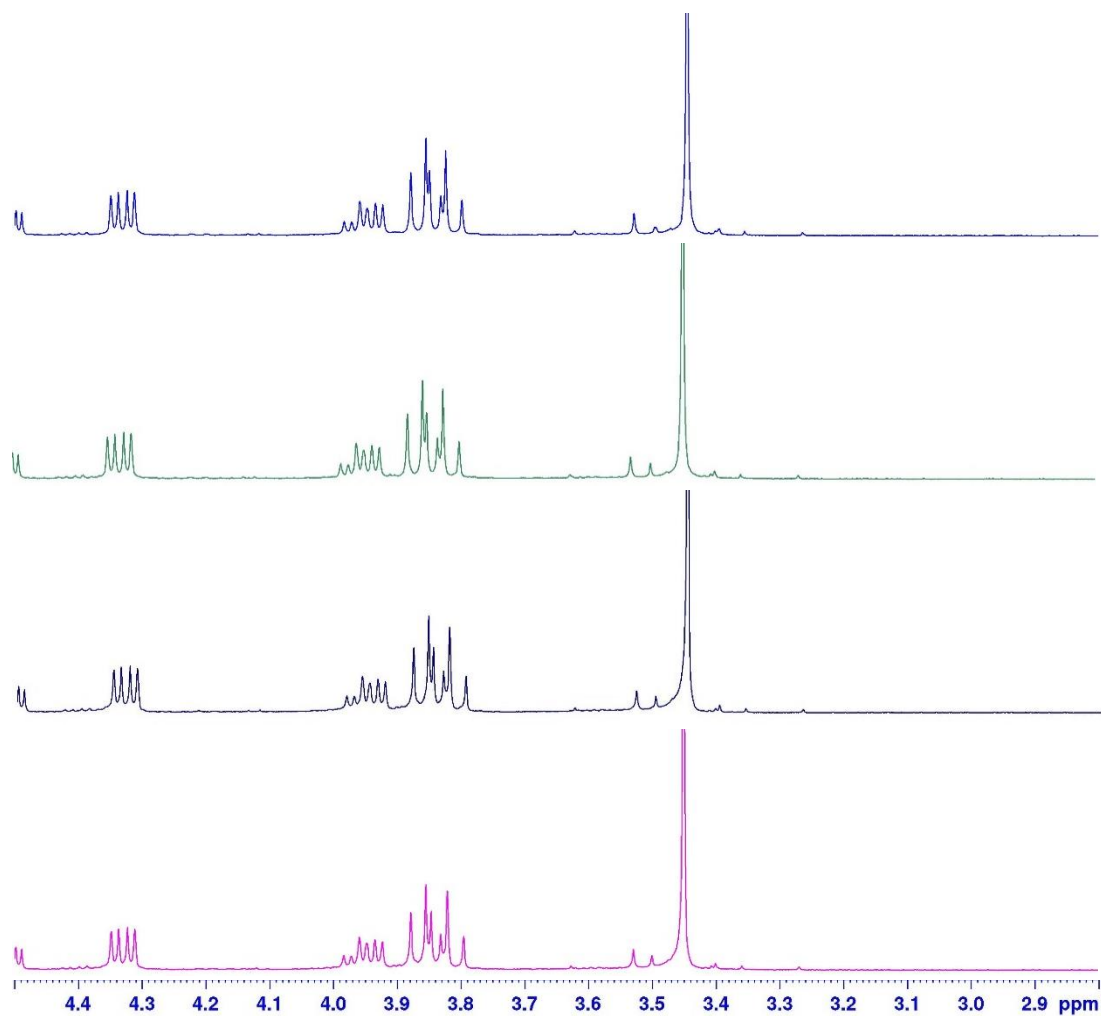
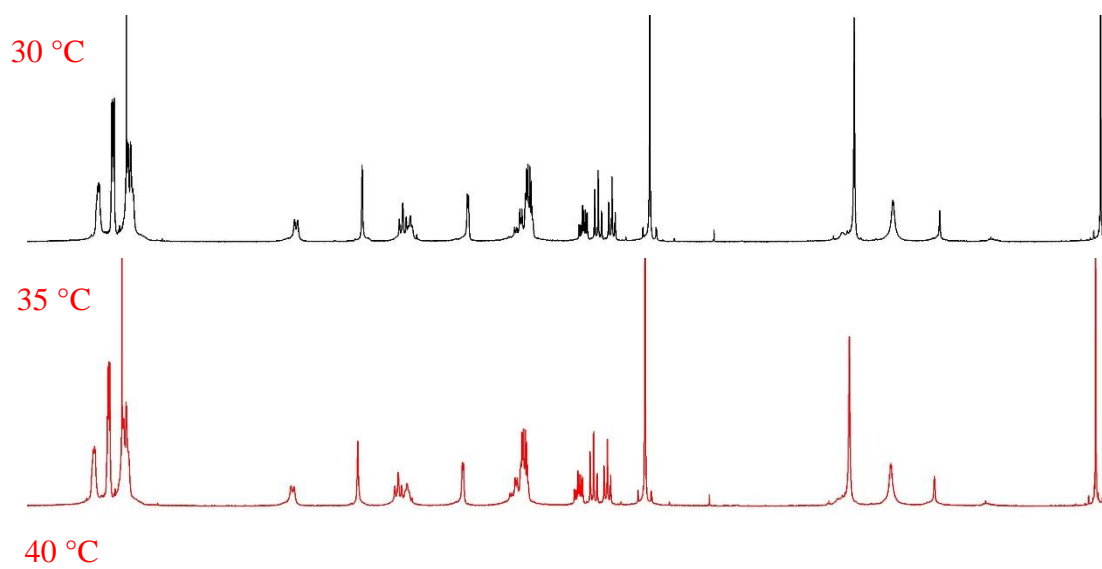


Fig. 32c) Variable temperature ^1H NMR (CDCl_3 , 400 MHz) study of compound **7** expansion from 2.8 to 4.5 ppm



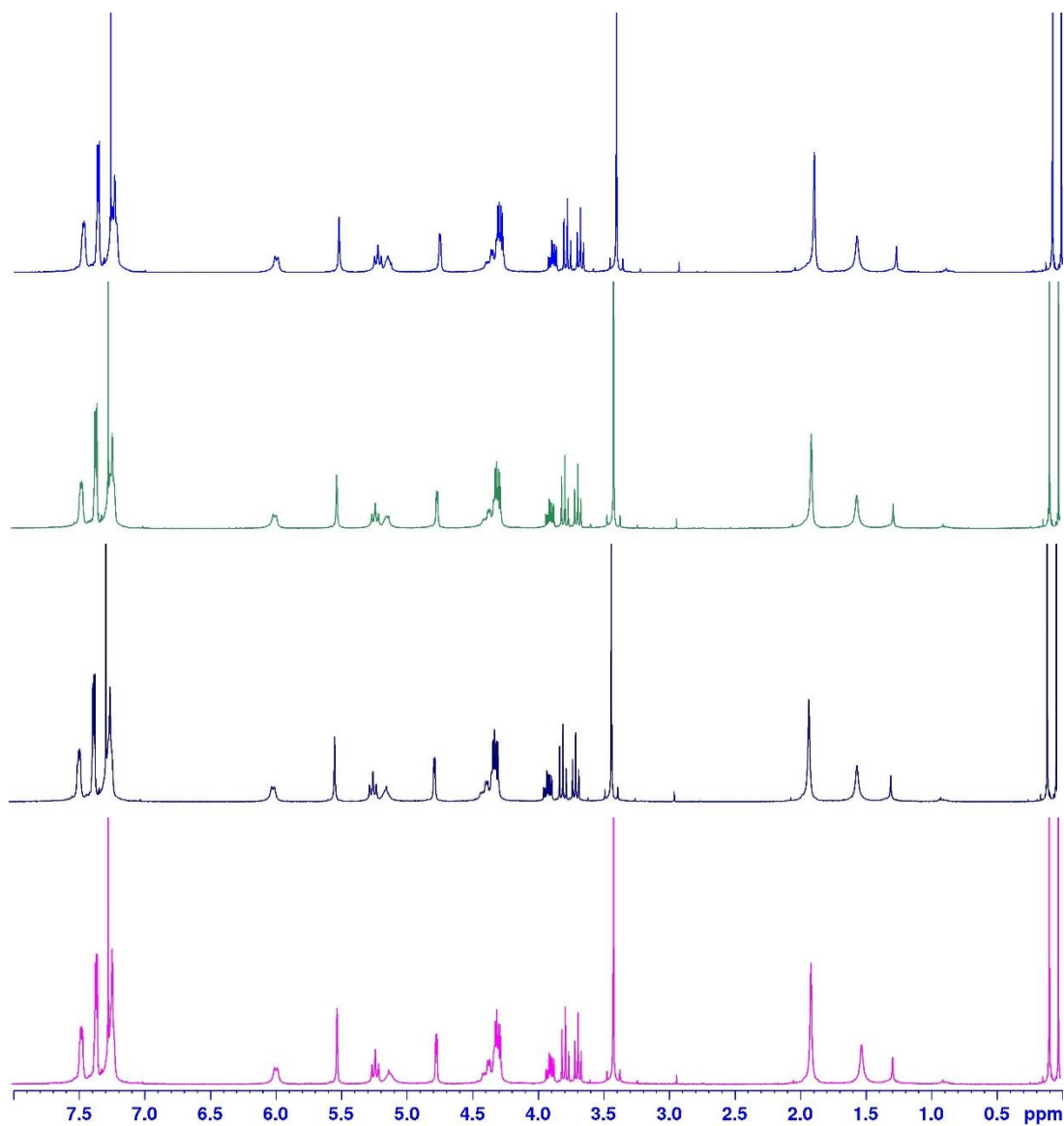
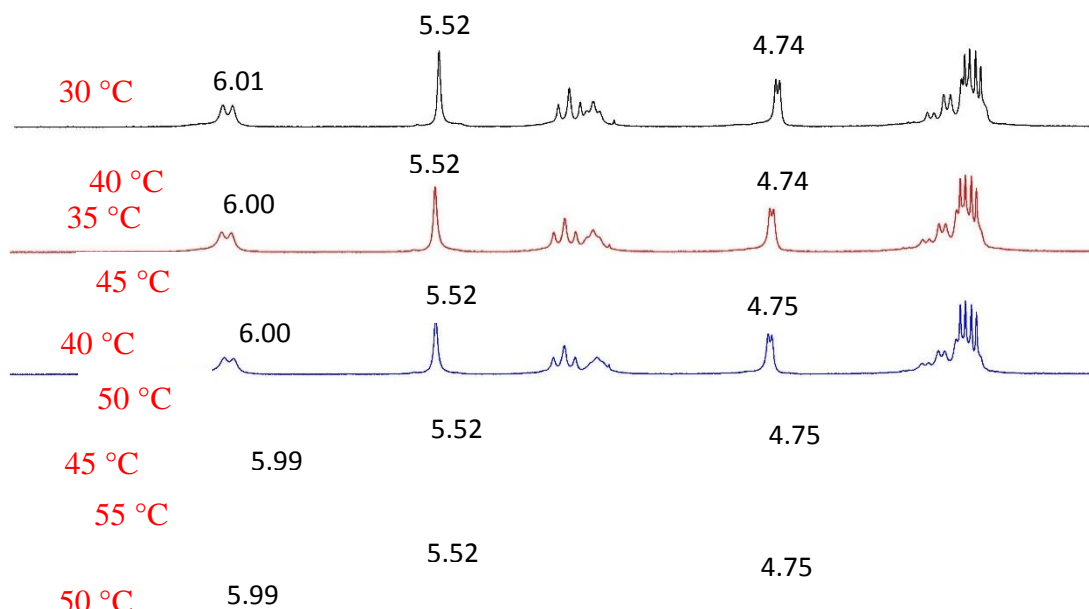


Fig. 33a Variable temperature ^1H NMR (CDCl_3 , 400 MHz) study of compound **14** from 0-8 ppm

b)



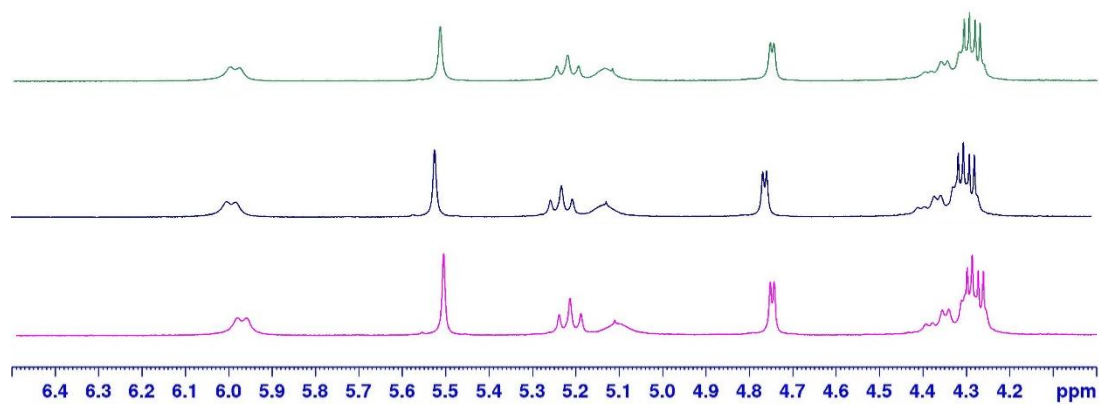


Fig. 33b Variable temperature ^1H NMR (CDCl_3 , 400 MHz) study of compound **14** expansion from 4.0 to 6.5 ppm.

c)

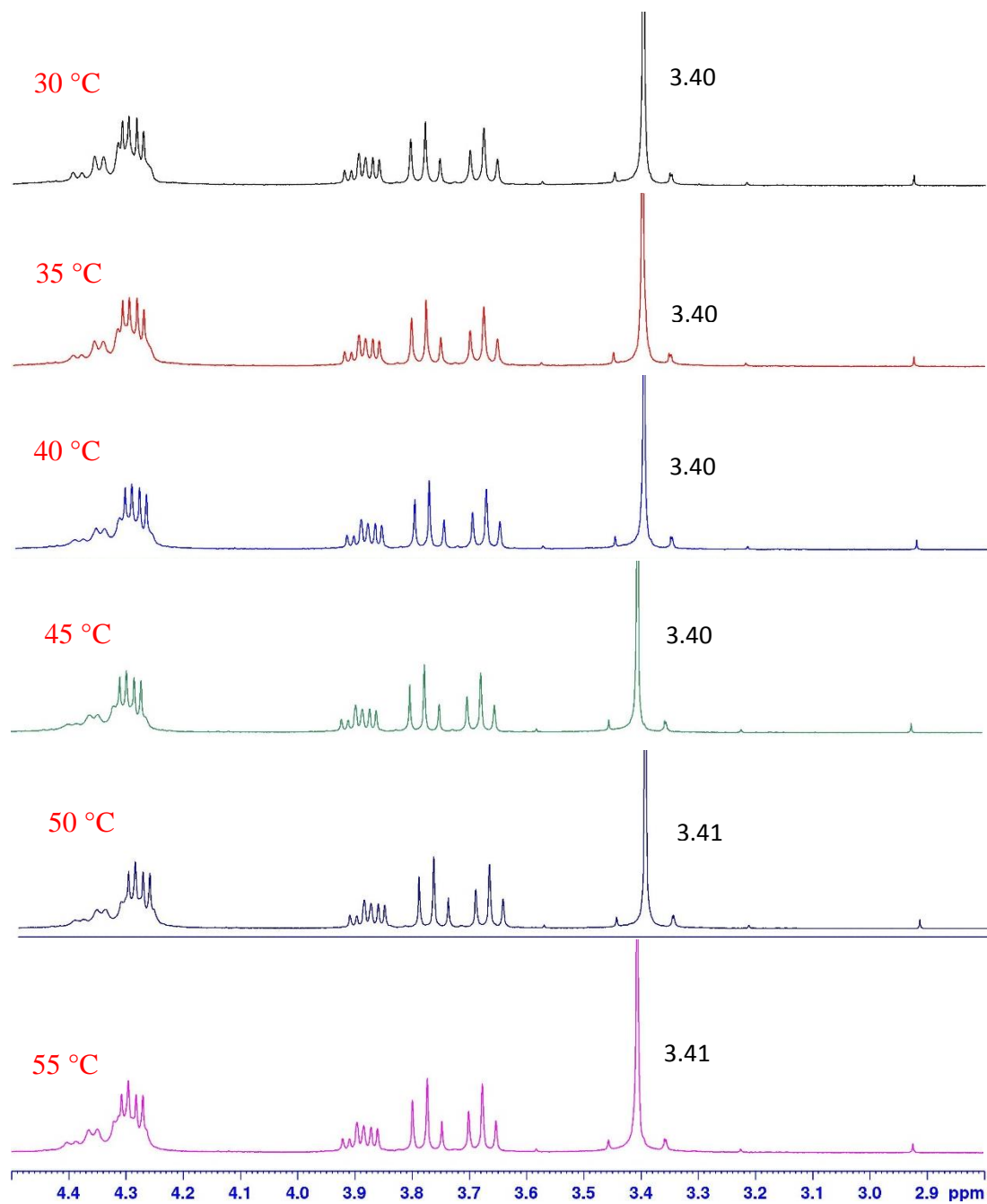


Fig. 33c Variable temperature ^1H NMR (CDCl_3 , 400 MHz) study of compound **14** expansion from 2.8 to 4.5 ppm.

We studied the rheological properties of the gels formed by the 3-ester and 3-carbamate derivatives. The gel formed by the *p*-methoxy ester compound **8** in 1:2 DMSO:H₂O had a higher storage modulus (G') than loss modulus (G'') at all frequencies tested (**Fig. 34**). This confirms the viscoelasticity of the gel. However, there was not a large difference between the loss modulus and the storage modulus. The storage modulus had a maximum of about 200 Pa. This shows that this gel possessed relatively weak mechanical strength.

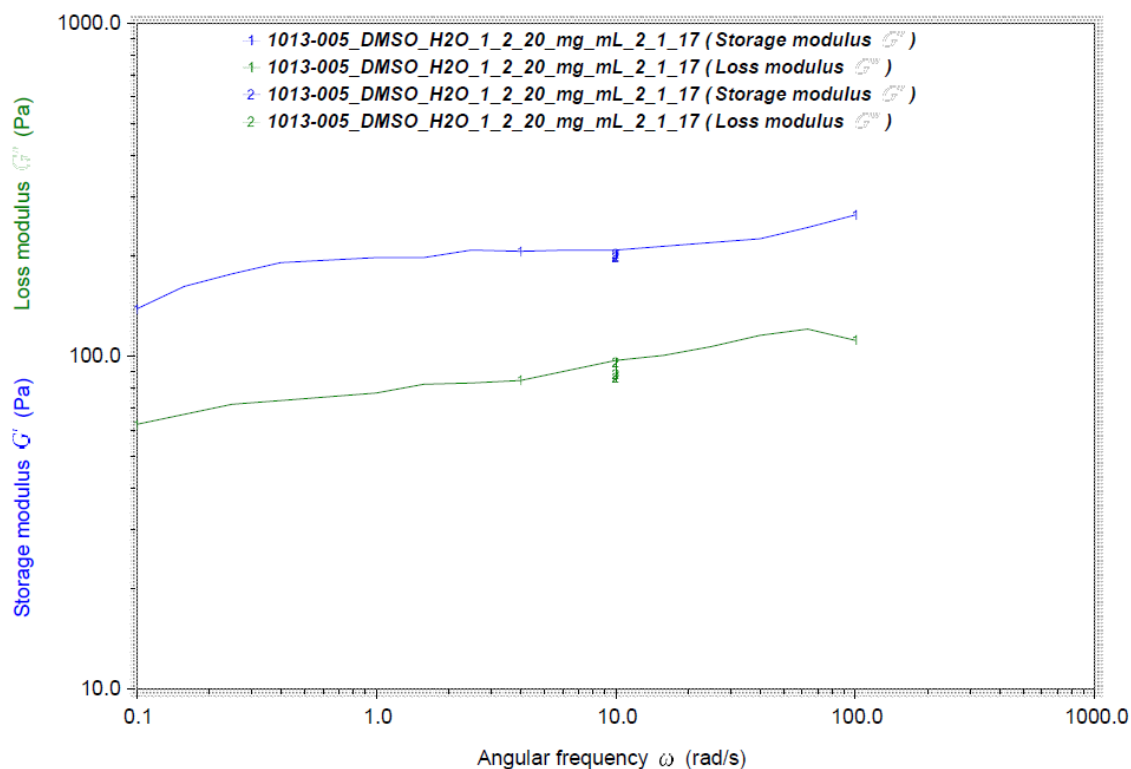


Fig. 34: Rheological properties of gel formed by compound **8** in DMSO:H₂O 1:2 (43.7 mM; 20 mg/mL)

The rheological studies of the gel formed by the phenyl ester compound **6** in 1:2 DMSO:H₂O showed that this gel possessed greater mechanical strength than the one formed by compound **8**. There is a greater difference between the loss and storage moduli (**Fig. 35**). The storage modulus is close to 1000 Pa throughout all the frequencies tested.

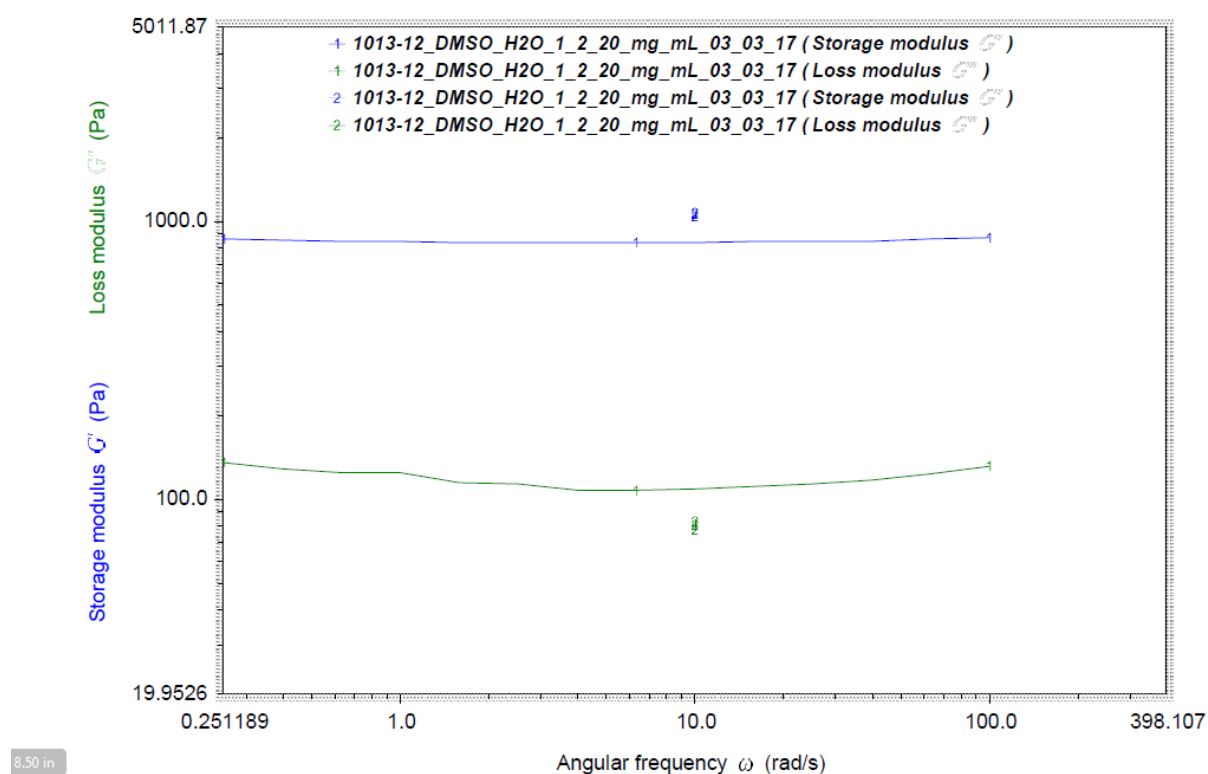


Fig. 35: Rheological properties of gel formed by compound **6** in 1:2 DMSO:H₂O (46.8 mM; 20 mg/mL)

The rheological studies gel formed by the cyclohexyl ester **12** in 1:1 DMSO:H₂O (**Fig. 36**) showed that this gel had very little mechanical strength. Although the storage modulus was

consistently greater than the loss modulus, both values were very low. The storage modulus remained around 100 Pa and the loss modulus was about 20 Pa.

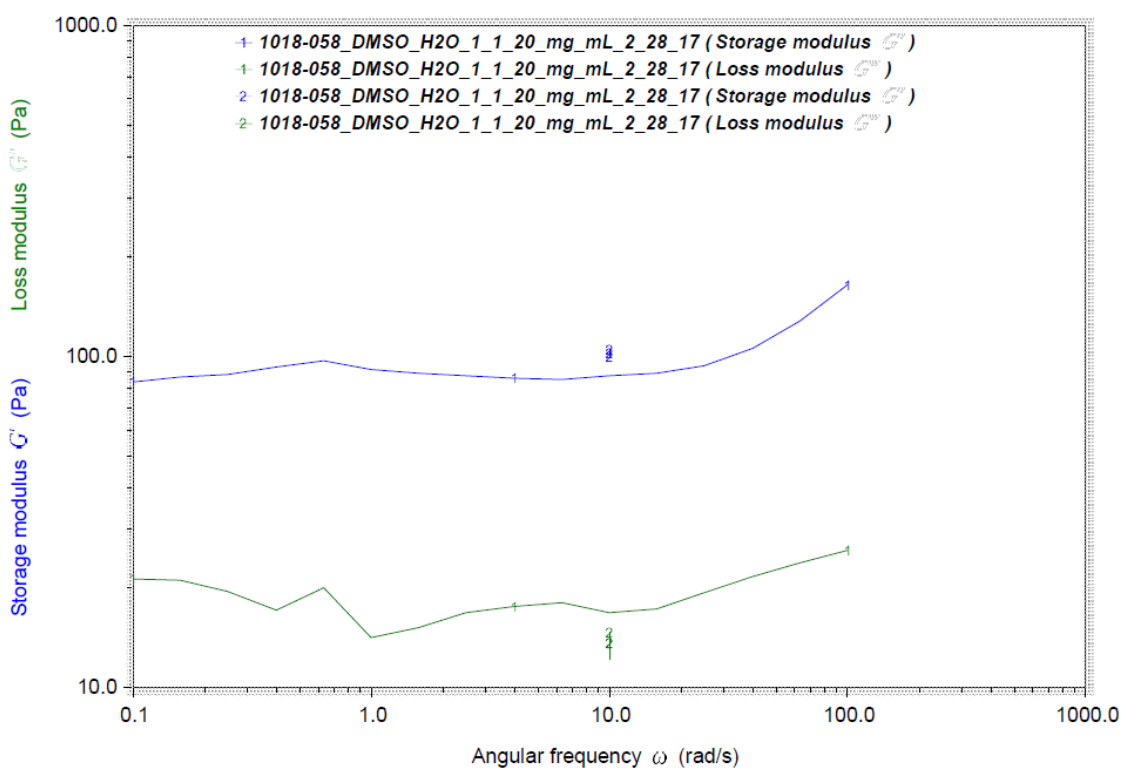


Fig. 36: Rheological properties of gel formed by compound **12** in 1:1 DMSO:H₂O (44.6 mM; 20 mg/mL)

The rheological properties of the gel formed by compound **12** in 1:1 DMSO:H₂O at a lower concentration was also tested (**Fig. 37**). The difference between the storage and loss moduli decreased even further, particularly at the higher frequencies. This shows that the mechanical strength of the gels decreases as the concentration decreases.

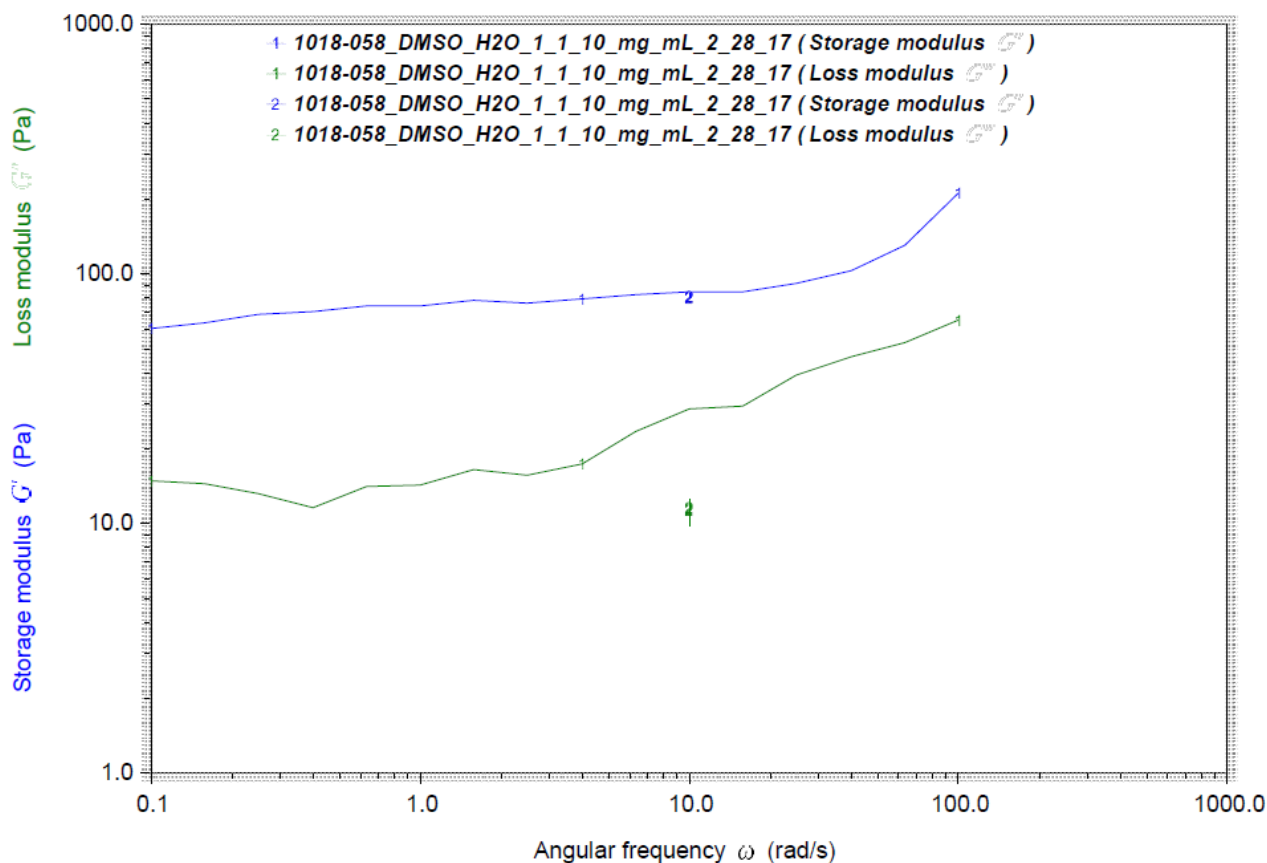


Fig. 37: Rheological properties of gel formed by compound **12** in 1:1 DMSO:H₂O (22.3 mM; 10 mg/mL)

We tested the gel formed by compound **14** in 1:2 DMSO:H₂O for its potential use in controlled drug release. The NSAID naproxen sodium was incorporated into the gel matrix. Aqueous solutions of the appropriate pH were made by adjusting the pH of DI water with aqueous NaOH. The DI water was pipetted on top of the gels containing naproxen sodium. The diffusion of naproxen into the aqueous phase was measured by UV/Vis. About one-third of the naproxen was released in the first thirty minutes. After that the rate of naproxen release slowed down

dramatically, with a very small amount diffusing out of the gel between 1 hour and 2 hours. After 24 hours only two-thirds of the naproxen had been released from the gel (**Fig. 38**).

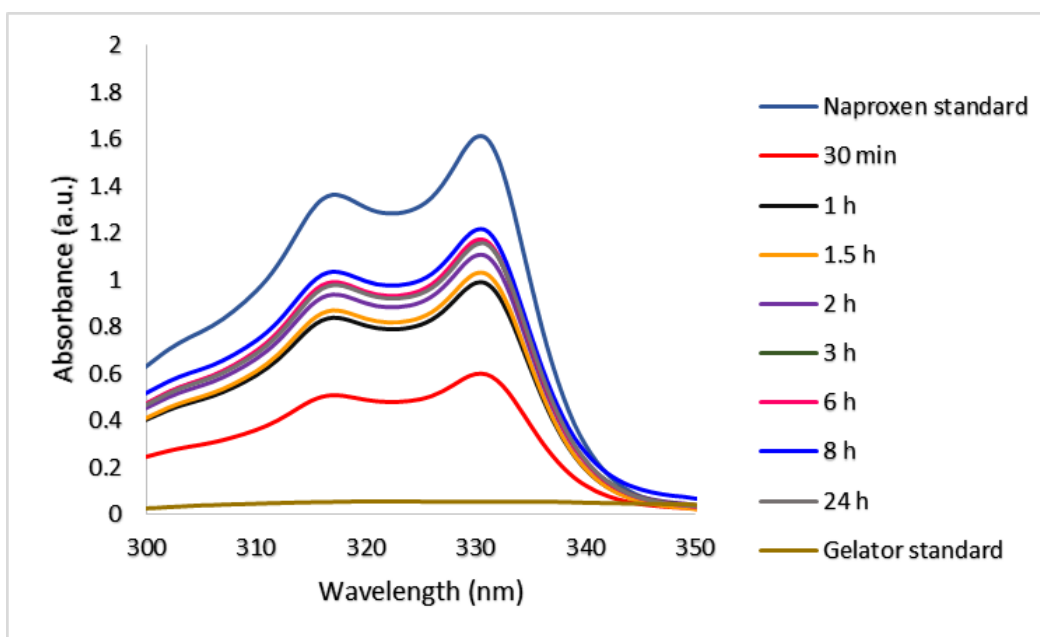
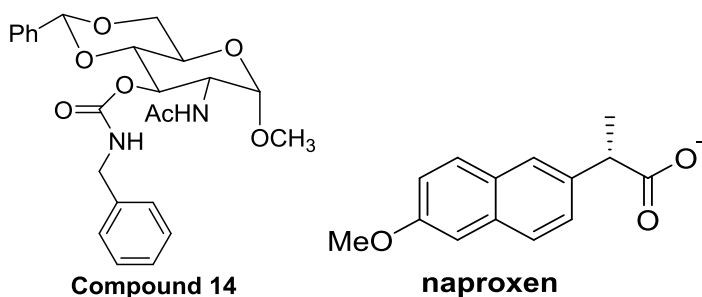


Fig. 38: Release of naproxen sodium from gel formed by compound **14** in the presence of pH 7 solution. 2 mg compound **14** (4.38 μmol) and 1 mg naproxen sodium (3.97 μmol) were dissolved in 0.2 mL 1:2 DMSO:H₂O with heating and sonication. Solution was cooled on the benchtop for ~20 min until a stable gel (21.9 mM of compound **14** and 19.9 mM of naproxen) formed. Naproxen standard is made by dissolving 1 mg naproxen (3.97 μmol) in 3 mL pH 7 solution to make a 1.32 μM solution.

The same experiment was repeated using a pH 10 solution. Carbamates can be hydrolyzed into amines by base. Therefore, it was expected that the gel would degrade at pH 10 and the naproxen would be released more quickly. Two-thirds of naproxen was already released in one hour. After three hours about 85% of the naproxen had been released (**Fig. 39**).

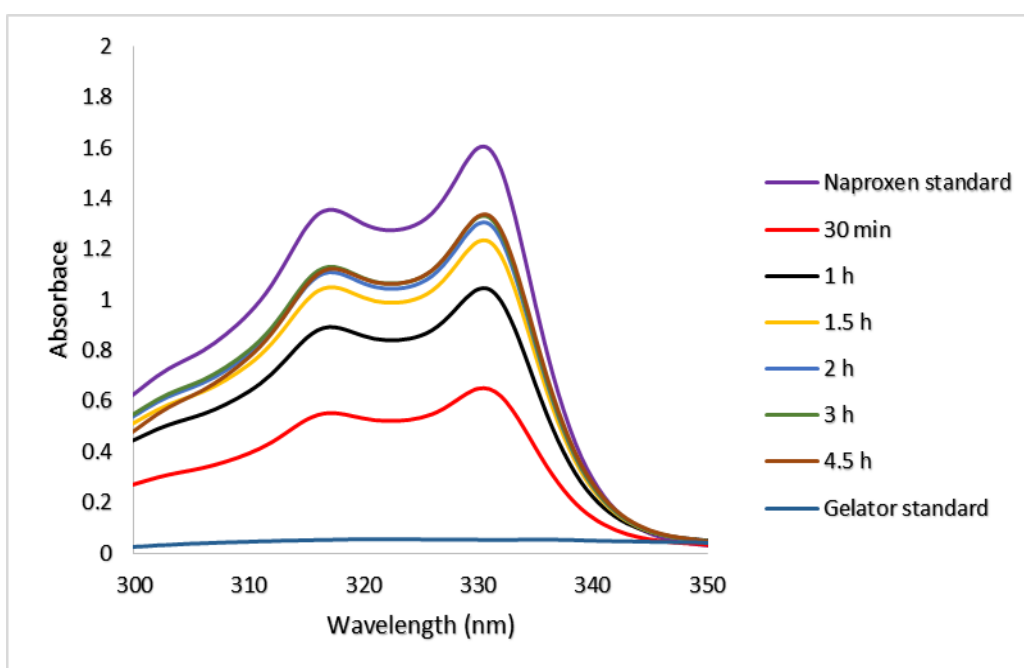


Fig. 39: Release of naproxen sodium from gel formed by compound **14** in the presence of pH 10 solution. 2 mg compound **14** (4.38 μmol) and 1 mg naproxen sodium (3.97 μmol) were dissolved in 0.2 mL 1:2 DMSO:H₂O with heating and sonication. Solution was cooled on the benchtop for ~20 min until a stable gel (21.9 mM compound **14** and 19.9 mM naproxen) formed. Naproxen standard is made by dissolving 1 mg naproxen (3.97 mmol) in 3 mL pH 10 solution to make a 1.32 μM solution.

A controlled release experiment was also done with the antibiotic chloramphenicol (**Fig. 40a**). Chloramphenicol was incorporated into the gel matrix and the release of chloramphenicol in the presence of a pH 7 solution was measured. About half of the chloramphenicol was released in 1.5 hours. After that, the rate of release decreased. There was little difference between the amount of chloramphenicol released at 2.5 hours and 3 hours. At 24 hours about 85% of the chloramphenicol was released from the gel. Visual inspection of the gel showed that the gel remained intact during the entire duration of the chloramphenicol release study.

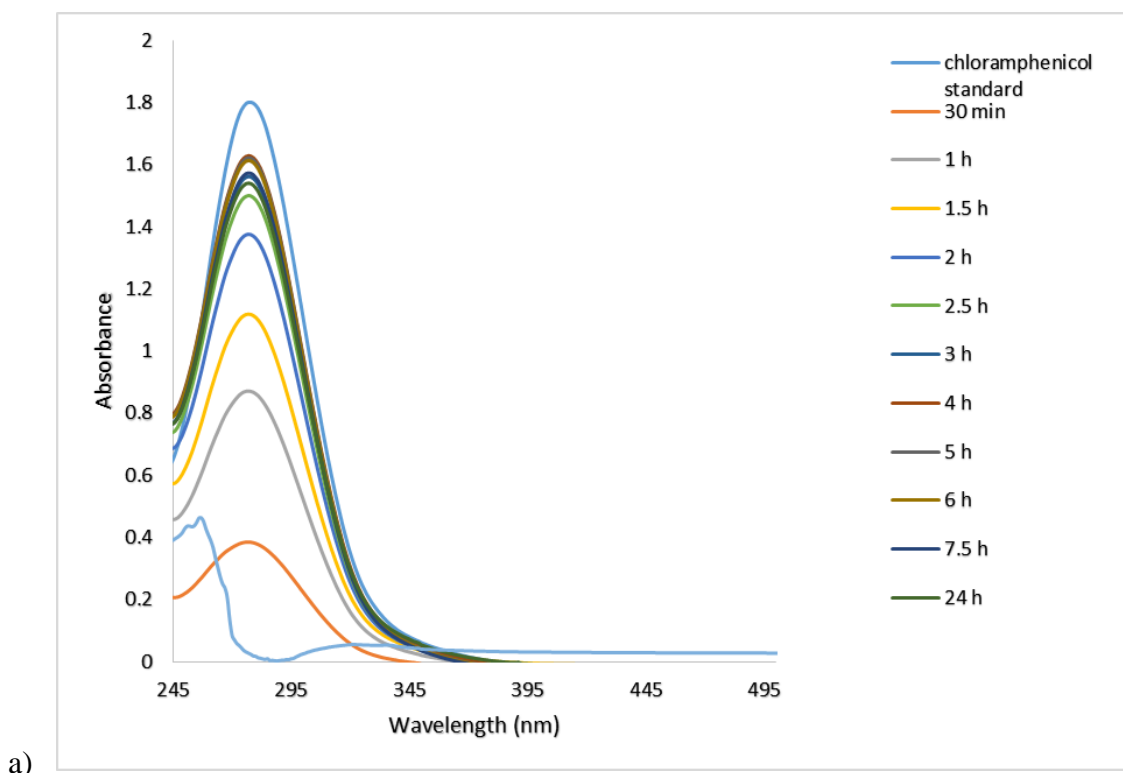
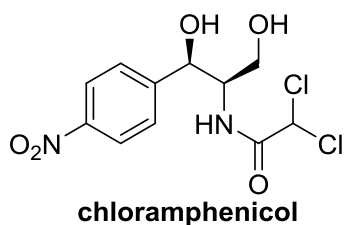


Fig. 40: a) Release of chloramphenicol from gel formed by compound **14** in the presence of pH 7 solution. 4 mg compound **14** (8.76 μM) was dissolved in 0.2 mL of a 3.1 mM (1 mg/mL) stock solution of chloramphenicol dissolved in 1:2 DMSO:H₂O. Solution was cooled on the benchtop until a stable gel (43.8 mM compound **14** and 3.11 mM chloramphenicol) formed. Chloramphenicol standard was made by dissolving 0.2 mL of the stock solution in 2.8 mL of pH 7 solution to make a .021 mM solution.

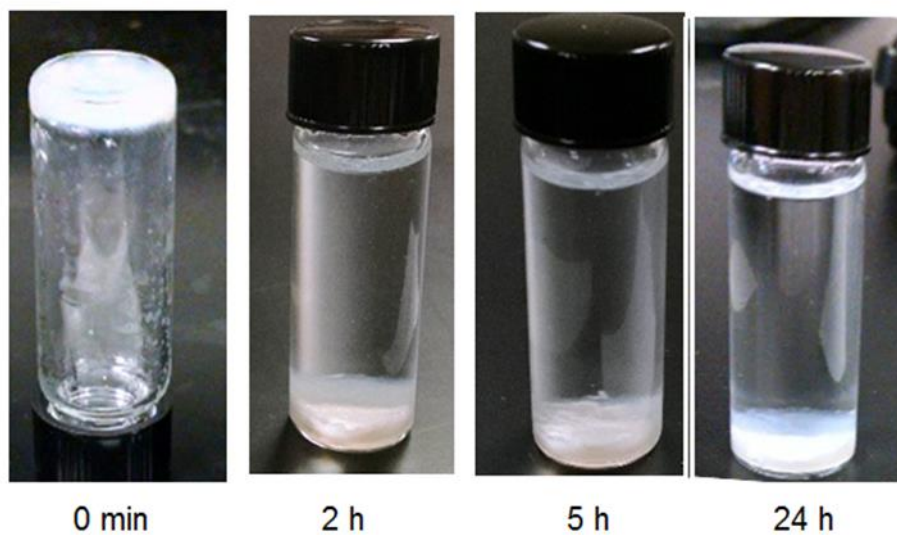


Fig. 40: b) Gel pictures from study of release of chloramphenicol from gel formed by compound **14** in the presence of pH 7 solution. 3 mL of deionized water was adjusted to pH 7 using NaOH with a pH meter.

When the study was repeated in the presence of a pH 10 solution, the chloramphenicol was completely released much more rapidly. (**Fig. 41a**). About half of the chloramphenicol was released in one hour. At 1.5 hours about two-thirds of the chloramphenicol was released and at 2 hours almost 90% of the drug was released. The chloramphenicol was 100% released in 2.5 hours. The gel appeared slightly unstable after the 2.5 hours.

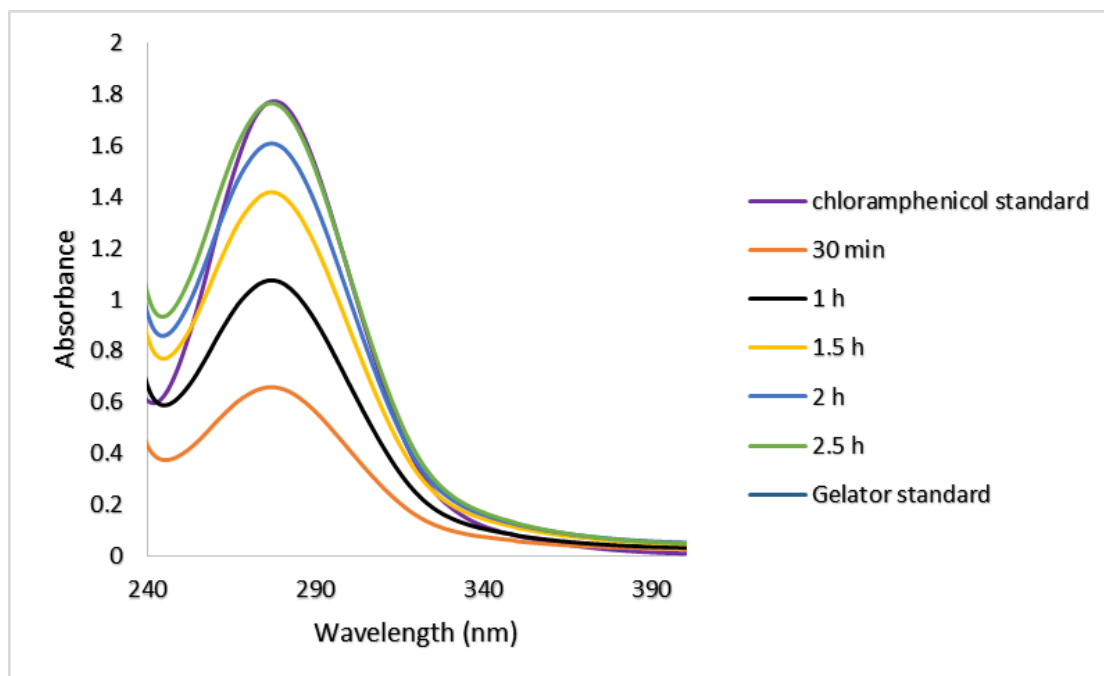


Fig. 41: a) Release of chloramphenicol from gel formed by compound **14** in the presence of pH 7 solution. 4 mg compound **14** (8.76 μM) was dissolved in 0.2 mL of a 3.1 mM (1 mg/mL) stock solution of chloramphenicol dissolved in 1:2 DMSO:H₂O. Solution was cooled on the benchtop until a stable gel (43.8 mM compound **14** and 3.11 mM chloramphenicol) formed. Chloramphenicol standard was made by dissolving 0.2 mL of the stock solution in 2.8 mL of pH 10 solution to make a 0.021 mM solution. The pH 10 buffer was prepared using NaOH with a pH meter.

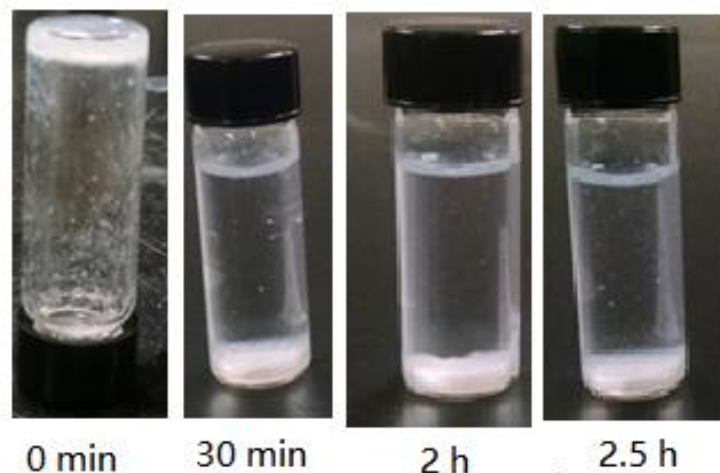


Fig. 41: b) Gel pictures from study of release of chloramphenicol from gel formed by compound **14** in the presence of pH 10 solution. Supernatant is DI water adjusted to pH 10. The pH 10 buffer was prepared using NaOH with a pH meter.

The release of chloramphenicol from the cyclohexyl ester **5** in the presence of a pH 7 solution was also measured (**Fig. 42a**). The release of chloramphenicol from compound **5** at pH 7 happened much faster than the release of chloramphenicol from compound **14** at the same pH. One-third of the chloramphenicol was released in 2 hours, and about half of it was released in 3 hours. Two-thirds of the drug was released in 4.5 hours and almost all of it was released in 7.5 hours. The gel remained stable during the duration of the study (**Fig. 42b**).

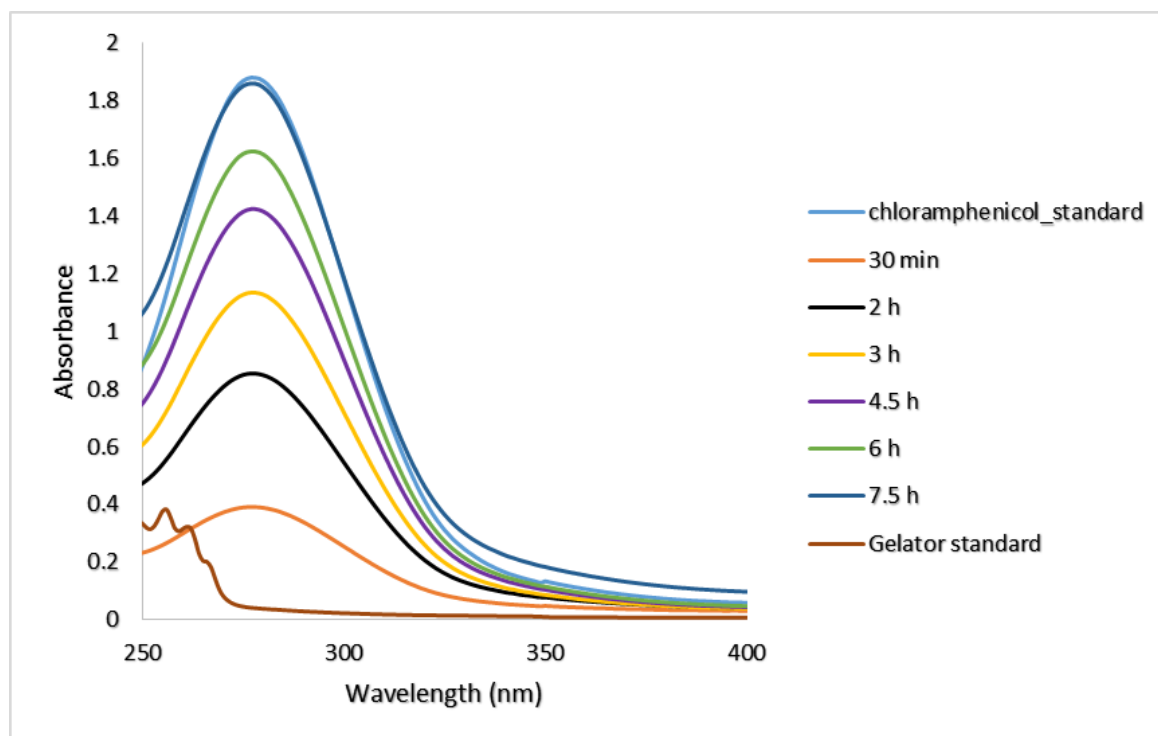
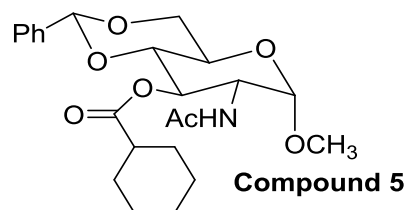


Fig. 42: a) Release of chloramphenicol from gel formed by compound **5** in the presence of pH 7 solution. 4 mg compound **5** (9.23 μmol) was dissolved in a 3.1 mM (1 mg/mL) stock solution of chloramphenicol dissolved in 1:2 DMSO:H₂O. Solution was cooled on the benchtop until a stable gel (46.2 mM compound **5** and 3.11 mM chloramphenicol) formed. Chloramphenicol standard was made by dissolving 0.2 mL of the stock solution in 2.8 mL of pH 7 solution to make a 0.021 mM solution.

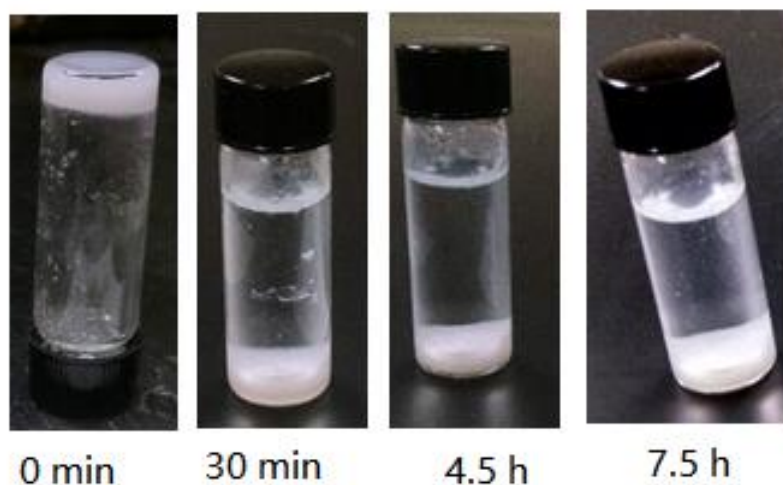


Fig. 42: b) Gel pictures of release of chloramphenicol from gel formed by compound **5** in the presence of pH 7 solution. Supernatant is DI water adjusted to pH 7.

The controlled release studies show that these compounds can form stable gels with naproxen sodium or chloramphenicol. When the gel containing the drug is kept at a neutral pH, the gel remains stable and therefore the drug is released very slowly. When the pH is raised to 10, the gel becomes unstable and therefore the drug is released much more quickly. Under these conditions, the drug is fully released in less than 24 hours. This shows that the gels formed from these ester and carbamate derivatives have potential use for controlled delivery in which the drug needs to be released under basic conditions.

3. CONCLUSIONS

A series of 3-ester and 3-carbamate derivatives of 4,6,-*O*-benzylidene acetal α -methyl-D-glucose were synthesized and characterized. Many of these compounds formed robust organogels, with the 3-carbamates forming more stable gels than the 3-esters. Optical microscopy showed that the gelators self-assembled into networks composed of uniform fibers. Rheological studies showed that the storage moduli G' of the gels was higher than the loss moduli G'' , which confirms the viscoelasticity of the gels. A comparison of gels formed by the same gelator in the same solvent system at different concentrations confirmed that gels with higher gelation concentration had greater mechanical strength. Measurement of the melting points of selected gels in 1:1 DMSO:H₂O showed that the gels melted at high temperatures and over a large range of temperatures. Gels with lower gelator concentrations showed a larger melting point range than those with higher concentrations. Comparison of the FTIR spectra of the solid gelators and their corresponding gels showed a change in intensity in peaks corresponding to aromatic C=C stretching and aromatic C-H bending. This suggests that intermolecular π - π stacking plays an important role in gel formation. The importance of intermolecular π - π stacking is supported by the 3D modeling, which shows the phenyl rings from the acetal protecting groups aligned parallel to each other. The 3D models also show the oxygen and nitrogen atoms oriented towards each other, which suggests intermolecular dipole-dipole interactions. ¹H NMR spectra taken at different temperatures changes in the NH, anomeric, acetal, and acetyl CH₃ signals. This suggests that these protons play a role in intermolecular hydrogen bonding interactions which contribute to gelation.

The release profile of naproxen and chloramphenicol from the gels formed by carbamate compound **14** and ester compound **5** in 1:2 DMSO:H₂O were studied at pH 7 and pH 10. At 24

hours, neither drug was completely released from compound **14** at pH 7. In both cases, the drugs were initially released quickly and then the rate of release slowed down to the point that the difference in the amount of drug released between one hour intervals was very small. When the pH was raised to 10, the gel formed by compound **14** and the drugs used in the study became less stable. This is likely due to basic hydrolysis of carbamates into amines. Naproxen was fully released in 4.5 hours and chloramphenicol was fully released in 2.5 hours. The rate of drug release remained constant for both drugs under basic conditions.

The gel formed by compound **5** with chloramphenicol was less stable than the one formed by compound **14** and therefore released the drug more quickly. Chloramphenicol was completely released from the gel formed by compound **5** in 7.5 hours. The rate of chloramphenicol remained constant throughout that time. Compound **5** was unable to form a stable gel with naproxen. The higher stability of gels formed from the carbamate compound and the drugs is likely due to the additional H-bonding groups in the carbamate compounds. These results suggest that compound **14** and the other carbamates may be useful for controlled drug release under basic conditions.

4. EXPERIMENTAL SECTION

4.1 Gelation Tests

2 mg of the solid compound was placed in a 1 dram vial. 200 μ L of the solvent being tested was added to the vial to make 20 mg/mL solution. The mixture was heated and sonicated to dissolve the compound, then allowed to cool on the bench for up to 20 minutes. The vial was inverted to see if the gel would remain on the bottom of the vial. If a stable gel was formed the solvent was added in 100 μ L increments. With each dilution the process of heating, sonicating, and cooling was repeated. This process continued until the compound could no longer form a stable gel.

4.2 Naproxen release study

NaOH was added to DI water to make aqueous solutions with pH 7 and 10. The gels were formed by weighing out 2 mg compound **14** and 1 mg naproxen sodium. 200 μ L 1:2 DMSO:H₂O was added and the mixture was heated, sonicated, and cooled to form a stable gel. 3 mL of the aqueous solution of appropriate pH was pipetted on top of the gel. The aqueous phase was periodically transferred to a quartz cuvette and the UV-Vis spectrum was measured. The naproxen standard was made by dissolving 1 mg naproxen sodium in 3 mL of the same pH solution used in each study. The gelator standard was made by dissolving 2 mg compound **14** in 3 mL of the solution of the pH being studied. All measurements were done on a Varian Cary 5000 UV-Vis-NIR spectrophotometer (version 1.12).

4.3 Chloramphenicol release study

A stock solution of 1 mg/mL chloramphenicol in 1:2 DMSO:H₂O was made by dissolving 10 mg chloramphenicol in 10 mL of the DMSO/H₂O mixture. 4 mg compound **14** or compound **5** was placed in a 1 dram vial. 200 μ L of the chloramphenicol stock solution was added to the vial. The mixture was heated, sonicated, and cooled to form a gel. 3 mL of the appropriate aqueous pH solution was pipetted on top of the gel. Diffusion of chloramphenicol into the aqueous phase was monitored by UV/Vis. The chloramphenicol standard was made by dissolving 200 μ L of the chloramphenicol stock solution in 2.8 mL of the same pH solution used in each study. Gelator standards were made by dissolving 2 mg compound **14** or compound **5** in the solution of the appropriate pH. All measurements were done on a Varian Cary 5000 UV-Vis-NIR spectrophotometer (version 1.12).

4.4 Synthesis of 4,6,*O*- α -methyl-N-acetyl-D-glucosamine

N-acetyl D-glucosamine was refluxed with Amberlite IR and methanol for 24 hours. Reaction mixture was filtered to remove resin and neutralized with NaHCO₃. The mixture was filtered again to remove NaHCO₃ and MeOH was removed under the rotovap. The resulting product was dissolved in DCM. 0.1 equiv. PTSA and 1.3 equiv. bezylidene dimethyl acetal was added to the reaction mixture. Reaction was stirred at 80 °C for 7 hours. Reaction was neutralized with NaHCO₃, filtered, and worked up with DCM and H₂O. Organic layer was combined and dried under the rotovap. Compound was recrystallized with hexane and ethanol. The mother liquor was concentrated and purified by column chromatography using a MeOH/DCM gradient.

4.5 General procedure for the synthesis of esters

The compounds **1-8** were synthesized and provided by Dr. Lalith Samankumara. The general method:

75 mg of 4,6,*O*- α -methyl-N-acetyl-D-glucosamine was added to a 50 mL round bottom flask and dissolved in 2 mL DCM. 2 equiv. pyridine was added and mixture was cooled to 0 °C. 1 equiv. acid chloride was added dropwise with stirring. Reaction was stirred for 4-10 hours from 0 °C to r.t. The crude mixture was concentrated on a rotary evaporator and purified by column chromatography using a hexane/ethyl acetate gradient.

4.6 General procedure for the synthesis of carbamates

The compounds **9-14** were synthesized and provided by Dr. Lalith Samankumara and Anji Chen. The general method:

75 mg of 4,6,*O*- α -methyl-N-acetyl-D-glucosamine and 0.3 equiv. DMAP were dissolved in anhydrous acetonitrile in a 50 mL round bottom flask. The mixture was stirred at r.t. for 15 min, then 1 equiv. isocyanate was added to the mixture. Reaction was stirred for 2-4 hours at r.t. Crude mixture was concentrated on the rotary evaporator and purified by column chromatography using a hexane/ethyl acetate mixture.

4.7 Measurement of melting point ranges of gels

The gelator was dissolved in a small vial at the minimum gelation concentration and heated to form the solution. The hot solution was transferred to the NMR tube, where it was allowed to cool down to form the gel. A metal ball was placed on top of the gel. The ball fell towards the bottom of the tube as the gel melted. The NMR tube was immersed in an oil bath which was heated

gradually. T1 is the temperature of the initial melting, T2 is the temperature at which the gel is estimated to be half melted, and T3 is the temperature at which the entire gel turned into a colorless liquid.

4.8 Water Tolerability Study

2 mg of solid gelator was weighed into a 4-dram vial and dissolved in 0.1 mL DMSO. 0.2 mL H₂O was added, causing spontaneous gelation. The bottom of the vial was heated with a heat gun to bring the gel back to the solution phase. 0.1 mL water was added and the vial was heated and sonicated to bring the gel back into the solution phase. The solution was allowed to cool for 20-30 min on the benchtop. This was repeated until a stable gel could no longer be formed.

4.9 Rheology

Rheological measurements were all done on a Discovery HR-2 hybrid plate rheometer. Gels were formed by dissolving the gelator in the appropriate solvent and allowing them to cool to form the gel. The gels were allowed to age for about 24 hours before measurements were taken.

4.10 Infrared Spectroscopy

All IR spectra were taken on a Bruker Alpha Platinum-ATR FTIR spectrometer. Solid samples were placed on the instrument arm down. Gel samples were measured once with arm down and once with arm up. Liquid samples were pipetted onto the instrument and the measurement was taken without placing the arm down.

4.11 3-D Modeling

3D modeling was done using Chem3D 16.0.

4.12 Variable Temperature ¹H NMR Studies

All samples were prepared at a concentration of 10 mg/mL in CDCl₃. Measurements were taken at 30 °C, 35 °C, 40 °C, 45 °C, 50 °C, and 55 °C on a Bruker Ascend 400 MHz NMR.

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