Prayogik Rasayan

Peptide-mimetic based supramolecular gel

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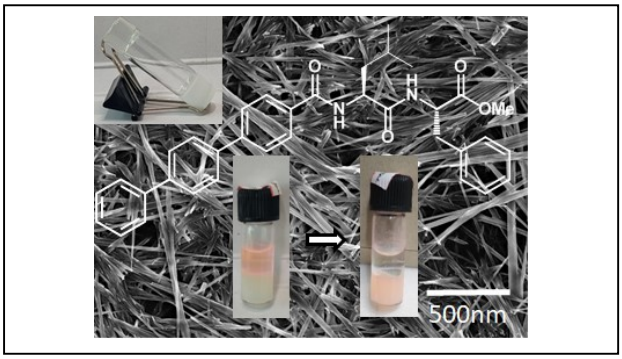
Abstract

We have reported the design, synthesis and gelation study of Leu-Phe peptide-mimetic 1 with 4-terphenylcarboxy protecting group at the N-terminus and C-terminus as methyl ester. The Suzuki-Miyaura cross-coupling reaction of biphenyl boronic acid and 4-bromo benzoic acid in presence of $Pd(OAC)_2$, urea and sodium carbonate in water results the *p*-terphenyl-4-carboxylic acid in excellent yield. The peptide-mimetic 1 in methanol solution show emission band at 380 nm on excitation at 292 nm. Interestingly, the peptide-mimetic 1 formed organogel in different organic solvents such as toluene, *p*-xylene, chlorobenzene, acetonitrile, nitromethane with minimum gelation concentration 5 mg/mL. However, the peptide-mimetic 1 fails to form organogel in hexane, DCM, EtOAc, MeOH, EtOH under same condition. The peptide-mimetic 1 based gels have high stability. From rheology study, the storage modulus of the organogel was approximately an order of magnitude larger than the loss modulus, which indicates the physical crosslink and the elastic nature of the gel. FESEM image of that xerogel exhibits entangled fiber network morphology. The gel may be use for removal of dyes from contaminated water. The maximum amount of Rhodamine 6G absorbed by gel is 4.5 mg/ g of gel.



Keywords: Peptide-mimetic, supramolecular, 4-terphenyl carboxylic acid, organogel, fibers

1. Introduction

LMWGs (low molecular weight supramolecular gels) are an important category of materials that can capture large amounts of solvents in entangled structures that are formed via the ordered assembly of individual molecules.[1] Amides, peptides, urea, peptoids, nucleobases, and various other small molecules have shown spectacular abilities to self-assemble. LMWGs gels have been used in various purposes such as water purification, in cosmetics, for the removal of organic dyes; oils, metal ions; as templates for nanoparticle fabrication; catalysts, drug delivery systems, dye-sensitized solar cells, etc. The self-assembly of peptide is achieved fortuitously from the last couple of decades, and it is proven that choosing individual amino acids properly can be capable of designing different self-assembled smart molecules. That's why even now the design of LMWGs is an important field of research due to their low expenditure value, availability, easy synthesis, biocompatibility, and multifunctionality. The supramolecular gels employed the building blocks to form larger self-assembled structures by various non-covalent interactions. Over the past few decades, extensive research has been performed for the fabrication of novel supramolecular gelators.[1] There are two classes of supramolecular gels: organogel and hydrogel. Supramolecular organogels are generally made by entangled fiber network fabricated by self-assembly of small organic molecules (commonly known as gelators) and encapsulated large amount of various organic solvents.[2-4] By definition, the supramolecular organogels are semi-solid in nature and can be tested by inverted test-tube technique.[5] The organogelators self-aggregated by various non-covalent interactions such as hydrogen bonding, C-H…π interactions, π-π stacking, ionic interactions, and Van der Waals interactions[6-9] to provide a fibrous network structure. The supramolecular organogels are dynamic as well as reversible in nature.[10] Moreover, the organogel matrix are highly capable to accommodate other important small molecules including nano-materials. The supramolecular organogels are

responsive towards external stimuli such as ultrasound, light, salts, solvent polarity, pH, as well as temperature.[11-28] The supramolecular organogels have diverse application in area of drug delivery,[29-30] tissue engineering,[31-33] medicine, biomedical applications,[34] material science, light harvesting and optoelectronics,[35-36] as well as smart materials.[37-39] Although a large number of organogelators with various functional groups have reported in the literature, yet the fabrication of a novel small molecule gelator is extremely important.[40] Our group had reported many supramolecular organogel.[41] Herein, we have reported the design and synthesis of a terminally protected peptide-mimetic 1 as a promising organogelator. The main aim of this investigation is to study the gelation propensities of Leu-Phe peptide-mimetic 1 with 4-terphenylcarboxy protecting group at the N-terminus and methyl ester protecting group at C-terminus (Figure 1). Interestingly, the peptide-mimetic 1 formed organogel in different organic solvents such as toluene, *p*-xylene, chlorobenzene, acetonitrile, nitromethane but fails to form gel in non aromatic solvents such as hexane, DCM, EtOAc, MeOH, EtOH under same condition. The gels have high stability for couple of months. The minimum gelation concentration for toluene, *p*-xylene, chlorobenzene is 5 mg/mL. From rheology study, the storage modulus of the organogel was approximately an order of magnitude larger than the loss modulus, which indicates the elastic nature of the gel and the physical crosslink. FESEM images of the xerogel exhibits twisted fiber morphology as well as dance fiber network.

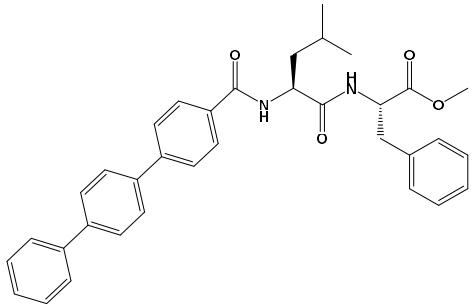


Figure 1. Schematic presentation of compound **1**.

2. Experimental

Synthesis of 4-triphenylcarboxylic acid

4-triphenylcarboxylic acid was synthesized following Suzuki-Miyaura cross-coupling reaction. First, 0.5 g of 4-bromobenzoic acid and 0.4 g of biphenyl boronic acid were dissolved in a 15 ml aqueous solution of sodium carbonate. The reaction mixture was heated to 50-70 °C. After five minutes, palladium catalyst (0.01 mol %) was added to the reaction mixture. After stirring for 1 hour, the product was precipitated out. The reaction mixture was kept at room temperature some time for cooling. Then it was quenched carefully with 1 M HCl. The crude product was filtered and washed with water and recrystallized from 1 M HCl and ethanol solution. Yield: 0.41 g (1.5mmol, 60%).

Peptide-mimetic **1** synthesis

Peptide-mimetics were synthesized using solution phase methods with racemization free fragment condensation strategy. Where the 4-triphenylcarboxy group was used for N-terminal protection and the C-terminal was protected as a methyl ester. Saponification method is used for deprotections of methyl ester. Couplings were done by using DCC/EDC. HCl and HOBt. All of the intermediates and final compounds were characterized by ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy, mass spectrometry and FT-IR spectroscopy.

Synthesis of Tri Ph-Leu-OMe

First of all, the C-terminal of Leu-OH was protected as a methyl ester (Leu-OMe). So, Leu-OH (1.3 g, 10 mmol) was dissolved in 20 ml MeOH in an ice-cold water bath and stirred. Inside the hood, 2mL $SOCl_2$ was added drop wise. This reaction stirred for 6-8 hours. Excess $SOCl_2$ was evaporated and thus Leu-OMe.HCl was obtained. Next TriPh-COOH (750 mg, 2.73 mmol) was dissolved in dry DCM in an ice-cold water bath. Leu-OMe. HCl (435 mg, 3 mmol) was dissolved in DCM and added 1 mL of triethylamine. It was then added to the reaction mixture, followed by immediate addition of 785 mg (4.1 mmol) EDC.HCl and 553 mg (4.1 mmol) of HOBt. The reaction mixture was allowed to come to room temperature and stired for 48 hours. After that, DCM was evaporated and the residue was dissolved in ethyl acetate. The organic layer was washed with 2 M HCl (3 × 50 mL), brine (3 × 50 mL), 1 M sodium carbonate (3 × 50 mL) and brine (2 × 50 mL) and dried over anhydrous sodium sulfate (Na_2SO_4). The solution was evaporated under vacuum to obtain the Tri Ph-Leu-OMe. The product was in white powder and further purified by column chromatography.

^{1}H NMR (400 MHz, chloroform-D) *δ* (ppm): 7.90 (d, *J* = 8.1 Hz, 2H), 7.67 (dd, *J* = 21.0, 6.1 Hz, 8H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 4.99 – 4.86 (m, 1H), 3.79 (s, 3H), 1.90 – 1.64 (m, 3H), 1.01 (dd, *J* = 7.7, 6.2 Hz, 6H).^{13}C NMR (101 MHz, chloroform-D) *δ* (ppm): 171.77, 171.56, 167.14, 143.98, 141.55, 140.32, 138.90, 135.65, 132.65, 129.32, 128.95, 128.63, 127.83, 127.73, 127.64, 127.14, 53.61, 52.27, 41.17, 38.35, 24.94, 23.00, 22.37.

*Synthesis of Tri Ph-Leu-Phe-OMe **1***

To protect the C-terminal of Phe-COOH as a methyl ester (Phe-OMe), Phe-COOH (115 mg, 0.7 mmol) was dissolved in MeOH in an ice-cold water bath and stirred. Inside the hood, 2mL $SOCl_2$ was added drop wise. This reaction was stirred for 6-8 hours. $SOCl_2$ was evaporated and Phe-OMe.HCl obtained**.** Then, Tri Ph-Leu-OH (269.30m g, 8 mmol) (Tri Ph-Leu-OMe hydrolyzed by NaOH in methanol followed by acidification with HCl) was dissolved in dry DCM in an ice-cold water bath. Phe-OMe.HCl (170 mg, 0.45 mmol) was dissolved in DCM and added 1 mL of triethylamine. It was then added to the reaction mixture, followed by immediate addition of 130 mg (0.675 mmol) EDC hydrochloride (EDC.HCl) and 92 mg (0.675 mmol) of HOBt. The reaction mixture was allowed to come to room temperature and stir for 48 hours. After that, DCM was evaporated and the residue was dissolved in ethyl acetate. This organic layer was washed with 2 M HCl (3 × 50 mL), brine (3 × 50 mL), 1 M sodium carbonate (3 × 50 mL) and brine (2 × 50 mL) and dried over anhydrous sodium sulfate. The solution was evaporated under vacuum to obtained the Tri Ph-Leu-Phe-OMe **1** as a white solid. The product was purified by column chromatography.

^{1}H NMR (400 MHz, chloroform-D) *δ* (ppm): 7.86 (d, *J* = 8.3 Hz, 2H), 7.78 – 7.61 (m, 8H), 7.54 – 7.43 (m, 2H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.24 – 7.14 (m, 2H), 7.09 (dd, *J* = 7.0, 2.2 Hz, 3H), 6.58 (d, *J* = 8.1 Hz, 2H), 4.88 (dd, *J* = 13.8, 6.2 Hz, 1H), 4.72 – 4.65 (m, 1H), 3.70 (ddd, *J* = 20.4, 13.9, 6.1 Hz, 3H), 3.12 (dd, J=7Hz, 1H) 2.95 (t, *J* = 7.7 Hz, 1H).1.84 – 1.58 (m, 3H), 0.95 (t, *J* = 7.7 Hz, 6H). ^{13}C NMR (101 MHz,

chloroform-D) δ (ppm): 171.77, 171.56, 167.14, 143.98, 141.55, 140.32, 138.90, 135.65, 132.65, 129.32, 128.95, 128.63, 127.83, 127.73, 127.64, 127.14, 53.61, 52.27, 41.17, 38.35, 24.94, 23.00, 22.37. Molar mass of Tri Ph-Leu-Phe-OMe 1 = 548.27, $[M+Na]^+$ = 571.8677.

NMR Experiments

All NMR experiments were performed on a Jeol 400 MHz and Bruker 500 MHz, spectrometer at 278 K. Compound concentrations were in the range 1–10 mM in $CDCl_3$ and DMSO-d_6.

FT-IR Spectroscopy

Solid-state FT-IR spectra using KBr disk method were measured in a Perkin Elmer Spectrum RX1 spectrophotometer at RT.

Mass spectrometry

Mass spectra of the peptide mimetics were recorded on a Q-Tof Micro YA263 high-resolution (Waters Corporation) mass spectrometer by positive-mode electrospray ionization.

UV/Vis spectroscopy

The absorption spectra of the peptide mimetics were recorded on a Perkin Elmer UV-Vis spectrophotometer.

Fluorescence spectroscopy

All fluorescence spectra of the peptide mimetics were recorded on a Perkin Elmer fluorescent spectrometer (LS 55) using 1 cm path length quartz cell. Slit widths 2.5/2.5 were used.

Rheology Experiments

To understand the mechanical strengths of the peptide mimetics gel, we performed rheological experiments on a MCR 102 rheometer (Anton Paar, Modular Compact Rheometer) using a steel parallel plate geometry with a 40 mm diameter at 25 °C. To control the temperature accurately during the measurement, the rheometer is attached to a Peltier circulator thermo cube. The storage modulus (G′) and loss modulus (G″) of the gels have been recorded.

Polarised optical Microscope

A small amount of solution of the peptide mimetic was placed on a clean glass cover slip and then dried by slow evaporation under open air, then visualized at 40×magnification (polarizer and CCD camera equipped Olympus optical microscope).

Field Emission Scanning Electron Microscopy

Field emission-scanning electron microscopy (FESEM) has used to know the morphologies of the reported peptide mimetics. A drop of peptide mimetic solution was placed on a clean microscopic glass slide and dried by slow evaporation. The dried materials were gold-coated, and the micrographs were taken in an FE-SEM apparatus (JEOL Scanning Microscope-JSM-6700F).

3. Result and discussion

The peptide-mimetic **1** was synthesized following standard solution phase peptide synthesis methodologies, purified and characterized by ^{1}H NMR, ^{13}C NMR, FT-IR and mass spectrometry analysis. Since the terminally protected peptide-mimetic TriPh-Leu-Phe-OMe **1** contains several intermolecular H-bonding sites and aromatic rings, we assumed the π-π stacking interactions on the aromatic ring in addition to the H-bonding could significantly modulate the self-assembly behavior of the peptide-mimetic 1 (Figure 1). Moreover, the hydrophobic and hydrophilic balance will be helpful for the organo-gelation.

To study the optical property, the absorption spectra of the peptide-mimetic 1 were recorded on a PerkinElmer UV-vis spectrophotometer. The self-assembly of the TriPh-Leu-Phe-OMe was examined by concentration dependent UV-VIS spectroscopy. The typical UV-VIS absorption spectra in methanol solution show absorption bands at 294 nm (Figure 2). With increasing the concentration, shift of the absorption band is also increasing. But the maximum wavelength is not changing.

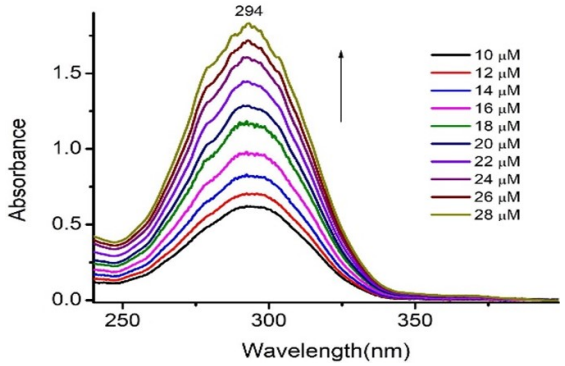


Figure 2: The absorption spectra of the peptide-mimetic 1**.**

We have also studied emission spectroscopy to know the optical behavior of peptide-mimetic 1, The typical emission spectra of compound in methanol solution show bands at 380 nm on excitation at 292 nm (Figure 3). The emission spectra show high intensity at low concentration and with increasing concentration, emission intensity decreases. But there is no shift of emission maxima (380nm).

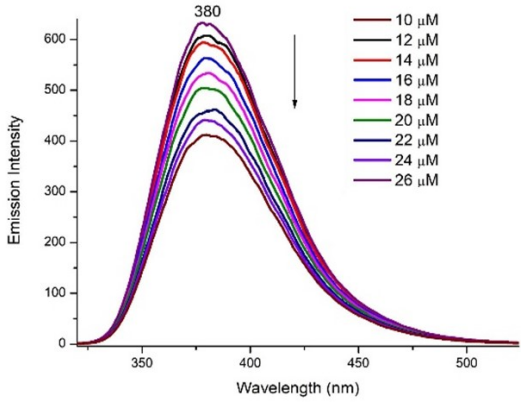


Figure 3: The emission spectra of the peptide-mimetic 1**.**

As the terminally protected peptide-mimetic TriPh-Ala-Phe-OMe **1** contains several intermolecular H-bonding sites and aromatic rings, we assumed the π-π interactions on the aromatic ring in addition to the H-bonding could significantly modulate the self-assembly behaviour of the peptide-mimetic 1 and helps in organogelation. The organogelation study was performed in different organic solvents. In order to check

the ability of the compound to form gels in different solvents, a weighted amount of the purified compounds was taken in micro centrifuge tubes and 0.5 mL of different solvents were added to them. The samples were heated in a heating block at temperatures ranging from 60–100°C and then they were subsequently cooled to room temperature and sonication was done. Gels were formed within a few minutes and were stable to inversion of the micro centrifuge tube. We observed that peptide-mimetic **1** forms organogel in toluene, *p*-xylene, chlorobenzene, acetonitrile, nitromethane by heating-cooling method (Figure 4). Organogel formation was confirmed by inverted vial test. Minimum Gelation Concentration (MGC) for peptide-mimetic **1** in toluene, *p*-xylene and chlorobenzene was found to be 5 mg/mL and in acetonitrile 7.2 mg/ mL. However, peptide-mimetic **1** does not form gel in solvents like hexane, DCM, EtOAc, MeOH, EtOH under similar condition even at comparatively high gelator concentration.

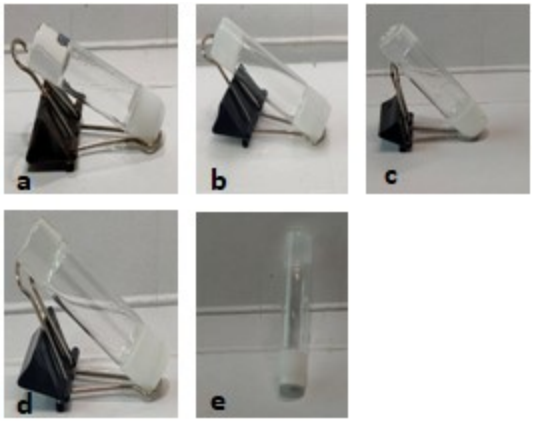


Figure 4: The organogel formed by peptide-mimetic TriPh-Ala-Phe-OMe **1** in (a) toluene, (b) acetonitrile (c) *p*-xylene, (d) chlorobenzene and (e) nitromethane.

Rheology helps to study mechanical behavior of material as stress-strain function, temperature, pressure based on viscosity, elasticity, time. Here Rheometer (Anton Paar, Modular Compact Rheometer) having a steel parallel plate geometry with 8 mm diameter was employed for rheology experiments at room temperature. In the amplitude graph there is a cross section that defines the gel form solution at that point. Rheology studies were carried out to examine the mechanical strength of the peptide-mimetic 1 based organogel. Rheology data of gel in toluene (5 mg/mL) was taken as a function of angular frequency and oscillatory strain. In rheology, there are two important parameters, elastic response ($G^{/}$) which is measured by storage modulus, it measured stored energy and the viscous response ($G^{//}$) which is measured by loss modulus, dissipated as the heat. However, in the frequency sweep experiment, the storage modulus $G^{/}$ is one order of magnitude higher than the loss modulus $G^{//}$ over the entire angular frequency range, which confirms formation of the strong gel (Figure 5a). But, in the amplitude sweep experiment, the loss modulus $G^{//}$ becomes greater than storage modulus $G^{/}$ at 1.1% oscillation strain, which exhibits that the gel breaks after this strain (Figure 5b). We have also measured the Rheology data of gel in acetonitrile as a function of angular frequency and oscillatory strain (Figure 6).

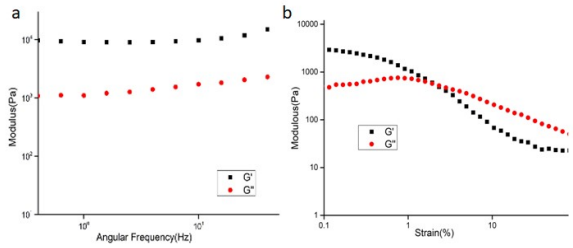


Figure 5: (a) Effect of angular frequency TriPh-Ala-Phe-OMe **1** in toluene. (b) Effect of strain TriPh-Ala-Phe-OMe **1** in toluene.

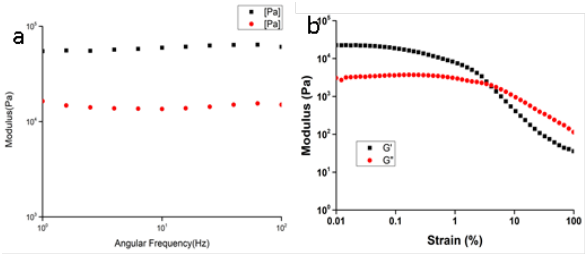


Figure 6: (a) Effect of angular frequency TriPh-Ala-Phe-OMe 1 in acetonitrile. (b) Effect of strain TriPh-Ala-Phe-OMe 1 in acetonitrile.

The morphology of the peptide-mimetic 1 organogel was studied by Polarised Optical Microscopy (POM) and Field-Emission Scanning Electron Microscopy (FESEM). The sample prepared from peptide-mimetic 1 solution in methanol drop casted on a glass slide followed by drying at 30°C for 48 h shows discrete fibers like morphology (Figure 7a) by POM. A slice of the peptide-mimetic 1 gel in *p*-xylene was placed on a microscopic glass slide and it was allowed to dry under reduced pressure at room temperature for two days. In FESEM image of that xerogel exhibits entangled fiber network morphology (Figure 7b).

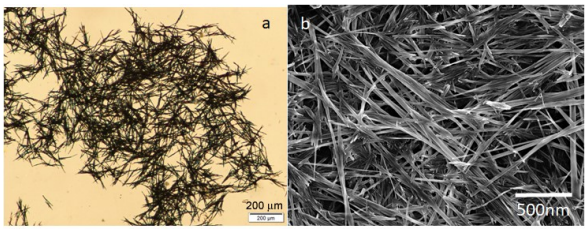


Figure 7: (a) POM image of peptide-mimetic 1 in methanol; (b) FESEM image of peptide-mimetic 1 gel in *p*-xylene.

Water pollution is one of the very rudimentary environmental problems faced by humanity at present. A critical source of water pollution is various organic dyes that are habitually utilized in several industries including the clothing industry. Dye and their byproducts are carcinogenic and harmful to the reproductive and immune systems. There have been methods of treating dye byproducts such as biological treatment, chemical precipitation, electrochemical techniques, absorption upon activated carbon, and others.

but they have their limitations due to their low sensitivity, high energy requirements, incomplete removal, and production of highly toxic sludge. Organogel-based soft materials offer an alluring alternative for the removal of dyes from contaminated water because of their large surface area for adsorption, and simplicity of use, along with their reusability and biodegradability. The peptide-mimetic 1 is rich in aromatic moieties and thus electron rich, so we thought they might be good contenders for cationic dye absorbance. An aqueous solution of Rhodamine 6g dye [10^{-4} (M)] was prepared and added to the organogel prepared from the compound in solvent *p*-xylene. This was kept still for 24 hours at room temperature, and the dye was totally absorbed in gel (Figure 8).

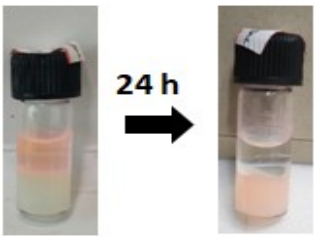


Figure 8: Removal of Rhodamine 6G dye from water by peptide-mimetic 1 gel in *p*-xylene.

Removal of dye molecules from their respective aqueous solutions was also examined by UV-visible spectroscopy. For Rhodamine 6G, 3 mL of 0.005 mM dye solution was treated with 5 mg of peptide mimetic **1** gel in *p*-xylene. The UV-visible spectroscopy shows that the maximum amount of the Rhodamine 6G (Figure 9) was absorbed by peptide-mimetic 1 gel leaving a nearly clear solution after 10 h. The maximum amount of Rhodamine 6G absorbed by gel is 4.5 mg/ g of gel.

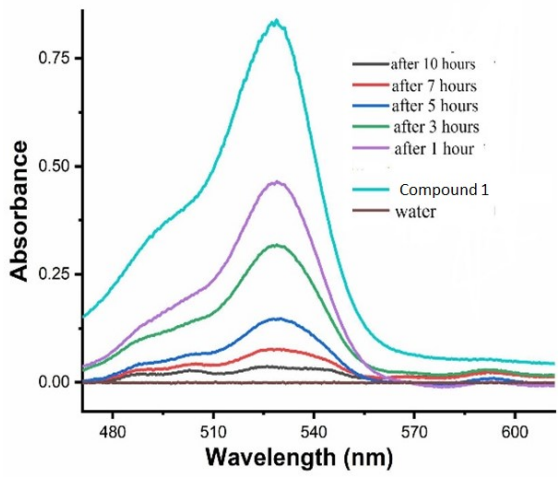


Figure 9: UV-vis spectra for time dependent absorption of Rhodamine 6G from aqueous solution by the peptide-mimetic 1 gel in *p*-xylene.

4. Conclusions

In conclusion, we have design, synthesized and studied the gelation properties of a peptide-mimetic 1 with methyl ester protecting group at C-terminus and 4-terphenylcarboxy protecting group at the N-terminus. Interestingly, the peptide-mimetic 1 formed organogel in different organic solvents such as in toluene, *p*-xylene, chlorobenzene, acetonitrile, nitromethane. The minimum gelation concentration for toluene, *p*-xylene, chlorobenzene is 5 mg/mL. However, the peptide-mimetic **1** does not form gel in hexane, DCM, EtOAc, MeOH, EtOH under similar condition. The terminally protected peptide-mimetic **1** based gels have high stability over couple of months. From rheology study, the storage modulus of the organogel was approximately an order of magnitude larger than the loss modulus, which indicates the physical crosslink and the elastic nature of the peptide mimetic **1** gel. FE-SEM images of the xerogel exhibits twisted fiber morphology and a danse fiber network. The peptide mimetic gel removed dyes from contaminated water. The maximum amount of Rhodamine 6G absorbed by peptide mimetic **1** gel is 4.5 mg/ g. The information will be helpful to develop new efficient low molecular weight gelators.

5. Acknowledgements

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6. Notes and References

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