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COMMUNICATION

Sugar Isoxazole Based Hydrogelators and Their Applications as Reusable Hydrogels for Dye Removal

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A series of eleven new glucosamine isoxazole derivatives were synthesized and analyzed for their self-assembling properties. These glycocojugates are gelators for several solvents and eight compounds are able to form hydrogels, representing the first class of isoxazole based molecular hydrogelators. The metallogel formation and dye removal application were also studied.

The self-assembly of small molecules through non-covalent interactions may lead to the formation of supramolecular gels. These compounds are referred to as low molecular weight gelators (LMWGs) or molecular gelators. Among these, the low molecular weight hydrogelators (LMHGs) are especially interesting due to their biocompatibility and potential biomedical and environmental applications.[1, 2] Using certain structural templates, effective LMWGs can be designed by balancing and adjusting various intermolecular forces such as hydrogen bonding, hydrophobic interactions, π-π stacking, and van der Waals forces. Among the many classes of compounds that are able to form supramolecular gels, carbohydrate derivatives have gained great attention due to their unique structures.[3] Heterocycle functionalized carbohydrate derivatives are useful for the formation of self-assembled networks and for the formation of LMWGs. We have found that triazole functional group is useful for the design of LMWGs through our previous work with per-acetylated glucose and glucosamine triazole derivatives (Figure 1, **A** and **B**).[4, 5] Eight glucose triazole derivatives **A** are organogelators and one is a hydrogelator.[4] Twelve glucosamine triazole derivatives **B** are organogelators and seven are hydrogelators.[5] The beta-glucosyl derivatives with triazole functional group linked through a 2 carbon spacer were also reported, some of the compounds are organogelators but the structure flexibility tend to make the molecules more soluble and less prone to form gels.[6] Isoxazoles are five membered ring heterocycles which can be synthesized via 2+3 cycloaddition reactions.[7, 8] We envisioned that the nitrogen and oxygen containing isoxazole heterocycle could be used for the design of sugar based molecular gelators through modification of template **B**. The five membered ring isoxazole exhibits strong dipole moment and can participate in hydrogen bonding through its nitrogen and oxygen, and the hetero-aromaticity contributes to π-π interactions. However, isoxazole based LMWGs are much less studied for gelation in comparison to triazole derivatives. Several isoxazole based organogelators have been reported.[9-11] A few rigid aromatic isoxazoles have been shown to form organogels but not hydrogels.[12-14] Certain isoxazole based organogelators were studied for phase selective oil gelation for oil spill cleanup.[9, 15] Isoxazoles have important biological activities and several glycosyl isoxazole conjugates have been synthesized due to their potential biological activities.[16-18] In the different applications of LMWGs, absorbing various dyes and drug molecules can have environmental applications.[19-21] Using sugar based gelators for dye absorptions have practical utilities since they are biocompatible.[22-25] LMWGs in particular those form gels in the presence of metal ions may have additional utilities. These metallogels have exhibited unique properties and have been explored for catalysis,[26-31] environmental applications of removal toxic metal or dyes,[32-34] and for preparation of new materials.[35, 36] To the best of our knowledge, isoxazole based hydrogelators have not been reported yet, and isoxazole sugar conjugates have not been studied for their molecular self-assembly and formation of supramolecular gels. To expand the structures of sugar derivatives for effective molecular gelators, we synthesized a series of isoxazole derivatives from N-acetyl-D-glucosamine with the general structure **C** and expect that they will be able to form hydrogels due to the structure similarity to the triazole based hydrogelators **B**. The systematic

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structure and gelation correlation can allow us to obtain a novel class of isoxazole based LMWGs.

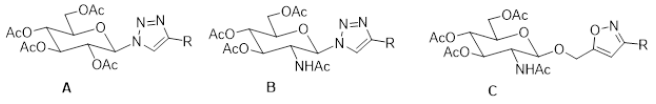
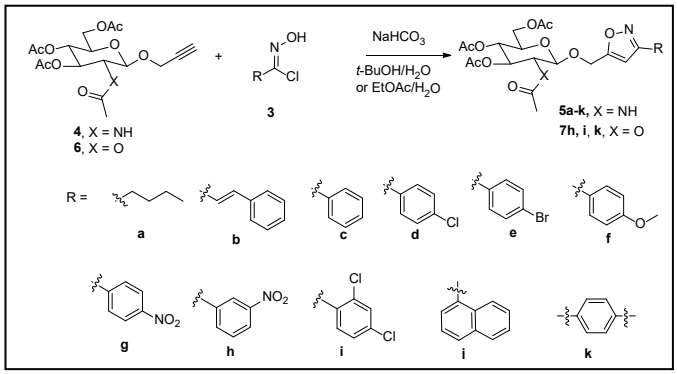


Figure 1. Structures modifications of triazole heterocycle derivatives to isoxazole derivatives

The isoxazole compounds **C** were synthesized using cycloaddition reactions of chloroximes with propargylated sugar headgroups (Scheme 1). The chloroximes **3** were prepared from the corresponding aldehyde **1** in two steps by forming hydroxylamines **2** and followed by N-chlorosuccinimide (NCS) oxidation (Scheme S1). Most of these compounds contain aromatic functional groups. In addition, three per-acetylated glucose derivatives, **7h**, **7i**, and **7k** were also synthesized.



Scheme 1. Synthesis of sugar isoxazole derivatives **5a-5k**, and **7h**, **7i**, and **7k**.

After these compounds were obtained, they were tested in a panel of solvents and the results are shown in Table 1. The gels are translucent to opaque, several representative images are shown in Figure 2. All glucosamine derivatives (**5a-5k**) were able to form gels in at least one of the selected test solvents, and remarkably, all compounds were found to be gelators for glycerol, forming clear or translucent gels. These compounds also formed gels in glycerol/ H_2O, DMSO/H_2O, or EtOH/H_2O mixed solvents. Four compounds formed stable gels in toluene, they are not effective gelators for isopropanol and ethanol. We were delighted to find that these compounds tend to form hydrogels, eight compounds formed stable gels in water. The most efficient hydrogelators are the 4-chlorophenyl derivative **5d**, 4-bromophenyl derivative **5e**, and 3-nitrophenyl derivative **5h**, forming hydrogels at 1.1, 1.2, and 2.0 mg/mL concentrations, respectively. All substituted phenyl isoxazoles are effective gelators in water, DMSO/H_2O (1:2) mixture, and in glycerol. These structural features enable them to form hydrogels can be a useful template for the design of effective low molecular weight hydrogelators. The non-substituted phenyl derivative **5c** and naphthyl derivative **5j** did not form hydrogels, the substituent on the phenyl ring contributed to intermolecular interactions more positively to enable gelation. The dimer **5k** on the other hand is not as effective gelator comparing to the monomeric isoxazole derivatives. It mainly formed gels in glycerol and EtOH/H_2O (1:1) mixture and partial gel like particles for the other solvents. This can be attributed to strong intermolecular forces from both isoxazole ring.

The glucose derivatives **7h** and **7k** mostly formed precipitates in the tested solvents. In comparison to the gelation properties of the glucosamine derivative **5h**, compound **7h** formed partial gels in glycerol and in water at 30 mg/mL. The dimeric glucose derivative **7k** didn't form gels in any tested solvents. This trend indicates that 2-amino group of the glucosamine headgroup is essential for the gelation properties. The ^{1}H NMR spectra of the compound **5h** at different concentrations showed that the amide NH signal shifted when concentration is increased, which is attributed to the intermolecular hydrogen bonding, as shown in Figure S2.

Table 1. Gelation properties of the isoxazole derivatives

No	Tol	IPA	EtOH	Glycerol	EtOH: H_2O (1:1)	EtOH: H_2O (1:2)	DMSO: H_2O (1:1)	DMSO: H_2O (1:2)	Gly:H_2O (1:1)	H_2O
5a	S	S	S	G6.7$_C$	S	S	G20$_O$	G20$_O$	G2.5$_O$	G20$_O$
5b	PG	P	S	G6.7$_T$	PG	PG	G20$_O$	G20$_O$	G2.2$_O$	G10$_O$
5c	P	P	PG	G20$_T$	PG	PG	PG	G20$_O$	G4.0$_O$	PG
5d	PG	S	P	G6.7$_C$	G10$_T$	G2.8$_T$	G20$_O$	G5.0$_O$	G2.8$_O$	G1.1o
5e	G20 $_C$	PG	G20$_O$	G2.0$_C$	G5.0$_O$	G5.0$_O$	G5.0$_O$	G5.0$_O$	G1.6$_O$	G1.2$_T$
5f	PG	P	P	G10$_T$	P	P	PG	G10$_O$	G2.5$_O$	G5.0$_O$
5g	G5.0$_T$	G10$_O$	G6.7$_O$	G4.0$_T$	G10.0$_O$	G5.0$_O$	G6.7$_T$	G6.7$_O$	G1.6$_O$	G3.3$_O$
5h	G10$_C$	PG	PG	G6.7$_C$	G20$_O$	G2.0$_T$	G10$_O$	G2.8$_T$	G1.2$_O$	G2.0$_T$
5i	G4.0$_C$	P	P	G5.0$_T$	P	G20.0$_O$	G10.0$_O$	G10.0$_O$	G3.3$_O$	G4.0$_O$
5j	P	S	P	G20.0	P	P	P	P	G2.8$_O$	I
5k	I	PG	PG	G3.3$_C$	PG	G2.5$_T$	PG	P	I	I
5gf	G13.0	P	P	G2.5$_T$	G5.0$_O$	G3.3$_T$	G10$_O$	G7.8$_O$	N/A	G5.6$_O$
7h	P	P	P	PG	P	P	P	P	N/A	P
7k	P	P	P	P	P	P	P	P	N/A	I

All compounds were tested starting from 20 mg/mL. G, stable gel at rt, the numbers are minimum gelation concentrations (MGC) in mg/mL; P, precipitation; S, soluble; I, insoluble; PG, partial gel; T, translucent; C, clear, O, opaque. **5gf** is a 1:1 mixture of **5g** and **5f**.

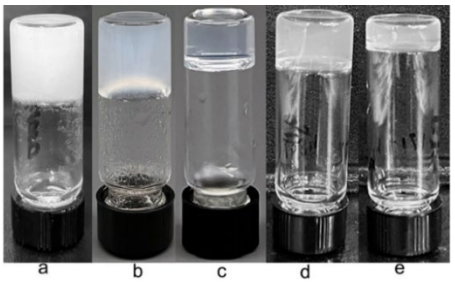
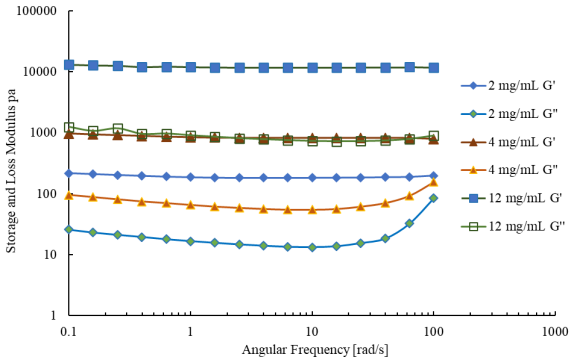


Figure 2. Gel appearances are opaque in a); translucent in b, d, and e; clear in c). a) **5d** in water at 1.1 mg/mL, b) **5e** in water at 1.2 mg/mL; c) **5e** in glycerol at 2.0 mg/mL, d) **5h** in H_2O at 2.0 mg/mL, e) **5h** in EtOH: H_2O (v/v 1:2) at 5.0 mg/mL.

The rheological properties of several hydrogels formed by gelator **5d** and **5h** are analyzed at different gelation concentrations. The p-chlorophenyl derivative **5d** at gelation concentrations in water at 1.1 mg/mL, 2.2 mg/mL, and 4.4 mg/mL (Fig. S3) and the 3-nitrophenyl derivative 5h at 2.0, 4.0 and 12.0 mg/mL (Fig. 3) were measured. For all hydrogels, the storage moduli G' are greater than the loss moduli G" for all frequencies and the storage moduli G' exhibited concentration dependence. At higher concentrations, the storage and loss moduli have higher values, indicating that the gels' stiffness and mechanical strengths are concentration dependent.

Figure 3. Rheology properties of the hydrogels formed by **5h** at 2.0, 4.0 and 12.0 mg/mL.



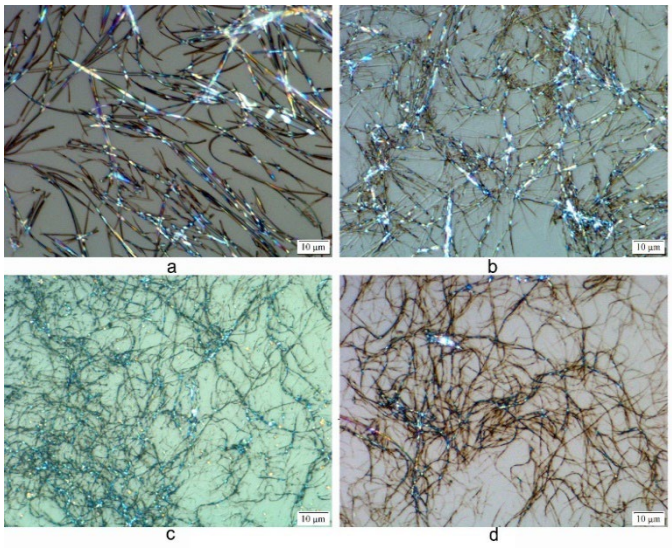


Figure 4. Optical micrographs of a few hydrogels. a-c) Compound **5d** in water at 1.1 mg/mL, b) with $Zn(OAc)_2{\cdot}2H_2O$, c) with $Cu(OAc)_2$, d) compound **5e** in water at 1.2 mg/mL.

Compound **5d** formed hydrogel at 0.11 wt%, this gelator was analyzed for its potential of gelation for metal ions. Several metal ions were tested, it was able to form stable gels in the presence of Ni^{2+}, Zn^{2+}, Cu^{2+}, Hg^{2+}, and Pb^{2+}, the gels are typically opaque as shown in Fig. S1. We also found that a two-component system formed by the 4-methoxylphenyl derivative **5f** and 4-nitrophenyl derivative **5g** (1:1 molar ratio) were effective gelators in several solvents (Table 1, **5gf**). This result indicates that the gelator molecule can be used to entrap a different small molecule and still maintain the molecular assembling structure.

The gel morphology was characterized using optical microscopy and scanning electron microscopy (SEM). A few representative images are shown in Figs. 4, 5 and Figs. S61-S62. Typically, the gels formed long fibrous networks. The Cl-compound **5d** showed long tubular fibers which are highly birefringent (Fig. 4a), the metallogels formed by this compound exhibited fibrous network as well, but typically narrower or smaller fibers, the additions of the metal ions didn't affect the hydrogelation. The hydrogel of **5d** in the presence of zinc ions and copper ions exhibited long and narrow fibrous network (Fig 4b-c). The SEM of hydrogels mostly exhibited fibrous network as well.

Compounds **5d** and **5h** formed stable hydrogels as indicated by the rheology studies. They were evaluated for applications in dye removal from aqueous solutions. The hydrogel was prepared in a syringe column and dye solution was eluted from the gel. UV-vis spectroscopy was used to analyze the amount of the dyes passing through the column. The hydrogel formed by **5d** at 4.4 mg/mL was used for the dye removal experiment. The

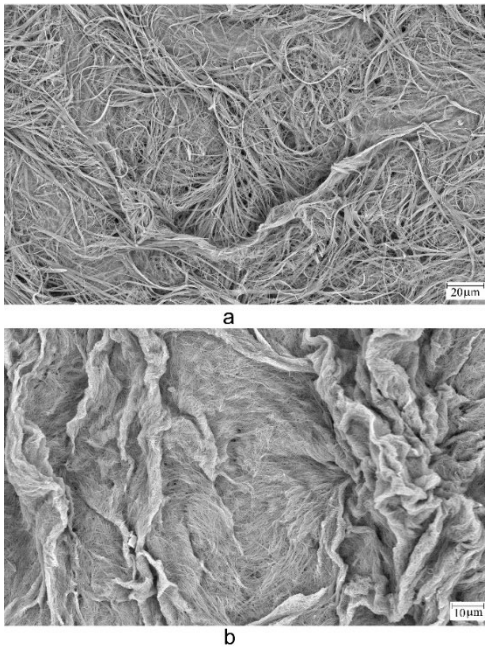


Figure 5. The scanning electronic micrographs of the hydrogels formed by: a) Compound **5d** at 1.1 mg/mL; (b) a mixture of compounds **5f** and **5g** at 5.6 mg/mL.

gel column was shown to absorbed 98% of toluidine blue dye (Fig. S16-17), and approximated 96% of rhodamine B (Fig. S18-19). Gelator **5h** was used to test the absorption of three dyes, including toluidine blue (TB), crystal violet (CV), and rhodamine B (RB). The gel formed by **5h** was stable to act as filtering matrix for the removal of dyes. As shown in Figs. S20-23, the dye absorption studies for TB and RB are analyzed first separately. Then a mixture the two dyes were tested using the hydrogel of **5h** at 8 mg/mL, as shown in Figures 6 and 7.

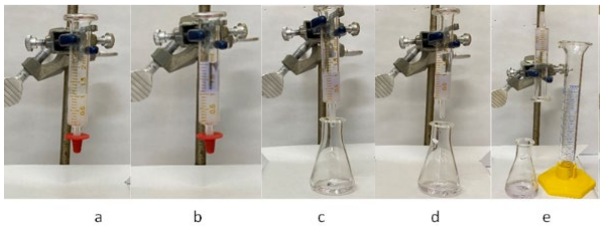


Figure 6. (a) Initial gel, 1.0 mL gel of **5h** in 8 mg/mL H_2O; (b) 1.0 mL dye mixture was added on top of the gel; (c) Gel column after passing dye; (d) after dye solution finished eluting, the gel was eluted with 1.0 mL of DI water; (e) inverted gel column after the completion of the experiment.

Besides the mixed dye experiment, we also tested the reusability of the gel column by sequentially loading three different dyes. First, crystal violet solution was loaded to the gel, after washing with water, RB, and lastly TB was added and eluted (Fig. S25-30). The gel column was stable after the eluting and washing cycles and was re-used for all three dyes. The same hydrogel of **5h** (1.0 mL, 8.0 mg/mL) was shown to be able to remove about 58%, then 56% RB, and 82% TB.

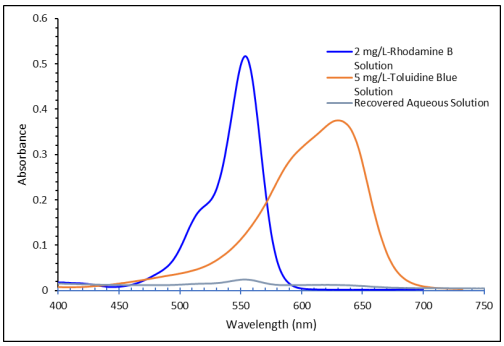


Figure 7. UV-vis spectra of eluted liquid from the gel column of **5h** and the initial dye solutions, about 79% RB and 82% TB were removed from the mixture.

In summary, we have synthesized and characterized a series of isoxazole glycoconjugates. The isoxazole glucosamine derivatives are effective LMWGs for at least one of the selected test solvents, and several of the derivatives are gelators for multiple solvents. Eight compounds are hydrogelators. Compound **5d** formed stable hydrogels as well as in the presence of different metal ions at 0.11 wt%. The gelators **5d** and **5h** were able to form gel columns for dye absorption. An advantage of using hydrogels for dye removal is that the water is an environmental benign solvent comparing to organic solvents. The hydrogels formed by **5h** was used for multiple dyes and showed effectiveness in removal of dyes from aqueous solution. The gel column can be reused several times demonstrating the reusability of the gels for dye absorption. Future studies will further evaluate these novel isoxazole derivatives for their biomedical and environmental applications. We thank the support from NSF grant 1808609.

Conflicts of interest

There are no conflicts to declare.

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