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Enhanced mechanical and thermal strength in mixed enantiomers based supramolecular gel

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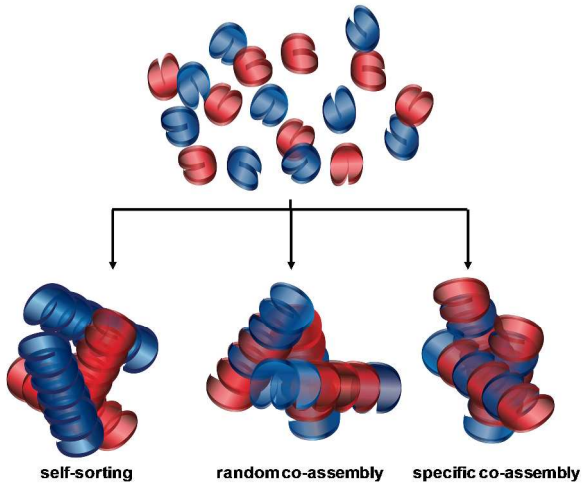
Supporting Information Placeholder

ABSTRACT: Mixing supramolecular gels based on enantiomers leads to re-arrangement of gel fibers at the molecular level, which results in more favorable packing and tuneable properties. Bis(urea) compounds tagged with a phenylalanine methyl ester in racemic and enantiopure forms were synthesized. Both enantiopure and racemate compounds formed gels in a wide range of solvents and the racemate (**1-rac**) formed a stronger gel network compared to the enantiomers. The gel (**1R+1S**) obtained by mixing equimolar amount of enantiomers (**1R** and **1S**) showed enhanced mechanical and thermal stability compared to enantiomers and racemate gels. The preservation of chirality in these compounds was analyzed by circular dichroism and optical rotation measurements. Analysis of the SEM and AFM images revealed that the network in the mixed gel is a combination of enantiomers and racemate fibers, which was further supported by solid state NMR. The analysis of the packing in xerogels by solid state NMR spectra and the existence of twisted-tape morphology in SEM and AFM images confirmed the presence of both self-sorted and co-assembled fibers in mixed gel. The enhanced thermal and mechanical strength may be attributed to the enhanced intermolecular forces between the racemate and enantiomer and the combination of both self-sorted and co-assembled enantiomers in the mixed gel.

INTRODUCTION

Supramolecular gels based on low molecular weight gelators (LMWGs)[1-9] have witnessed a tremendous growth over the last decade due to their emerging potential applications[10-16] such as dynamic gels, biological applications using gels as cell growth scaffolds and also as a medium to control crystal growth, drug delivery etc. Although the majority of these gelators are based on individual molecules, gels based upon multi-component systems have emerged as smart materials due to their application in tuning gel state properties.[17-30] Multi-component gels are formed when two or more components are mixed together in a well-defined stoichiometry and also by introducing an external entity such as nanoparticles,[31] graphene,[32, 33] carbon nanotubes,[34] clay nanosheets,[35] liquid crystal,[36] surfactants[37, 38] and polymers[39-41] to an individual system to trigger gelation process. Multi-component gels based on mixing individual gels are less explored, which will lead to the co-assembly or self-sorting of individual gels either constructively or destructively resulting in mixtures of gel and crystals[42] or "multi-gelator" gels.[20, 43-45] The self-sorting processes of multi-component gels can be analyzed by various analytical methods (NMR, XRD etc.)[8, 45, 46] and also by direct and real-time imaging of self-sorted supramolecular fibers.[47] However, predicting the formation of co-assembled or self-sorted multicomponent gels is challenging due to the differences in their mutual interactions and the gelation conditions. The co-assembly and self-sorting is often dictated by the structural similarity between individual gels.[18] An excellent strategy is to use enantiomers, for example chiral gels to design multi-component systems with structurally similar components.



Scheme 1. Self-assembly modes in mixed gels.

Chiral LMWGs have proved to be an excellent class of soft materials [14, 43, 48-50] due to their potential applications in the field of asymmetric catalysis, chiral nano-materials and chiral recognition. Gel fibers often show chirality at a mesoscopic scale, which is evident from their morphology (helical cylinders or multiple heli-

ces)[48] and Gunnlaugsson and Pfeffer's group showed that chirality of the gelator dictates the self-assembly processes of gels resulting in the formation of helical materials.[51] Chirality plays an important role in controlling and mediating the self-assembly of LMWGs, which clearly explains the occurrence of stereogenic centers[14, 43, 48, 49, 52] in most LMWGs. LMWGs based on enantiomerically pure chiral molecules display strong gelling ability compared to their racemates.[43, 46, 53, 54] Interestingly, when pure enantiomers are less efficient gelators or non-gelators, a reverse phenomenon is observed.[55-62] A racemate LMWG can be considered as a multi-component gel, where two structurally similar compounds are present in stoichiometric ratio. Mixing enantiomers lead to self-recognition at the molecular level and pure enantiomers would interact with enantiomers, which may lead to more favorable packing and better gels.[18, 63-65]

Multi-component self-assembled gels obtained by mixing enantiomers have shown different properties compared to the individual gels.[63, 65-69] For example, Schneider's group reported mixing an equimolar ratio of enantiomers enhanced the mechanical strength of amino acid based gels.[67, 70] This is due to the structural similarity of enantiomers, which will either self-sort or co-assemble depending upon the environment. Self-sorting occurs when enantiomers independently assemble and retain their chirality, whereas in the case of co-assembly it may result in random or specific co-assembly similar to its racemate (Scheme 1). In a mixed enantiomer system, the interaction of enantiomers with the same conformation results in separate aggregates via self-sorting, which may lead to conglomerate formation.[18] Based on their studies on amphipathic peptides, Nilsson and co-workers proposed that enantiomers form co-assembled rippled β-sheet fibrils rather than self-sorting.[63] In this work, we have designed multicomponent gels based on amino acid compounds to analyze the difference between the self-assembly of pure and mixed enantiomers. Enantiomeric multicomponent gels based on amino acid derivatives are ideal candidates due to their availability in enantiomeric and racemic forms, easily accessible, relatively cheap and easiness in modifying the substituent groups.[64]

EXPERIMENTAL SECTION

Materials and Methods

All starting materials and reagents were commercially available (Sigma Aldrich) and used as supplied. Deionised water was used for gelation test and solvent chloroform was distilled over P_2O_5, and methanol over Mg turnings in presence of small amount of iodine.

Synthesis

*Methyl-**rac-**phenylalaninate*: 5 g (30.0 mmol) of ***rac-***phenylalanine was dissolved in 70 mL of methanol and 2 mL of conc. H_2SO_4 was added. The solution was refluxed overnight and then cooled to room temperature. Methanol was evaporated and the white oil obtained was stirred with 2% $NaHCO_3$ solution. The solution was extracted with DCM (3 x 75 mL), the combined organic layers were dried over Na_2SO_4 and evaporated to yield the ester as white powder. Yield: 4.99 g, 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.32-7.18 (m, 5H), 3.74 (dd, J=8.0, 5.2, 1H), 3.72 (s, 3H), 3.09 (dd, J=13.5, 5.1, 1H), 2.86 (dd, J=13.5, 7.9, 1H), 1.47 (s, 2H).

General Synthesis of R-R bis(urea) (**1R**) and *S-S bis(urea)* (**1S**) compounds: The phenylalanine methyl ester hydrochloride (1.3 g, 6.0 mmol, either **R** or **S**) was dissolved in 60 mL chloroform and 3 mL of trimethylamine was added. A solution of 1,6-disocyanatohexane (482 µL, 3.0 mmol) in chloroform (40 mL) was added dropwise under N_2 atmosphere over a period of one hour. The solution was then refluxed at 60 °C overnight, cooled to room temperature and the solvent was evaporated to yield a white oil. The oil was dried in air and suspended in 50 mL distilled water and stirred. The suspension was filtered, washed with ethyl acetate and dried to yield the desired product as white powder.

1R: Yield: 1.50 g, 95.0%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 – 7.13 (m, 10H), 6.11 (d, *J* = 8.2 Hz, 2H), 6.05 (t, *J* = 5.7 Hz, 2H), 4.39 (td, *J* = 8.0, 5.6 Hz, 2H), 3.59 (s, 6H), 2.99 – 2.82 (m, 8H), 1.35 – 1.16 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.19, 157.49, 137.19, 129.21, 128.34, 126.62, 54.09, 51.74, 39.15, 37.71, 29.94, 26.13. HRMS (APCI) Calcd for $C_{28}H_{38}N_4O_6$ 526.28; found 549.26 $[M+Na]^+$.

1S: Yield: 1.46 g, 92.3%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38 – 7.07 (m, 10H), 6.12 (d, *J* = 8.2 Hz, 2H), 6.06 (t, *J* = 5.9 Hz, 2H), 4.40 (td, *J* = 8.0, 5.6 Hz, 2H), 3.59 (s, 6H), 2.93 (m, *J* = 17.1, 8.9, 7.9 Hz, 8H), 1.42 – 1.09 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.20, 157.52, 137.20, 129.22, 128.35, 126.64, 54.11, 51.76, 39.17, 37.73, 29.96, 26.14. HRMS (APCI) Calcd for $C_{28}H_{38}N_4O_6$ 526.28; found 549.26 $[M+Na]^+$.

Synthesis of racemic bis(urea) **(1-rac)** The *rac*-phenylalanine methyl ester (1.11 g, 6.2 mmol) was dissolved in 60 mL chloroform and 2 mL of trimethylamine was added. A solution of 1,6-disocyanatohexane (500 µL, 3.1 mmol) in chloroform (40 mL) was added dropwise under N_2 atmosphere over a period of one hour. The resulting mixture was refluxed at 60 °C overnight, cooled to room temperature and a similar reaction workup for **1R** was followed to yield desired product as white powder. Yield: 1.57 g, 96.3%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 – 7.12 (m, 10H), 6.11 (d, *J* = 8.2 Hz, 2H), 6.05 (t, *J* = 5.7 Hz, 2H), 4.39 (td, *J* = 8.1, 5.6 Hz, 2H), 3.59 (s, 6H), 3.00 – 2.82 (m, 8H), 1.34 – 1.24 (m, 4H), 1.24 – 1.15 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.22, 157.55, 137.21, 129.24, 128.37, 126.66, 54.13, 51.78, 39.18, 37.74, 29.97, 26.15. HRMS (APCI) Calcd for $C_{28}H_{38}N_4O_6$ 526.28; found 549.26 $[M+Na]^+$.

Gelation details

Gelation test: 10 mg of gelator was taken in a test tube and 1 mL of the appropriate solvent was added, the solution was heated until the compound completely dissolved. The test tube was then sonicated and left undisturbed for gelation and the gel formation was confirmed by inversion test.

Minimum gel concertation (MGC): 10 mg of the gelators **1R**, **1S** or **1-rac** was placed in a vial and 1 mL of solvent was added. The vial was heated until a clear solution was obtained. The solution was then sonicated and left to cool to room temperature for gelation. Additional solvent was added in portions and the gelation process was repeated until a small amount of solvent was left on top of the gel, the excess solvent was then decanted and MGC was calculated by weight. Similar experiments were performed for the **1R+1S** mixed gel, which was prepared by mixing equal amount of **1R** and **1S**.

T_{gel} experiment: 10 mg of the gelator (**1R**, **1S** or **1-rac**) was taken in a standard 7 mL vial and 1 mL of appropriate solvent was added. The solution was heated and sonicated to dissolve the compound and allowed to stand undisturbed. After 24 hours, a small spherical glass ball (92 mg) was placed on the top of the gel. The vial was placed over an oil bath equipped with a magnetic stirrer and a thermometer. The oil bath was gradually heated and the observation was noted. The temperature at which the glass ball touched the bottom of the vial was recorded as T_{gel}. Similar experiments were performed for the **1R+1S** mixed gels by mixing 5 mg of each **1R** and **1S**.

Rheology: The rheological study was performed by using a TA Instruments Advanced Rheometer 2000 and toluene was selected as the gelling solvent. The gels of **1R**, **1S** and **1-rac** were prepared by heating 50 mg of corresponding gelator in 1 mL toluene and the resulting solutions were kept at room temperature without disturbing for one hour. The **1R+1S** gel was prepared by mixing equal amount of **1R** and **1S** (25 mg in 0.5 mL toluene), heated and left at room temperature without disturbing for one hour. A stainless steel cone-plate geometry (20 mm, 2° angle, truncation 64 μm) was used. Viscoelastic properties were evaluated by oscillatory measurements, using a frequency sweep between 0.1 and 10 Hz within the linear viscoelasticity domain (0.05% deformation). Complex moduli (G*) and tanδ were evaluated. Mechanical properties were determined by uniaxial compression measurements using a TA HD Plus Texture Analyzer (Stable Micro Systems, UK) with a stainless steel 0.5 mm probe. The probe penetrated 80% of the initial height using a crosshead speed of 1 mm/s.

Scanning Electron Microscopy (SEM): 20 mg of the gelator (**1R**, **1S** or **1-rac**) was dissolved in 1 mL of toluene/ethyl acetate by heating and sonicating. The solution was allowed to stand undisturbed to form the gel. After 24 hours, it was filtered through filter paper and the residue was dried in air. The **1R+1S** xerogel was prepared by same procedure from the gel obtained by mixing equal amount of **1R** and **1S.** The xerogels were gold coated and placed on a Leo Supra 25 microscope for scanning electron microscopy and the morphologies of the dried gels were examined by SEM. The EtOH/water xerogels were lightly dusted onto double sided carbon tape and was then coated with a 30 nm layer of platinum using a Leica EM ACE600, where the thickness was monitored using a film thickness monitor. The SEM imaging for EtOH/water gels were undertaken on a NanoSEM 230 fitted with a through lens detector at an operating voltage of 5 kV, with a working distance of between 4.9-5.7 mm.

Atomic Force Microscopy: Gels of **1R**, **1S** (0.7 wt%), **1-rac** (0.15 wt%) and **1R+1S** (0.3 wt%) were dispersed in appropriate solvent (toluene or EtOH/water), heated to dissolve and the gels were formed in 5 minutes after cooling. The solutions were diluted 5 x (100 μL + 400 μL solvent) and 10 x (100 μL + 900 μL solvent), One drop of the organogel in its solution phase was cast onto a mica substrate, followed by spreading of the drop over the mica using a glass slide, with the excess liquid wicked away using capillary action. Samples were left to dry overnight before imaging. Imaging was undertaken on a Bruker Mulitmode 8 Atomic Force Microscope in Scanasyst Air (PeakForce Tapping) mode, which is based upon tapping mode AFM, but the imaging parameters are constantly optimized through the force curves that are collected, preventing damage of soft samples. Bruker Scanasyst-Air probes were used, with a spring constant of 0.4–0.8 nm and a tip radius of 2 nm.

Circular Dichroism: The data was collected using a ChirascanPlus CD spectrometer (Applied Photophysics, UK) scanning between wavelengths of 180–500 nm with a bandwidth of 1 nm, 0.6 s per point, and step of 1 nm. The gels of **1R**, **1S**, **1-rac** and **1R+1S** were prepared at their minimum gel concertation in EtOH/water (1:1 v/v). After 24 hours the gel was dispersed in EtOH/water (1:1 v/v) to obtain various concentrations (0.005, 0.025 and 0.05 wt%) for CD experiments. CD experiments in solution state were performed by dissolving 2.5 mg of the gelator (either **1R**, **1S**, **1-rac** or **1R+1S**) in 10 mL of absolute ethanol.

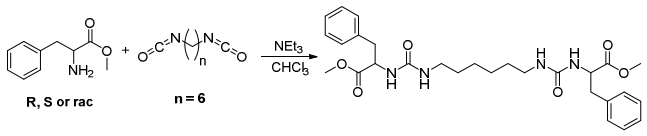
Optical rotation measurements (OD): The OD experiments for both enantiomers, the racemic mixture and the mixed gel (at 50/50 wt/wt) were carried out at 589 nm, on an Autopol V from Rudolph research analytical, in both a gelling solvent (toluene) and a non-gelling solvent (2-butanol). Due to the opaque nature of the gel, the concentration was kept under the minimum gel-concentration.

NMR Experiments: The solution state ^{1}H and ^{13}C-NMR spectra were recorded on Bruker Advance 400 spectrometer (^{1}H-NMR: 400 MHz, ^{13}C-NMR: 100 MHz). The solid state NMR spectra were recorded on Bruker Avance III 700 MHz spectrometer on xerogels of **1R**, **1S**, **1-rac** and **1R+1S** in toluene at 1 wt%.

RESULT AND DISCUSSION

We have selected the bis(urea) moiety as a hydrogen bonding backbone, which has been extensively used as a supramolecular synthon for the self-assembly of gelators in LMWGs with tuneable properties.[71-76] Compounds based on bis(urea) ligands form a α-urea tape structure, which will result in a 1-dimensional tape like network (fibrils) and these fibrils aggregate to form an interconnected, entangled 3-D framework capable of immobilizing solvent molecules thereby inducing gelation in small molecules.[7, 77-81] Enantiopure *R-R* (**1R**) and *S-S* (**1S**) bis(urea) compounds based on amino acid derivatives were synthesized by reacting 1,6-diisocyanatohexane and corresponding methyl ester protected

amino acid hydrochloride in chloroform.[81-83] The racemate bis(urea) compound (**1-rac**), which is a statistical mixture of *R-S*, *R-R* and *S-S* (see supporting information) was synthesized by reacting racemate phenylalanine methyl ester with 1,6-diisocyanatohexane in chloroform (Scheme 2). The gelation properties of these compounds were tested in a series of solvents.



Scheme 2. Synthesis of **1R**, **1S**, **1-rac** bis(urea) compounds

Gelation experiments: The initial screening was performed in a series of solvents with 1 wt% of the compound. In a typical experiment, the compounds were heated and sonicated in a particular solvent to get a clear solution, cooled to room temperature and the gel formation was confirmed by inversion test (Figure 1). All the three bis(urea) compounds (**1R**, **1S** and **1-rac**) formed gels in 1,2-dichloroethane, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, chlorobenzene, ethyl acetate, 2-butanone and nitrobenzene. This is quite interesting that all the three forms (both enantiomeric and racemate) show gelation for a wide range of solvents. Generally, selective gelation is observed with either the enantiomers or racemate,[46, 53, 54, 56, 84] but gel formation of both enantiomers and racemate are rare.[56, 57, 85, 86] The selective gelation of **1-rac** at 1 wt% was observed in cyclohexanone and mesitylene. (Table S1, see supporting information) The occurrence of partial gels prompted us to check the gelation of the compounds at higher concentrations, and gels were obtained at higher wt% for **1R** and **1S** in mesitylene (2 wt%). Gels were formed at 2 w% for the racemate **1-rac** in isopropanol, 2-pentanol and n-pentanol and in ethanol at 3 wt%. We have also checked the gelation properties in aqueous solution by using 50% (v/v) of water and a co-solvent (either methanol, ethanol, DMA, DMF and DMSO) to dissolve the compounds. Hydrogels were obtained at 1 wt% for most of the cases except for **1-rac** in DMF/water and DMSO/water, where gelation occurred at 2 wt%.

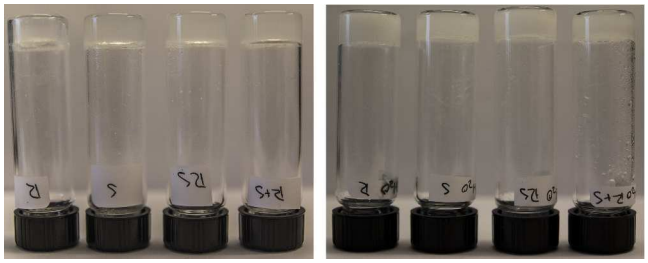


Figure 1. Gel images (left) in toluene and (right) EtOH/water (50%, v/v).

The minimum gel concentration of the gelators were evaluated in solvents such as ethyl acetate, 2-butanone, toluene, chlorobenzene, xylenes (*ortho*-, *meta*- and *para*-) and nitrobenzene (Table S2, see supporting information). Interestingly, **1-rac** compounds formed gels at lower concentration compared to the **1R** and **1S**. The **1-rac** gels formed in toluene, chlorobenzene and xylenes (*ortho*-, *meta*- and *para*-) can be classed as super gelators. Specifically, less than half the concentration was required to form the gels for **1-rac** gels compared to enantiomerically pure gels, indicating that the presence of both isomers increases gelling ability. This may be attributed to the π–π interaction between the solvents and gelator molecules in the 3-D network, within which the solvent molecules are entrapped. Furthermore, the α-sheet like structure of the urea network could be preserved due to the absence of the strong hydrogen bonding moieties. These results clearly indicate that both **1R** and **1S** self-assemble to form a strong network in the racemate form **1-rac**. This lead to an interesting question, what happens when two enantiomers are mixed? Will **1R** and **1S** undergo self-sorting or co-assembly to form conglomerate or racemate? This prompted us to evaluate the gelation property of mixed enantiomers, which was performed by mixing equal amount of **1R** and **1S** in a series of solvents at 1 wt% resulting in mixed gels. The mixed gel turned out to be an excellent multicomponent gel and gels were formed in 23 solvents. Analyzing the gelation results revealed that **1R+1S** formed gel at 1 wt% in solvents such as acetonitrile, tetrahydrofuran, acetone, 2-butanol, n-butanol and 1,4-dioxane and 2 wt% in n-propanol respectively, whereas **1R**, **1S** and **1-rac** did not form gel in these solvents (Table S1, see supporting information). The experiments performed on mixed gels prepared by mixing equimolar solutions of **1R** and **1S** resulted in similar gelation properties.

Table 1. Gel-Sol transition temperature (°C) of the enantiomers, racemate and mixed gels at 1 wt%.

Solvent	1R	1S	1-rac	1R+1S
Toluene	91.0	86.5	85.0	106.5
Ethyl acetate	55.0	54.5	61.0	73.5
p-xylene	94.0	91.0	98.0	102.0
m-xylene	99.0	95.0	97.0	102.0
o-xylene	92.0	91.0	90.0	99.0
2-butanone	38.0	37.5	40.0	55.5
Chlorobenzene	73.0	70.5	75.5	90.5
EtOH/Water	51.5	44.5	52.5	55.5

Gel strength: The thermal stability of the gel network was evaluated using gel to solution transition temperature test (T_{gel}). In order to compare gel strength, we have selected solvents such as toluene, ethyl acetate, xylenes (*ortho*-, *meta*- and *para*-), 2-butanone, chlorobenzene and EtOH/water (50% v/v) and the gel concentration was fixed at 1 wt%. Analysis of the results revealed that T_{gel} of **1R** in toluene, m-xylene and p-xylene is higher compared to **1S** and **1-rac** gels (Table 1). In other cases, the **1-rac** gel displayed the highest T_{gel} value indicating a thermally stronger network whereas **1S** showed similar or lower values than **1R**. Interestingly, there is a distinct difference in **1R+1S** mixture T_{gel}, which is higher than pure enantiomers and racemate in all cases (Table 1). A difference of 10 to 20 °C was observed for toluene,

ethyl acetate and 2-butanone. This clearly indicate that the 3-D network in the enantiomers and the mixed gels are different. This was confirmed by variable temperature rheology experiments in toluene (Figure S1, see supporting information). We have also compared the T_{gel} of the hydrogels obtained from EtOH/water (1:1, v/v) and **1R+1S** gels showed greater thermal stability compared to the enantiomers and the racemate gels. The enhanced thermal stability of the mixed gel (**1R+1S)** gel may be attributed to the self-assembly of these components into a new or mixed network as compared to the enantiomer and racemate fibrils. The T_{gel} experiments performed on 1 wt% of mixed gels by varying the concentration of both **1R** and **1S** revealed that the gel formation of **1R+1S** depends on **1R** and **1S** concentrations respectively (Figure 2).

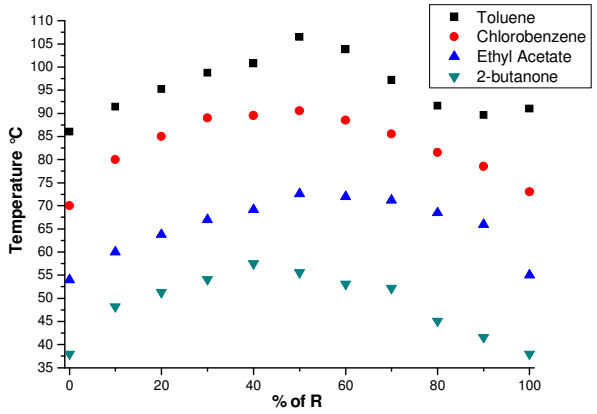


Figure 2. T_{gel} of **1R+1S** gels by varying the concentration of both **1S** and **1R** in toluene, ethyl acetate chlorobenzene and 2-butanone.

Rheology: Rheology was used to evaluate the structural characteristics of supramolecular gels, which enables us to elucidate information regarding factors controlling the gelation, gel strength and the solid-like properties of pure gels. For example, Adams and co-workers reported the combination of self-sorted LMWGs and photo responsive gelators offer the possibility of spatially controlling the rheological properties of LMWG.[45] We performed frequency sweep experiments to compare the relative gel behavior of **1R**, **1S**, **1-rac** and **1R+1S** in toluene at 5 wt%. Elastic ($G´$) and viscous ($G´´$) moduli were evaluated, as well as the complex modulus ($G^* = \sqrt{G´^2 + G´´^2}$) and tanδ ($G´´/G´$).

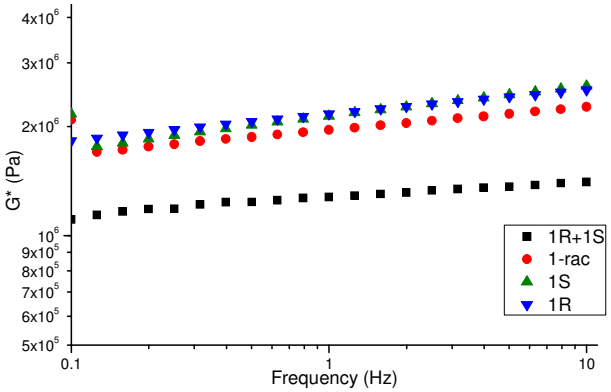


Figure 3. Complex modulus G* for gels produced with **1R**, **1S**, **1-rac** and **1R+1S** in toluene at 5 wt%.

It is worth mentioning that a strain sweep was also carried out to determine the linear viscoelastic region. This ensured that the systems did not undergo an irreversible deformation during the experiments and the original structure of the organogels can be evaluated. All organogels showed gel-like behavior with no frequency dependence (Figure 3). The **1R**, **1S** and **1-rac** gels exhibited very similar G* behavior. However, the **1R+1S** gel had a slightly lower complex modulus (G^*) value, indicating the presence of a weak fibrous network in comparison to the other gels. It should be noted that the **1R+1S** $G´$ values were not so different from the other gels, but the viscous contribution ($G´´$) was higher for **1R**, **1S** and **1-rac** systems, leading to higher values of G^*. Indeed, tanδ results presented lower values for the **1R+1S** system, while the other gels remained very close to each other (Figure S2, see supporting information). The lower tanδ value indicates a prevailing elastic modulus ($G´$), i.e. more solid characteristic, which will enable the network to withstand higher applied forces without irreversible deformation. The mechanical strength of all gels was compared by evaluating the force required to penetrate a certain distance through a gel, force vs distance was plotted (Figure 4). Unlike rheological analysis, mechanical properties measure high and irreversible deformation, complementing the rheological results, which are performed at small deformations. These results clearly indicate that **1R**, **1S** and **1-rac** showed similar behavior with maximum forces with same magnitude. On the other hand, a higher maximum force was observed for the mixed gels (**1R+1S)**. Moreover, a larger area under the curve also means a stronger structure, which was observed for **1R+1S**, indicating that this gel was stronger in comparison to the other systems. Mechanical results corroborated rheological tests, showing that **1R+1S** presented more solid character with higher resistance to applied forces.

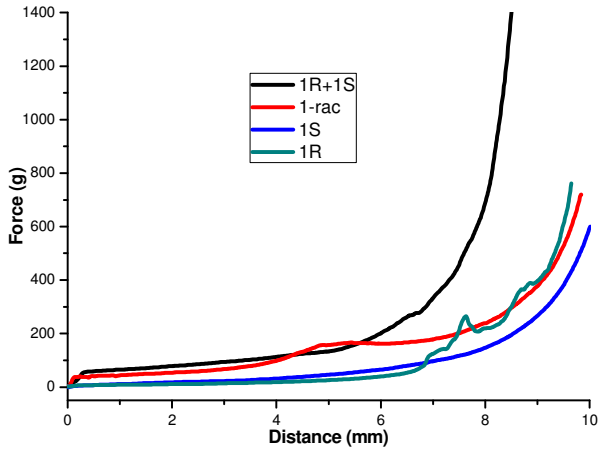


Figure 4. Comparison of mechanical strength for gels **1R**, **1S**, **1-rac** and **1R+1S** in toluene at 5 wt%.

Gel morphology: The morphologies of all gels were analysed by scanning electron microscopy (SEM). All gels were prepared at 2 wt% in toluene and ethyl acetate, then filtered and dried under a fume hood for 2-3 days. A small portion of the dried gel was placed on a pin mount with graphite planchets on top and was coated with gold for three minutes. The SEM images revealed that all xerogels display a typical fibrous and helical network (Figure 5 and 6). The SEM images of xerogels from ethyl acetate showed that **1R** and **1S** form helical fibrous network (Figure S3). The individual fibrils form helical fibrous aggregates with varying dimensions and the thickness of each helical fibers varied from 25 to 40 nm. The larger bundles of 100 nm to 150 nm are formed by wrapping of individual fibers around each other in a helical manner resulting in a physically entangled networks, this type of twisting is often observed in chiral compounds.[84, 87, 88] The helicity of single fibers for **1R** and **1S** clearly indicate that molecular chirality had been successfully transferred to the hierarchical aggregates (Figure 5a). The morphology of racemate xerogel **1-rac** is different from its enantiomers and tape like fibers were observed (Figure 5b). The thickness of each fiber varied from 50 to 200 nm with few fibrils wrapped around each other. Interestingly, a twisted tape like architecture was observed in **1R+1S** with bundles of varying dimension from 50 to 200 nm indicating the presence of both enantiomers and racemate (Figure 6a). The SEM of xerogels obtained from toluene showed similar morphologies, both **1R** and **1S** form helical fibrous network with a thickness of 30 to 70 nm (Figure S4, see supporting information). These small fibers merge with each other to form a thicker helix of diameter 150 – 200 nm.

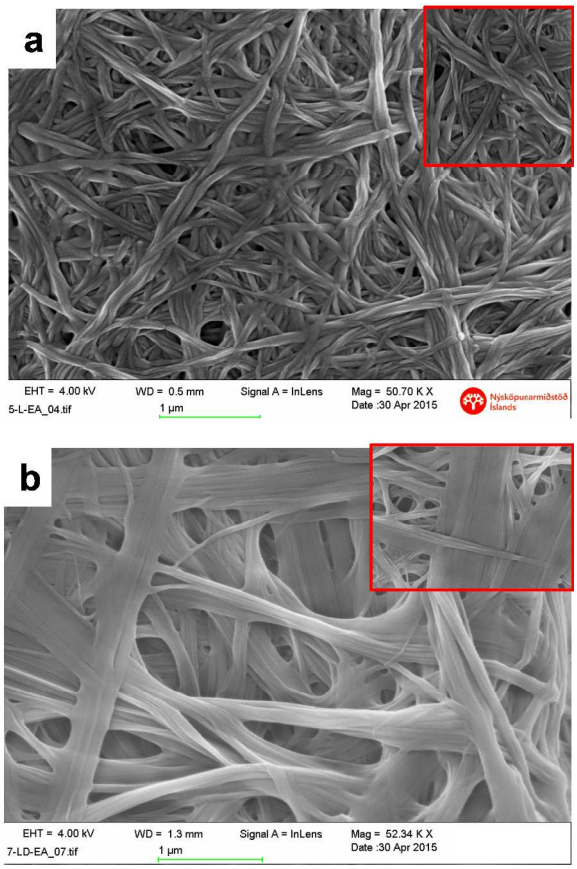


Figure 5. SEM images of (a) **1S** and (b) **1-rac** xerogels in ethyl acetate, inset shows the magnified images.

Xerogels of **1-rac** from toluene shows similar tape like morphology (Figure S5, see supporting information) The **1R+1S** xerogel displayed twisted tape morphology similar to ethyl acetate gels and the diameter of the fibers were found to be 100 – 250 nm. The SEM analysis of xerogels obtained from EtOH/water (50% v/v) also support the presence of mixed network in **1R+1S** gels (Figure S6, see supporting information). The presence of two types of networks in the SEM images corroborate well with the rheology results. In mixed networks, elastic character of the gel network was increased due to higher entanglement, which is evident from the rheology results of **1R+1S** compared to other gels.

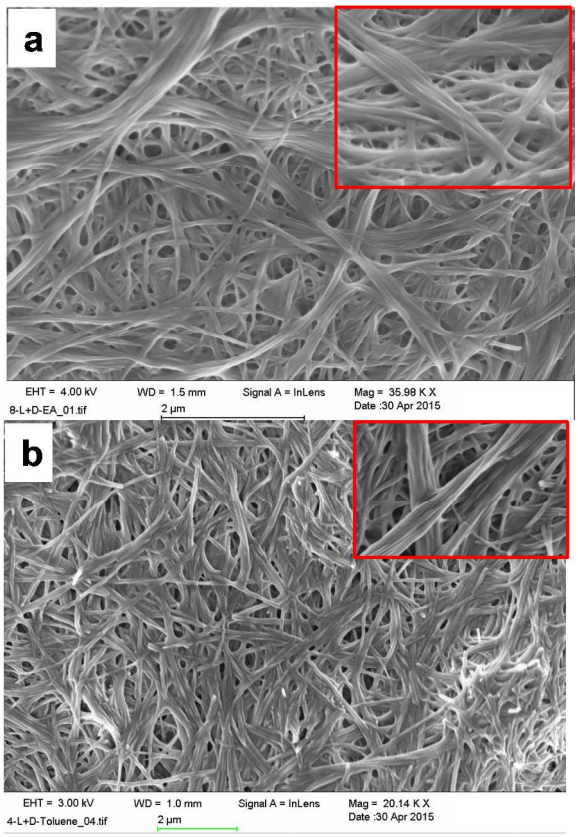


Figure 6. SEM images of **1R+1S** xerogels in (a) ethyl acetate and (b) toluene, inset shows the twisted tape morphology.

Atomic Force Microscopy (AFM): The morphology of the gel fibers was further analyzed by AFM studies. The gels were made by dissolving the **1R** (0.7 wt%), **1S** (0.7 wt%) and **1-rac** (0.15 wt%), in toluene. The **1R+1S** gel was prepared by dissolving individual **1R** and **1S** in toluene (0.3 wt%) and then heated. All these gels were further dispersed in toluene (10x), dropped on a plate, dried at room temperature and analyzed by AFM. Analysis of the AFM images of **1R** and **1S** revealed that both the enantiomer have twisted single helix with uniform right and left-handed morphology respectively (Figure 7). However, a tape like morphology was observed for **1-rac**, which clearly indicate that the helicity was cancelled due to the co-assembly of both **R** and **S** fibrils (Figure 8).

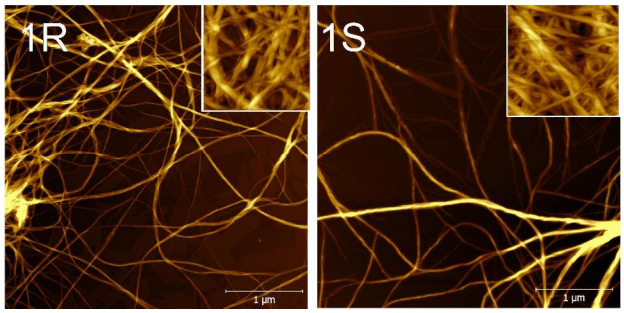


Figure 7. AFM images of **1R** and **1S** showing the left and right handed helical fibers; inset shows the magnified images.

Interestingly, the mixed gel **1R+1S** showed both twisted and tape like morphology. This may be attributed to self-sorting and co-assembly of **1R** and **1S** fibrils when they are mixed and heated together. Similar morphologies were observed for EtOH/water (50%, v/v) gels and the AFM images of **1R** and **1S** showed helical fibers, a tape like morphology for **1-rac** and both twisted and tape like morphology for **1R+1S** (Figure S9-S10, see supporting information).

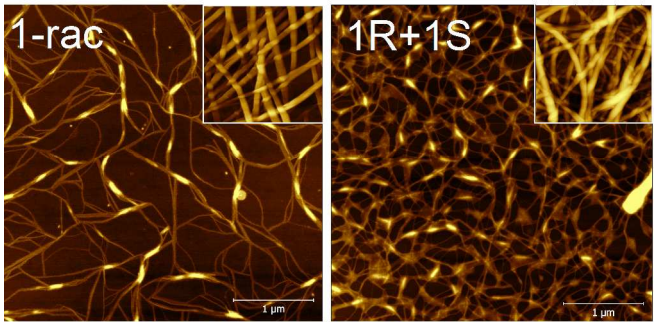


Figure 8. AFM images showing tape like architecture in **1-rac** and a mixture of tape and helical morphology in **1R+1S**; inset shows the magnified images.

Circular dichroism (CD): The sensitivity of CD to chiral perturbations will provide information about molecular chirality and the difference between CD signals of self-assembled and isolated state will enable us to elucidate the structural information of the assembled hierarchical structure.[89] Although, we screened a series of solvents, which are capable of forming gels with **1R**, **1S** and **1-rac**, these solvents were discarded due to background absorption. We have selected EtOH/water mixture for our studies, which showed an absorption cut-off at around 190-200 nm. The CD experiments were performed at various concentrations in dispersed gel state and weak signals were observed below 0.005 wt% for all gelators. On the other hand, increasing the concentration above 0.05 wt% resulted in saturation of CD signals. Thus, we selected 0.025 wt% as the optimum concentration for the enantiomers, racemate and the mixed gels (Figure 9a). The CD signal maxima was observed at 200 nm and 220 nm for **1S** may be attributed to the existence of π–π stacking interactions from the

aromatic units.[90, 91] The CD spectrum of **1R** showed negative signals, which is similar to the mirror image of the CD signal of **1S**. The gels of **1-rac** and **1R+1S** (50% v/v) displayed linear CD signal indicating the presence of both enantiomers in the gel state. In order to get an insight to the self-assembly process the CD of these compounds in the solution state was also analyzed (Figure 9b) and compared to the gel state CD, which indicate the formation of self-assembled networks in gel state. The small peak at 240 nm observed in the gel state CD is likely due to stacking of the aromatic phenylalanine groups within the gel. We have also performed the CD experiments of **1R+1S** by varying the concentration of 1R and 1S. The CD spectrum of **1R+1S** (75% **1R** v/v) mixture displayed negative maxima indicating the presence of excess **1R** (Figure S11, see supporting information). Similarly, the experiments with **1R+1S** (25% **1R** v/v) displayed positive maxima.

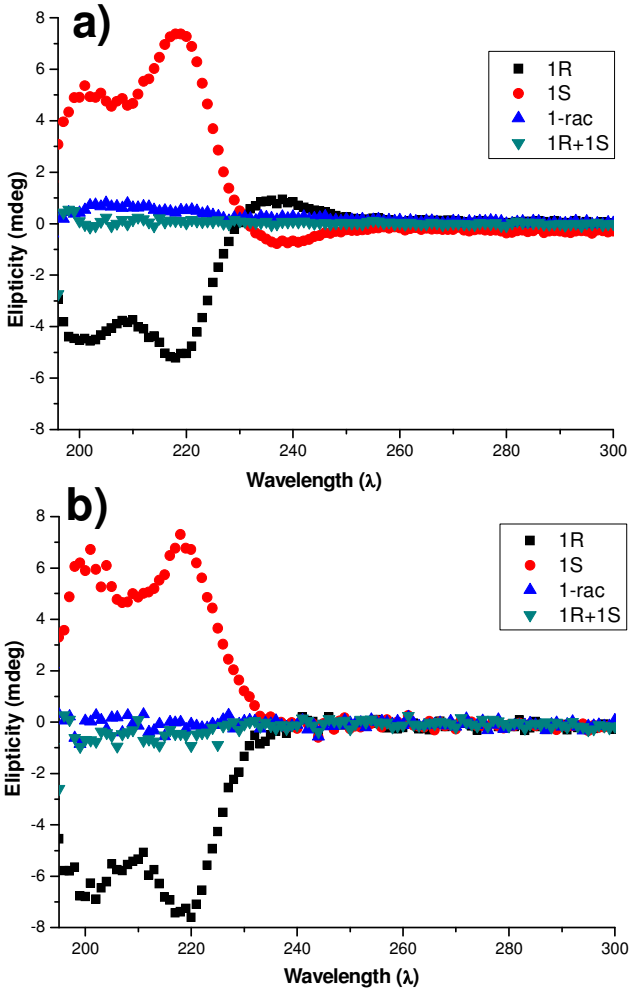


Figure 9. CD spectra of **1R**, **1S**, **1-rac** and **1R+1S** in dispersed gel state (a) and in solution state (b).

We have also performed optical rotation measurements for **1R**, **1S, 1-rac** and **1R+1S** at 589 nm in solution (2-butanol) and gelling solvent (toluene) at concentrations below minimum gel concentrations (Table S4, see supporting information). The observations were similar to that of the CD experiments.

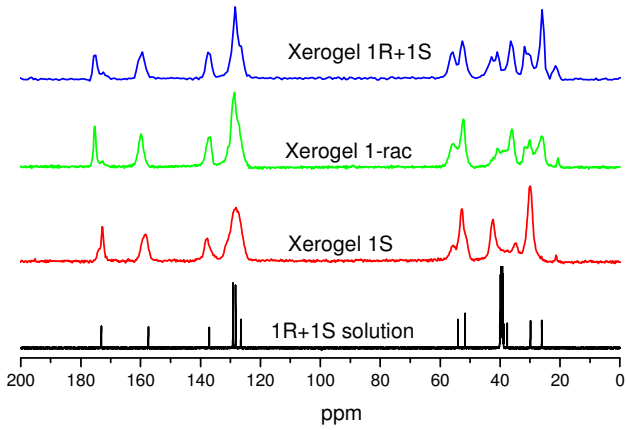


Figure 10. Comparison of the solid state and solution state ^{13}C NMR of **1R**, **1S**, **1-rac** and **1R+1S**.

Nuclear Magnetic Resonance Spectroscopy (NMR): The self-assembly of **1R**, **1S**, **1-rac** and **1R+1S** were studied by NMR spectroscopy. The ^{1}H and ^{13}C NMR of **1R**, **1S**, **1-rac** and **1R+1S** in solution state was recorded in DMSO-d_6 and similar NMR spectra suggest that enantiomers, racemate and mixed enantiomers have an identical environment in the solution state (Figure S12 and S13, see supporting information). In order to analyze their self-assembly in the gel state, solid state NMR was performed on the xerogels of **1R**, **1S**, **1-rac** and **1R+1S** by filtering 1 wt% gels, followed by drying and compared with the solution state NMR (Figure 10).

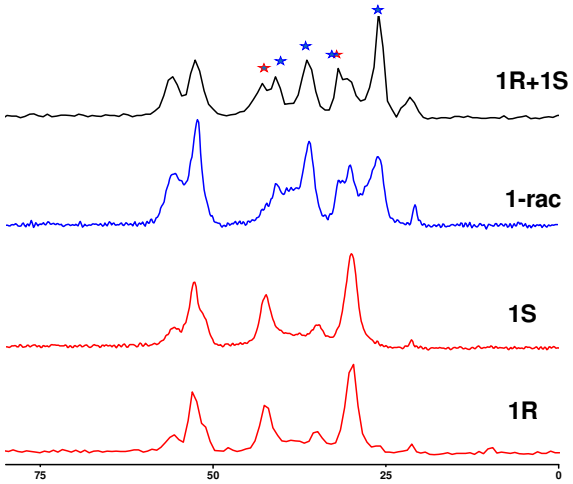


Figure 11. Comparison of the solid state ^{13}C NMR of **1R**, **1S**, **1-rac** and **1R+1S** for the aliphatic region showing the mixed net-

work in solid state for **1R+1S** (*indicates the corresponding peaks in enantiomers and racemate).

Analysis of the ^{13}C NMR of the four samples revealed that the solid state packing of the xerogels are not identical (Figure S14, see supporting information), which may be attributed to the difference in molecular self-assembly. Generally, the morphology and molecular arrangement of original gels are translated to the xerogels but in some cases the removal of solvent may result in artefacts due to dissolution and recrystallization, changes in morphology or polymorphic phase transition.[9] The NMR spectrum of enantiopure **1R** and **1S** were identical due to the similar 3-dimensional packing in these structures because of their mirror image. This observation corroborates nicely with the SEM and AFM images, where a helical fibrous network was observed for **1R** and **1S**. However, the peak at δ = 42.5 ppm was missing in racemic **1-rac** but more peaks were observed at δ = 26.0, 31.8, 36.3 and 40.9 ppm (Figure 11). Thus, the self-assembly in the racemate is different from its enantiomers and is evident from the tape like fibers in SEM and AFM images. The packing mode of **1R+1S** was analyzed by comparing the NMR spectra of **1R**, **1S** and **1-rac** with **1R+1S** (Figure 11). It is clear from the spectrum that **1R+1S** network is a mixture of fibers from both enantiomers and the racemate, which indicates the presence of both self-sorted and co-assembled fibers in **1R+1S**.

Conclusions

We have successfully synthesized the enantiopure (**1R**) and racemic (**1-rac**) forms of bis(urea) based phenylalanine methyl ester. The known enantiomeric form (**1S**) was also synthesized and all the isomers were found to be excellent gelators capable of gelling a wide range of solvents. Multi-component gels based on enantiomers were prepared by mixing the equal amount of pure enantiomers as well as varying individual enantiomer concentrations. The gels were characterized using standard gelation techniques and the morphology was analyzed by SEM, AFM and solid state NMR. The mixed gel displayed higher thermal and mechanical strength compared to the enantiomer and racemate gels. CD experiments performed in the solution sate and gel state revealed the preservation of chirality in the gel fibers. The enantiopure gels displayed helical fibers and the racemate showed tape like architecture indicating co-assembly of individual enantiomers. The mixed gel of the enantiopure gels displayed twisted tapes indicating the presence of both enantiomers and the racemate gels. This was also confirmed by solid state NMR studies where the NMR spectrum of the xerogel of mixed gel displayed both the forms. This clearly indicates that in mixed gels system the fibrils rearrange to form self-sorted and co-assembled fibers. The enhanced mechanical and thermal stability of the mixed gel compared to the enantiomer and racemate gel may be attributed to the presence of both self-sorted and co-assembled fibers. The tuning of mechanical and thermal strength as a function of self-assembly will enable supramolecular chemists to design multi-component systems with enhanced mechanical and thermal stability.

ASSOCIATED CONTENT

Supporting Information

Further gelation test, MGC experiments, T_{gel} experiments, SEM and AFM images, CD and OD experiments, rheology and NMR spectra. "This material is available free of charge via the Internet at http://pubs.acs.org."

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Notes

The authors declare no competing financial interests.

KEYWORDS

Supramolecular gel, Multi-component gel, Enantiomers, Racemate, Self-assembly, Self-sorting and Co-assembly

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