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ARTICLE

Gel-based Supramolecular ON-OFF Switch from Aryl-triazolyl Peptides with Excellent Chiro-optical-, Thixotropic-, and Self-healing Characteristics

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Systematic structure-property optimization of an achiral gelator (Aryl-triazolyl homo dipeptide, **1.0**) through a fragment replacement approach led to the identification of a new chiral system (Aryl-triazolyl dipeptide **1.4** having leucine as the C-terminal residue) which exhibit consistent and perfectly reversible chiro-optical response on Sol-Gel transition that can work like an ON-OFF switch. The gelator **1.4** could also direct the assembly of **1.0** in a sergeant-soldier mode to give similar CD responses. In addition, its gels are mouldable, self-healing and highly thixotropic, making it important from an application standpoint.

Introduction

Chirality or 'handedness' is intimately associated with functional aggrandization in biomolecules which form the pillars of life.[1] While secondary structural preferences of natural and synthetic peptides can be directly related to their monomer composition and configuration, evolution of supramolecular chirality is more difficult to foresee as it is guided by diverse array of secondary interactions which are environment-dependant and dynamic.[2] Low Molecular Weight compounds which cause gelation of the medium through hierarchical assembly have special significance in supramolecular chemistry because of their potential application as stimuli responsive molecular switches.[3] There have been enormous interests to identify systems which reversibly respond to stimuli like temperature, additive, solvent polarity, pH with characteristic changes in CD signals.[4-6] Chirality transfer from a gelator to achiral additive, amplification of chirality from trace amount of chiral additive through achiral gelator, and symmetry breaking during the assembly of achiral molecules are the frontiers in this rapidly developing area of science.[3]

Hierarchical preferences during self-assembly of achiral systems require a bias during molecular packing. This can be induced by circularly polarized light (L or R), external fields, stirring, or electrochemical method.[7-13] In addition to supramolecular chirality in bulk phase, similar preferences have also been realized at gas/liquid, gas/solid, liquid/solid and liquid/liquid interfaces under specific conditions.[2, 14-18]

Results and Discussion

Our group has been working on the design and development of Low Mol Wt. Gelators with a focus to understand structural features that determine solvent preferences and bulk properties.[19-21] Interest in chiro-optical switching in aryl-triazolyl peptides started when we looked into the CD profile of the dipeptide **1.0** in different gel forming organic solvents (CCl_4, Toluene, Mesitylene etc.). Its CCl_4 gel (0.2 wt%) at room temperature gave two positive signals at 260 nm and 290 nm (Figure 1). There was no response when it was bought to solution state (at 60 °C) but the signal was regained on decreasing the temperature to 50 °C (ESI, Figure S1a). Heating-cooling cycles did not change the sign or magnitude of the signal suggesting that the primary aggregates existing in solution is nucleating the growth in subsequent cycles.

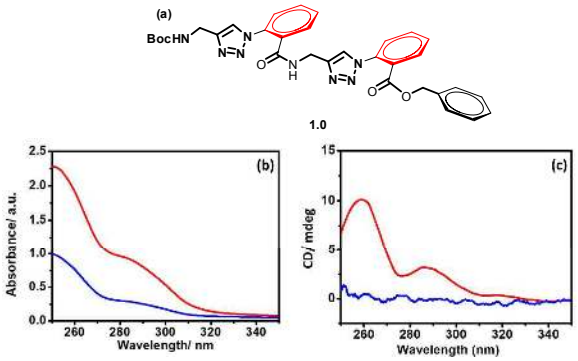

Fig. 1 a) Structure of **1.0**; b)its absorption spectrum in CCl_4 solution (blue,) and in gel state (red); c) CD spectra of **1.0** in CCl_4 solution (blue) and in gel state (red).

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It was possible to find an opposite signal from another sample of **1.0** (ESI, Figure S1b), which also retained the sign during repeated heating-cooling cycles. To know whether this arises as a result of chiral preference during self-assembly, its LD spectrum was recorded under similar conditions (ESI, Figure S2). The data showed prominent LD effect, and suggested that macroscopic alignment of transition dipole moments during gelation is most likely contributing to the observed CD.[11-12] Although this did not support a chiral preference, what made **1.0** important as a new functional system is the ready reversibility and reproducibility of signals in response to gelation. No detectable CD signal in the solution state, and a well-defined signal on gelation gave us impetus to fine-tune the structure to make the process more predictable (Figure 2). Introduction of a chiral centre without altering the properties was the next challenge. Towards this, the analogs **1.1**-**1.4** with **Gly**, **Phe**, **Val**, **Leu** at the C-terminus were synthesized and subjected to gelation and chiro-optical analysis. They have comparable N-terminal region as that of **1.0** but were expected to show some difference in self-assembly and gelation preferences in accordance with the difference in the C-terminal side chain. The synthetic details of these compounds are discussed in supporting material.

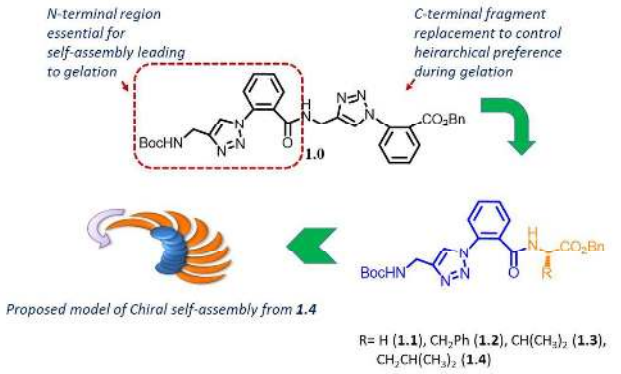

Fig. 2 Flow scheme showing strategy adopted for identifying aryl-triazolyl hybrid dipeptide **1.4** as a LMWG for hierarchical preference.

Among **1.1-1.4,** only the Leucine-based **1.4** was able to gel a wider range of solvents; details of these preliminary assessment are given in Figure 3 and ESI-Table 1. Whereas **1.0** formed gels mainly from aromatic solvents, CCl_4 and IPA, **1.4** could gel oils and hydrocarbon solvents like n-heptane, dodecane in addition. Gel pictures of some selected solvents are presented in Figure 3. Furthermore, the morphological characteristics of xerogels of **1.4** from DCM-Hexane, Mesitylene and Heptane were analysed by SEM which showed entangled fibrous networks as seen in other gel-forming systems (ESI-Figure S8).

Temperature-dependant CD studies involving **1.4** were conducted in n-Heptane and CCl_4 as it formed transparent gels in both these solvents at 0.1 wt%. At low temperature (5 °C), its heptane gel showed a bisignated signal with negative maximum at 268 nm zero crossing at 251 nm and positive maximum at 220 nm (Figure 4a).

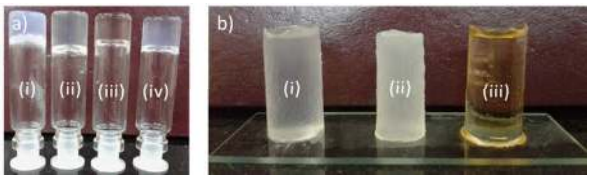

Fig. 3 a) Inverted vials showing immobilized gels of **1.4** from (i) n-Heptane (2 wt%), (ii) Diesel (2 wt%), (iii) Tetralin (2.5 wt%), (iv) CCl_4 (2.5 wt%); b) its self-standing gels from i) Mesitylene, ii) CCl_4, iii) Tetralin.

As the temperature was increased, the signal intensity started collapsing and decreased to the lowest level at 55 °C (Figure 4c) and remained more or less unchanged on further increase in temperature (till 75 °C). It was possible to execute this temperature-dependent sol-gel transition with characteristic change in CD signals in the form of an ON/OFF switch. As evident from Figure 4d, even after 10 cycles, no change was observed in the intensity of CD signal. For comparing the chiral preferences, the R- isomer of **1.4** was also synthesized using D-Leucine benzyl ester in the coupling step. The CD profile of heptane gel of (*R*)-**1.4** at 0.1 wt% was then recorded. An exactly opposite mirror images signal compared to that of (*S*)-1.4 was observed in this case and is shown in Figure 4a.

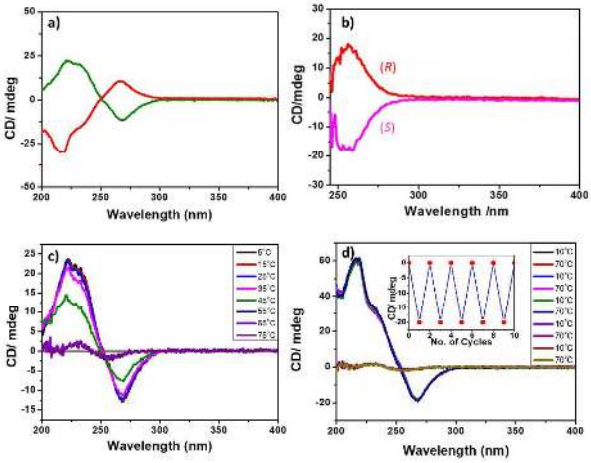

Fig. 4 a) CD spectra of n-Heptane gel of **1.4** (*S*- isomer, green), *R*-isomer (red), 0.1 wt%) at 5 °C; b) CD spectra of enantiomers of **1.4** in CCl_4 (0.1 wt%); c) VT CD spectra of **1.4** in n-Heptane showing disruption of supramolecular chirality with increasing temperature; d) Chiro-optical switching (ON/OFF) executed between 10 °C (gel state) and 70 °C (sol state) for 10 different cycles (inset image showing chiroptical switching at 268 nm).

Similar experiments involving CCl_4 gels of **1.4** (both *R* and S isomers, at 0.1 wt %) were done in the wave length range 250-350 nm (Figure 4b). To rule out orientational effects, LD spectra were also recorded in CCl_4 gel at 0.1 wt% and the outcome is presented in ESI-Figure S3b-c. The results indicated that LD artefacts are insignificant, and the observed CD preferences in these cases arise as a result of asymmetric packing during gelation process, dictated by chirality in individual molecules.

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Secondary interactions which assist the self-assembly of **1.4** was then studied using temperature dependent ^{1}H NMR, FTIR and PXRD techniques. Formation of supramolecular structures involves secondary interactions such as π- stacking, hydrogen bonding etc. ^{1}H NMR spectroscopy, especially in a temperature- or solvent dependant mode, is a reliable method to understand the groups involved in such interactions as they show characteristic changes in signals in response to such effects. Figure 5 presented below shows the down-field shift of NH (amide) and triazolyl protons of **1.4** (Toluene-d_8, 5 wt%) on decreasing the temperature, indicative of their involvement in H-bonding during gelation.

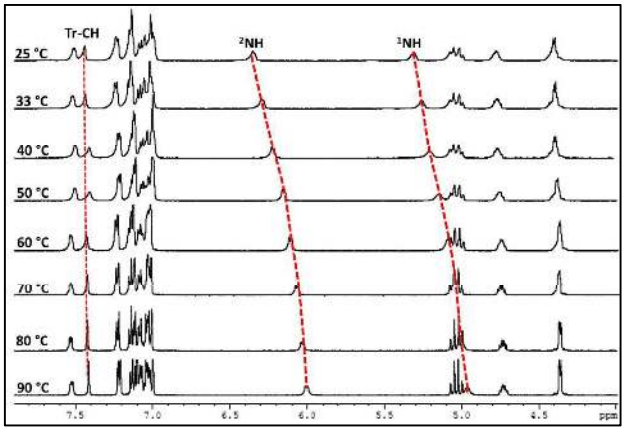

Fig. 5 Variable temperature ^{1}H NMR spectra of **1.4** in Toluene-d_8 (5 wt%) showing evidences of hydrogen bonding involving NH and triazolyl protons during gelation.

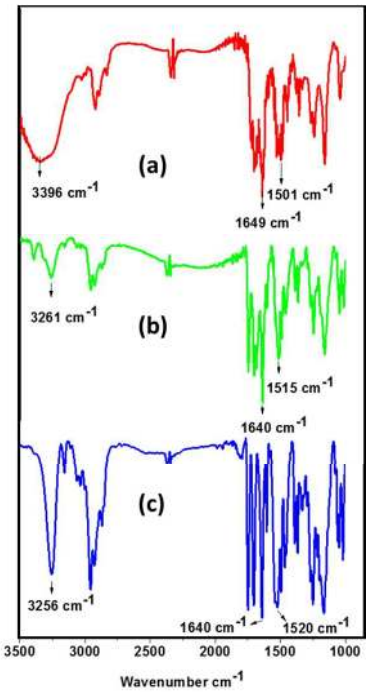

Fig. 6 Comparison of IR spectra of **1.4** from (a) $CHCl_3$ (2 wt%) neat, (b) heptane xerogel (1 wt%), (c) CCl_4 xerogel (2.5 wt%)

This was further supported by FT-IR data. The IR spectrum of **1.4** drop-casted from chloroform solution showed transmission bands at 3396, 1649, and 1501 cm^{-1} (Figure 6a) which are characteristic of non-hydrogen bonded NH (stretching), carbonyl (stretching), and NH (bending). However, its xerogels from Heptane and CCl_4 had these bands at 3261, 1640, 1515 cm^{-1} (Figure 6b) and 3256, 1640, 1520 cm^{-1}(Figure 6c) respectively. Lowering of stretching frequencies of NH and C=O groups, accompanied by an increase in the amide bending frequency clearly attest the hydrogen bonding involving these groups in the xerogel. Further, a reflection in the PXRD spectrum of **1.4** (xerogel from CCl_4) at 2θ of 23.29 corresponding to π–π distance of ~ 3.81 Å (ESI Figure S6) showed that N-terminal region has an important role in assembly process.

In addition to their supramolecular chiral preferences, gels of **1.4** and **1.0** possess some unique thermal and mechanical properties, relevant from an application stand point. Although the CGC value of the Mesitylene gel of **1.4** was higher (1.7 wt%) than that for **1.0** (0.1 wt %), the T_{gel} of the former was considerably lower (ESI- Figure S5). The increase in T_{gel} with respect to gelator concentration was also less in the case of **1.4** which makes it thermally processable even at higher gelator concentration (ESI, Figure S5). This is remarkable since only a slight increase in temperature (from 30 °C to 40 °C) is sufficient to convert the strong gel to a solution, which on cooling to room temperature (25 °C), regained the original strength. A similar behaviour was also shown by tetralin gel of **1.4**. In recent years, there have been lot of research activities to identify gel-forming systems with superior self-healing properties.[22-29] Based on our observation of decreased dependence of *Tgel* on gelator concentration in the case of **1.4**, we set out to explore the self-healing property on a larger scale as shown in Figure 7. Towards this, 5 wt% gel discs of mesitylene and Tetralin with **1.4** were first prepared. As shown in Figure 7a&e, they were self-standing and shape persistent in nature. These discs were then cut into four equal pieces (Figure 7b&f). After keeping these pieces in close contact, it was slightly warmed with a heat gun for ~2s.

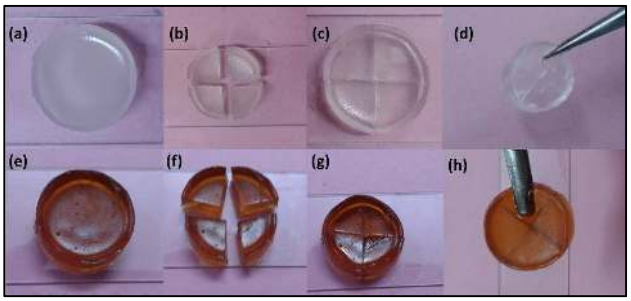

Fig. 7 a-d) Demonstration of self-healing property in 5 wt% Mesitylene gel disc from 1.4(S); e-h) similar images from its 5 wt% Tetralin gel.

Within 10 minutes (on reverting to room temperature) it again became a single block which was stable for handling and to normal mechanical stress (Supporting Video 1). Essentially, all these gels behaved like wax which could be melted and re-joined easily, and

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offer great promise as next generation functional materials with good processability. The viscoelastic behaviour of Tetralin gel of **1.4** (5 wt%) was also studied through strain sweep and frequency sweep rheology experiments. The storage modulus G' dominated loss modulus over the range of 0.01-10% strain (Figure 8) till the critical strain of 0.09% was reached. Similarly, in the frequency sweep experiment performed at 0.01% strain, the storage modulus remained superior throughout 0.4-300 rad/s and both these moduli were independent of angular frequency in this range (ESI-Figure S7b).

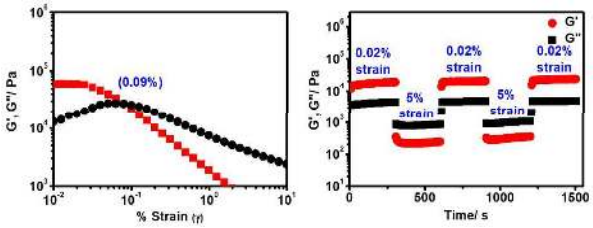

Fig. 8 Results from thixotropy experiments involving Tetralin gel of **1.4**.

The re-establishment of network and the extent of self-healing was then analysed by thixotropy experiments. In these step-strain experiments, the change in storage and loss moduli was analysed at 0.02% strain (before gel collapse; G'> G") and at 5% strain (after collapse; G"> G'). As evident from Figure 8b, there was perfect regaining of G' and G'' after each cycle. Consistent regaining of storage modulus indicates strong gel with efficient network formation each time (Figure 8). The fact that G' remain superior to G'' even in the vicinity of yield strain shown the superior viscoelastic property of this gel.

Comparison of properties of 1.0 with 1.4 and development of their hybrid network

While chiro-optical switching through sol-gel transition itself is rewarding, we went ahead to explore the possibility of developing hybrid network of **1.0** and **1.4** to expand the application potential of this class of gelators. Apart from having identical N-terminal region that contributes significantly to the gelation process, their dependence on Kamlet-Taft solvatochromic parameters,[30] especially α and β, was also comparable (Figure 9a,b) which indicated their possible compatibility in a gel matrix. In preliminary assessment (based on solvent preference), the polarizability (π^*) was found to be less significant in the gelation of **1.0**, whereas lower polarizability with minimal H-bond donating acidity (α) and minimal H-bond accepting basicity (β) favoured gelation of **1.4** (eg. CCl_4, n-heptane, Dodecane etc.; ESI-Figure S4 and Table 2). Solvents having zero α, and lower β values, which doesn't disrupt gelator-gelator hydrogen bonding networks seems to have positive influence on both these gelators (Figure 9a and b). Solvents with positive α values which could disrupt gelator-gelator interactions (EtOH, IPA, *t*BuOH etc.) appear to compromise the gelation ability of **1.4** because of higher solvation effects (Figure 9d). On the other hand, primary aggregates of **1.0** having better avenues for π-π interaction are able to outrun the solvation effects and could form gels in these solvents (Figure 9c).

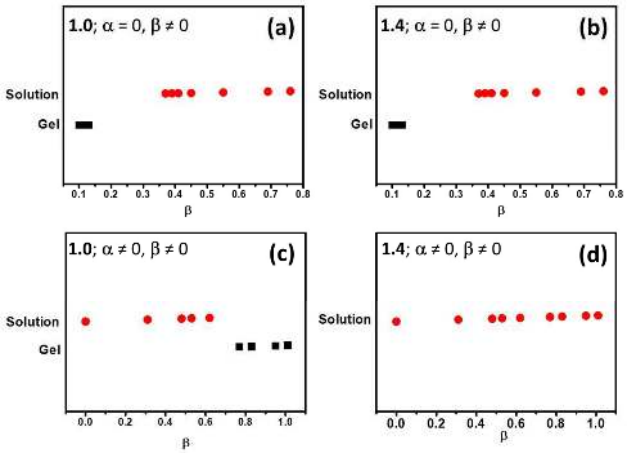

Fig. 9 Gelation behaviour of **1.0** and **1.4** assessed on the basis of kamlet-taft parameters of solvents: a&c) behaviour of **1.0** when β is nonzero; b&d) the corresponding results from **1.4**.

Based on this, gel formation by a mixture of **1.0** and **1.4** (R or S) in CCl_4 gel was first confirmed, and subsequently the process was analysed by CD spectroscopy. The cotton effect from 1:1 mixture of **1.0** with *R*-**1.4** and *S*-**1.4** were complementary to one another which were reproducible, unlike the situation with **1.0** alone (Figure 10).

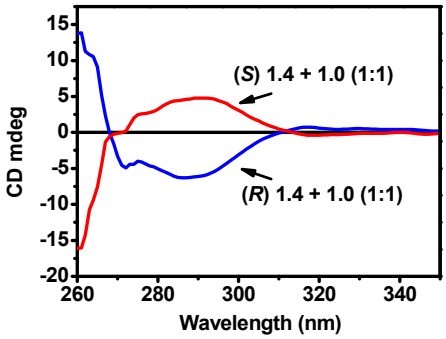

Fig. 10 CD spectra showing chiral preferences of achiral dipeptide **1.0** in the gel state when used in combination with the chiral dipeptide **1.4** in R or S forms

Although this suggested direct influence from **1.4**, the question of whether it operates through a co-assembly or a sergeant-soldier mode needed further exploration. Towards this, variable temperature NMR experiments with 1:1 mixture of **1.0** and **1.4** (S) in CCl_4 was performed using DMSO-d_6 as the reference. After assignment of individual peaks in their ^{1}H NMR based on a combination of 1D- and 2D experiments, the spectrum was first recorded at 25 °C, which had signals only from **1.4** as shown in Figure 11; peaks from **1.0** were absent showing its predominance in gelation process. On increasing the temperature (25 °C to 65 °C;

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Figure 11 and ESI-Figure S18), the signals from **1.0** became more and more prominent which once again confirms its larger contribution in network formation. This, when correlated with the consistent temperature-dependant reversible CD responses from their mixture, suggest that a sergeant-soldier type of assembly modulation is responsible for the hierarchical preference.

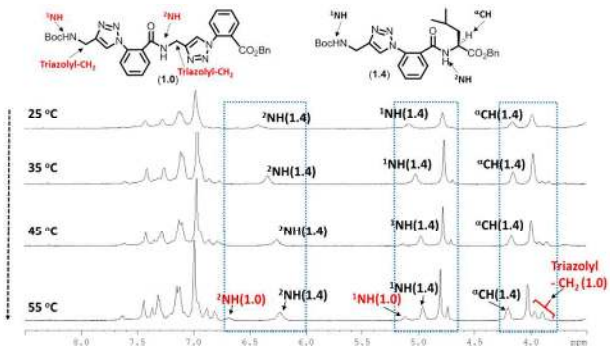

Fig. 11 Temperature dependent ^{1}H NMR of a 1:1 mixture of **1.0** and **1.4** showing gelator network formation predominantly from **1.0** at lower temperature.

The temperature-dependant ^{1}H NMR, FT-IR results and PXRD data discussed previously (Figure 5, Figure 6 and ESI Figure S6) show that the N-terminal region of **1.4** has a prominent role in its self-assembly. The chiral preference during this process is directly linked to the asymmetry in the C-terminal region, as pictorially shown in Figure 2. The chiral bias in the assembly of **1.0** in presence of **1.4** could arise because of a co-assembly in the nucleation stage in which the handedness is dictated by **1.4**. The self-healing property was also retained in the tetralin gel prepared from a 1:1 mixture of **1.0** and **1.4** (2.5 wt% each) as demonstrated in Figure 12. In a typical experiment, a 5 mL gel disc was made first and then it was cut into four pieces (Figure 12a-b) which was able to re-join on applying a little heat and bringing down to room temperature, as shown in Figure 12c.

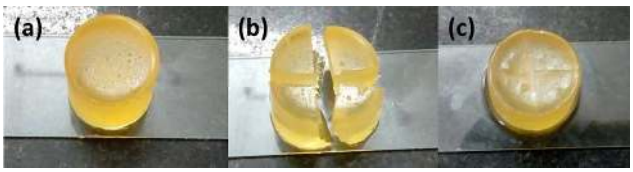

Fig. 12 Demonstration of self-healing property in the Tetralin gel disc from 1:1 mixture of **1.0** and **1.4** (a-c)

Design of supramolecular functional materials requires a good control over molecular packing or the network of secondary interactions. In the case of soft systems like gels, involvement of solvent in the process result in equilibrating aggregates which bring additional kinetic and thermodynamic influences compared to more static systems. Hierarchical preference during self-assembly offer great promise in the development of stimuli-responsive materials, and their application potential increases if the process can be executed reversibly without effecting signal quality over several cycles. This requires re-establishment of secondary interaction networks with high efficiency, each time. The present work is an excellent demonstration of how such LMWOG-based chiro-optical ON-OFF switches can be identified through stepwise structure-property optimization of an achiral system, and is part of our on-going efforts to find guiding principles for rational gel design with specific functional characteristics.

Conclusions

In summary, the achiral gelator **1.0** exhibited a reversible CD response during sol-gel transition which was attributed to orientational effects through LD analysis. Based on this, structure refinement through C-terminal fragment replacement with natural amino acids residues was done without compromising the gelation efficiency. This led to the identification of leucine-based aryl-triazolyl peptide **1.4** with excellent chiro-optical switching ability between gel and sol states through hierarchical preferences during self-assembly. It was also able to direct the assembly of **1.0** in a 'sergeant-soldier' mode using **1.4** with consistent and reproducible CD response. Apart from having excellent thermo-mechanical properties including rheological characteristics, the gels from **1.4** are mouldable, fast self-healing and thixotropic which makes it attractive for the design of new supramolecular functional materials.

Conflicts of interest

The Authors declare no conflict of interest.

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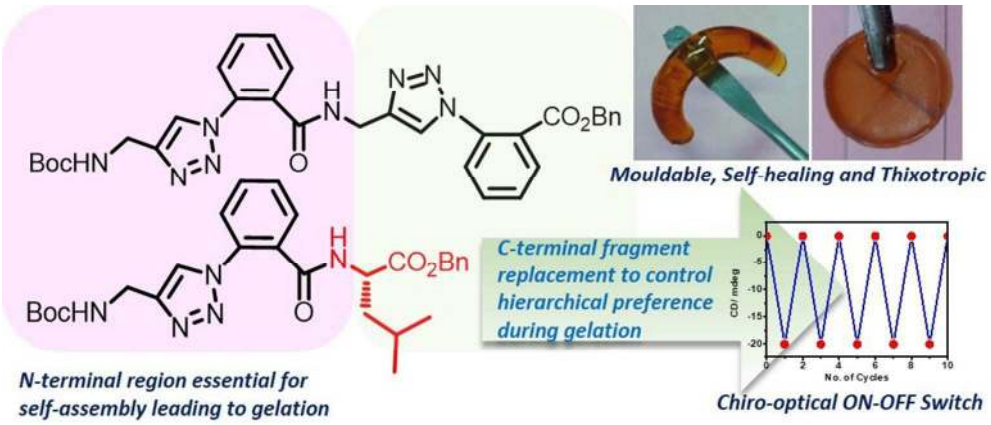

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