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Synthesis and Self-assembly of Novel *s*-Tetrazine-based Gelator

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The design, synthesis and self-assembly of new symmetrical 3,6-bis(4-(3,4,5-tris(dodecyloxy)benzoate)phenyl)-1,2,4,5-tetrazine were described. The novel gelator, *sym*-tetrazine, was prepared by addition reaction of 4-cyanophenol with hydrazine monohydrate followed by oxidation reaction to afford the corresponding 3,6-bis(4-hydroxyphenyl)-1,2,4,5-tetrazine which was then subjected to esterification reaction with 3,4,5-tris(dodecyloxy)benzoic acid. The chemical structure of the *sym*-tetrazine gelator was confirmed by elemental analysis, fourier-transform infrared spectroscopy (FT-IR), and nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectral measurements. It was confirmed to exhibit relatively strong gelation ability to produce supramolecular assemblies in several polar alcoholic organic solvents, such as *n*-butanol, *n*-octanol and 1,6-Dihydroxyhexane. The π-π stacking and van der Waals mediated self-assembly of tetrazine-based organogelator were studied by scanning electron microscopy images of the xerogel to reveal that the obtained organogel consists of fibrillar aggregates. Investigation of FT-IR and concentration-dependent ^{1}H NMR spectra confirm that the intermolecular van der Waals interactions and π-π stacking were the key driving forces for self-assembly during gelation process of *s*-tetrazine molecules.

Keywords: *s*-Tetrazine • Organogel • Self-assembly • Gelation properties

Introduction

s-Tetrazines are a distinguished class of aromatic heterocycles that have been used in different research fields including anti-tumor activity [1, 2], coordination specially in metallosupramolecular assemblies [3], molecular self-assembly [4], insecticides [5], electrochemistry [6], fluorescence [7], conductive materials [8], bioorthogonal labeling [9], and cell detection applications [10]. Tetrazines represent the most electron deficient aromatic group of materials. They provide unusual high electron affinity and charge transfer potential as conjugated molecular structures [11]. They display

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bright colors and electron rich materials have the ability to selectively quench their fluorescence emission [1, 12]. Tetrazines have been valuable as stimuli-responsive smart materials in the molecular identification of environmental pollutants [13], as anion binders [14], and in metal complexation [15]. Tetrazines readily react in inverse demand Diels-Alder reactions [16]. High-nitrogen energetic 1,2,4,5-tetrazine-based materials were also recognized for their use in propellants, explosives, and pyrotechnic ingredients [17-19].

Supramolecular gels are soft materials mainly consist of a fluid, but exhibit solid-like viscoelastic characteristics which can be attributed to the existence of a gelator able to assemble into three-dimensional arrangements. These systematic networks can be created in the form of chemical bonding via crosslinking or polymerization, or physical bonding via self-assembly, phase transition or entanglements. Recently, low molecular-weight organogelators (LMOGs) have attracted considerable interest due to the large diversity of gelators giving rise to thermally reversible organogels in different solvents [20-24]. The distinct capability of small organogelator to solidify and hold organic liquids via weak non-covalent interactions such as π-π stacking, push-pull systems, hydrogen bonding, and van der Waals interactions, has received significant attention [25-27]. It is significant to control such intermolecular forces in a way that the gelator molecules can self-assemble into fibrous higher order assemblies but without switching into dense crystals [25]. LMOGs are characterized by their potential function in a wide range of applications, such as rheology improvers in cosmetics and food industries; polymer crystal nucleating agents; production of inorganic nanoporous materials; multifunctional sensors; soft materials for drug delivery and medical regeneration in tissue engineering; and removal of pollutants [28, 29]. The structure-property relationship of LMOGs has proven to be complex. It has been found that small variations in the molecular structure, such as the number of carbon atoms in an *n*-alkyl chain or introducing branches or cyclic moieties can have remarkable influences on the gelation performance, such as the organogel transition temperature or the range of solvents that are gelled [25-29].

Many structure prototypes of LMOGs have been reported recently [25-29]. Surprisingly, to the best of our knowledge; there is no report of LMOGs based on *sym*-tetrazines. We observed that long alkoxy chain substituted *sym*-tetrazine can be self-assembled into supramolecular architectures. Herein, we report the first pattern of thermally reversible tetrazine-based LMOGs via cooperative van der Waals and π-stacking induced supramolecular assembly. In this LMOG, the self-assembly of appropriate organic molecules by the process of non-covalent forces results in the formation of fibrillar supramolecular structures that were further intertwined to afford sample-spanning networks capable of supporting the solvent. The synthesis of the newly designed tetrazine diphenylester gallate (TZ-DEG) and its gelatinization behavior in a variety of organic solvents was described.

Results and Discussion

Synthesis and characterization

The 3,4,5-tris(dodecyloxy)benzoic acid **3** was prepared according to literature procedures starting from ethyl 3,4,5-trihydroxybenzoate **1** [30, 31]. The dihydrotetrazine **5** and 3,6-bis(4-hydroxyphenyl)-1,2,4,5-tetrazine **6** were prepared according to literature procedures starting from 4-hydroxybenzonitril **4** [32, 33]. As can be seen in Scheme 1, compound **1** was refluxed with 1-bromododecane (3.2 equiv.) in presence of anhydrous potassium carbonate and potassium iodide as

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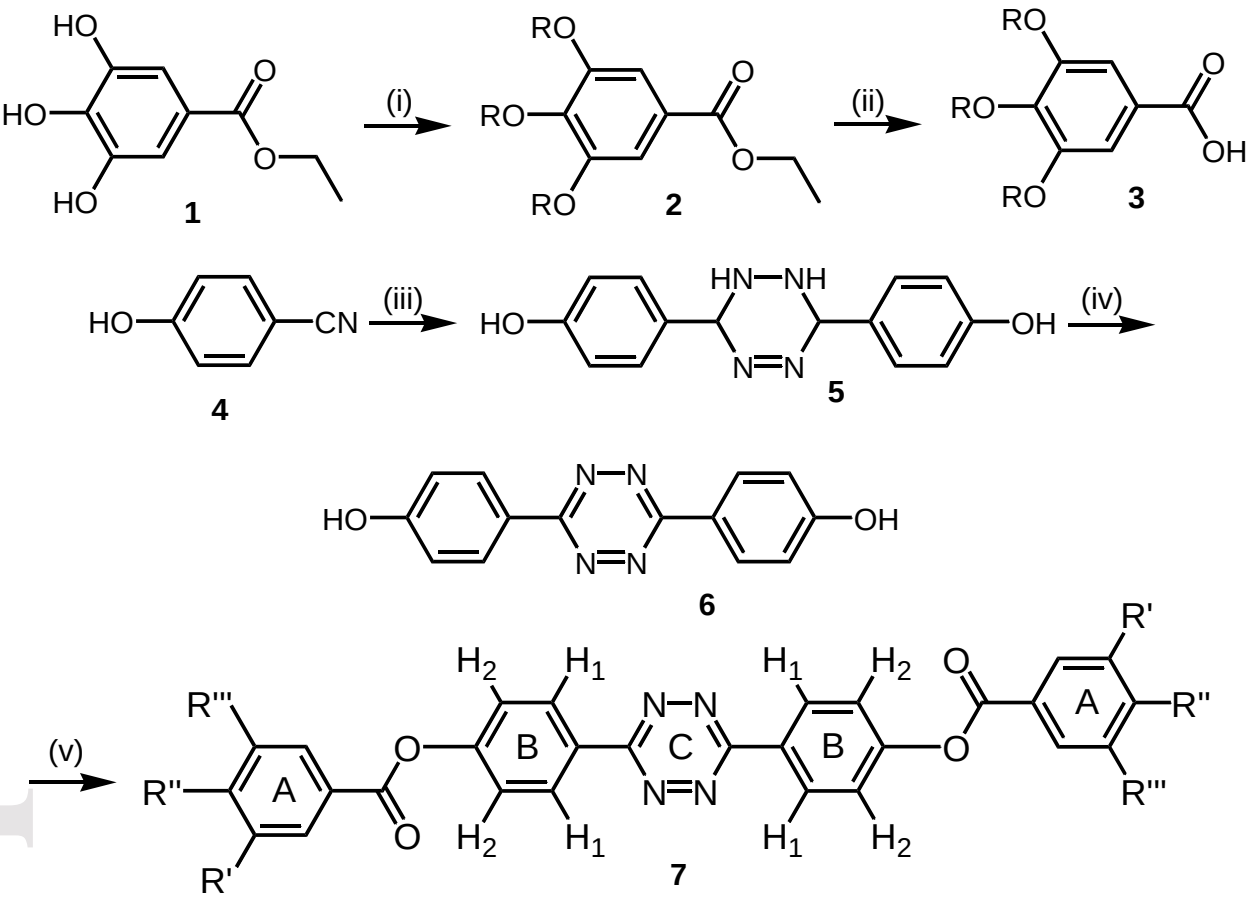
a catalyst to afford ethyl 3,4,5-tris(dodecyloxy)benzoate **2** which was subjected to saponification via hydrolysis under basic conditions, where sodium hydroxide acts as a nucleophile, while an ethoxide is the leaving group affording compound **3** ethanol by-product. Based on literature procedure, the dihydrotetrazine **5** was prepared from 4-hydroxybenzonitril **4** via addition reaction with hydrazine monohydrate followed by oxidation using sodium nitrite to afford compound **6**. The reaction of 3,6-bis(4-hydroxyphenyl)-1,2,4,5-tetrazine **6** with 3,4,5-tris(dodecyloxy)benzoic acid **3** was performed via *Steglich* esterification employing *N*,*N*'-dicyclohexylcarbodiimide (DCC) as a *coupling* reagent and 4-(dimethylamino)pyridine (DMAP) as a catalyst to produce our novel *sym*-tetrazine gelator (TZ-DEG **7**).



Scheme 1. Synthetic route for novel *sym*-tetrazine organogelator **7** (R = $C_{12}H_{25}$). Reagents and conditions: (i) $C_{12}H_{25}Br$, acetone, K_2CO_3, KI, reflux 36 h; (ii) NaOH, acetone, 12 h; (iii) $NH_2NH_2.H_2O$, 90˚C 16 h; (iv) CH_3COOH, $NaNO_2$ [O]; (v) **3**, DCC, DMAP, dry THF.

In ^{1}H NMR spectra, the peak at 7.37 ppm was assigned for the two equivalent gallate moieties (A). Although symmetrical molecular structure of compound **7**, the two *para*-substituted benzene rings (B) displayed two different doublet peaks at 8.68 and 7.41 ppm. This is due to the different surrounding electronic environments around protons H_1 and H_2 as a result of both inductive and resonance effects applied on both protons H_1 and H_2. Furthermore, a weak CH---N hydrogen bonding could be experienced between protons H_1 and the corresponding nitrogen atoms of the tetrazine

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ring, and therefore, doublets were only observed and not the expected doublets of doublets [33]. The IR spectra of **7** display a weak aromatic stretch peak at 3073 cm^{-1}. Another two strong peaks appeared at 2921 and 2851 cm^{-1} assigned for CH aliphatic asymmetric stretch and CH aliphatic symmetric stretch, respectively. The carbonyl ester stretch group appeared at 1734 cm^{-1}.

Gelation properties

The gelation behavior of TZ-DEG were examined in a variety of solvents by means of the ''stable to inversion'' technique and the minimum gel concentration (MGC) values were recorded. In the ''stable to inversion'' technique, the glass vial containing the formed gel is inverted upside down to indicated the absence of fluid solvent which was immobilized due to the construction of the soft gel (Fig. 1). Compound **7** selectively formed gels mainly in polar solvents. TZ-DEG showed lower MGC in protic alcoholic solvents compared to non-protic polar solvents which could be attributed to the hydrogen bonding between the alcoholic hydrogen of the protic polar solvent and the ester oxygen of TZ-DEG gelator. The MGCs is known to decrease upon increasing the length of terminal alkyl chains leading to better gel ability [34]. It was found that **7** did not generate a gel following typical heating-cooling procedure in tetrahydrofuran, dimethylformamide, ethyl acetate or dimethyl sulfoxide in which the solubility is too high. Similarly, **7** cannot gel in toluene or cyclohexane owing to the very low solubility. However, TZ-DEG acts as a gelator in pure alcohols which indicated that **7** is a successful gelator for various alcohols. A series of mixed non-alcohols were also inspected. It was found that an organogel of **7** can be produced in a number of mixed solvents such as chloroform/cyclohexane (v/v = 1/3) and acetone/cyclohexane (v/v = 1/1). The gelation studies of the minimum gel concentration values are displayed in Table 1. The minimum gelation concentration values demonstrate solvent dependent performance and occur in the range of 2.38 and 9.63 mM which is comparable to a variety of reported organogelators containing long alkoxy side chains [27, 34-37]. In addition, the *n*-butanol gel formed from the TZ-DEG gelator was found to be stable for a number of weeks at room temperature and atmospheric pressure, while under similar circumstances, the acetone/cyclohexane gel was stable for only few days.

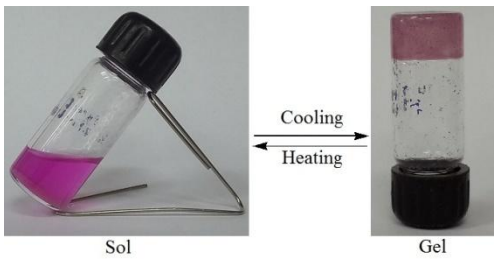

Figure 1. Reversible sol-gel phase transition of the organogel of TZ-DEG in *n*-butanol.

The above results elucidate that the long alkoxy side chains of the TZ-DEG gelator not only improve its solubility in organic liquids but also support assembly between the generated nanofibrous architectures, via van der Waals forces, and consequently organogel creation. However, the strong solvation of the alkoxy chain may also reduce the intermolecular affinity required for self-assembly.

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As indicated in the literature, the long alkoxy chain is an essential feature on the aromatic core for creating a high-quality gelator [34]. These results signify the important function of the side dodecyloxy chains in the gelation capability. The six dodecyloxy side chains of **7** increase its solubility in various solvents; therefore, the strong solvation probably brings about the low intermolecular affinity of the self-association in non-polar and non-protic polar solvents.

Table 1. The minimum gel concentration (MGC) of TZ-DEG in different solvents.

Solvent	MGC in mM
Methanol	sol
Ethanol	ppt
n-Propanol	ppt
n-Butanol	G (3.06 mM)
n-Octanol	G (2.82 mM)
1,2-Dihydroxyethane	G (4.95 mM)
1,3-Dihydroxypropane	G (3.21 mM)
1,6-Dihydroxyhexane	G (2.38 mM)
Acetic acid	sol
Formic acid	sol
Benzyl alcohol	ppt
Toluene	insol
Cyclohexane	insol
Chloroform/Cyclohexane (v/v = 1/3)	G (5.26 mM)
Chloroform	ppt
Acetone	ppt
Ethyl acetate	sol
THF	sol
Dimethylformamide	sol
Dimethyl sulfoxide	sol
Acetone/Cyclohexane (v/v = 1/1)	G (9.63 mM)

G: gel; sol: soluble; insol: insoluble; ppt: precipitation. The minimum gel concentration in mM is shown in parenthesis.

The UV-Vis absorption spectra of TZ-DEG in both solution and gel states were recorded in *n*-butanol (Fig. 2). The main absorption peak undergoes a bathochromic shift from 310 nm for the solution phase to 316 nm for the gel phase (ca. 6 nm shift value). Such red-shift of the absorption peak of TZ-DEG gel phase to longer wavelength compared with that in dilute solution indicates that the molecules packing have the J-aggregate form.

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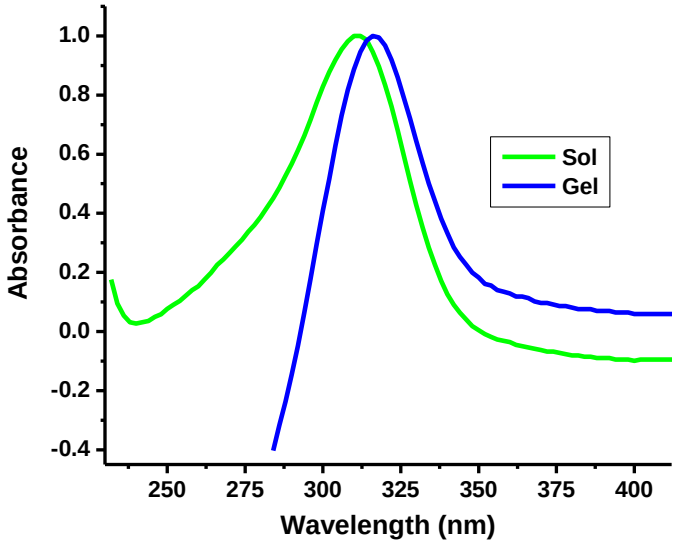

Figure 2. Normalized UV-Vis absorption spectra of TZ-DEG 7 in both solution (green curve) and gel (blue) states in *n*-butanol.

Morphology and structure of assemblies

To gain a macroscopic insight of the aggregation mode of TZ-DEG gelator in organogelation process, the *n*-butanol xerogel (after complete solvent evaporation) was investigated by using scanning electron microscopy. The SEM images display the development of 3D entangled arrangements (Fig. 3) in which the self-assembled tape-like structural morphology was monitored with widths of 180-350 nm and lengths. SEM inspection of the xerogel gives an insight into higher order nanofibrous arrangements able to bundle and generate the network. Creation of long nanofibers signifies that strong directional intermolecular interactions might exist. The xerogel displays strongly developed supramolecular morphology with high porosity responsible for holding and immobilizing solvent molecules. This microscopic aspect of the xerogel affords three-dimensional nanofibrous network produced by the intertwined nanofibers able to immobilize and hold organic solvent and result in the construction of the gel.

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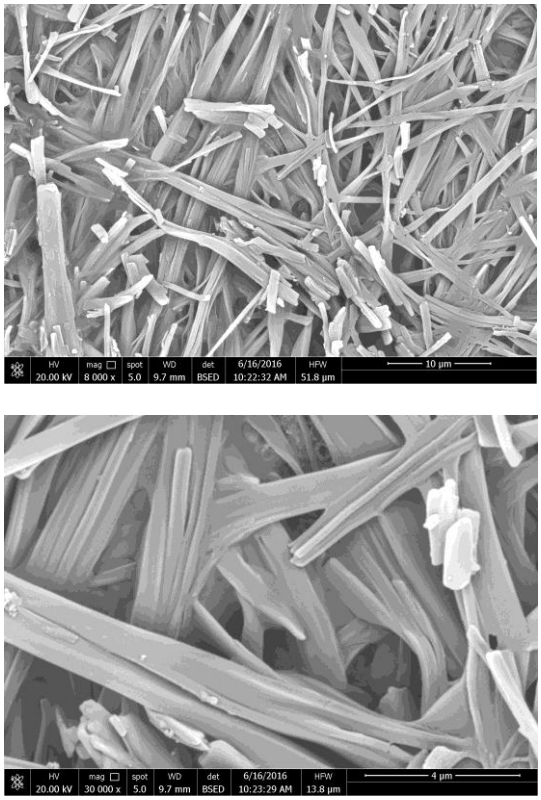

Figure 3. SEM images for the dried xerogel of TZ-DEG obtained from *n*-butanol (3.06 mM).

In order to discover the motivating forces for the self-assembly of the supramolecular nanofibrous architectures, FT-IR and concentration-dependent ^{1}H NMR spectroscopic experiments were carried out. The development of expanded tape-like nanofibrous aggregates proves that the self-assembly of TZ-DEG is motivated by strong directional intermolecular interactions. The π-π stacking interaction forces of the aromatic gallate unit in solution were verified by ^{1}H NMR spectroscopy. No gelation behavior was monitored upon increasing the minimum gel concentration of TZ-DEG in chloroform. However, nanofibrous precipitate was formed upon cooling. Therefore, chloroform can be considered as a suitable solvent to study self-assembly behavior using ^{1}H NMR spectroscopy. Upon regular increase of concentration (Deuterated chloroform solution of **7)** from 0.5 to 25 mmol L^{-1}, the gallate ring protons slightly shifted upfield from 7.37 to 7.34 ppm (Fig. 4). This is strong evidence for the creation of stacked molecules in which the protons of the gallate aromatic ring are shielded by aromatic rings of adjacent molecules due to the π-π stacking interactions between the aryl rings are engaged in the gel development process.

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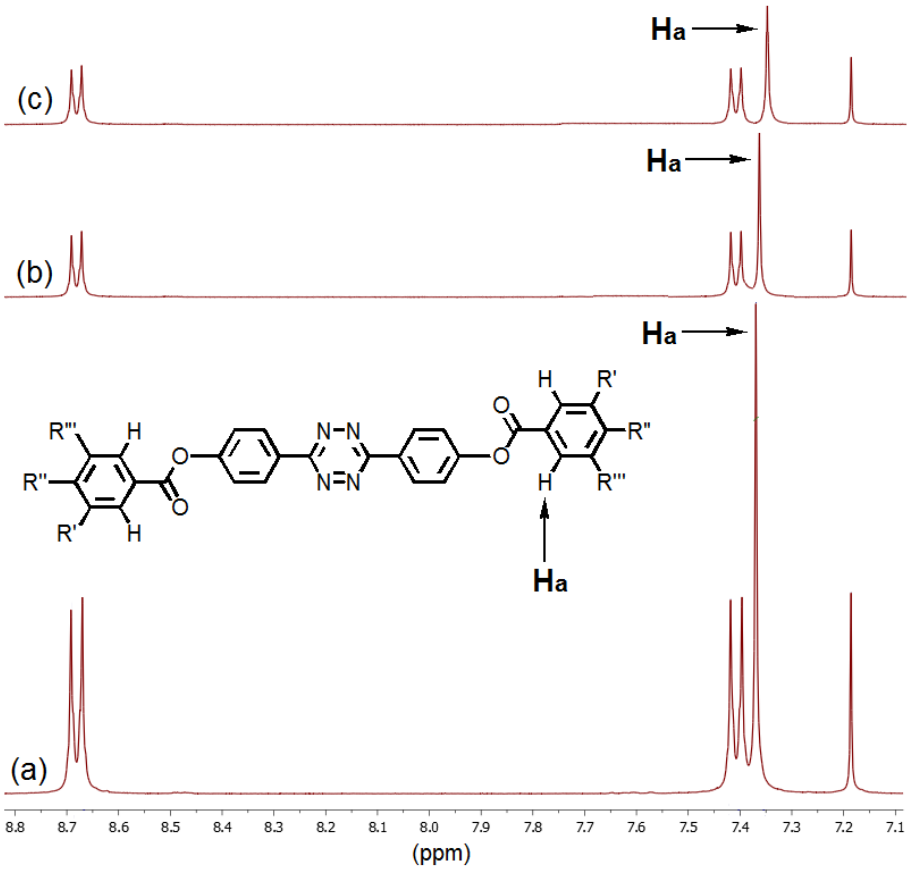

Figure 3. Set of partial ^{1}H NMR spectra of TZ-DEG in $CDCl_3$ at different concentrations of (a) 0.5 mmol L^{-1}, (b) 10 mmol L^{-1}, and (c) 25 mmol L^{-1} at room temperature.

Furthermore, both of *symmetric* and *antisymmetric* methylene stretching vibrational modes of TZ-DEG was employed to detect alkyl chain conformations. With the alkyl chain length expanding, for TZ-DEG xerogel, the $(CH_2)_{sym}$ and $(CH_2)_{anti}$ were shifted from 2851 cm^{-1} (solid) to 2849 cm^{-1} (xerogel) and from 2921 cm^{-1} (solid) to 2917 cm^{-1} (xerogel), respectively, indicating a significant population of the *trans* conformation (Fig. 8S) [34]. The decreased wavenumber values reflect a reduced fluidity of the alkyl chains due to the physically powerful association of the alkyl units via van der Waals forces. Accordingly, the motivating forces of the organogelation process are π-π stacking interaction forces of the aromatic gallate ring in cooperation with van der Waals forces among the terminal alkyl chains.

The thermal stability of the TZ-DEG organogel in *n*-butanol was explored by determining the concentration-dependent gel-to-sol transition temperature (Fig. 5). An increase in the organogel melting temperature was detected within the temperature range 33-47°C upon increasing the gelator concentration in *n*-butanol from 3.06 to 10.17 mmol L^{-1}. However, the organogel melting temperature decreases upon increasing the gelator concentration (gelator concentration > 10.17 mmol L^{-1}). The reason for the reduced thermal stability at gelator concentration > 10.17 mmol L^{-1} is not obviously understood. The improved thermal stability at gelator concentration lies between 3.06-10.17 mmol L^{-1}; can be assigned to the higher amount of gelator molecules incorporated in the

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nanofibrous aggregates. In other words, the increased gel→sol transition temperature is correlated to the expansion of one-dimensional nanofibrous aggregates, which exhibits them more flexibility, leading to more fiberous entanglements, and that way rising the transition temperature.

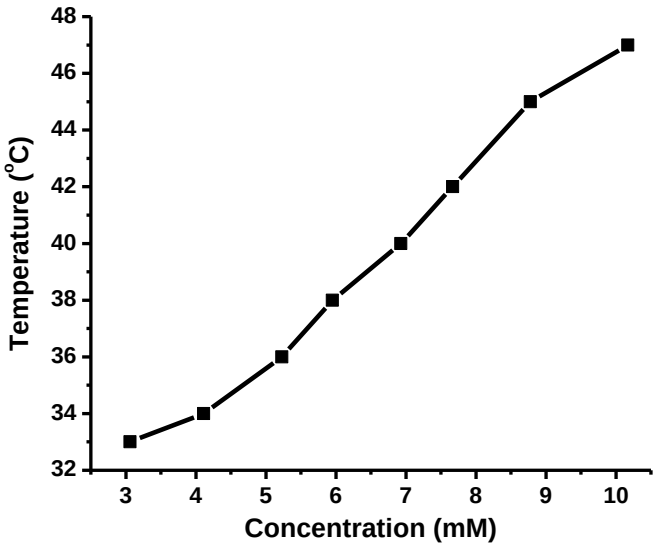

Figure 5. Gel-to-sol transition temperature profile of TZ-DEG gelator in *n*-butanol as a function of gelator concentration.

To gain insight into the sol-to-gel transition reversibility, we conduct the temperature-dependent gel-to-sol transition. The gel was subjected to heating around the boiling point (118˚C for *n*-butanol) until a clear homogeneous solution appears, and the gel-to-sol transition temperature was reported at the initial collapse of the gel. The mixture was then allowed to stand at room temperature (at 25˚C) within few minutes to allow the gel to reform. The formation of gels was confirmed by "stable to inversion of a glass vial" technique which was indicated by the absence of fluid solvent. The process can be repeated by numerous cycles of heating and cooling (Fig. 9S). No changes were observed in the gel-to-sol transition temperature, indicative of the fully thermal reversibility of the sol-to-gel conversion.

Conclusions

Novel *sym*-tetrazine containing gallate unit was successfully designed, synthesized and characterized. According to SEM clarification, FT-IR and ^{1}H NMR spectroscopic techniques, we have demonstrated the systematic investigation of the gelation properties in different solvents for novel *sym*-tetrazine-based gelator assembled to form the macromolecular morphology. Upon studying the minimum gel concentration, assemblage morphology of organogel, and gel formation driving forces, the results show that both of π-π stacking and van der Waals forces are the key driving forces for the

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development of self-assembled organogel. The temperature-dependent gel-to-sol transition indicated fully thermal reversibility of the sol-to-gel conversion**.**

Experimental Section

Materials and methods

All experimental results were collected at room temperature (25˚C) unless stated otherwise. Solvents used in this study were obtained from Fluka and Aldrich for syntheses and spectroscopic measurements (spectroscopic grade) and were employed without further purification. Compound **3** was prepared according to literature procedures starting from ethyl 3,4,5-trihydroxybenzoate **1** commercial material [30, 31]. Compounds **5** and **6** were prepared according to literature procedures starting from the commercial compound **4** [32, 33]. Compounds **1** and **4** were purchased from Sigma-Aldrich. All reactions were monitored by thin layer chromatography (TLC) using Merck aluminum plates pre-coated with silica gel PF254; 20x20 cm, 0.25 mm, and detected by visualization of the plate under UV lamp (254 or 365 nm). Compounds were purified through crystallization or using flash column chromatography which was performed on Scharlau silica gel, packed by the slurry method.

Synthesis of 3,6-bis(4-(3,4,5-tris(dodecyloxy)benzoate)phenyl)-1,2,4,5-tetrazine 7

In a 250 ml round bottom flask; a mixture of 3,6-bis(4-hydroxyphenyl)-1,2,4,5-tetrazine **6** (650 mg, 2.24 mmol), 3,4,5-tris(dodecyloxy)benzoic acid **3** (3.37 g, 5.0 mmol, 2.05 equiv.), 4-dimethylaminopyridine DMAP (30 mg, 0.25 mmol) and dicyclohexylcarbodiimide DCC (1.03 g, 5.0 mmol) was stirred in an anhydrous THF (80 mL) overnight. The mixture was concentrated under reduced pressure, filtered over multiple times from dichloromethane, and re-crystallized from methanol to afford a purple solid (2.78 g, yield 72%). mp 107-108˚C; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.68 (d, 4H Ar-H), 7.41 (d, 4H Ar-H), 7.37 (s, 4H Ar-H), 4.00 (m, 12H aliphatic), 1.74 (m, 12H aliphatic), 1.43 (m, 12H aliphatic), 1.20 (m, 96H aliphatic), 0.81 (t, 18H aliphatic);

^{13}C NMR (400 MHz, $CDCl_3$), δ (ppm): 164.60 (C=O), 163.38 (C), 154,84 (B), 153.07 (A), 143.40 (A), 129.45 (B), 129.30 (B), 123.41 (A), 122.89 (B), 108.75 (A), 73.64 (R’’), 69.36 (R’ and R’’’), 31.96 (R’’), 31.93 (R’ and R’’’), 30.38 (R’’), 29.77 (R’ and R’’’), 29.75 (R’’), 29.74 (R’ and R’’’), 29.71 (R’’), 29.67 (R’ and R’’’), 29.65 (R’’), 29.58 (R’ and R’’’), 29.41 (R’’), 29.37 (R’ and R’’’), 29.33 (R’’), 26.10 (R’ and R’’’), 26.08 (R’, R’’ and R’’’), 22.71 (R’, R’’ and R’’’), 22.69 (R’, R’’ and R’’’), 14.11 (R’, R’’ and R’’’). IR (neat, v/cm^{-1}): 3073 (CH aromatic stretch), 2921 (CH aliphatic asymmetric stretch), 2851 (CH aliphatic symmetric stretch), 1734 (C=O ester stretch), 1591 (C=N), 1506 (C=C aromatic bend), 1333 (C-O ester), 1190 (CH_2 aliphatic deformation bend), 1124 (CH_3 aliphatic deformation bend), 863 (CH aromatic bend), 720 (CH_2 aliphatic bend rocking); Elemental analysis calculated for $C_{100}H_{162}N_4O_{10}$ (1579.23): C 76.00, H 10.33, N 3.55; Found: C 75.89, H 10.36, N 3.61

Gelation procedure

The gelation tests were performed by dissolution of *sym*-tetrazine in solvent by heating in a sealed glass vial around the boiling point until a clear solution appeared. The mixture was then allowed to stand at room temperature for 1 hour. The gels formed in 10-25 minutes depending on the gelator concentration and the employed solvent. The formation of gels was confirmed by “stable to inversion of a glass vial” technique which was indicated by the absence of fluid solvents when the

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glass vial was inverted. The sol-to-gel transition reversibility was also investigated as the vial containing the gel was kept upside down in a paraffin oil bath. The temperature was increased at a rate of 2°C/minute and the temperature at which the gel fell under gravity was recorded as the gel melting temperature. This procedure was repeated for several cycles.

Characterization and measurements

Melting points

All melting points were determined on *Stuart SMP30* digital apparatus and were reported uncorrected in °C.

FT-IR spectroscopy

FTIR spectra were recorded using a JASCO FT/IR-4700 spectrophotometer with a resolution of 4 cm^{-1} and in the wavenumber region of 4000-400 cm^{-1}. The measurements were made at room temperature (25˚C).

Elemental analyses

Elemental analyses (C, H, N) were performed with PerkinElmer 2400 analyzer (PerkinElmer, Norwalk, CT, USA) at the Microanalytical Center, Cairo University.

^{1}H and ^{13}C NMR spectra

NMR spectra were recorded using a BRUKER AVANCE 400 spectrometer at 400 MHz; chemical shifts were reported in ppm relative to tetramethylsilane internal standard at 295°K.

UV/Vis absorption spectra

The UV/Vis absorption spectra were recorded with an HP-8453 spectrophotometer.

Scanning Electron Microscope (SEM)

In case of scanning electron microscopy, the gel formed from TZ-DEG in *n*-butanol was scooped up and placed on carbon tapes pasted on aluminum stubs and allowed to dry at room temperature in a desiccator connected to vacuum pump. The dried sample was then annealed overnight in an oven at 45°C, followed by application of a 10 nm gold-coating before recording images. SEM images were obtained using Hitachi S-2600N operating at 20 kV.

Procedure for concentration-dependent ^{1}H NMR measurements

The concentration-dependent ^{1}H NMR was carried out by gradually increasing the concentration of TZ-DEG solution in $CDCl_3$. The initial concentration of TZ-DEG **7** was 5 x 10^{-4} mol L^{-1}, the concentration was then adjusted by direct addition of correct quantity of **7** into the $CDCl_3$ solution at concentrations of 10 and 25 mmol L^{-1}.

Supplementary Material

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/MS-number.

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Authors Contribution Statement

T. A. Khattab designed and performed the experiments, analyzed the data, and wrote the manuscript.

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