

pH-Responsive Properties of Bis-urea-based Supramolecular Hydrogels

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Physical hydrogels exhibit sol-gel reversibility, which is affected by external stimuli such as variations in pH and temperature. One class of hydrogelators, known as the low-molecular-weight gelators, can form fibrillar networks through noncovalent self-assembly, resulting in the formation of physical gels. This study aims to investigate the pH-responsive properties of bis-urea-based supramolecular hydrogelators. A series of bis-urea compounds containing an aromatic linker and various end groups were synthesized *via* a one-pot condensation reaction. Gelation of the compounds in water was conducted at pH 2–13, whereby the inversion technique was used to confirm the hydrogel formation. The compound bearing an *m*-picoyl end group effectively forms gels within the pH 3–12 range. The gelator also exhibits decreasing critical gel concentration with increasing pH, presumably due to the ionizability of the pyridyl groups. Rheological analysis of the gels determined the storage modulus (G') to be greater than the loss modulus (G''), which indicated the expected solid-like behavior of the hydrogel at low strain. The morphology of the gel obtained by scanning electron microscopy revealed a fibrous aggregated structure. Results obtained from this study may suggest the applicability of bis-urea compounds as pH-sensitive physical hydrogelators.

Keywords: bis-urea derivatives, gelators, physical hydrogels, self-assembly, sol-gel reversibility

INTRODUCTION

Physical hydrogels are composed of an aqueous solvent entrapped in a gel matrix stabilized by noncovalent forces such as hydrogen bonding, π - π stacking, electrostatic interactions, and van der Waals forces (Yamanaka 2013; Terech and Weiss 1997). These types of gels gelate at relatively milder conditions and exhibit sol-gel reversibility in response to different external factors such as changes in pH and temperature, thus making them ideal for stimuli-sensitive applications in drug delivery, biosensing, controlled release of substances, etc. (Bahram et al. 2016; Jones and Steed 2016).

Depending on the matrix composition, physical hydrogels can be divided between polymeric gels composed of long

polymeric chains and supramolecular gels composed of low-molecular-weight gelators (LMWGs). Over the years, the former has been widely studied for its gelation properties; however, the noncovalent cross-linking holding the gelation network often results in nonspecific interactions, which makes it difficult to control their properties such as sol-gel reversibility and stability for higher precision applications (de Loos et al. 2005b; Paderes et al. 2020). In contrast, supramolecular gelators are capable of noncovalent specific self-assembly to form well-ordered gel matrices, in which gelation properties can be fine-tuned through modifications in a priori design of the gelator molecular structure (Esch et al. 1999; Chivers and Smith 2019; Liu 2022).

Supramolecular gelators derived from urea-based compounds are widely investigated due to their highly stable noncovalent self-assembly and ease of synthesis.

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Intermolecular hydrogen bonds between the oxygen and hydrogen atoms in stacking ureide groups result in a directional assembly to form supramolecular polymeric fibers (van Lommel *et al.* 2020; Yokoya *et al.* 2020; Yamanaka 2013). Synthesis of the urea compounds involves readily available isocyanates and amines at low temperatures and, hence, is easily conducted (Delebecq *et al.* 2013). Aromatic bis-urea compounds, in particular, are well-known to be effective hydrogelators due to their capability to form rigid one-directional self-assembly and stability in forming intermolecular hydrogen bonds (Esch *et al.* 1999). Featuring modifiable cyclic linkers and end groups, these compounds are highly versatile, rendering them easily adjustable according to targeted specific properties for gelation.

Symmetric bis-urea gelators have the ability to gelate within a wide range of polar and nonpolar organic solvents (de Loos *et al.* 2005a; Esch *et al.* 1999). Recently, we reported the applications of symmetric bis-urea derivatives in the fabrication of functional supramolecular gels in cosmetic solvents (Genio and Paderes 2021), surfactant formulations (Magdato and Paderes 2023), and aqueous solutions (Rutgeerts *et al.* 2019), wherein robust gels with promising rheological properties were obtained. This study was conducted to investigate the gelation properties of the bis-urea compounds in aqueous solvents of varying pH. Results may provide insights into the effects of different functional end groups of the gelators on the properties of the urea-based hydrogel. Furthermore, the study may offer a better understanding of the rheological behavior of the hydrogels in varying pH and aqueous solvent components. As such, overall findings from this study may aid in the development of fine-tunable hydrogels suitable for drug delivery, biosensing, and controlled release of substances.

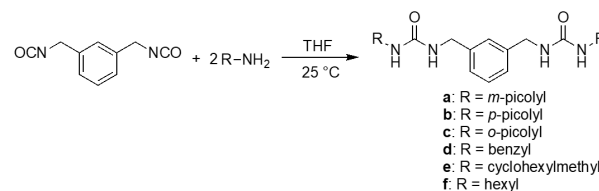
MATERIALS AND METHODS

Reagents

Bis-urea compounds were prepared by reacting 1,3-bis(isocyanatomethyl)benzene (TCI, > 98%) to various amine end groups. Amines used were 2-picolylamine (Sigma Aldrich, 99%), 3-picolylamine (TCI, > 99%), 4-picolylamine (TCI, > 98%), benzylamine (Sigma-Aldrich, 99%), cyclohexylamine (TCI, 99%), and hexylamine (Sigma-Aldrich, 99%). Anhydrous tetrahydrofuran (Scharlau, 99.5% anhydrous w/ molecular sieves, max 0.005% H₂O) was used as a solvent for the reaction, whereas diethyl ether (RCI Labscan) was used to wash the solid products. For gelation experiments, distilled water was used as the aqueous solvent, whereas

pH was adjusted using hydrochloric acid (Duksan) for acidic and sodium hydroxide (RCI Labscan, > 99%) for basic environments.

Synthesis and Characterization of Bis-urea Compounds



Scheme 1. General scheme for the synthesis of the bis-urea molecules a–f.

As shown in Scheme 1, the synthesis of the gelators involved the preparation of 1 g of the diisocyanate linker and the corresponding amine end group in a ~ 1:2.1 ratio by moles. The amine was then placed in a dried 100-mL round-bottom flask along with 40-mL anhydrous THF solvent under an inert nitrogen atmosphere. The diisocyanate linker was then added dropwise to the solution at room temperature while stirring. After 1 h, the solvent was removed using a rotary evaporator. The precipitate formed was filtered and washed twice with 20 mL of diethyl ether and then dried under reduced pressure.

Synthesized compounds were characterized using nuclear magnetic resonance (NMR) and Fourier transform infrared (FTIR) spectroscopies. ¹H NMR and ¹³C NMR spectra were obtained using Agilent Varian 500 MHz Spectrometer operating at 500 and 126 MHz for each respective nucleus. FTIR spectroscopy was recorded using a Shimadzu IR Prestige-21 Spectrometer with an attenuated total reflectance attachment. The melting point range of the compounds was obtained using a Cole Parmer Electrothermal IA9200.

Gelation Tests

Aqueous solvents from pH 2–12 were prepared using hydrochloric acid and sodium hydroxide and then measured using a Milwaukee MW100 pH meter. Gelation tests were conducted at 1 wt/v% with 5 mg of gelator added to 0.5 mL of the corresponding aqueous solvent in a 7-mL glass vial. The mixture was sonicated for 1 h under room temperature using an MRC SCG-200H Ultrasonicator operating at 40 kHz (P = 200 W). The bath temperature was maintained at an ambient temperature using an ice pack. The mixture was then heated for another hour (or until dissolution) at an estimated 95 °C in an oil bath. After which, the solution was immediately cooled to room temperature in an iced bath. Gel formation was then determined by the ability of the sample to resist

gravity flow upon vial inversion. Critical gel concentration (CGC) for gelled samples was determined by adding increments of the aqueous solvent until the samples failed the inversion test.

Gel Characterizations

Scanning electron microscopy (SEM). An SEM xerogel sample was prepared by mixing 4 mg of bis-urea compound a in 1 mL (~ 0.4 wt/v%) of an aqueous solvent at pH 12. Dissolution of the gelator was done *via* sonication and heating, then allowed to cool in the freezer at 0 °C overnight. The gel was lyophilized to form xerogel and SEM images were taken from magnifications of 5000–25000x using a Hitachi SU8230 FESEM.

Rheological measurements. Hydrogels for rheology measurements at 5 wt/v% were prepared in 20-mL vials with 9.5 mL of aqueous solvent at pH 12 and 50 mg of the gelator. Rheological tests were performed on a TA AR3 Hybrid Rheometer using a 40-mm parallel (flat) geometry plate with a 1.05-mm gap. Strain sweep measurements for the oscillation amplitude test were performed by varying the applied strain between 0.02–2000% strain at a constant angular frequency of 10.0 rad/s and a constant

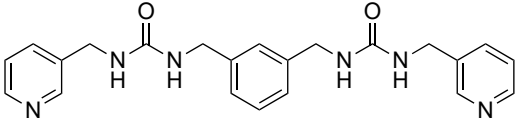
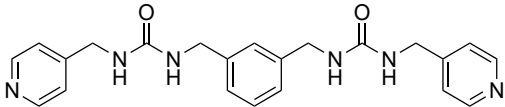
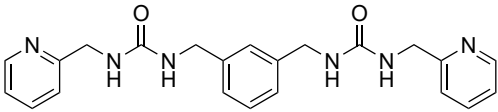
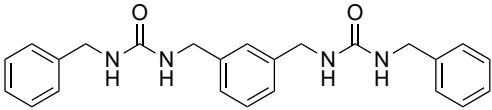
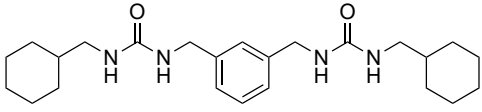
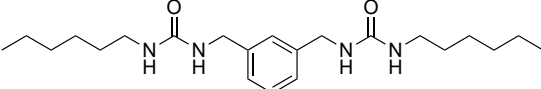
temperature of 25 °C. Frequency sweep measurements for the oscillation frequency test were performed by varying the angular frequency between 0.01–100.0 Hz at a constant oscillation displacement of 0.001 rad at a constant temperature of 25 °C.

RESULTS AND DISCUSSIONS

Synthesis of Bis-urea Compounds

Six bis-urea hydrogelators, as summarized in Table 1, were synthesized from a 1,3-bis(isocyanatomethyl) benzene linker and their corresponding amine end groups in quantitative yields (91–99%). The design of compounds a–c was based on our initial study on the gelation of phenyl bis-urea picolylamine isomers, differing in the position of the pyridyl N-group (Rutgeerts *et al.* 2019). Due to the basic nature of pyridyl end groups, the gels are allowed to be responsive to changes in pH. In a highly acidic environment, the pyridine nitrogen atoms become protonated, thereby increasing the hydrophilicity and solubility of the compound. Deprotonation at a more basic pH, however, will decrease their solubility. Another factor

Table 1. Structures of synthesized bis-urea gelators and % yield.

Compound	Structure	% yield ^a
a		94
b		91
c		96
d		99
e		95
f		93

^a% yield reported are isolated yields

that was considered in the design of these compounds is the contribution of π - π stacking interactions to gel stability (Genio and Paderes 2021). Gel formation of compounds a–d would presumably involve stacking within the aromatic groups, adding stabilization to the linear self-assembly of the gel network (Pandurangan *et al.* 2014). Compounds e and f, on the other hand, contain aliphatic end groups known to stabilize gels *via* solvophobic effects (Genio and Paderes 2021).

Gelation Tests

Gelation tests were initially conducted at 1 wt/v% in aqueous solvents of varying pH. All gels were sparingly soluble, but some dissolved after sonication and heating. Gel formation was confirmed *via* the inversion test, and

CGC was determined for the gels formed. Table 2 below summarizes the results from the gelation tests for all six compounds.

Among the six bis-urea compounds, compound a effectively formed gels in water at various pH. Although compounds a–c have similar structures, they only differ in the placement of the N atom in the pyridyl group, compounds b and c failed to form gels. To rationalize the observed hydrogelation of compound a, the proposed supramolecular assembly is shown in Figure 1a. The supramolecular hydrogelation is primarily driven by intermolecular hydrogen bonding interactions between two urea moieties (Rutgeerts *et al.* 2019). Additional stabilization is achieved through the cooperative effects of π - π stacking of phenyl linkers and C-H \cdots N hydrogen

Table 2. Gelation test results of phenyl bis-urea compounds^a.

Gelator	Solvent pH											
	2	3	4	5	6	7	8	9	10	11	12	
a	S	0.5	0.5	0.4	0.2	0.3	0.2	0.2	0.2 ^b	0.2	0.2 ^b	
b	S	PS	I	I	I	I	I	I	I	I	I	
c	PS	I	I	I	I	I	I	I	I	I	I	
d	–	–	–	I	I	I	I	I	–	–	–	
e	–	–	–	I	I	I	I	I	–	–	–	
f	–	–	–	I	I	I	I	I	–	–	–	

Abbreviations used: [S] soluble, [PS] partially soluble, and [I] insoluble; ^bunstable gels (started to flow within 24 h); values given are the critical gel concentration in wt/v%; [–] no gelation test was conducted

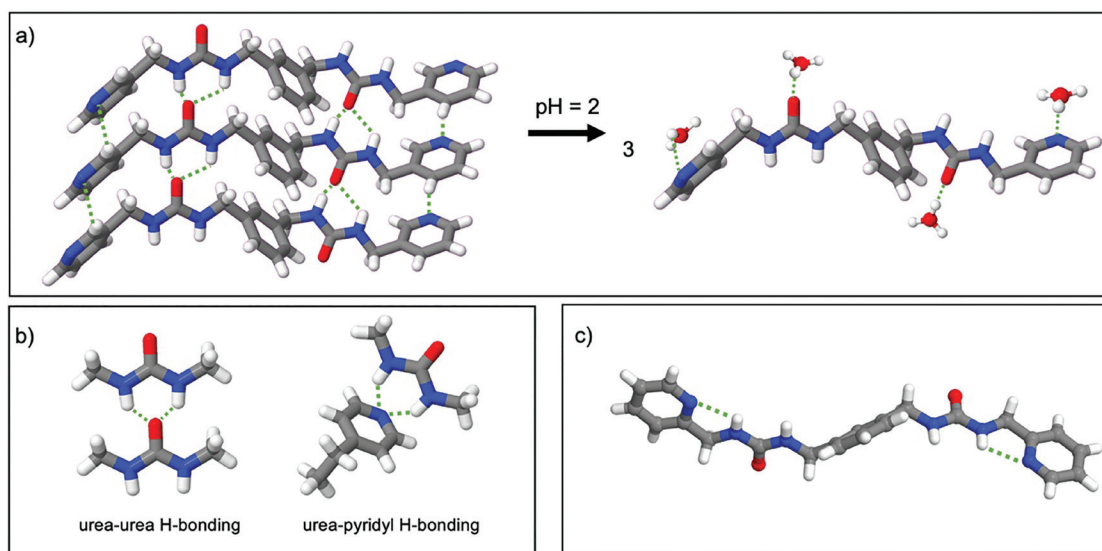


Figure 1. [a] Possible one-dimensional supramolecular assembly of bis-urea compound a showing H-bonding between the urea groups (O=CNH \cdots O=CNH) and pyridyl groups (C-H \cdots N). At pH 2, the network assembly is disrupted due to protonation of C=O and pyridyl N, which results to dissolution of compound a; [b] significant H-bonding interactions observed from MD simulations (van Lommel *et al.* 2020), with intermolecular urea-pyridyl H-bonding as potentially the predominant interaction for compound b; [c] possible intramolecular H-bonding in compound c, which disfavored network formation.

bonding between the pyridyl groups (Rutgeerts *et al.* 2019; Jones *et al.* 2017; Rotger *et al.* 2008). Alternatively, in addition to the urea-urea H-bonding, the self-assembly could also involve the formation of hydrogen bonds between water molecules and the pyridyl groups, linking together the bis-urea monomer units as shown in Figure A17 of the appendices (Schlücker *et al.* 2001).

In the study conducted by van Lommel *et al.* (2020), the gelation behavior of picolyl-containing bis-urea compounds was investigated using a combination of computational techniques – including the density functional theory, molecular dynamics (MD) simulation, and non-covalent interaction index. In the initial stages of the self-assembly process, two types of H-bonding interactions were observed – [1] urea-urea ($\text{O}=\text{CNH}\cdots\text{O}=\text{CNH}$) and [2] urea-pyridyl ($\text{O}=\text{CNH}\cdots\text{NPyr}$) (Figure 1b). Urea-urea H-bonding is a crucial factor that induces the formation of supramolecular aggregates, whereas the latter interaction could impede the one-dimensional network assembly. MD simulations revealed that both *o*- and *p*-picolyl substituted bis-urea compounds exhibit significant urea-pyridyl ($\text{O}=\text{CNH}\cdots\text{NPyr}$) H-bonding due to their favorable conformations, with intramolecular interactions being particularly prominent in the *o*-picolyl derivatives (Figure 1c). Because this specific interaction could disrupt the network formation, this offers a plausible explanation for the observed difference in the gelation behaviors of compounds a–c, wherein no gels were formed for compounds b and c.

The solubility of compounds a–c was shown to increase with decreasing pH as a result of the protonation of the basic picolyl and urea carbonyl groups (Estroff and Hamilton 2000) (Figure 1a). Although they were either insoluble or gelled at pH 3–12, all three compounds dissolved at pH 2, with compound a not being able to form gels. It could be that the degree of ionization of the picolyl groups is too high that the molecule becomes too soluble to gelate.

Compounds d–f, on the other hand, feature nonpolar end groups with benzyl, cyclohexyl, and hexyl groups attached, respectively. They bear non-polar end groups that may have been too hydrophobic to dissolve in the aqueous solvent.

The gels obtained were easily destroyed by mechanical agitation. However, the reformation of the gels even after repeated heating and cooling of the sol-gel system indicates thermoreversibility, which is an important feature of LMWG-based gels (de Loos *et al.* 2005b). It was also observed that the CGC of gels from pH 3–12 decreased from 0.5 to 0.2 wt/v%, with the gel at pH 12 capable of forming an unstable gel at 0.1 wt/v%. The decreasing CGC values of the gels with increasing pH

may be attributed to the presence of basic ionizable picolyl groups in compound a (Milanesi *et al.* 2011). Decreasing the pH of the solvent may have caused decreased hydrogen-bonding capabilities of the urea and pyridine end group due to ionization, possibly disrupting the network assembly (Srivastava *et al.* 2005). Thus, gelation results signify that the pyridine-mediated hydrogen bonding of the end groups is also an important factor in gel formation, which supports the proposed orthogonal self-assembly (Rutgeerts *et al.* 2019).

Hydrogels obtained from compound a appeared white and translucent at all pH levels. Figure 2 shows the gels of compound a formed at pH 3 and 12.

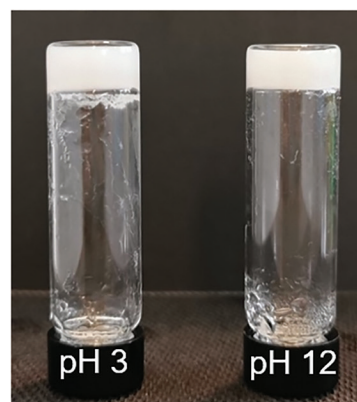


Figure 2. Gels of compound a at 1.0 wt/v% at pH 3 and 12.

Gel Characterizations

Scanning electron microscopy (SEM) imaging.

SEM was used to determine the gel matrix structure of compound a. The gel of compound a at pH 12 was used since it had the highest physical observable stability at its lowest CGC value. The hydrogel was lyophilized to produce xerogels, which were then prepared for imaging analysis. The SEM image shown in Figure 3 features intertwined nanofiber bundles with an average width of ~ 200–250 nm. Space pockets shown may be from the entrapment of the solvent during the gelation process. At high magnification (x25000), the nanostructures of the gels looked like tangled and twisted threads, which is still comparable to the images seen by Rutgeerts *et al.* (2019). This stable three-dimensional structure with secured spaces for solvent molecules may be the reason for the solid-like rheological property of the gel.

Rheological measurements. Viscoelastic properties of the gel of compound a were determined through an oscillatory amplitude test and an oscillatory frequency sweep, with results plotted in Figure 4. Gel samples were prepared at 5 wt/v% in a pH 12 aqueous solvent. The

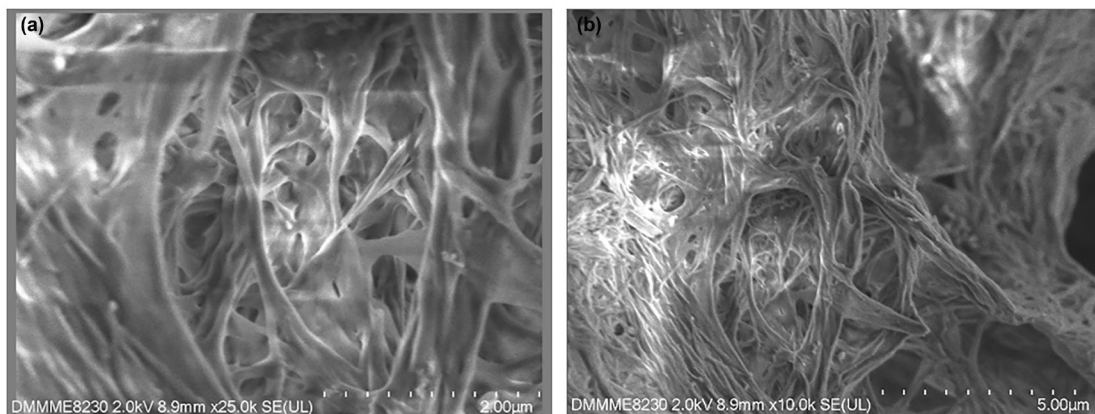


Figure 3. SEM images of xerogel of compound a at pH 12 at a magnification of [a] x25000 and [b] x10000.

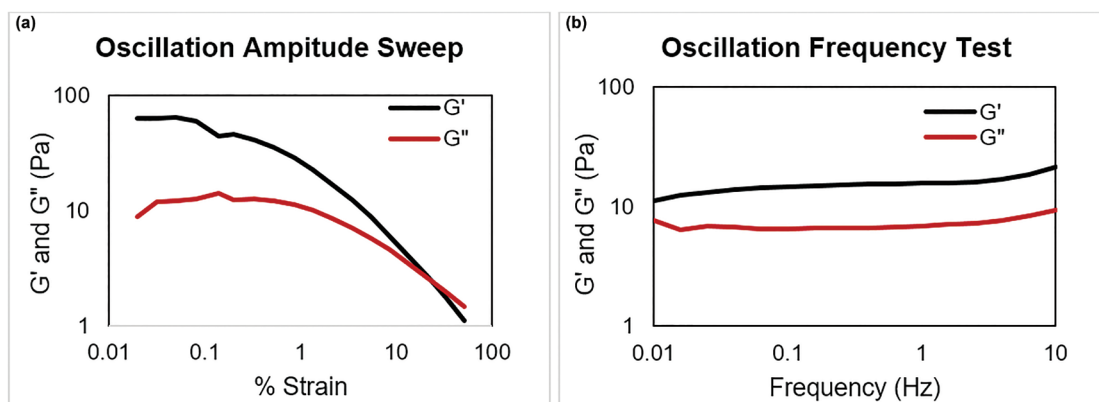


Figure 4. [a] Oscillation amplitude sweep and [b] oscillation frequency test of gel of compound a at pH 12.

oscillation amplitude test showed initial storage (G') and loss (G'') modulus values to be equal to 63.9 and 8.85 Pa, respectively (Figure 3a), and the oscillation frequency sweep showed parallel-like pattern for G' and G'' , where G' remains larger than G'' throughout the frequency range (Figure 3b). The oscillation amplitude sweep showed $G' > G''$ confirming the expected solid-like behavior of the hydrogel at low strains. The crossover point in the oscillatory amplitude plot, where G' becomes equal to G'' , showed a strain value of 23.2% – indicating the level of strain applied at which the gel network breaks apart and gel-sol transition occurs (G'' becomes greater than G'). This behavior is called shear thinning, a property important to some commercial and biomedical applications (Chen *et al.* 2017). Additionally, the oscillation frequency test also confirmed the solid-like nature of the gel with $G' > G''$, with both values showing very little dependence on the frequency, which is also another common property observed in other supramolecular gels.

CONCLUSION

The gelation properties of six low-molecular-weight phenyl bis-urea hydrogelators were explored in varying pH. Variations in the peripheral substituents of the gelators were employed, causing differences in the gelating ability of each hydrogelator. Nonpolar substituents were shown to be completely insoluble at all pH, whereas compounds bearing the ionizable picolyl end groups modulated the solubility of the gelator, which increased with decreasing pH. Based on the results, *m*-picolyl bis-urea compounds were found to be effective gelators over a wide pH range of pH 3–12. A decreasing trend for the critical gelation concentration was observed with increasing pH due to the ionizing property of its picolyl end groups. The para and ortho isomers, along with the other compounds bearing nonpolar substituents, however, did not form gels at all pH ranges – indicating the importance of molecular structural design responsible for self-assembly in gel formation. A sample gel matrix as viewed under SEM was composed of intertwined nanofiber aggregates, which confirmed the formation of a three-dimensional network during gelation.

Rheological tests confirmed the solid-like nature of the gels with $G' > G''$ at low strains and the ability to flow at higher strains. Findings in this study may be useful in hydrogel applications requiring pH sensitivity, such as in drug delivery and biosensors. To further understand how pH influences the gelation properties, morphology, and rheological behavior of the bis-urea hydrogelators, future studies are directed toward refining the molecular structure by employing other types of aromatic and aliphatic linkers, as well as more polar end groups.

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STATEMENT ON CONFLICT OF INTEREST

The authors declare no conflict of interest.

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