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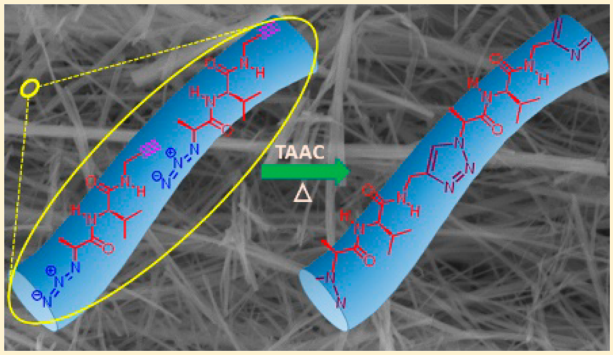
Topochemical Azide–Alkyne Cycloaddition Reaction in Gels: Size-Tunable Synthesis of Triazole-Linked Polypeptides

Baiju P. Krishnan and Kana M. Sureshan*

School of Chemistry, Indian Institute of Science Education and Research Thiruvananthapuram, CET Campus, Thiruvananthapuram, Kerala 695016, India

Supporting Information

ABSTRACT: Though topochemical reactions are attractive, the difficulty associated with crystallization such as low yield, unsuitability for large-scale synthesis, etc. warranted the exploitation of other self-assembled media for topochemical reactions. We synthesized a dipeptide gelator decorated with azide and alkyne at its termini, N_3-Ala-Val-$NHCH_2$-C≡CH, which is designed to self-assemble through intermolecular hydrogen bonds to β-sheets thereby placing the azide and alkyne motifs in proximity. As anticipated, this peptide forms gels in organic solvents and water via hydrogen-bonded β-sheet assembly as evidenced from IR spectroscopy and PXRD profiling. The microscopic fibers present in organogel and hydrogel have different morphology as was evident from scanning electron microscopy (SEM) imaging of their xerogels, XG_h (xerogel made from hydrogel) and XG_o (xerogel made from organogel). Heating of xerogels at 80 °C resulted in the topochemical azide–alkyne cycloaddition (TAAC) polymerization to 1,4-triazole-linked oligopeptides. Under identical conditions, XG_o produced larger oligopeptides, and XG_h produced smaller peptides, as evidenced from MALDI-TOF spectrometry. We have also shown that degree of TAAC polymerization can be controlled by changing gel fiber thickness, which in turn can be controlled by concentration. SEM studies suggested the morphological intactness of the fibers even after the reaction, and their PXRD profiles revealed that both XG_h and XG_o undergo fiber-to-fiber oligomerization without losing their crystallinity. In contrast to crystals, the xerogels undergo TAAC polymerization in two distinct stages as shown by DSC analyses. Interestingly, XG_h and XG_o undergo spontaneous TAAC polymerization at room temperature; the latter shows faster kinetics. This is not only the first demonstration of the use of xerogels for thermally induced topochemical polymerization but also the first report on a spontaneous topochemical reaction in xerogels.



INTRODUCTION

Supramolecular gels formed by self-assembly of small molecules in appropriate solvents through various noncovalent interactions such as hydrogen-bonding, π···π stacking, cation···π, dipole···dipole, van der Waals interactions, etc.[1] have gained much attention due to their reversibility, ease of synthesis, and tunability. These supramolecular gels hold great potential for many applications in different fields[2] such as sensors,[3] soft optics,[4] stimuli-responsive materials,[5] drug delivery systems,[3,6] electronics,[7] catalysis,[8] templated synthesis,[9] oil-spill recovery,[10] pollution control,[11] etc. One important application of these noncovalent polymers is their exploitation in topochemical reactions. Though such high-yielding, solvent-free, catalyst-free, regio/stereospecific, and proximity-driven reactions are done in crystals,[12] the similarity between crystallization and gelation in organization of molecules prompted researchers to exploit gels for topochemical reactions.[13] This is indeed a remarkable evolution in the field of topochemical reactions as it obviates the necessity of crystallization which is often difficult, time-consuming, low-yielding, and unsuitable for large-scale preparation.[13n] Notable demonstrations of this strategy include light-induced transformations such as polymerization of diacetylenes to PDA,[13] dimerization of anthracene,[14] and 2 + 2 cycloaddition of alkenes,[15] in the gel or xerogel states. Translation of noncovalent polymers in gels or other ordered media to covalently linked polymers via topochemical polymerization is an excellent strategy to synthesize polymers.[13,16,17] However, only photopolymerization of diacetylenes to PDA was successful for this, to date. Herein, we report the first thermal topochemical polymerization reactions of xerogels of a gelator formed by its self-assembly in organic solvents and water (Figure 1).

RESULTS AND DISCUSSION

There is growing interest in the synthesis of peptidomimics in view of their improved stability, ease of preparation, and attractive properties[18] over traditional peptides. Since triazole is one of the best bioisosteres of the peptide bond,[19] pseudopeptides having a triazole linkage as surrogate for

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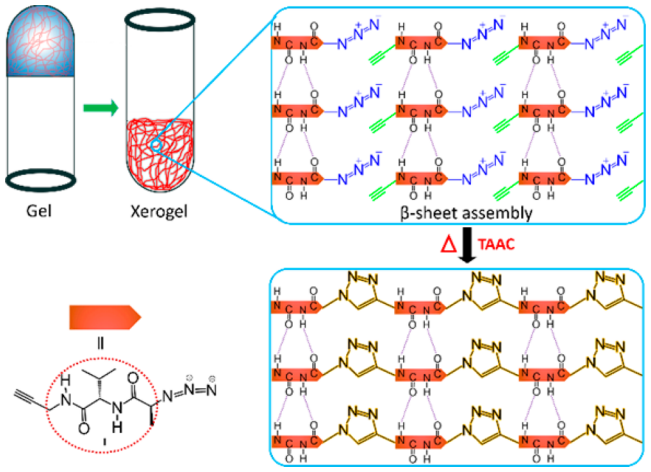

Figure 1. Probable packing arrangement of dipeptide **1** in xerogel and subsequent thermal topochemical reaction. Chemical structure of dipeptide **1** is also shown.

amide bond have received much attention.[20] Though a Cu(I)-catalyzed azide−alkyne cycloaddition (click) reaction can be employed for the introduction of one or a few triazole units, this solution-phase method is impractical for synthesis of higher oligomers containing many triazole units due to poor solubility, difficult purification, etc. Pursuing our interest in topochemical reactions,[21] we have recently reported the crystal-to-crystal topochemical polymerization of dipeptide **1** to pseudoproteins of molecular weights up to 7 kDa.[22] We have relied on the formation of hydrogen-bonded β-sheet assembly of Ala or Val containing a small peptide for the design of the dipeptide **1**.

As many small peptides form hydrogen-bonded gels in various solvents, we have investigated the gelation abilities of dipeptide **1**. Dipeptide **1** was found to be an efficient gelator capable of congealing not only organic solvents but also water (Figure 2A,B). The critical gelation concentration (CGC) varied from 0.6 to 4.8 wt % (Table S1, SI). FT-IR spectroscopy studies gave evidence for the role of intermolecular hydrogen bonding in gelation. While the NH stretching bands in the IR spectrum of dipeptide **1** in its dissociated state [solution in a nongelling solvent (DCM)] peaked at 3449 and 3399 cm^{-1} as sharp signals, in its self-assembled states (viz., benzene gel, xerogel made from benzene gel, and xerogel made from hydrogel), they were not only red-shifted but also appeared as broad signals in the ranges 3426−3044, 3391−3171, and 3403−3175 cm^{-1}, respectively (Figure S2, SI). This suggests that amide NHs are intermolecularly hydrogen-bonded in self-assembled states in both organogel and hydrogel. The concentration-dependent ^{1}H NMR experiment showed a gradual downfield shifting of signals due to amide protons with an increase in concentration, providing additional evidence for the intermolecular hydrogen-bonding being responsible for the self-assembly leading to gelation (Figure S1, SI).

The amide I and amide II bands in the IR spectra of xerogels (1642 and 1553 cm^{-1} for XG_o, and 1643 and 1551 cm^{-1} for XG_h) were very similar to those of crystals (1640 and 1550 cm^{-1}, respectively) of dipeptide **1** suggestive of β-sheet arrangement in the xerogels as in the case of the crystals (Figure 2C).[13f,16e] We have investigated the morphologies of microstructures formed in organogel and hydrogel by scanning electron microscopy (SEM) of their xerogels. While the xerogel made from benzene gel (XG_o) showed an entangled fibrous network (Figure 2D), xerogel made from hydrogel (XG_h)

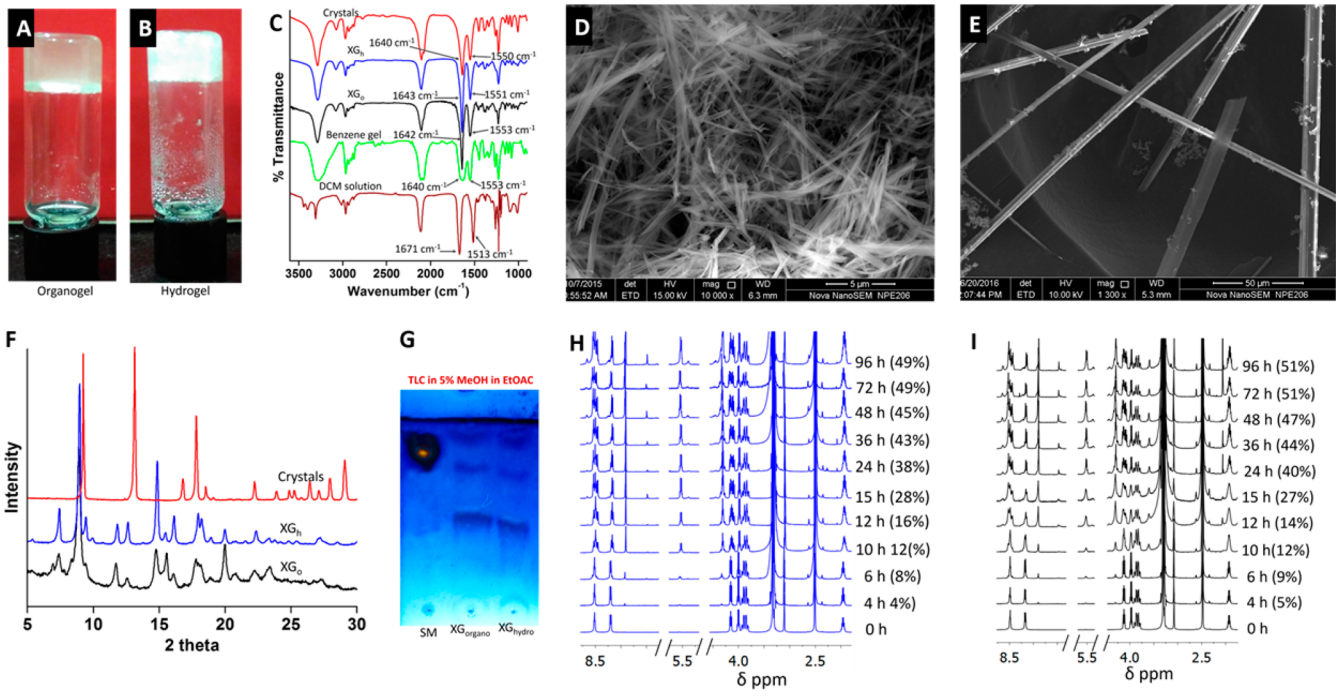

Figure 2. Photographs of (A) benzene gel (2.5 wt %) and (B) hydrogel (2.5 wt %). (C) FT-IR comparison of DCM solution, benzene gel, xerogels (of organogel and hydrogel), and crystals. SEM images of xerogels of (D) benzene gel (2.5 wt %) and (E) hydrogel (2.5 wt %). (F) Comparison of PXRDs of xerogels with that of crystals. (G) TLC showing the consumption of monomer and formation of oligomers in xerogels after heating for 48 h at 80 °C. Kinetics of the TAAC reaction of (H) XG_h and (I) XG_o at 80 °C monitored by ^{1}H NMR spectroscopy. Only relevant parts of the spectra are shown for brevity, and the full spectra are in the SI. The figures are color-coded as XG_o, black, and XG_h, blue.

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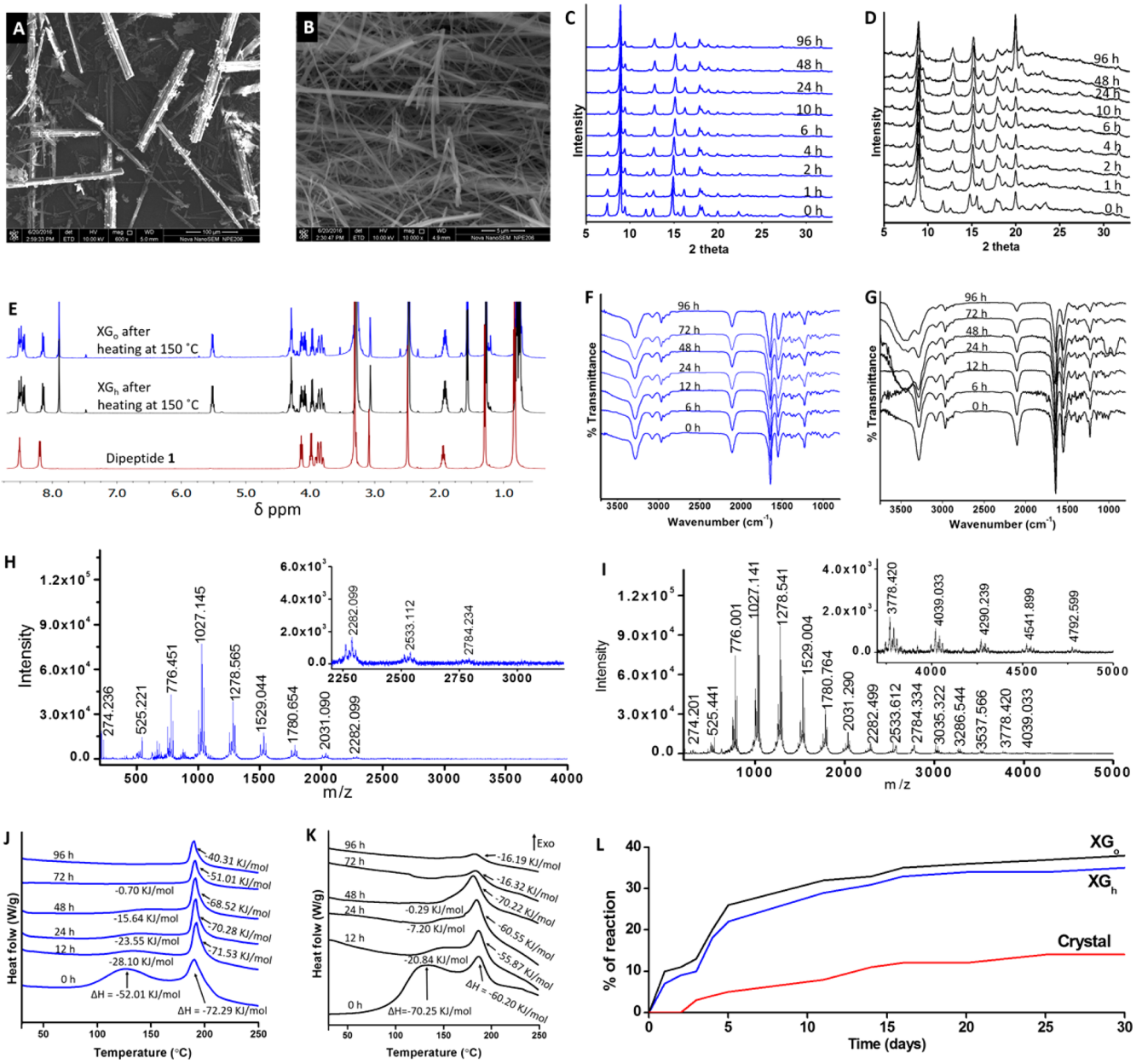

Figure 3. SEM images of (A) XG_h (magnification: 600×) and (B) XG_o (magnification: 10 000×) after the TAAC reaction. Time-dependent PXRD spectra of (C) XG_h and (D) XG_o kept at 80 °C for various durations. (E) ^{1}H NMR spectra of xerogels after heating for 10 min at 150 °C in comparison with that of dipeptide **1**. Time-dependent FT-IR spectra of (F) XG_h and (G) XG_o kept at 80 °C. MALDI spectra of (H) XG_h and (I) XG_o after being kept at 80 °C for 96 h. Time-dependent DSC analyses of (J) XG_h and (K) XG_o during TAAC reaction (kept at 80 °C). (L) Comparison of kinetics of TAAC at room temperature (rt) of xerogels, XG_o and XG_h, with that of crystal. The figures are color-coded as XG_o, black, XG_h, blue.

showed a thick rod-like morphology (Figure 2E). Interestingly, the PXRD profiles of XG_o and XG_h were almost similar but different from that of crystals suggesting that they are different polymorphic forms of dipeptide **1** (Figure 2F and Figure S3, SI). Though the molecules in organogel, hydrogel, and crystals are self-assembled in β-sheet arrangement, there could be minor differences in packing leading to different polymorphs.

As one of the two polymorphs, viz., crystals underwent TAAC reaction,[22] we were curious to know the possibility of topochemical reaction in the other polymorph, viz., xerogels. In order to investigate this, we have heated xerogels XG_h and XG_o (2.5 wt %) at 80 °C for 2 days, which were then analyzed by TLC after dissolution in methanol. TLC analysis showed the consumption of the starting material and formation of polar oligomers suggesting that both XG_h and XG_o underwent azide−alkyne cycloaddition reaction in the xerogel state (Figure 2G). ^{1}H NMR spectra of these heated XG_h and XG_o samples showed the emergence of new signals due to the triazolyl proton at δ 7.91 ppm, with a methyne proton connected to triazole at δ 5.53 ppm and methylene protons at δ 4.39 ppm as a result of the formation of the 1,4-triazole-linked peptides, as in the case of TAAC reaction of crystals of dipeptide **1** (Figure S4, SI).[22] The regiospecific formation of only 1,4-triazole suggests that, in both cases (XG_h and XG_o), the cycloaddition happens under topochemical control. The kinetics of these solid-state cycloaddition reactions were monitored by time-

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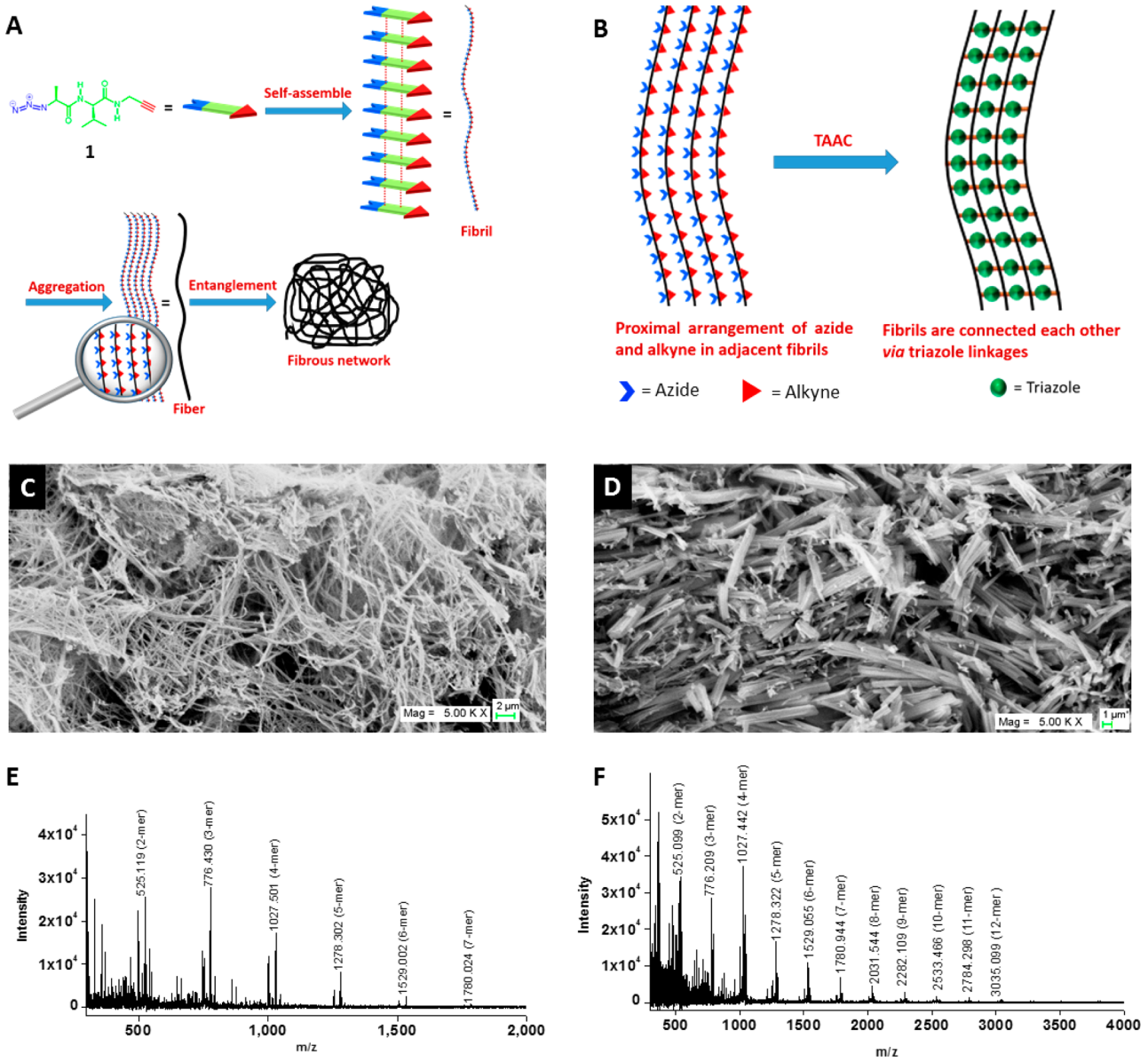

Figure 4. (A) Schematic representation of formation of fibrillar network by dipeptide **1**. (B) Probable direction of TAAC reaction in fibers. SEM images of xerogels obtained from organogels of different concentrations: (C) 1.6 wt % and (D) 10 wt %. (E, F) MALDI spectra xerogels obtained from 1.6 and 10 wt % gels after heating at 80 °C for 72 h, respectively.

dependent ^{1}H NMR spectroscopy. Thus, samples of XG_h and XG_o were kept at 80 °C, and small portions were withdrawn at different times and analyzed by ^{1}H NMR spectroscopy. The relative intensities of the signals due to the products increased, and that of monomer **1** decreased with time; the reaction attained a state of stagnancy after 72 h (Figure 2H,I and Figure S5A,B, SI). As expected for topochemical reactions, both the reactions followed sigmoidal kinetics (Figure S5C, SI). However, heating a solution of **1** in DMSO at 80 °C for 40 h did not result in any reaction, confirming the necessity of self-assembly (Figure S7, SI). On the other hand, heating the DMSO solution of **1** at 120 °C for 40 h resulted in a complex mixture of products due to the formation of 1,4- and 1,5-linked triazoles in a random fashion (Figure S8, SI). Thus, it is clear that, for high degree of 1,4-selectivity, self-assembly is essential.

SEM images of XG_h and XG_o kept at 80 °C for 96 h showed that their initial morphologies were unaffected even after the polymerization reaction, confirming the topochemical nature of the reaction (Figure 3A,B, Figure S6, SI). Time-dependent PXRD analyses of XG_h and XG_o that were kept at 80 °C showed the gradual appearance of new peaks and disappearance of some of the parent peaks, suggesting that both reactions proceed without losing crystallinity (Figure 3C,D).

It is interesting to note that the reaction proceeded even at very high temperature with complete topochemical control. Thus, NMR spectroscopy of xerogels kept at 150 °C for 10 min revealed that the reaction has progressed much faster and regioselectively giving the 1,4-triazole-linked oligomers (Figure 3E). Morphology of xerogels did not change even after this high-temperature reaction as evidenced from SEM analysis (Figure S9, SI). On the other hand, heating of crystals at this temperature led to an uncontrolled reaction leading to the formation of both 1,4- and 1,5-regioisomers (Figure S10, SI).

Time-dependent FT-IR spectroscopy of XG_h and XG_o kept at 80 °C revealed that the azide stretching band at 2108 cm^{-1} gradually decreases with duration of heating, suggesting gradual

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consumption of azide due to azide−alkyne cycloaddition reaction (Figure 3F,G). MALDI-TOF spectra of XG_h and XG_o kept at 80 °C for 96 h showed the presence of oligomers up to 11-mers in the former (Figure 3H) and oligomers up to 19-mers in the latter (Figure 3I). This could be due to the optimal orientation of the reacting groups in the case of XG_o, enabling it to undergo easy topochemical reaction.

Time-dependent DSC profiles of XG_h and XG_o kept at 80 °C were compared. At the beginning (duration of prior heating = 0), the DSC profiles of XG_h and XG_o were similar but different from the DSC profile of crystals of dipeptide **1** (Figure S11, SI). While the crystals showed only a single exothermic peak at 153 °C, both of the xerogels showed two exothermic peaks: a broad peak with an onset before 100 °C and a sharp peak at 178 °C (Figure 3J,K). This suggests that the xerogels have very different reactivity than crystals and the oligomerization in xerogels happens in two distinct stages. As expected, the intensities of these exothermic peaks decreased with duration of prior heating due to the consumption of azide and alkyne in the TAAC reaction during prior heating (Figure 3J,K).

MALDI-TOF spectra of xerogels after heating for 24 h at 80 °C revealed the presence of a large amount of dimer as compared to other oligomers (Figure S12, SI). It may be recalled that the DSC profiles of xerogels after heating for 24 h showed only one exothermic peak, i.e., the peak at 178 °C. With a combination of these two observations, it is clear that the exothermic peak at around 100 °C is the heat released in the TAAC reaction of monomer to mainly dimers. MALDI-TOF spectra of these xerogels after heating for 96 h at 80 °C showed negligible amounts of the dimer (Figure 3H,I), and at this stage, its DSC profile showed a much less intense exothermic peak at 178 °C suggesting that the peak at 178 °C is probably due to the heat released in the uncontrolled polymerization of the initially formed dimer. Remarkably, the intensities of the peak at 178 °C did not vary considerably up to 48 h, suggesting that, up to 48 h, mainly the topochemical dimerization happens, and then there is further topochemical reaction of these dimers to higher oligomers. This is in stark contrast to the topochemical polymerization of the crystals of **1**, which happens in a single stage.[22]

A comparison of the DSC profiles of crystal, XG_o, and XG_h revealed that both the xerogels react at lower temperature than the crystal (Figure S11, SI). Since xerogels start reacting at lower temperatures compared to crystals, it is anticipated that they might undergo spontaneous topochemical reaction at room temperature. In order to test this, crystals, XG_o, and XG_h were kept at room temperature, and the reaction was monitored at regular intervals by withdrawing a small portion of these samples and recording their ^{1}H NMR spectra. As anticipated, both the xerogels underwent spontaneous TAAC reaction at room temperature, and the rate of the reaction was faster for the XG_o sample. The crystals reacted very slowly (Figure 3L and Figures S13−S15, SI). These experiments also suggest that, though the organogel and hydrogel are formed by self-assembled β-sheet arrangement (similar molecular packing), the assembly in XG_o is easier to react.

Though the extent of polymerization can be tuned by choosing XG_h or XG_o, another way of tuning the extent of polymerization would be by limiting the number of molecules aligned along the direction of the reaction. A probable mechanism for the formation of fibrillar network is in Figure 4A. Thus, hydrogen-bonded assembly leading to β-sheets would form long fibrils (β-tape), and the assembly of such fibrils through lateral interaction (which can bring the azide and alkyne of adjacent fibrils at proximity) would lead to fibers. Thus, it is probable that the reaction direction is along the breadth (thickness) of the fibers (Figure 4B). As the fiber thickness can be tuned by changing concentration of the gelator in the gel, it might be possible to control the degree of polymerization. To test the effect of thickness of gel fibers on the extent of TAAC reaction, we have prepared xerogels from 1.6 and 10 wt % benzene gels, which formed thinner and thicker fibers, respectively, as evidenced by SEM images of these xerogels (Figure 4C,D). Both of the xerogels were heated at 80 °C for 72 h and were analyzed by MALDI-TOF spectrometry. As anticipated, thinner fibers (xerogels from 1.6 wt % gel) reacted forming oligomers up to 7-mer and the thicker fibers (10 wt % gel) up to 13-mer (Figure 4E,F). Both of the fibers conserved their morphologies even after the reaction as shown by their SEM images (Figure S16, SI). Thus, modulating the fiber thickness is a convenient way to tune the degree of polymerization, which is rather difficult with crystals.

CONCLUSION

In summary, the modified dipeptide, N_3-Ala-Val-$NHCH_2$-C≡CH, which was designed to pack in β-sheet arrangement through intermolecular hydrogen-bonded self-assembly, was found to congeal both water and organic solvents. The xerogels made from both organogels and hydrogel underwent smooth TAAC reaction leading to the regiospecific formation of 1,4-triazole-linked oligopeptides upon thermal activation. This is the first report of thermally activated topochemical polymerization in xerogel states. The xerogels showed different reactivity and followed different pathways for the topochemical reaction than the crystals of dipeptide **1**, which is a different polymorph. Though many topochemical polymerizations have been reported in crystals or other ordered media, to the best of our knowledge, there is no study on control of the extent of polymerization in topochemical reactions. Interestingly, under similar activation, the XG_o showed a relatively high degree of polymerization (DP = 19) as compared to that of XG_h (DP = 11), suggesting that DP can be tuned by choosing the appropriate solvent for gelation. We have also shown, for the first time, that the extent of polymerization can be tuned by the changing thickness of gel fibers. Remarkably, both of the xerogels underwent spontaneous TAAC reaction at room temperature, making this the first report on spontaneous topochemical reaction in a gel platform. The only known gel-templated topochemical polymerization of diacetylene to PDA has been exploited for the synthesis of many functional materials, and it is anticipated that our demonstration of a thermal polymerization using gel platform would ignite application oriented research in this area.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b11549.

Details of characterization of the gel of dipeptide **1**; DSC, PXRD, IR, NMR, TGA, and MALDI-TOF results (PDF)

AUTHOR INFORMATION

Corresponding Author

*kms@iisertvm.ac.in

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ORCID

Kana M. Sureshan: 0000-0002-4005-3655

Notes

The authors declare no competing financial interest.

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