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PII: S0022-4596(19)30532-8

DOI: https://doi.org/10.1016/j.jssc.2019.121027

Reference: YJSSC 121027

To appear in: Journal of Solid State Chemistry

Received Date: 22 September 2019

Revised Date: 19 October 2019

Accepted Date: 22 October 2019

Please cite this article as: P. Yadav, A. Ballabh, N-(thiazol-2-yl)benzamide derivatives as a new series of supramolecular gelators: Role of methyl functionality and S…O interaction, *Journal of Solid State Chemistry* (2019), doi: https://doi.org/10.1016/j.jssc.2019.121027.

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ABSTRACT

A new series of N-(thiazol-2-yl) benzamide derivatives were synthesized, characterized and investigated for their gelation behavior with the aim to elucidate the role of methyl functionality and multiple non-covalent interactions on gelation/non-gelation behavior using Crystal engineering approach. Interestingly, two amides, namely, 3-methyl-N-(thiazol-2-yl) benzamide (**1c**) and 3-methyl-N-(5-methylthiazol-2-yl) benzamide (**3c**) displayed gelation behavior towards ethanol/water and methanol/water mixture with good stability and low minimum gelator concentration (MGC). The single crystal structure of gelator (**1c**) displayed the helical assembly driven by π - π interaction along with cyclic N-H...N and S...O interaction, whereas single crystal structure of gelator (**3c**) displayed 2D hydrogen bonded network without any π - π interaction.

KEYWORDS: Crystal engineering, supramolecular gelators, S...O interaction, helical architecture, thiazole amide derivatives

INTRODUCTION

2-aminothiazole and its derivatives, a simple heterocyclic compound, with huge biological implication are at the forefront of research and development since many decades.¹ Surprisingly, the use of 2-aminothiazole as structural motif for crystal engineering and supramolecular assembly is not addressed to its fullest.^{2,3} In our quest for new supramolecular gelators, we serendipitously discovered 2-aminothiazole as a versatile structural motif for design and synthesis of new Low Molecular Weight gelators (LMWGs).⁴⁻⁸ LMWGs are special class of supramolecular materials capable of immobilizing solvent (water, organic or mixture) through weak non-covalent interactions such as hydrogen bonding, π - π , van der Waals forces, etc. In last two decades, design, synthesis and application of new LMWGs have gained considerable interest due to its potential applications in various areas of research ranging from material science to biomedical applications.⁹⁻¹⁵ Even though, most of the LMWGs were discovered serendipitously but crystal engineering approach proved to be a reliable tool for designing new LMWGs.^{16,17}

Recently, we found series of compounds, which can be classified as LMWGs based on 2aminothiazole capable of immobilizing water¹⁸ and organic solvents.^{19,20} Our studies on aliphatic amides of 2-aminothiazole displayed many interesting properties such as dependence of gelation behaviour on the position of methyl functionality on 2-aminothiazole as well as number of methylene group in the aliphatic backbone, i.e., even number of methylene groups (-CH₂) displayed gelation, whereas odd number of –CH₂ group was found to be deterrent to gelation behaviour.¹⁹

Inspired by our success with 2-aminothiazole based LMWGs (salts, amides, metal complex), we decided to design new series of compounds containing the 2-aminothiazole moiety, amide linkage and aromatic backbone (**Chart 1**). These set of compounds may provide an opportunity

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to study the role of π - π interaction in inducing supramolecular gelation along with other weak non-covalent interactions such as (methyl) C-H... π , (methyl) C-H...N, (methyl) C-H...S (**Scheme 1**). Our studies on 2-aminothiazole based LMWGs displayed frequent occurrence of intermolecular cyclic N-H...N interaction and intramolecular (amide) O.....S (thiazole) interactions (**Scheme IA**). Surprisingly, S...O interaction is rarely explored as supramolecular glue in crystal engineering related studies²¹ as compared with its prevalence in biological system.²²⁻²⁶

In the present study, series of thiazole based amide having aromatic backbone were synthesized and characterized by various physicochemical methods. The effect of position of methyl functionality (thiazole moiety and benzene ring) on crystalline packing and gelation behavior was evaluated. Out of 12 compounds synthesized two (**1c** and **3c**) displayed excellent gelation behavior towards ethanol/water and methanol/water mixture (1:1). The single crystal structure of two gelators (**1c** and **3c**) and non-gelators (**1b**, **1d**, **3b** and **3d**) were compared to understand the cause of gelation/ non-gelation behavior based on hydrogen bonding pattern and synergistic effect of other weak non-covalent interaction such as S...O, C-H... π , π ... π , etc.



Chart I: List of N-(thiazol-2-yl)benzamide derivatives synthesized in the present study



Scheme 1: Probable supramolecular synthons in amides and thiazole containing amides

Experimental Section

Materials and physical measurements

2-Aminothiazole (97%), 2-Amino-5-methylthiazole (98%), 2-Amino-4-methylthiazole (98%), benzoic acid (97%), 2-toluicacid (98%), 3-toluic acid (98%), 4-toluicacid (99%) (All Chemical were purchased from Aldrich) were used as received. The other chemicals were of the highest commercial grade available and were used without further purification. The solvents used for the preparation of gels were reagent grade. All solvents used in the synthesis were purified, dried and distilled as required. FTIR Spectra were recorded on a Perkin Elmer -RX FTIR instrument. Solid samples were recorded as an intimate mixture with powdered KBr. Microanalysis was performed on Perkin Elmer elemental analyzer (Series II, 2400). The ¹H- NMR spectra were measured by using a Bruker AVANCE, 400MHZ for ¹H-NMR with TMS as internal standard. Morphologies of all reported gel materials were investigated using Scanning Electron Microscopy (SEM) (JEOL JSM5610 LV microscope). For SEM study, the gel samples were dried at room temperature (25°C) to obtain xerogel, followed by recording the micrographs. Single crystal X-ray study was carried out on Single Crystal X-ray diffractometer (Xcalibur, EOS, Gemini diffractometer). All structures were solved and refined using the Olex2²⁷ software and ShelXL²⁸ refinement package Graphics are generated using MERCURY 3.9. All structures are solved by direct methods and refined in a routine manner. In all cases, non-hydrogen atoms are treated anisotropically. Whenever possible, the hydrogen atoms are located on a difference Fourier map and refined. In other cases, the hydrogen atoms are geometrically fixed.

Rheological study: Sample **1a** and **1c** were subjected to rheological study by amplitude sweep methods using TA instruments (Model- ARES G2) at 25°C. Rheometer has parallel plate geometry with a plate diameter of 50 mm maintained at a gap of 1mm. The gel samples were

subjected to frequency variation of 10 rad/s. The storage (G') and loss modulus (G'') of the samples were evaluated with respect to oscillation strain (in %).

Gelation Study

A weighted amount of potential gelator and a measured volume of selected pure organic solvent were placed into a test tube, and the system was heated in oil or water bath until all solid materials were dissolved. The solution was cooled to room temperature and finally, the test tube was turned upside down to observe if the solution inside could still flow. A positive test is obtained if the flow test is negative. Systems in which only solution remained until the end of the tests are referred as solutions (S). Systems that are clear solutions when they are hot but precipitation or crystallization occurs when they are cooled down to room temperature are denoted by P (precipitation) and R (recrystallization), respectively. Temperatures of gel-to-sol transition (T_{gel}) were determined by using a conventional "falling ball" method. In a typical T_{gel} measurement experiment, a small glass ball (63mg) was carefully placed on the top of the gel sample in a test tube. The tube was slowly heated in a thermostated oil bath until the ball fell to the bottom of the test tube. The temperature at which the ball touched the bottom of the test tube was recorded as gel-sol transition temperature (T_{gel}) for a given gelator-solvent system.

Synthetic procedure

Synthesis method of N-(thiazol-2-yl) benzamide derivatives

Oxalyl chloride (2 mL, 20 mmol) was added slowly to a solution of monocarboxylic acids (2 mmol) in dry dichloromethane (10 mL) under a nitrogen atmosphere with continuous stirring and reaction mixture was kept for 12 hours under inert atmosphere. Excess oxalyl chloride and solvent were removed by distillation under reduced pressure. The acid chloride obtained was

dissolved in dry dichloromethane (10 mL) and subsequently, added to the 2-aminothiazole (2 mmol) and triethylamine (0.3ml, 2.15mmol) mixture in a RB flask. The mixture was stirred under a nitrogen atmosphere for more than 12 hours .The reaction mixture was then added to dilute hydrochloric acid (5%), and extracted with chloroform. The product obtained after removing chloroform was further purified by repeated crystallization from ethanol.

Synthesis and Characterization: All the synthesized compounds were characterized various physicochemical studies. The IR studies of compounds **1a-1d**, **2a-2d** and **3a-3d** showed amide I (C=O) stretching peak in the range of 1611-1688 cm⁻¹ and N-H stretching frequency in the range of 3452-3182 cm⁻¹ (see supporting information). All the compounds were further characterized by ¹H NMR spectroscopy and elemental analysis.

RESULTS AND DISCUSSION

Gel Formation and morphology studies

All the synthesized compounds were subjected to gelation test in various solvents with varied polarity ranging from highly polar solvents such as water, ethanol, methanol, etc. to very less polar solvents such as toluene and n-octadecane (**See supporting information Table S1**). Out of 12 synthesized compounds only two (**1c** and **3c**) turned out to be good gelator for ethanol/water (1:1) and methanol/water (1:1) mixture. **1c** and **3c** showed quite low minimum gel concentration (MGC) for the gelation of methanol/water and ethanol/water mixture (**Table S1**).

A graph of T_{gel} versus concentration of gelator molecules in wt % (w/v) showed a gradual increase in T_{gel} up to a certain concentration of gelator then plateau was observed (**Figure 1**).Understandably, the increase in gelator concentration improves the self-aggregation and stability of supramolecular assembly but not beyond certain critical concentration. The nature of

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the graph for T_{gel} versus concentration of gelator is frequently observed for supramolecular gelators.



Figure 1: Sol-to-gel transition temperature (T_{gel}) versus change in concentration (wt % w/v) graph for gelator 1c and 3c in ethanol/water mixture

To study the morphology of gelator fibres a detailed SEM analysis was carried out on xerogel (dried gel) of **1c** and **3c** obtained from ethanol/water (1:1) gel (**Figure 2**). SEM image of xerogel of **1c** displayed highly crossed linked twisted fibres. However, the xerogel of **3c** showed a well-defined independent assembly of rod like morphology. Presumably, such loose collections of crystalline tubes immobilize solvents, resulting in a weak gel (high MGC). Understandably, highly cross linked network of fibres in **1c** would be capable of hardening a solvent easily than a bundle of rods, which lacks a junction point and or/cross linking (**3c**).



Figure 2: SEM images of xerogel of (A)1c and (B) 3c from 1:1 ethanol/water mixture

The gel made from the gelators 1c and 3c were further characterized by rheological experiments. The magnitude of the storage modulus (G') was found to be an order of magnitude higher that the loss modulus (G'') for both the gel samples. This represents the true behaviour of the viscoelastic gel materials (**Figure 3**).



Figure 3: Rheological studies of the gel formed from A) 1c and B) 3c in ethanol/water mixture (1:1)

Single crystal X-ray studies of compounds (1b-1d and 3b-3d)

2-methyl-N-(thiazol-2-yl) benzamide (1b): 1b crystallizes in the orthorhombic space group Pccn. Asymmetric unit of **1b** contains one molecule of 2-methyl-N-(thiazol-2-yl) benzamide. Two molecules of **1b** are strongly hydrogen-bonded with each other through cyclic N-H.....N (thiazole) (N....N =2.951 Å, \angle N-H.....N=175.93⁰) and N-H...N (thiazole) (N....N=2.951 Å, \angle N- H...N =175.93⁰) interactions, along with the intramolecular bond between the carbonyl oxygen atom and the thiazole sulphur atom (O....S=2.719Å), resulting in a zero-dimensional (0D) network. The 0D network extends to 1D through the bifurcated short contacts between the benzene ring i.e. C-H.... π (C... π =3.722 Å, \angle C-H... π =158.01°; C... π =3.753Å, \angle C-H... π =150.02°). Interestingly, C-H... π interaction was observed between two thiazole ring (C-H...Centroid (C_g) = 2.825 Å, \angle C-H...C_g= 132.8 °C) which propagates packing of **1b** to twodimensional network (2D). (**Figure 4A**). A critical examination of the crystal structures suggests the overall twisted packing (**Figure 4B**).



Figure 4: View of A) hydrogen bonded helical network of **1b** in ball and sticks model and B) Space fill model

3-methyl-N-(thiazol-2-yl) benzamide (1c): 1c crystallizes in the triclinic space group P-1. The asymmetric unit of **1c** contains two molecules of 3-methyl-N-(thiazol-2-yl) benzamide. The two molecules of **1c** are hydrogen-bonded with each other through cyclic N-H.....N(thiazole)(N....N =2.927 Å, \angle N-H.....N=150.02°) and N-H...N (thiazole) (N....N= 3.008 Å, $\angle N$ -H....N=151.79°) interactions. The hydrogen bonded assembly of four molecules of **1c** were held together with C-H...O interaction and two $\pi ... \pi$ interaction (Centroid....Centroid= 3.893Å) between thiazole molecule and benzene ring. The assembly of 4 molecules were extended to 1D network through S...S (S....S =3.461Å) interaction. Surprisingly, non-bonded interaction S...S interaction is not reported in the crystal engineering of organic molecules to the best of our knowledge. Interestingly, the self-assembly of **1c** displayed double helical structure (**Figure 5**).



Figure 5: view of A) hydrogen bonded double helical network of **1c** in ball and sticks model and B) Space fill model

4-methyl-N-(thiazol-2-yl) benzamide (1d): 1d crystallizes in the triclinic space group P-1. The asymmetric unit of **1d** contains two molecules of 4-methyl-N-(thiazole-2-yl) benzamide. The two molecules of **1d** are held together by cyclic N-H.....N(thiazole) (N....N =2.955 Å, \angle N-H.....N=155.91°) and N-H...N (thiazole) (N....N=2.934 Å, \angle N-H.....N=166.84°) interactions,

along with the intramolecular bond between oxygen atom and sulphur atom(O....S=2.668Å), resulting in a 0D network. Various short contacts such as C-H.....S (C....S =3.884 Å, \angle C-H.....S=171.84⁰) and C-H.....N (C....N =3.428Å, \angle C-H.....N=150.94⁰) interactions propagates the 0D network into 1D hydrogen bonded twisted structure (**Figure 6A**), While C-H..... π (C....C=3.841Å, \angle C-H.....C= 133.39⁰) interactions propagates, leading to 2D hydrogen bonded network (**Figure 6B**).



Figure 6: view of hydrogen bonded network of **1d**, resulting twisted structure A) space fill model and B) ball and sticks model

2-methyl-N-(5-methylthiazol-2-yl) benzamide (3b): 3b crystallizes in the triclinic space group P-1. One molecule of 3b was found in the asymmetric unit of 3b. The two molecules of 3b are held together by strong supramolecular synthon N-H...N (N....N =2.871Å, \angle N-H.....N=155.91⁰) interactions, along with the intramolecular bond between the carbonyl oxygen atom and the thiazole sulphur atom (O....S=2.769Å), resulting in a 0D network. 0D network of **3b** is retained by multiple C-H...O interaction between two molecules of **3b**. The 0D network extends to 1D network through C-H...O (C....O =3.484 Å, \angle C-H....O=145.06°)interaction between two molecules of **3b** one above and one below the plane A weak van der Waals interaction between the C-H...C is also observed in the crystal structure leading to overall 2D network having twisted hydrogen bonded network (**Figure 7**).



Figure 7: view of A) hydrogen bonded network of **3b** in ball and sticks model and B) Space fill model

3-methyl-N-(5-methylthiazol-2-yl) benzamide (3c): **3c** crystallizes in the monoclinic space group P 21/c. The two molecules of **3c** are held together by strong supramolecular synthon N-H...N (N....N =2.934Å, \angle N-H....N=177.08⁰) interactions, along with the intramolecular bond between the carbonyl oxygen atom and the thiazole sulphur atom (O....S=2.684Å), resulting in a 0D network. The 0D network extends to 2D network through C-H...O (C....O =3.544 Å, \angle C-

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H.....O=154.53°) interaction and weak van der Waals interaction between the C-H...C (C....C =3.672 Å, \angle C-H....C=178.15°), C-H...C (C....C =3.544 Å, \angle C-H....C=151.50°) (Figure 8).



Figure 8: view of A) hydrogen bonded network of **3c** in ball and sticks model and B) Space fill model

4-methyl-N-(5-methylthiazol-2-yl) benzamide (3d): **3d** crystallizes in the monoclinic space group I 2/a. The asymmetric unit of **3d** contains one molecules of 4-methyl-N-(5-methylthiazol-2-yl) benzamide. The two molecules of **3d** are bonded through hydrogen bonding supramolecular synthons with each other i.e. cyclic N-H.....N(thiazole) (N....N =3.996 Å, \angle N-H.....N=148.97°) and N-H...N (thiazole) (N....N=2.991Å, \angle N-H.....N=149.51°) interactions, along with the intramolecular bond between the carbonyl oxygen atom and the thiazole sulphur atom(O....S=2.696 Å), resulting in a 0D network. 0D network of 3d extends to 2D through various short contacts such as (methyl)C-H..... π (centroid...C-=3.657 Å, \angle C-H.....C=159.55°), C-H....O (C....O =3.312Å, \angle C-H.....O= 132.80°). Even though, the self-assembly of **3d** did not propagated in twisted manner but it showed consecutive double turn conformation (**Figure 9**).



Figure 9: view of hydrogen bonded twisted network of 3d in capped stick model

A critical analysis of weaker interactions (Table 1 and supporting information Table S3 and Figure S1) clearly shows the presence of robust cyclic (amide) N-H...N (thiazole) supramolecular synthon leading to 0-D hydrogen bonded network in all the crystal structures (Scheme 1, synthon A). None of the structure displayed the presence of amide-amide linkage, suggested the preference of cyclic N-H...N interaction over amide-amide supramolecular synthon (Scheme 1, synthon B and C). However, intramolecular O....S interaction was found in all the crystal structures of thiazole amide, with or without a methyl functional group, leading to restricted C-C bond rotation between thiazole moiety and amide functional group. To understand the effect of position of methyl group on benzene ring as well as thiazole moiety, we carry out measurement of angles between the planes passing through the aromatic and thiazole ring. We observed the drastic variation in angles between two planes (plane passing through aromatic ring and thiazole ring) for the two series of compounds i.e. 1b-1d and 3b-3d, ranging from 8.78° to 88.67°. Understandably, such change in angles may be attributed to close proximity of methyl group to thiazole amide dimer (see supporting information Table S4 and Figure S2).

	1b		1c		1d		3b		3с		3d	
	Bond length (Δ^0)	Bond angle	Bond length	Bond angle	Bond length	Bond angle	Bond length	Bond angle	Bond length	Bond angle	Bond length	Bond angle
	(11)	(0)	(A ⁰)	(0)	(A ⁰)	(⁰)	(A ⁰)	(0)	(A ⁰)	(⁰)	(A ⁰)	(0)
0S	2.719		2.675		2.668		2.769		2.683		2.696	
Cyclic	2.951	175.93	2.927	150.02	2.955	155.91	2.871	155.91	2.935	173.39	3.996	148.97
N-HN	2.951	175.93	3.008	151.79	2.934	166.84	2.871	155.91	2.935	173.39	2.991	149.51
С-Нπ	3.722	158.01						Q				
С-Нπ	3.753	150.02					5					
(methyl)C- HO			2.683	126.71		.0	3.439	140.25	3.555	157.42		
ππ			3.391									
SS			3.461									
C-HS					3.884	171.84						
C-HN					3.428	150.94						
(methyl)C- Hπ									3.575	147.50	3.685	171.06
(methyl)C- Hπ			5						3.575	147.50	3.578	145.49

Table 1: Critical analysis of non-bonded interactions present in single crystal X-ray structures

As ortho position of methyl group on phenyl ring brought the maximum change in angle between the planes passing through aromatic and thiazole ring, i.e. **1b** (59.84°) and **3b** (88.67°), whereas the para position of methyl group to phenyl ring brought the least deviation in the angles between the planes, especially in the series of compounds, **3b-3d**. It is difficult to make a comment on the series of compounds (**1b-1d**) as **1c** and **1d** both contain two molecules each in asymmetric unit with drastically different angle between the planes passing through the aromatic and thiazole ring.



Scheme 2: Schematic representation of a plausible mechanism of gelation (1c and 3c) and nongelation (2c).

Interestingly, the series containing methyl group at meta position of phenyl ring (1c and 3c) turned out to be hydrogelator. Compound 1c turned out to be an excellent gelator for alcohol/water mixture, whereas compound 3c was found to be a weak gelator of solvent mixture, suggesting the position of methyl group on the thiazole moiety play a crucial role in gelation process (Scheme 2). Understandably, the suitable position of methyl groups (on thiazole moiety and phenyl ring) facilitate the formation of extended hydrogen bonding network through multiple weak non-covalent interactions such as C-H...O, C-H...N, etc. The series of 4-methylthiazole amide having phenyl ring with ortho, meta and para $-CH_3$ group turned out to be non-gelator for the solvent studied (Scheme2). Furthermore, the good gelation property of 1c in water/ethanol and water/methanol mixture (based on its single crystal structure) may be attributed to the presence of multiple weak non-covalent interactions such as C-H...O, π ... π ,

S...S along with cyclic N-H...N and S...O interactions, which are invariably present in all the crystal structures (gelator and non-gelators). On the other hand, the single crystal structure of weak gelator 3c also contains multiple weak interactions such as two C-H... π and one C-H...O interactions. Comparative analysis of weak non-bonded interactions present in gelators (1c and 3c) suggests greater number of auxiliary non-bonded contacts than non-gelators molecules (1b, 1d, 3b and 3d). This prompted us to propose that along with N-H...N (cyclic dimeric supramolecular synthons) and S...O (intramolecular) interactions multiple weak non-bonded contacts play a crucial role in controlling the overall supramolecular assembly.

The single crystal structure of thiazole amide displayed plethora of weak non-bonded interactions such as C-H... π , C-H...O, C-H...N, C-H...S, S...S, etc., suggested more detailed research is required before we can choose the robust supramolecular synthons for designing a new material with interesting properties especially in thiazole based compounds.

CONCLUSIONS

A new series of LMOGs based on thiazole amide moiety decorated with aromatic ring was designed and synthesized using the concept of crystal engineering. Out of 12 amides synthesized two molecules namely **1c** and **3c** turned out to be good gelling agent for ethanol/water (1:1) and methanol/water (1:1) mixture. Some interesting facts were observed in the single crystal structure of gelator/non-gelator. All the structure show the recurrence of two supramolecular synthons i.e. N-H...N (cyclic) and intramolecular S...O interaction. The single crystal structure of gelator (**1c**) displayed the presence of π - π interaction along with S...O and N-H...N interactions (absence of π - π interaction). The intramolecular

S...O interaction seems to bestow rigidity and planarity to the structures and cyclic N-H...N interaction makes 0-D supramolecular assembly. Surprisingly, the additional π ... π interaction or C-H...O interaction proved to be crucial factor in inducing the gelation properties in these series of compounds. The present studies open an avenue to design a new set of LMWGs based on present design strategy of thiazole derivatives-amide linker-benzene derivatives to any heterocyclic compounds-hydrogen bonding linker-aromatic backbone. Furthermore, these studies show how crystal engineering approach may help in designing and understanding the supramolecular assembly of new LMWGs. We believe the weak S...O interaction observed in thiazole based compounds need to be strengthen further before it can be used as reliable designing tool in crystal engineering.

ASSOCIATED CONTENT

Supporting Information. Physicochemical data of compounds 1a-1d, 2a-2d and 3c-3d, gelation study table, crystallographic parameter table of 1b(CCDC No. 958804), 1c (CCDC No. 972288), 1d(CCDC No. 964475), 3b(CCDC No. 994091), 3c (CCDC NO. 1890271) and 3d(CCDC No. 994092), ORTEP diagram and table of hydrogen bonds with symmetry operation (1b-1d and 3b-3d), table containing inter-planar angles between aromatic ring and thiazole moiety in the crystal structures (1b-1d and 3b-3d). ¹H NMR and IR spectra of compounds 1a-1d, 2a-2d and 3a-3d.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ACKNOWLEDGMENT

Authors would like to acknowledge the DST-PURSE program funding for the Single Crystal Xray Diffractometer at Faculty of Science, The Maharaja Sayajirao University of Baroda, Vadodara and NMR facility to DST-FIST (Phase I) program of Department of Chemistry, Faculty of Science, The Maharaja Sayajirao University of Baroda, Vadodara. AB would like also like to acknowledge The Head, Department of Chemistry, Faculty of Science, M. S. University of Baroda for moral support and providing infrastructural facility. Solvay Research and Innovation Centre (R &I), Vadodara is gratefully acknowledge for their help in Rheological characterization of gel samples.

ABBREVIATIONS

MGC Minimum Gelator Concentration, LMWG Low Molecular Weight Gelator, $T_{\rm gel}$ gel-sol transition temperature

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Declaration of interests

 \boxtimes The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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