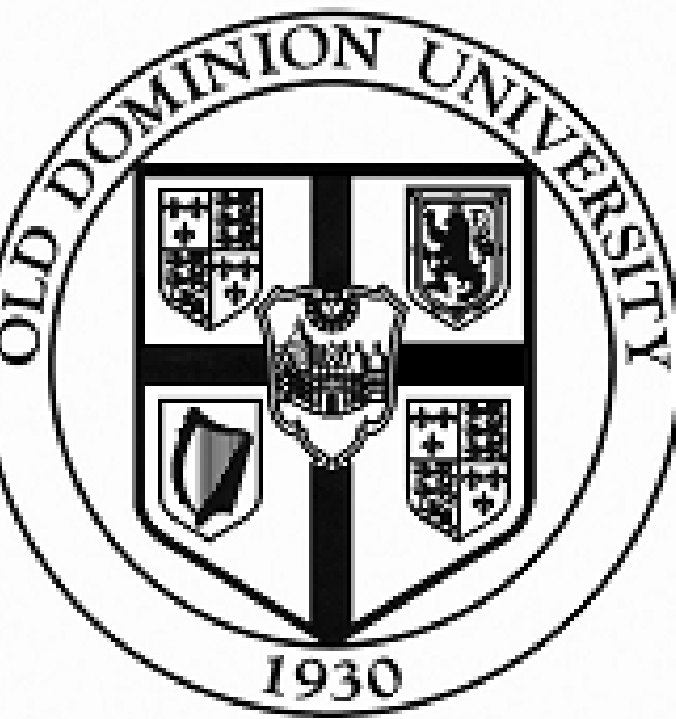


Synthesis and self-assembling property of a series of D-glucose and D-galactose triazole derivatives



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Abstract

Carbohydrate based low molecular weight gelators (LMWGs) have gained extensive interests due to their interesting applications in the areas of biomedical sciences, environmental remediation and optical electronic devices etc. Many monosaccharides have been used in the design of LMWGs in recent past. The self-assembly of the sugar molecules is attributed to the non-covalent forces like hydrophobic interactions, hydrogen bonding, π - π interactions and CH- π interactions. Previously, we have found that certain D-glucose and D-glucosamine derivatives were effective LMWGs. In this study, we carried out further structure modifications on peracetylated glycosides containing triazole moieties and studied their tendencies of gelation. The influence of distance between triazole and the anomeric carbon of sugars on gelation ability is reported.

Introduction

LMWGs are small molecules that can self-assemble to form gels in a variety of organic solvents (organogels) or in water (hydrogels).¹ The structures of LMWGs encompass a broad range of functionalities. Carbohydrates are biocompatible and naturally abundant. Moreover, they can serve as chiral templates for further functionalization to afford advanced materials. We have systematically functionalized monosaccharides and disaccharides through copper (I) catalyzed azide and alkyne cycloaddition reactions (CuAAC), click chemistry, and introduced triazole moiety in the structure to obtain effective LMWGs as shown in Figure 1.²⁻⁴ It has been found that the β -triazolyl derivatives of peracetylated glucose **1**, glucosamine **2**, and maltose **3** formed organogels in solvents like toluene and alcohols as well as in the aqueous mixtures of ethanol and dimethyl sulfoxide. The gelation properties of these compounds depend on the structures of the sugars and the R groups.

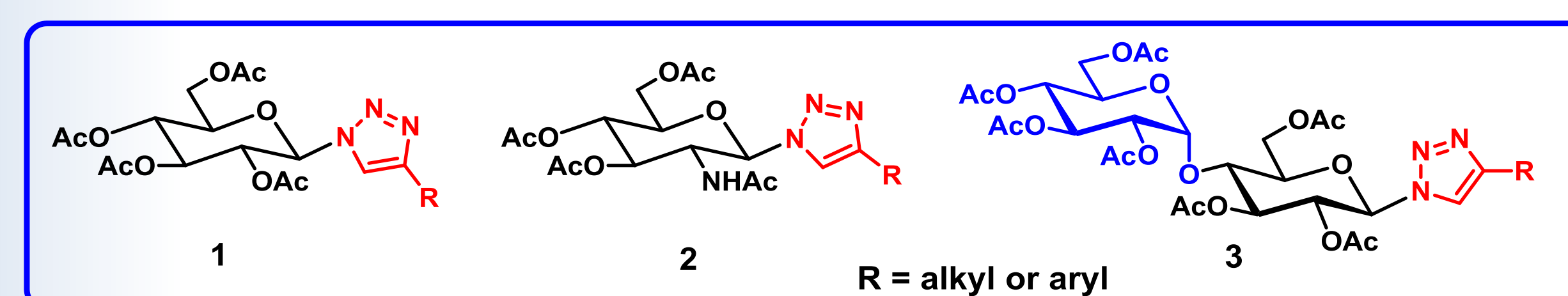


Figure 1. General structures of several carbohydrate based LMWGs.

Results and Discussions

In order to further understand the structural influence on molecular self-assembly and gelation properties, in this study we inserted 2-3 methylene groups between the anomeric oxygen and the triazoles. As shown in Schemes 1 and 2, we synthesized and characterized two series of sugar triazole derivatives containing either two or three carbon spacers. The glucose **4** and galactose **12** were treated with acetic anhydride and sodium acetate, followed by glycosylation with either chloroethanol or chloropropanol afforded chloro derivatives **6-7** and **14-15**. The chloro group was then displaced with azide, which was reacted with various terminal alkynes using the CuAAC. These compounds were synthesized and characterized. A ¹H NMR spectrum for compound **11a** is shown in Figure 2. Their gelation properties in several solvents were tested and some of the results are shown in Table 1.

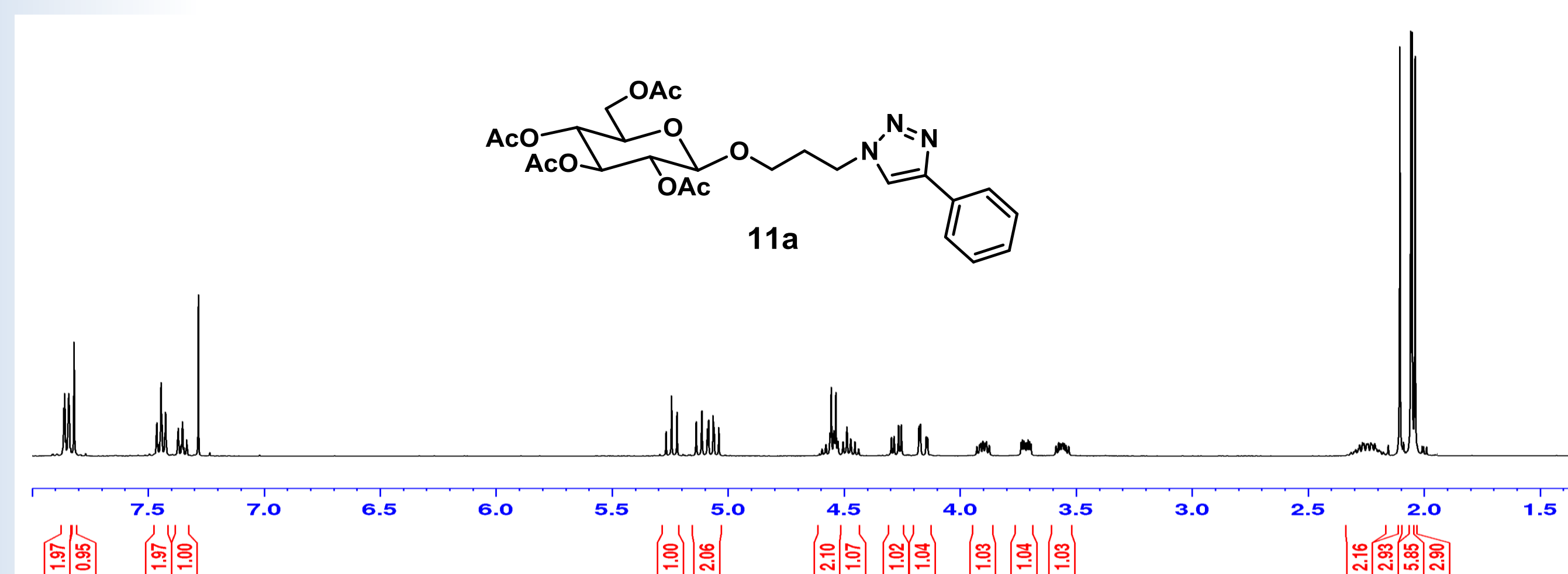
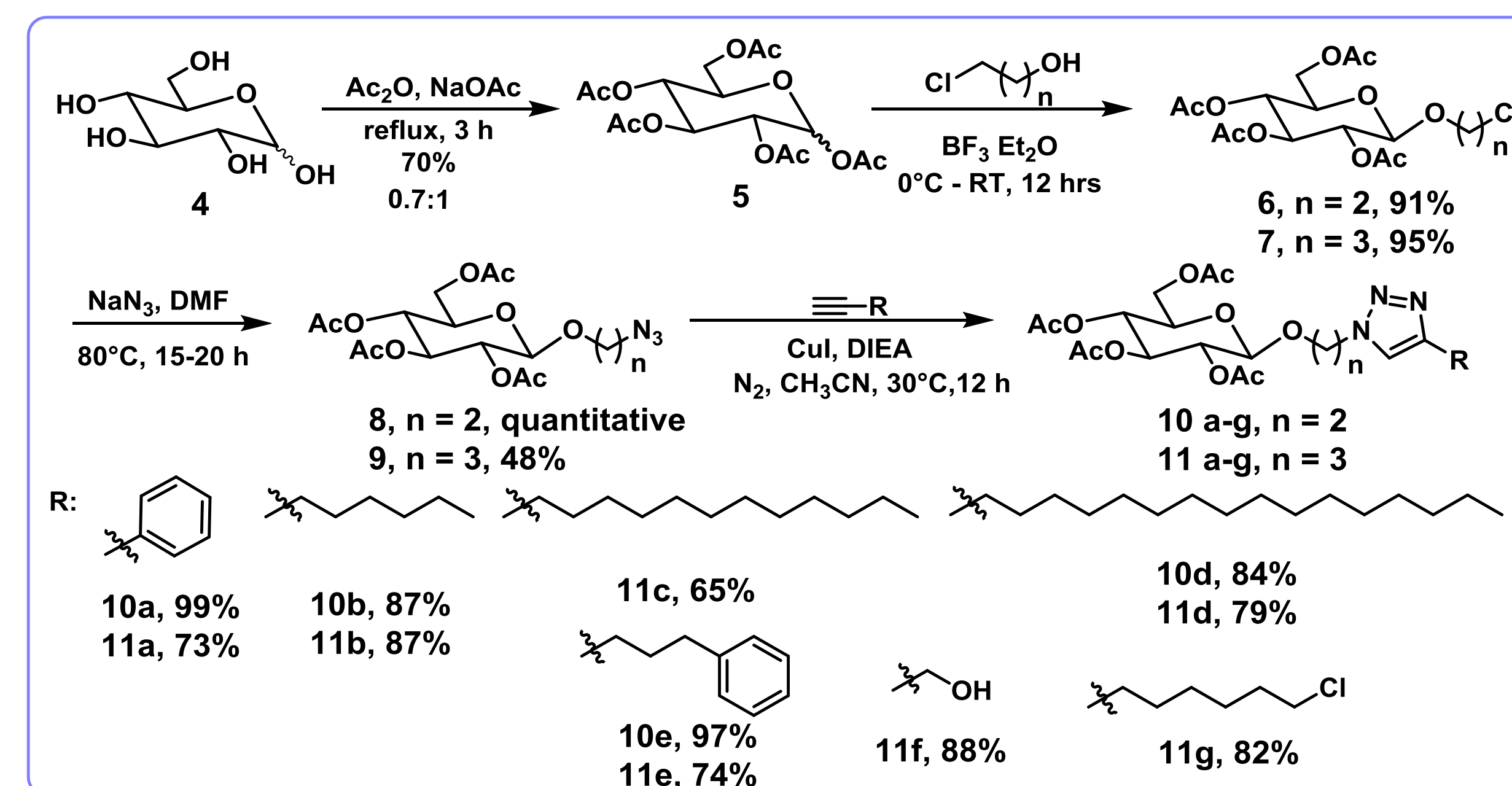
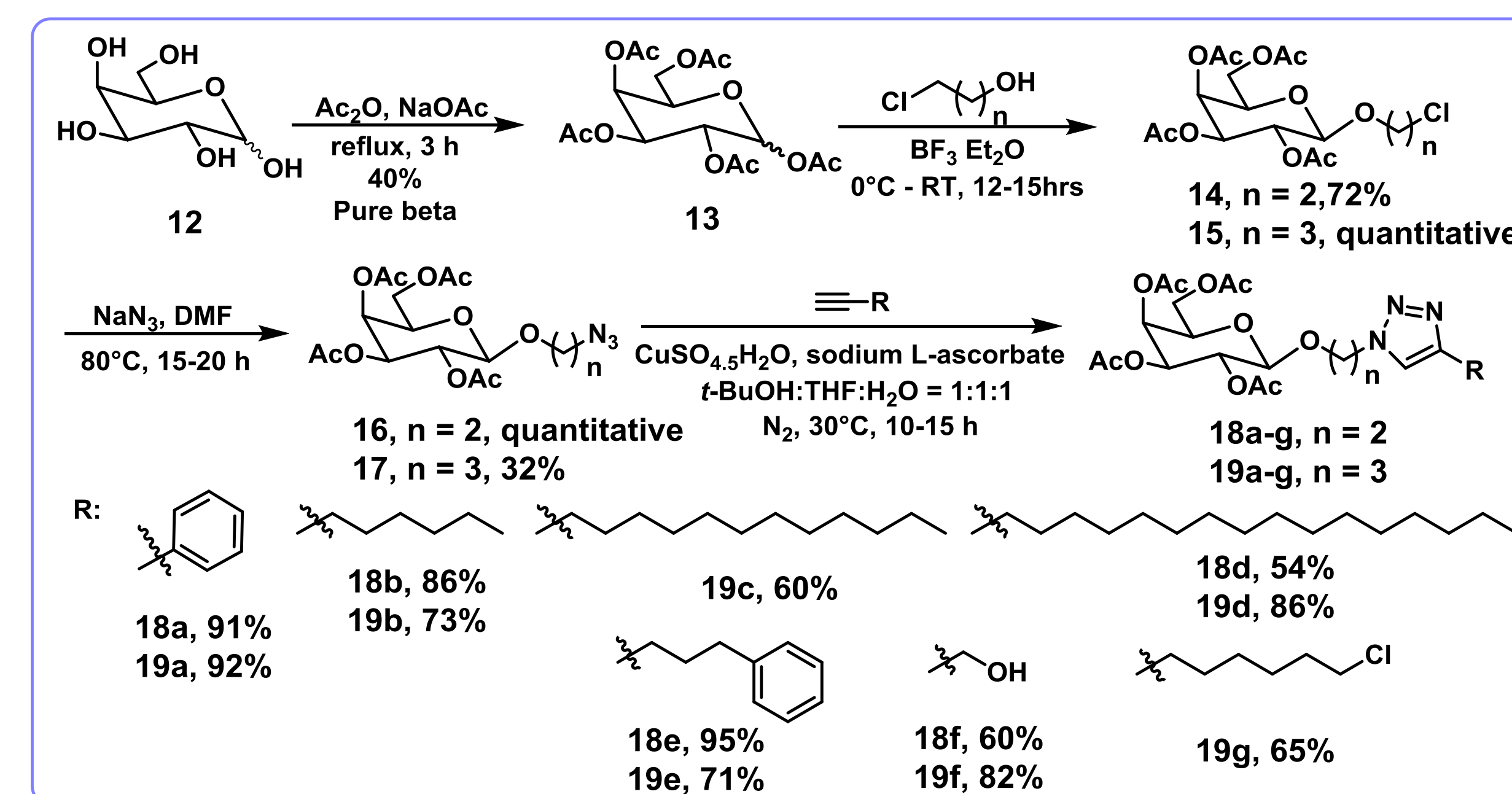


Figure 2. ¹H NMR spectrum of compound **11a** in CDCl₃, 400 MHz.



Scheme 1. Synthesis of β -triazolyl glucosides **10a-g** and **11a-g**.



Scheme 2. Synthesis of β -triazolyl galactosides **18a-g** and **19a-g**.

In general, we noticed that D-galactose derivatives were not as effective gelators as the D-glucose derivatives. As shown in Table 1, the galactose derivatives did not function as gelators for either two or three carbon spacer series. However, a few galactose derivatives without spacers were effective gelators, though not as effective as glucosamine analogs. This difference can be attributed to the difference in stereochemistry at C-4 position of the sugar rings. The glucose derivatives with three carbon spacers were more effective than the corresponding derivatives with two carbon linkers. When R group contains more hydrophobic functional groups, they typically form gels in aqueous mixtures. The viscoelastic properties of a few gels are shown in Figure 3. A few representative images of the gels formed by these compounds are shown in Figure 4.

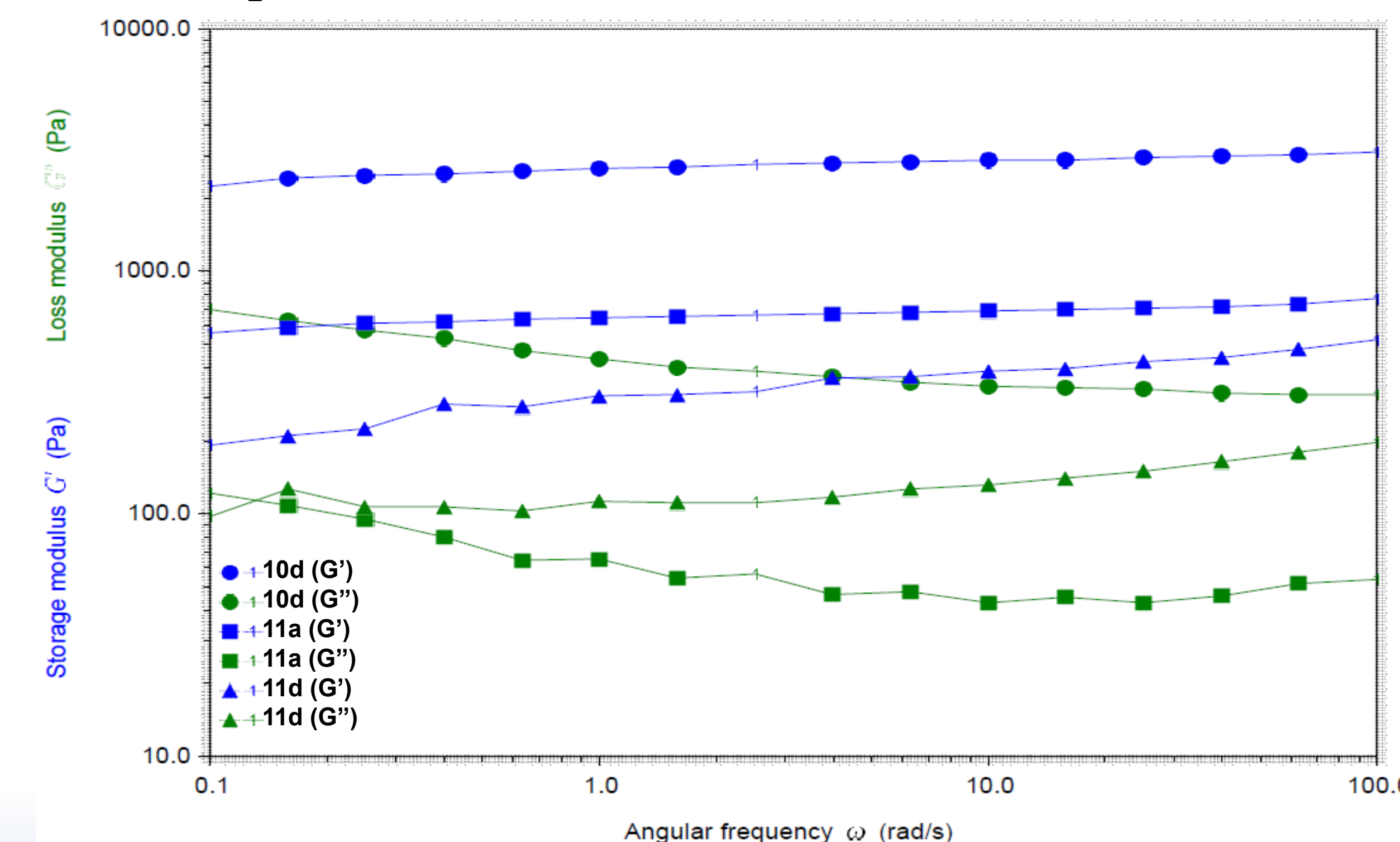


Figure 3. The rheological measurement of the gel formed by compounds **10d** (DMSO:H₂O v/v 1:1, 10.0 mg/mL), **11a** (H₂O, 5.0 mg/mL) and **11d** (EtOH:H₂O v/v 1:1, 3.3 mg/mL).

Table 1. Gelation test results of the triazole analogs synthesized.

Cpd.	Toluene	i-PrOH	EtOH:H ₂ O (1:1)	EtOH:H ₂ O (1:2)	DMSO:H ₂ O (1:1)	DMSO:H ₂ O (1:2)	Glycerol	Ethylene Glycol	H ₂ O
10a	S	S	S	G 10 ⁰	G 10 ⁰	G 10 ^T	S	G 20 ⁰	I
10b	S	G 20 ^C	S	I	G 20 ⁰	G 20 ^T	S	S	I
10d	S	S	G 10 ⁰	S	G 10	P	S	G 10 ⁰	P
11a	S	G 20 ⁰	S	G 6.7 ⁰	G 4 ⁰	G 2.2 ⁰	S	S	G 5 ⁰
11b	S	S	S	S	G 10 ⁰	P	S	S	I
11c	S	S	G 10 ⁰	G 20 ⁰	G 3.3 ⁰	G 4 ⁰	G* 5 ⁰	G 4 ⁰	P
11d	S	S	G* 2.8 ⁰	UG 20 ^T	UG 20 ⁰	UG 20 ⁰	S	G* 10 ⁰	P
11e	S	S	S	S	S	S	S	S	S
11f	S	S	S	S	S	S	S	S	S
11g	S	S	S	I	I	I	S	S	S
19a	S	S	S	P	P	P	P	S	P
19b	S	S	S	S	S	S	S	S	S
19c	S	S	S	S	G* 20 ⁰	I	S	S	S
19d	S	S	P	P	P	P	S	G 6.6 ⁰	S
19e	S	S	S	S	S	I	G* 20 ⁰	S	S
19f	S	S	S	S	S	S	S	S	S
19g	S	S	S	S	S	I	S	S	I

All compounds were tested starting from 20 mg/mL. UG, unstable gel at room temperature, G, stable gel at room temperature, the numbers are MIC in mg/mL; P, precipitation; S, soluble; I, insoluble; G* Gels were formed after 10-12 h of standing at room temperature. Gel appearance: C for clear or transparent; T, translucent; O, opaque.

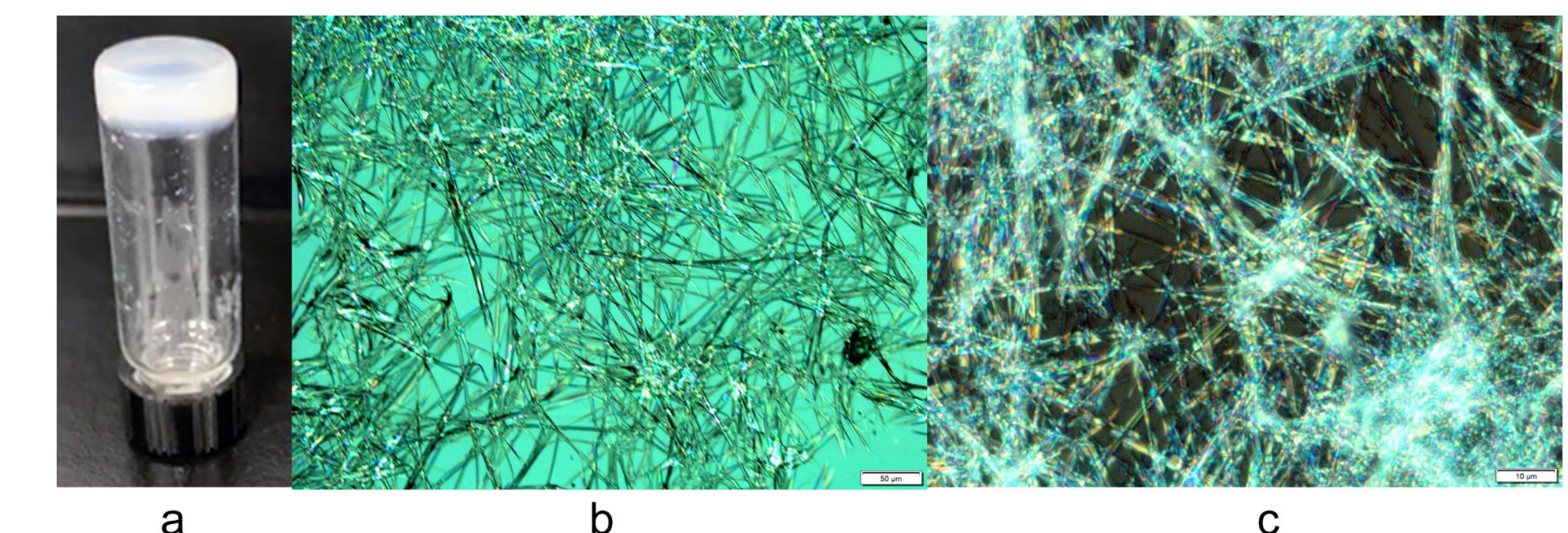


Figure 4. a) An opaque gel formed by compound **11c** in DMSO:H₂O (1:2) at 4.0 mg/mL; b) An optical micrograph of the gel in a); c) An optical micrograph of the gel by compound **11d** in EtOH:H₂O (1:1) at 3.3 mg/mL.

Conclusions and Future Studies

We have synthesized and studied novel β -triazolyl glycosides of D-glucose and D-galactose with two and three carbon spacers. Several effective gelators were obtained from the glucose series and the gels were characterized using optical microscopy and rheology. The introduction of galactose seems to diminish the gelation tendencies of triazolyl glycosides. Also, the introduction of polar functional groups makes the compounds ineffective towards gelation tendencies. This suggests that when designing effective gelators, there should be a balance of the intermolecular forces for the selection of R groups. These compounds will be further studied for applications as matrices for controlled delivery of drugs or biomolecules, and stimuli-responsive smart materials.

References

1. a) Du, X.; Zhau, J.; Shi, J.; Xu, B. *Chem. Rev.*, **2015**, *115*, 13165–13307. b), Krishnan, B. P.; Sureshan, K. M. *J. Am. Chem. Soc.*, **2017**, *139*, 1584–1589.
2. Okafor, I. S.; Wang, G. *Carb. Res.*, **2017**, *451*, 81–94.
3. Mangunuru, H. P. R.; Yerabolou, J. R.; Liu, D.; Wang, G. *Tetrahedron Lett.* **2015**, *56*, 82–85.
4. Mangunuru, H. P. R.; Yerabolou, J. R.; Wang, G. *Tetrahedron Lett.* **2015**, *56*, 3361–3364.

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