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Anion-induced Mechanical Properties of Stimuli-Responsive Supramolecular Gels based on *N*-oxide amides

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ABSTRACT

Supramolecular gels are an excellent class of stimuli-responsive materials where the self-assembly process can be turned ON/OFF by external stimuli such as heat, sound, light, ions, and pH. However, creating stimuli-responsive low molecular weight gelators (LMWGs) with predictable properties can be difficult because the self-assembly and gelation properties depend on various experimental conditions. Our group has reported that modifying a known gelator will help us understand the self-assembly process, enabling us to design new gelators with predictable properties. We have modified LMWGs of pyridyl amides namely *N*-(4-pyridyl)isonicotinamide and *N*-(4-pyridyl)nicotinamide, to di-*N*-oxides such as *N*-(4-pyridyl)isonicotinamide *N*-oxide (PINNox) and *N*-(4-pyridyl)nicotinamide *N*-oxide (PNNox) respectively. In this work, we evaluate the effect of anions on the mechanical properties of isomeric PINNox and PNNox, which were performed using rheological experiments. This will help to evaluate the role of positional isomers on the mechanical properties of *N*-oxide gels in the presence of an external entity.

INTRODUCTION

Supramolecular gels based on low-molecular-weight organic molecules (LMWGs)[1-10] are a fantastic category of stimuli-responsive materials that have alluring potential applications such as tissue engineering, dynamic gels, sensors, tissue engineering and as media for catalysis and crystal growth.[10-18] In forming the gel network, the gelator's non-bonding interaction and molecular structure play a critical role. However, it is challenging to predict the mechanism of the self-assembly process and the gel structure because the non-covalent interactions are dynamic in nature and the self-assembly process depends on the spatial orientation of the functional groups. Understanding the role of functional groups/building blocks and the nature of the non-bonding interactions will aid researchers in designing smart materials based on LMWGs with fascinating properties. LMWGs based on amide groups are an excellent class of stimuli-responsive material, and their gelation ability can be tuned by applying external stimuli such as heat, sound, light, ions, and pH.

The incorporation of pyridyl amide groups has the potential to produce many isomers that are determined by the specific arrangement of the pyridyl nitrogen atom, which could enhance the stimuli-responsive properties.[7, 19-22] In addition, they offer other benefits, including the convenience of obtaining crystalline materials and the ease of synthesis. By substituting the pyridyl group with pyridyl-*N*-oxide, the gelation characteristics of bis-pyridyl LMWGs can be adjusted, leading to the formation of pyridyl-N-oxide LMWGs.[23] Compounds based on pyridyl-

N-oxide moieties have various applications in synthetic and bio-chemistry and in medicinal science.[24-27] The incorporation of pyridyl-*N*-oxides moieties helps to enhance the hydrogen bonding and solubility in water [28-29], making them a good hydrogelator, but there are only a few reports of LMWGs based on pyridyl-*N*-oxides moieties.[28, 30-31]

The relative position of the functional groups plays a crucial role in gel network formation. For example, in pyridyl-amide/urea gelators, compounds derived from *N*-(4-pyridyl) moiety are mostly proved to be superior gelators over the other positional isomers.[32-33] The relative position of *N*-oxide moieties could also play an important role in the self-assembly process and the gelation properties of LMWGs.[23, 34] We have reported the gelation ability of mono-/bis-pyridyl-*N*-oxide compounds of *N*-(4-pyridyl)isonicotinamide (4PINA)[28] and have shown that bis-pyridyl-*N*-oxide displayed enhanced mechanical and thermal properties. We have also reported that the relative position of *N*-oxide moieties is crucial for the effective interaction of the gelator with salts/ions, resulting in LMWGs. In this work, we evaluate the effect of anions on the mechanical properties of isomeric PINNox and PNNox, which were performed by rheological experiments. This will help to evaluate the role of positional isomers on the mechanical properties of *N*-oxide gels in the presence of an external entity. We are analyzing the role of *N*-oxide moieties in gel network formation by comparing the gelation ability of isomeric pyridyl-*N*-oxide amides in water.

EXPERIMENTAL SECTION

We have commercially purchased all the starting materials and solvents from Sigma-Aldrich, Fluorochem, and TCI-Europe, and they were used as supplied. The gelation experiments were conducted using deionized water. The Bruker AVANCE 400 spectrometer was used to record the ^{1}H and ^{13}C NMR spectra. Rheological tests were conducted using an Anton Paar MCR 302 rheometer. A Peltier hood was utilized for temperature control during the rheological experiments.

Synthesis: The *N*-Oxides PNNox and PINNox were synthesized by oxidizing N-(4-pyridyl)-nicotinamide and *N*-(4-pyridyl)-isonicotinamide, respectively, using 3-chloroperoxybenzoic (Figure 1).[23, 28]

Gelation test: In a standard 7.0 mL vial with an inner diameter of 1.5 cm, about 10.0 mg of the compound was taken, and 1.0 mL of solvent/solvent mixture was added. The vial was sealed, sonicated and slowly heated to dissolve the substance. The gelation was tested using a vial inversion test. The procedure was repeated at various higher concentrations of the compound (until 50.0 mg).

Gel-sol transition temperature (T_{gel}): T_{gel} measurements were performed with the hydrogels of ligands PNNox AND PINNox. A small spherical glass ball (100.0 mg) was carefully placed on top of the gel, 24 hours after the gelation. The vial was submerged in an oil bath with a magnetic stirrer and thermosensor attached to control the temperature. The oil bath's temperature was raised by approximately 10.0 °C per minute. The temperature at which the glass ball contacts the vial's bottom after being heated progressively and submerged in the gel was measured and recorded as the T_{gel}.

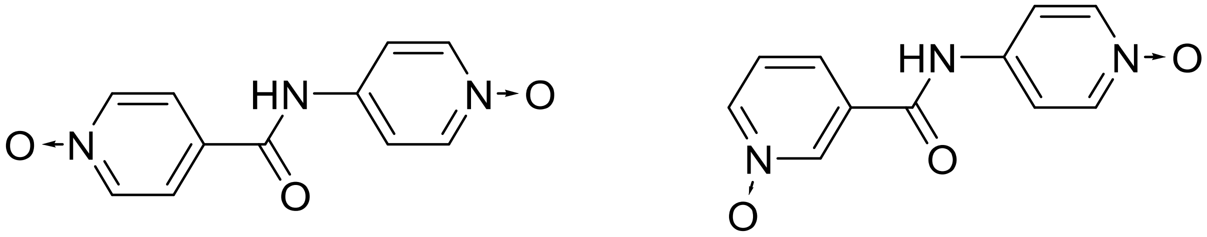
Rheology: The mechanical strengths of the hydrogels with PNNox and PINNox were measured in an Anton Paar MCR 102 modular compact rheometer utilizing a stainless-steel parallel plate geometry design with a diameter of 25.0 mm. Gels of PNNox and PINNox were prepared at 40.0 mg and 18.0 mg of the corresponding gelator in 1.0 mL of water. The experiments involved placing around a 1.0 mL portion of the gel onto the plate. Oscillatory experiments were conducted at a constant temperature of 20.0 °C to examine the viscoelastic characteristics.

Amplitude sweeps were carried out at a set frequency of 1.0 Hz and with a logarithmic ramp strain (γ) ranging from 0.01% to 100%. Frequency sweeps were performed between 0.1 and 10.0 Hz within the linear viscoelasticity range, using a strain of 0.02%. To conduct frequency and amplitude sweeps, a Peltier temperature control wrap was used to prevent evaporation and keep the temperature at a constant 20.0 °C.

Anion sensing: Anion sensing experiments were performed with the hydrogels of PNNox and PINNox, which were prepared at 40.0 mg and 18.0 mg with 1.0 equiv. of various potassium and sodium salts. The standard procedure for gelation was performed to check the effect of salts/ions on the gelation properties of these compounds.

RESULTS AND DISCUSSION

We have shown that the relative position of *N*-oxide moieties plays an important role in anion sensing for PINNox and PNNox,[23] but the effect of anions on gel state properties has not been studied. Hence, we have synthesized PINNox[28] and compared the gelation properties with the already reported PNNox (Figure 1).[23]



PINNox **PNNox**

FIGURE 1: Structures of *N*-(4-pyridyl)isonicotinamide *N*-oxide (PINNox) and *N*-(4-pyridyl)nicotinamide *N*-oxide (PNNox)

The gelation experiments were performed in water, and both **PINNox** and **PNNox** were found to be hydrogelators (Figure 2). The minimum gelator concentration (MGC) of PINNox was higher than PNNox (Table 1), which indicates that PNNox gelled at a lower concentration than PINNox.

TABLE 1. *Gel to sol transition temperature (T_{gel}) and MGC of PINNox and PNNox in water.*

Gelator	MGC (wt%)	T_{gel} (^{0}C)
PINNox	4.0	71.8
PNNox	1.8	76.9

By employing the "dropping ball" method to record the gel to sol transition temperature (T_{gel}), the thermal stability of the gel network was determined. The PNNox, which gelled at 1.8 wt%, had a T_{gel} of 76.9 ^{0}C, while the PINNox at 4.0 wt% showed a lower thermal strength of 71.8 ^{0}C. The thermal strength analysis revealed that the relative position of *N*-oxide can influence the gelation properties.

FIGURE 2: Hydrogel of PINNox at 4.0 wt% in water.

Rheology has been used to analyze the flow characteristics and gel deformation in supramolecular gels.[35-36] The relative position of *N*-oxide moieties in the presence of anions could play a vital role in the gel state properties, and we have analyzed the effect of anions on the mechanical properties of these LMWGs with/without anions by performing the amplitude- and frequency-sweep experiments on the hydrogels. The gel network undergoes reversible deformation inside the linear viscoelastic region (LVER), so it is important to perform amplitude sweep experiments to determine the LVER. This was done by making measurements at a constant oscillation amplitude and temperature whilst measuring over a range of oscillation frequencies. The results indicated that the storage modulus G' declined after 0.02 % of the shear strain, demonstrating that both the hydrogels had a narrow LVER (Figure 3).

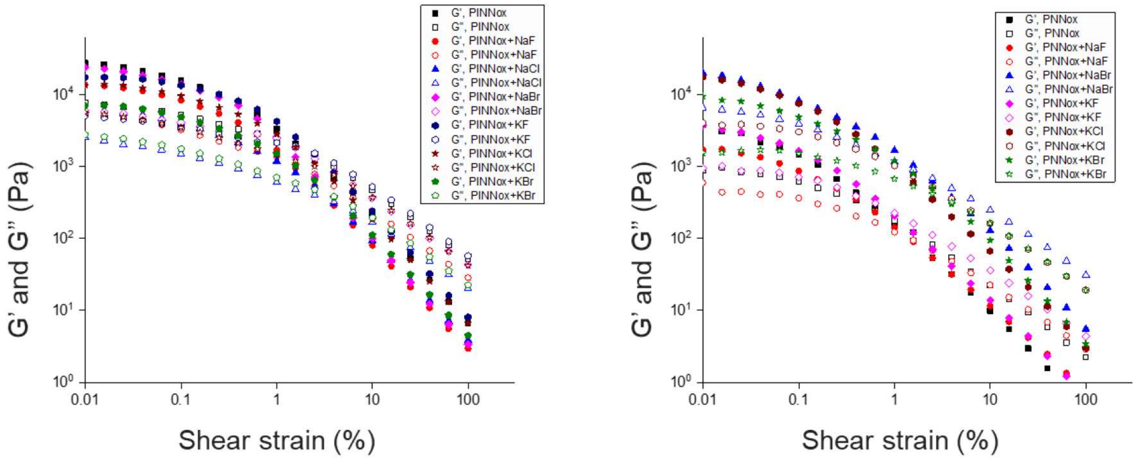


FIGURE 3: Amplitude sweep experiments with gels of PINNox at 4.0 wt% and PNNox at 1.8 wt% with/without anions in water at 20.0 °C with a constant frequency of 1.0 Hz.

Frequency sweep experiments were performed on the hydrogels at MGC in the presence/absence of anions to evaluate the effect of anions on the mechanical strength of the gelators (Figure 4). The comparison of mechanical strength revealed that the gel network of PINNox (4.0 wt%) was weakened in the presence of anions (Table 2). Similar results were observed for potassium salts, indicating that the effect of cation is nominal for PINNox gels.

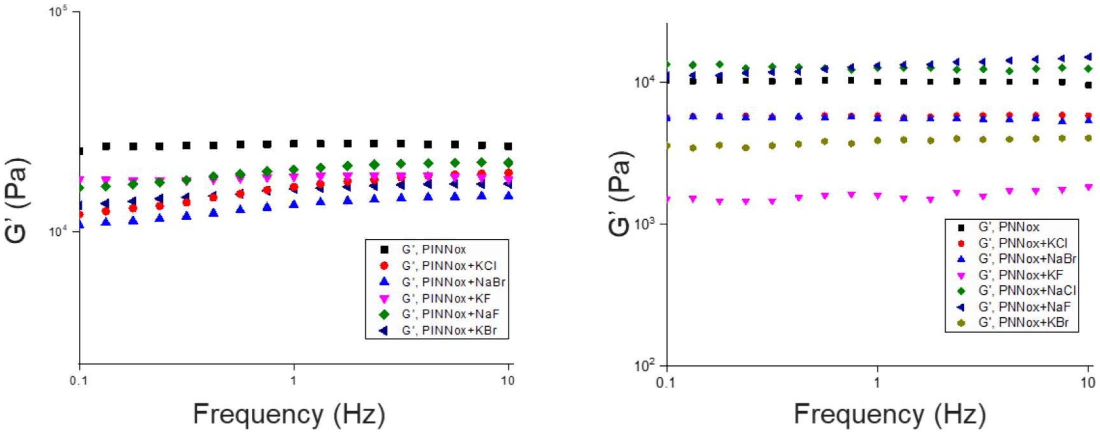


FIGURE 4: Frequency sweep at a constant strain of 0.02 % with (a) PINNox and (b) PNNox at 4.0 wt% in the presence of various anions in water.

However, anion-responsive gel properties were observed for PNNox hydrogel (Table 2), and the mechanical strength was affected by the size of the anions. The comparison of the elastic (G′) and viscous (G″) moduli indicated that smaller anions, such as fluoride and chloride ions, enhanced the mechanical strength of PNNox, but a reverse trend was observed for larger anions, such as bromide. The gel network collapsed in the presence of iodide salts, and these results indicate that mechanical strength depends on the electronegativity of the halide salts.

TABLE 2. *The effect of anions on the storage modulus in comparison to the blank corresponding hydrogels*

Salts	Equivalence of salt	PNNox (1.8 wt%)	PINNox (4.0 wt%)
No Anion	0	1	1
NaF	1	1.6	0.8
KF	1	0.2	0.7
NaCl	1	1.3	0.7
KCl	1	0.6	0.8
NaBr	1	0.6	0.6
KBr	1	0.4	0.7

The comparison of the results indicates that PNNox formed a stronger gel network than PINNox gels, indicating that the mechanical strength depends on the relative position of *N*-oxide moieties. Furthermore, the relative position of the functional groups plays an important role in the anion-sensing ability because the nature of anions did not affect the PINNox. However, a drastic change was observed for PNNox, and the mechanical strength depends on the size of the anions. We repeated the experiments for PNNox with potassium salts, and a similar trend was observed. Mechanical strength analysis revealed that potassium salts weakened the gel network compared to sodium salts. This prompted us to evaluate the cation sensing application of PNNox gels, and the effect of cation on the mechanical strength of PNNox gels is ongoing.

CONCLUSION

We have synthesized two di-*N*-oxide derivatives of isonicotinamide and nicotinamide, PINNox and PNNox, respectively. Gelation studies revealed that both PINNox and PNNox were hydrogelators with MGCs of 4.0 and 1.8 wt%, respectively. Rheological studies showed that anions lowered the mechanical strength of PINNox gels. Anion-responsive mechanical strength was observed for PNNox gels, and enhanced mechanical strength was observed in the presence of NaF and NaCl. However, a reverse trend was observed for bromide and iodide salts. These results indicate that positional isomers play an important role in the mechanical properties in the presence of anions. PNNox also displayed a similar trend towards potassium salts, indicating the possibility of a cation sensor. The studies based on the cation sensing capabilities of the PNNox gels are ongoing.

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REFERENCES

1. Banerjee, S.; Das, R. K.; Maitra, U., Supramolecular gels 'in action'. *J. Mater. Chem.* **2009,** *19* (37), 6649-6687.
2. Dastidar, P., Supramolecular gelling agents: can they be designed? *Chem. Soc. Rev.* **2008,** *37* (12), 2699-2715.

3. de Loos, M.; Feringa, B. L.; van Esch, J. H., Design and Application of Self-Assembled Low Molecular Weight Hydrogels. *Eur. J. Org. Chem.* **2005,** *2005* (17), 3615-3631.

4. Estroff, L. A.; Hamilton, A. D., Water Gelation by Small Organic Molecules. *Chem. Rev.* **2004,** *104* (3), 1201-1218.

5. George, M.; Weiss, R. G., Molecular Organogels. Soft Matter Comprised of Low-Molecular-Mass Organic Gelators and Organic Liquids†. *Acc. Chem. Res.* **2006,** *39* (8), 489-497.

6. Hirst, A. R.; Escuder, B.; Miravet, J. F.; Smith, D. K., High-Tech Applications of Self-Assembling Supramolecular Nanostructured Gel-Phase Materials: From Regenerative Medicine to Electronic Devices. *Angew. Chem. Int. Ed.* **2008,** *47* (42), 8002-8018.

7. Steed, J. W., Anion-tuned supramolecular gels: a natural evolution from urea supramolecular chemistry. *Chem. Soc. Rev.* **2010,** *39* (10), 3686-3699.

8. Yu, G.; Yan, X.; Han, C.; Huang, F., Characterization of supramolecular gels. *Chem. Soc. Rev.* **2013,** *42* (16), 6697-6722.

9. Chivers, P. R. A.; Smith, D. K., Shaping and structuring supramolecular gels. *Nat Rev Mater* **2019,** *4* (7), 463-478.

10. Kumar, D. K.; Steed, J. W., Supramolecular gel phase crystallization: orthogonal self-assembly under non-equilibrium conditions. *Chem. Soc. Rev.* **2014,** *43* (7), 2080-2088.

11. Truong, W. T.; Su, Y.; Meijer, J. T.; Thordarson, P.; Braet, F., Self-assembled gels for biomedical applications. *Chem. Asian J.* **2011,** *6* (1), 30-42.

12. Foster, J. A.; Damodaran, K. K.; Maurin, A.; Day, G. M.; Thompson, H. P.; Cameron, G. J.; Bernal, J. C.; Steed, J. W., Pharmaceutical polymorph control in a drug-mimetic supramolecular gel. *Chem. Sci.* **2017,** *8* (1), 78.

13. Zhu, J.; Wang, R.; Geng, R.; Zhang, X.; Wang, F.; Jiao, T.; Yang, J.; Bai, Z.; Peng, Q., A facile preparation method for new two-component supramolecular hydrogels and their performances in adsorption, catalysis, and stimuli-response. *RSC Adv.* **2019,** *9* (39), 22551-22558.

14. Qu, R.; Shen, L.; Qu, A.; Wang, R.; An, Y.; Shi, L., Artificial Peroxidase/Oxidase Multiple Enzyme System Based on Supramolecular Hydrogel and Its Application as a Biocatalyst for Cascade Reactions. *ACS Appl. Mater. Interfaces.* **2015,** *7* (30), 16694-16705.

15. Zhang, X.; Liu, J.; Gao, Y.; Hao, J.; Hu, J.; Ju, Y., Multi-stimuli-responsive hydrogels of gluconamide-tailored anthracene. *Soft Matter* **2019,** *15* (23), 4662-4668.

16. Yan, L.; Li, G.; Ye, Z.; Tian, F.; Zhang, S., Dual-responsive two-component supramolecular gels for self-healing materials and oil spill recovery. *Chem. Commun.* **2014,** *50* (94), 14839-14842.

17. Patterson, A. K.; Smith, D. K., Two-component supramolecular hydrogel for controlled drug release. *Chem. Commun.* **2020,** *56* (75), 11046-11049.

18. Buerkle, L. E.; Rowan, S. J., Supramolecular gels formed from multi-component low molecular weight species. *Chem. Soc. Rev.* **2012,** *41* (18), 6089-6102.

19. Lloyd, G. O.; Piepenbrock, M.-O. M.; Foster, J. A.; Clarke, N.; Steed, J. W., Anion tuning of chiral bis(urea) low molecular weight gels. *Soft Matter* **2012,** *8* (1), 204-216.

20. Piepenbrock, M.-O. M.; Lloyd, G. O.; Clarke, N.; Steed, J. W., Metal- and Anion-Binding Supramolecular Gels. *Chem. Rev.* **2010,** *110* (4), 1960-2004.

21. Lloyd, G. O.; Steed, J. W., Anion-tuning of supramolecular gel properties. *Nat. Chem.* **2009,** *1* (6), 437-442.

22. Piepenbrock, M.-O. M.; Lloyd, G. O.; Clarke, N.; Steed, J. W., Gelation is crucially dependent on functional group orientation and may be tuned by anion binding. *Chem. Commun.* **2008,** (23), 2644-2646.

23. Jayabhavan, S. S.; Kristinsson, B.; Ghosh, D.; Breton, C.; Damodaran, K. K., Stimuli-Responsive Properties of Supramolecular Gels Based on Pyridyl-N-oxide Amides. *Gels* **2023,** *9* (2), 89.
24. Reddy, L. S.; Babu, N. J.; Nangia, A., Carboxamide–pyridine N-oxide heterosynthon for crystal engineering and pharmaceutical cocrystals. *Chem. Commun.* **2006,** (13), 1369-1371.
25. Mfuh, A. M.; Larionov, O. V., Heterocyclic N-oxides-an emerging class of therapeutic agents. *Curr. Med. Chem.* **2015,** *22* (24), 2819-2857.
26. Saikia, B.; Khatioda, R.; Bora, P.; Sarma, B., Pyridine N-oxides as coformers in the development of drug cocrystals. *CrystEngComm* **2016,** *18* (43), 8454-8464.
27. Puttreddy, R.; Beyeh, N. K.; Ras, R. H. A.; Trant, J. F.; Rissanen, K., Endo-/exo- and halogen-bonded complexes of conformationally rigid C-ethyl-2-bromoresorcinarene and aromatic N-oxides. *CrystEngComm* **2017,** *19* (30), 4312-4320.
28. Ghosh, D.; Mulvee, M. T.; Damodaran, K. K., Tuning Gel State Properties of Supramolecular Gels by Functional Group Modification. *Molecules* **2019,** *24* (19), 3472.
29. Sauvée, C.; Ström, A.; Haukka, M.; Sundén, H., A Multi-Component Reaction towards the Development of Highly Modular Hydrogelators. *Chem. Eur. J.* **2018,** *24* (32), 8071-8075.
30. Ghosh, D.; Deepa; Damodaran, K. K., Metal complexation induced supramolecular gels for the detection of cyanide in water. *Supramol. Chem.* **2020,** *32* (4), 276-286.
31. Ghosh, D.; Ferfolja, K.; Drabavičius, Ž.; Steed, J. W.; Damodaran, K. K., Crystal habit modification of Cu(ii) isonicotinate–N-oxide complexes using gel phase crystallisation. *New J. Chem.* **2018,** *42* (24), 19963-19970.
32. Kumar, D. K.; Jose, D. A.; Dastidar, P.; Das, A., Nonpolymeric Hydrogelator Derived from N-(4-Pyridyl)isonicotinamide. *Langmuir* **2004,** *20* (24), 10413-10418.
33. Kumar, D. K.; Jose, D. A.; Das, A.; Dastidar, P., First snapshot of a nonpolymeric hydrogelator interacting with its gelling solvents. *Chem. Commun.* **2005,** (32), 4059-4061.
34. Ghosh, D.; Bjornsson, R.; Damodaran, K. K., Role of N–Oxide Moieties in Tuning Supramolecular Gel-State Properties. *Gels* **2020,** *6* (4), 41.
35. Goodwin, J. W.; Hughes, R. W., *Rheology for chemists: an introduction*. Royal Society of Chemistry: 2008.
36. Guenet, J.-M., *Organogels: Thermodynamics, structure, solvent role, and properties*. Springer: 2016.