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Synthesis and characterization of monosaccharide lipids as novel hydrogelators

Guijun Wang,* Sherwin Cheuk, Kristopher Williams, Vibha Sharma,
Lousi Dakessian and Zeus Thorton

Department of Chemistry, University of New Orleans, New Orleans, LA 70148, USA

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Abstract—Self-assembly of small molecules is a useful strategy for forming functional supramolecular structures. Three new series of methyl α-D-glucopyranoside derivatives, including esters and carbamates, have been synthesized and characterized. Several of these compounds are excellent hydrogelators and formed interesting self-assembled network structures, including birefringent fibers and tubules. The gelation properties depend on the acyl chain length and the headgroup structures. Small molecule sugar-based hydrogelators have potential applications in drug delivery and enzyme immobilization.

Keywords: Monosaccharides; Lipids; Self-assembly; Hydrogelators; Organogelators

1. Introduction

Carbohydrates are abundant natural products and readily available chiral compounds. They contain all of the important elements necessary to prepare highly functional and synthetically flexible units, but they are the most complex and structurally dense of all naturally occurring materials. Attempts to overcome this complexity and integrate the rich functionality and the chirality of carbohydrates into structural units that self-assemble into grand architectures are very important to advance carbohydrate chemistry. Soft materials formed by carbohydrates and lipids are biocompatible and have potential uses in many biomedical areas and as biodegradable materials.

Small molecule self-assembly through non-covalent forces can afford interesting soft materials, such as hydrogels or organogels. Low molecular weight organogelators (LMWOs) are small molecules that can form gels in organic solvents or water.[1–3] The gelation processes are typically reversible because of the non-covalent interactions between the molecules. These molecules have potential applications in forming liquid crystalline materials, as templates for synthesizing other novel materials, and as matrices for separating peptides and amino acids.[4,5] Polymer hydrogels are useful for drug delivery, tissue engineering, enzyme immobilization, and controlled release of other biological agents.[6a,b,7a,b] Polysaccharide gels have been widely utilized for DNA and protein purification and enzyme immobilization. Supramolecular hydrogels are formed by LMWOs in water through non-covalent forces. They are a interesting new class of soft materials that also have important applications in biomaterials and pharmaceutical research.[8–10] These self-assembled supramolecular gels have the advantage that the monomers are easy to prepare and the resulting materials can have tunable physical properties. Small molecules can be synthesized and purified to give materials with a single molecular weight, as compared to polymers, which have a distribution of molecular weights. Their structure can also be readily modified to introduce functional groups that can give rise to desired physical properties. Reversible physical gelation may also have the advantage of

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* Corresponding author. Tel.: +1 504 280 1258; fax: +1 504 280 6860; e-mail: gwang2@uno.edu

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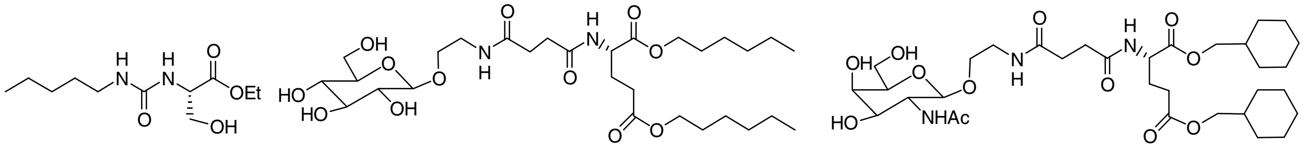
entrapping biomolecules in the matrix, without affecting the properties of the entrapped agents. The non-covalent interactions between the molecules make the gels easier to dissolve or break down than polymer gels, thus allowing the entrapped substances to be separated readily.

Low molecular weight hydrogelators have a variety of structures, including, but not limited to, ureas,[11,12] saccharides,[13a,b,14–16] amino acids,[17,18,19a–d,20–22] nucleotides,[23] nucleosides,[24] and other structural classes.[25–29] Many of them were discovered by serendipity, while some were discovered by rational design or combinatorial chemistry.[8,16] Several examples of existing hydrogelators (**1**–**3**) are shown in Figure 1. Mono-urea serine derivative **1** can form gels in pure water at a concentration of 0.8–1 wt %.[12] The hydrogen bonds between the urea moiety allow the molecules to self-assemble into a one-dimensional array and the short alkyl group provides flexibility. The short chain glucose and galactose amino acid lipids **2** and **3** were discovered by combinatorial chemistry and shown to be effective hydrogelators.[8,16] They can be used to immobilize enzymes and form protein microarrays. From an examination of the structures of small molecule hydrogelators, the common features of good hydrogelators that are apparent is a rigid region that can form hydrogen-bonding interactions, and a flexible short alkyl chain that will allow the molecules to interact with each other through hydrophobic forces.

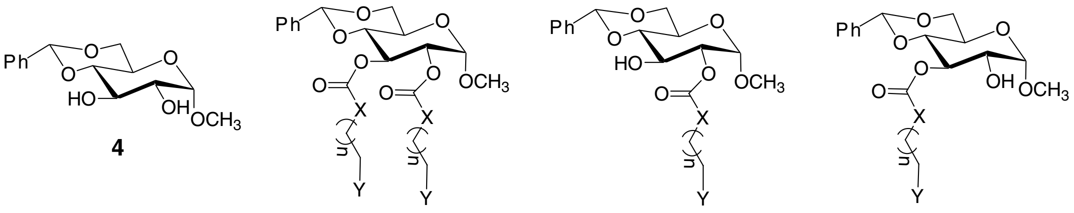
Because of the great potential of hydrogelators, we are interested in discovering new biocompatible hydrogelators with straightforward structures, which will render large-scale synthesis more feasible. Carbohydrates are ideal starting materials because they are abundant natural chiral compounds with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

Many glycolipids and other small sugar derivatives can form gels in organic solvents, but less frequently in water. Compound **4** is a simple and commercially available glucose derivative, which can form gels in organic solvents but not in water.[9] Modifying its structure by introducing short alkyl chains could potentially lead to good gelators in water or organic solvents. The structures of three molecular classes, (**A**, **B**, and **C**, Fig. 2) depending on the positions of functionalization, are shown in Figure 2. Inspired by the structures of hydrogelators **1**–**3**, we envisioned the incorporation of short chain fatty acyl unit to the 2 or 3-hydroxyl groups via ester or carbamate linkages (**B** and **C**) could potentially lead to small molecule hydrogelators and the diester or dicarbamate **A** could be potential organogelators. The hydroxyl groups and amide groups can provide hydrogen-bonding interactions. The incorporation of terminal acetylene groups may reduce the acyl chain packing order and therefore increase solubility to some extent. It can also be used as a group that allows further structural modification.



1 **2** **3**

Figure 1. Structures of some hydrogelators (**1**–**3**).



4 **A** **B** **C**

X = NH, CH_2, Y = CH_3, or C≡CH n = 0-5

Figure 2. Structures of the designed hydrogelators.