

Massive Molecular Motion in Crystal Lattice Leads to an Unexpected Product in a Topochemical Polymerization

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ABSTRACT: We synthesized a designed proline-derived monomer decorated with azide and alkene for topochemical ene-azide cycloaddition (TEAC) polymerization. The monomer, in its crystal, assembles as supramolecular helices along the ‘a’ axis by exploiting various non-covalent interactions. Along the ‘c’ axis, the molecules are head-to-tail arranged in a wave-like topology such that the azide and alkene of adjacent molecules are proximally and anti-parallelly organized, obeying Schmidt’s criteria for topochemical reaction. This ready-to-react arrangement, resembling the transition-state arrangement for their cycloaddition, is expected to facilitate a smooth topochemical polymerization forming 1,4-triazoline-linked polymer along the ‘c’ direction. Upon heating, the monomer underwent regio- and stereospecific TEAC polymerization in a single-crystal-to-single-crystal fashion, as evidenced by SCXRD analysis. Surprisingly, it produced an unexpected 1,5-disubstituted-triazoline-linked covalent helical polymer along the ‘a’ axis rather than the expected 1,4-disubstituted-triazoline-linked wave-like polymer along ‘c’ axis. The polymerization linked the monomer molecules within the supramolecular helix via the cycloaddition between azide and alkene groups that are neither

proximal nor in a suitable orientation. Interestingly, the crystal avoided a ready-to-react arrangement and chose an unexpected path involving a massive rotation of 134° of the alkene group, leading to a transient but new reactive arrangement followed by TEAC polymerization. This is the first regiospecific ene-azide cycloaddition reaction that yielded the 1,5-disubstituted product. This study cautions that the use of topochemical postulates for the prediction of reactivity can sometimes be misleading.

In recent years, solid-state organic reactions have attracted researchers in the context of greener synthetic strategies, sustainability, and cost-effectiveness.¹⁻⁸ Topochemical reactions, a subset of the solid-state reactions that occur under strict lattice-control, are more attractive due to their high yield, regiospecificity, stereospecificity, and the ability to yield unique products that cannot be obtained *via* conventional solution-phase organic synthesis.⁹⁻³⁴ Unlike in solution, the molecules have very limited freedom of movement in the crystal lattice, and hence, the proximity of the reactive groups in the crystal lattice and their proper orientation are crucial for any topochemical reaction. Schmidt realized that crystal structure can be used to predict both the possibility of a topochemical reaction and the molecular structure of the product.³⁵ According to Schmidt, the distance between centroids of two reactive groups should be less than 4.2 Å, and the reactive groups should be aligned face-to-face for orbital overlap.³⁵ Additionally, such a reaction will involve the nearest-reacting pairs in the crystal lattice and take place with minimal atomic/molecular movements. While these postulates have served as the guiding principle for the rational design of molecular crystals for many successful topochemical reactions,^{12,14,19-21,30,36-47} there are examples of inert crystals despite satisfying topochemical postulates.⁴⁸⁻⁵² There are also many topochemically reactive crystals that do not meet these criteria.^{32,33,53-60} Such reactivity is due to various stimuli-induced molecular motions, within the crystal lattice, leading to the transient attainment of reactive arrangements. However, in all these cases, the molecules undergo various motions to attain a reactive

orientation due to the absence of a pre-existing favorable arrangement satisfying Schmidt's criteria. Here, we report an interesting case where a crystal ignored a pre-existing ready-to-react arrangement meeting the topochemical criteria but reacted unusually and regiospecifically after extensive molecular motion to give an unexpected product. More interestingly, despite the large molecular motion, the polymerization occurred in a single-crystal-to-single-crystal manner.

We have exploited the Topochemical Azide-Alkyne Cycloaddition (TAAC) reaction for the successful synthesis of many crystalline polymers,⁶¹⁻⁶³ including mimics of polysaccharides,⁶⁴⁻⁶⁶ proteins,⁶⁷⁻⁷² and nucleic acids.^{73,74} We recently introduced the Topochemical Ene-Azide Cycloaddition (TEAC) reaction,^{75,76} which allows the synthesis of polymers whose backbone can be modified post-synthetically *via* the denitrogenation of the triazoline ring formed in the cycloaddition reaction. Additionally, as a new chiral center is generated in the ene-azide cycloaddition reaction, the TEAC reaction can be potentially regiospecific and stereospecific. The fascinating properties of collagen, possessing a primary sequence of repeated triad Gly-Xxx-Yyy, where Xxx is usually proline and Yyy is any amino acid, attracted us to synthesize polymers having such repeated triads. We designed and synthesized monomer **M** (Fig. 1a), mimicking Gly-Pro-Gly by appropriately modifying the terminal groups as azide and alkene for TEAC polymerization (Scheme S1, Fig. S3-13). We obtained colorless single crystals by the slow evaporation of a solution of the monomer **M** in 5:1 toluene: acetone mixture (Fig. 1b).

The monomer **M** crystallizes in an orthorhombic space group $P2_12_12_1$ with one molecule in the asymmetric unit (Fig. 1c, Table S1, S2). The simulated PXRD pattern matches with the experimental PXRD pattern of the bulk sample, ensuring the absence of any other crystal forms (Fig. 1d). The methylene groups of the proline ring are disordered due to the *endo* and *exo* conformations as a result of ring puckering, as expected (Fig. 1c). The monomer adopts a C-shaped conformation in the crystal (Fig. S1), and this conformation is stabilized by weak

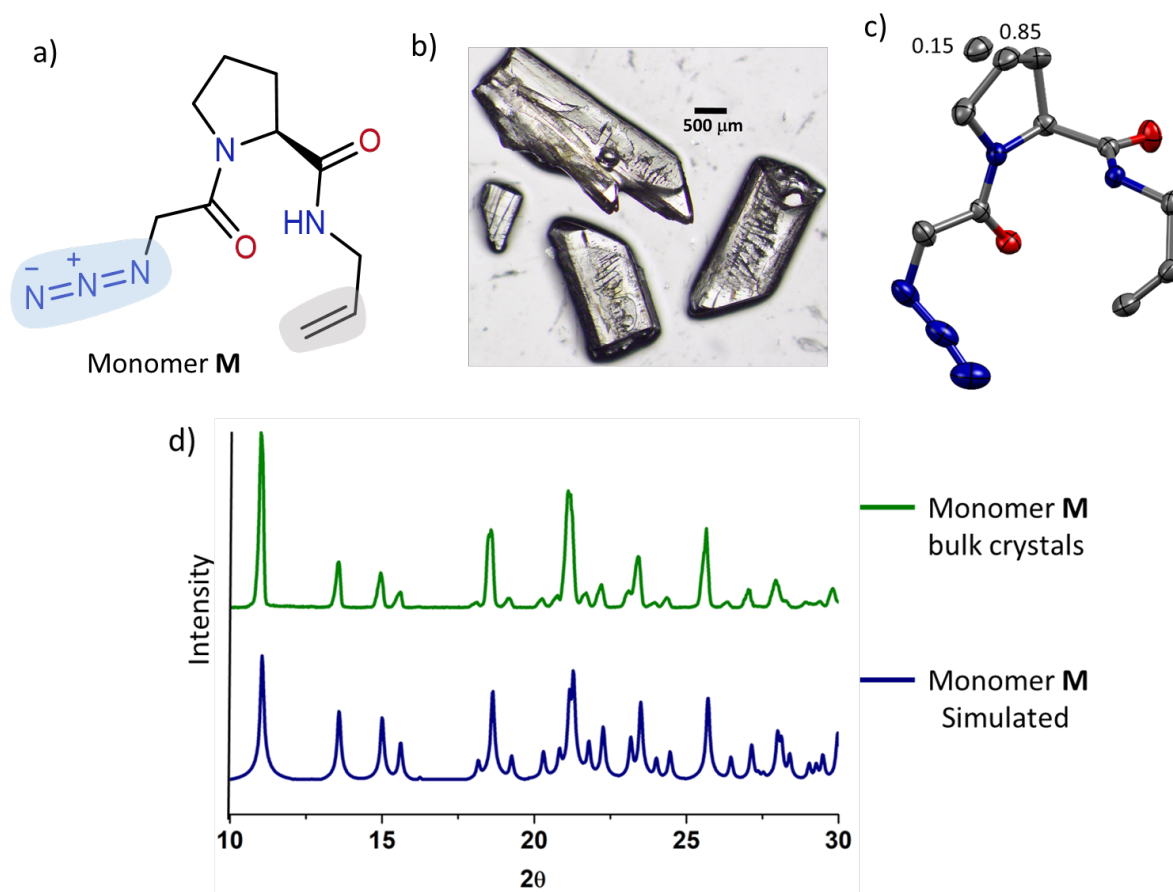


Figure 1. a) Chemical structure of the monomer **M**. b) Optical microscopic image of the single-crystals of monomer **M**. c) ORTEP diagram of the monomer **M** (ellipsoids at 50% probability level). d) Comparison of PXRD profile of bulk crystals of monomer **M** with simulated PXRD.

intramolecular interactions such as azide...oxygen interaction⁷⁷ between β -N of the azide and carbonyl oxygen and a C-H...O hydrogen bond between the vinylic hydrogen and carbonyl oxygen. Along the crystallographic '*a*' axis, the molecules are connected predominantly by N-H...O hydrogen bond, azide...oxygen interaction,⁷⁷ and CH...N hydrogen bond, forming a supramolecular helix (Fig. 2a,b, Table S2). Such supramolecular helices are arrayed coaxially through weak non-covalent interactions such as C-H...O, C-H...N, and van der Waals interactions, and each helix is surrounded by six such helices (Fig. 2c, Table S2). The azide and alkene of adjacent molecules in a helix are neither arranged proximally (termini distance of 5.9 & 6.9 Å and 5.8 & 5.1 Å) nor are their orientation supportive of TEAC reaction within

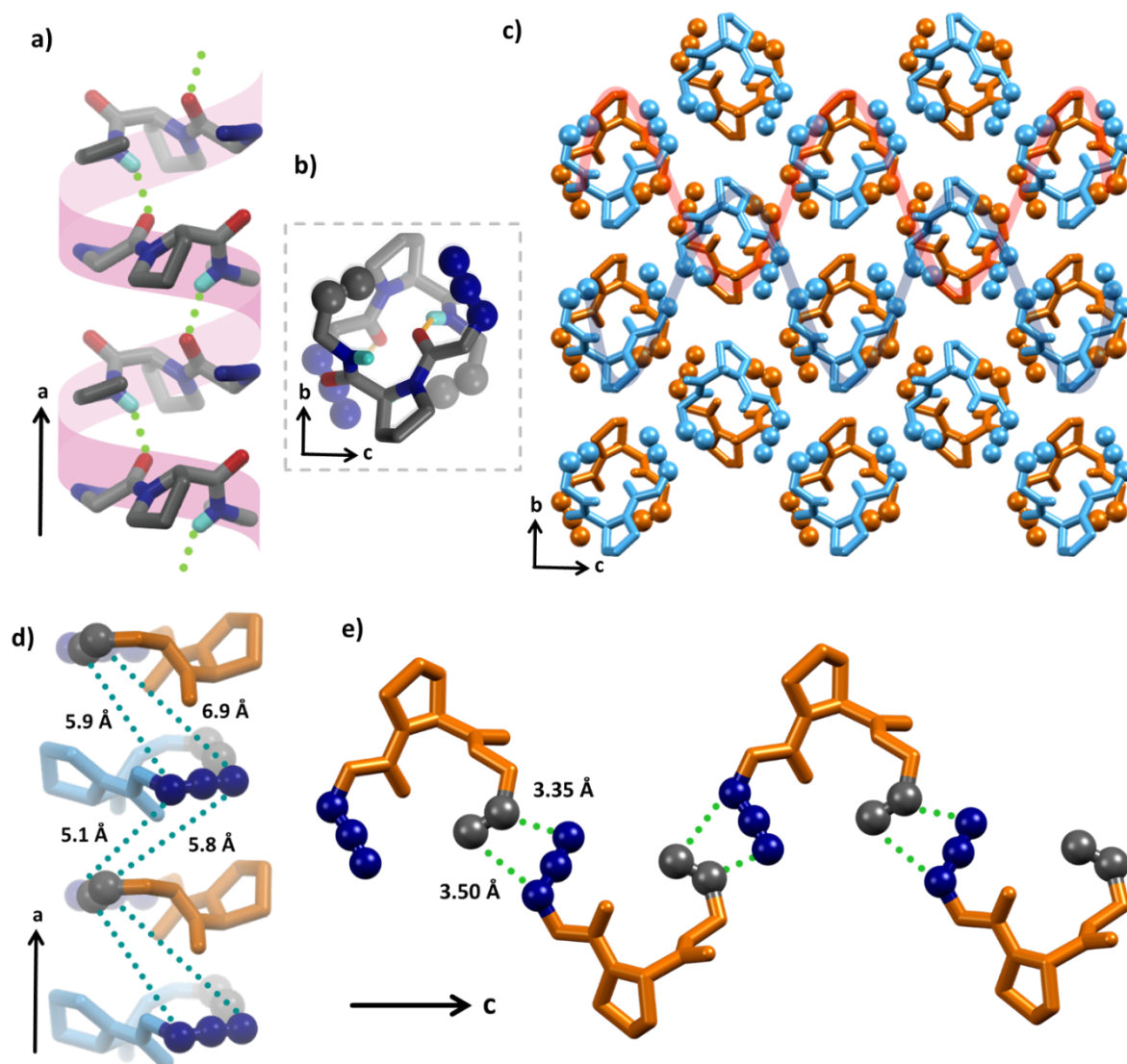


Figure 2. a) N-H...O H-bonded molecules forming a 1D H-bonded supramolecular helix along 'a' direction. (Green dotted lines indicate N-H...O H-bonds). b) View of a supramolecular helix along its axis. c) Crystal packing showing the hexagonal arrangement of supramolecular helices. Azide and alkene units are highlighted in the ball and stick model. d) Non-reactive arrangement of molecules within a supramolecular helix showing unsuitable distance and orientation for TEAC reaction. e) Reactive arrangement of molecules between supramolecular helices, showing suitable distance and orientation for TEAC reaction. (H atoms are hidden for clarity).

the supramolecular helix, along 'a' axis (Fig. 2d). On the other hand, molecules are arranged in a head-to-tail manner as supramolecular waves with proximally placed azide and alkene along crystallographic 'c' axis (Fig. 2c,e). The distances between the termini of alkene and azide units are 3.4 Å and 3.5 Å (centroid-centroid distance 3.4 Å), and they are nearly in an anti-parallel orientation resembling the transition state-like arrangement for their cycloaddition reaction. Based on this crystal packing that satisfies Schmidt's criteria,³⁵ the monomer **M** is expected to undergo smooth TEAC polymerization to yield 1,4-triazoline-linked polymer having a wave-like conformation in the crystal lattice.

We investigated the topochemical reactivity of the monomer **M**. The single crystals were stable at room temperature for two months and did not react. We heated the single crystals of monomer **M** in a glass vial at different temperatures to check their reactivity. The optimum temperature for the topochemical reaction was found to be 60 °C. The crystals heated at 60 °C for five days were only partially soluble in common solvents like dichloromethane, ethylacetate, chloroform, acetone, ethanol, methanol, isopropanol, tetrahydrofuran, DMF, and DMSO. The ¹H NMR spectra of the sparingly soluble samples exhibited only the signals corresponding to the monomer **M**, suggesting that the product formed is insoluble. After eight days of heating at 60 °C, the crystals were completely insoluble in common solvents. Unlike the monomer **M** crystals, which show a melting point of 95 °C, the crystals heated for eight days did not melt but started charring at a temperature above 255 °C. The DSC analysis also agreed with these observations (Fig. 3a); while the monomer **M** shows a sharp endothermic peak at 95 °C (melting point) followed by a broad exothermic peak ascribable to the heat released in the ene-azide cycloaddition reaction in the molten state, the heated crystals (60 °C, 8d) did not show any heat change till 250 °C. The exothermic peaks after 250 °C correspond to the heat released in the denitrogenation and decomposition. TGA analysis of monomer **M** revealed a weight loss of 11.34% in the temperature window of 98-215 °C, which corresponds

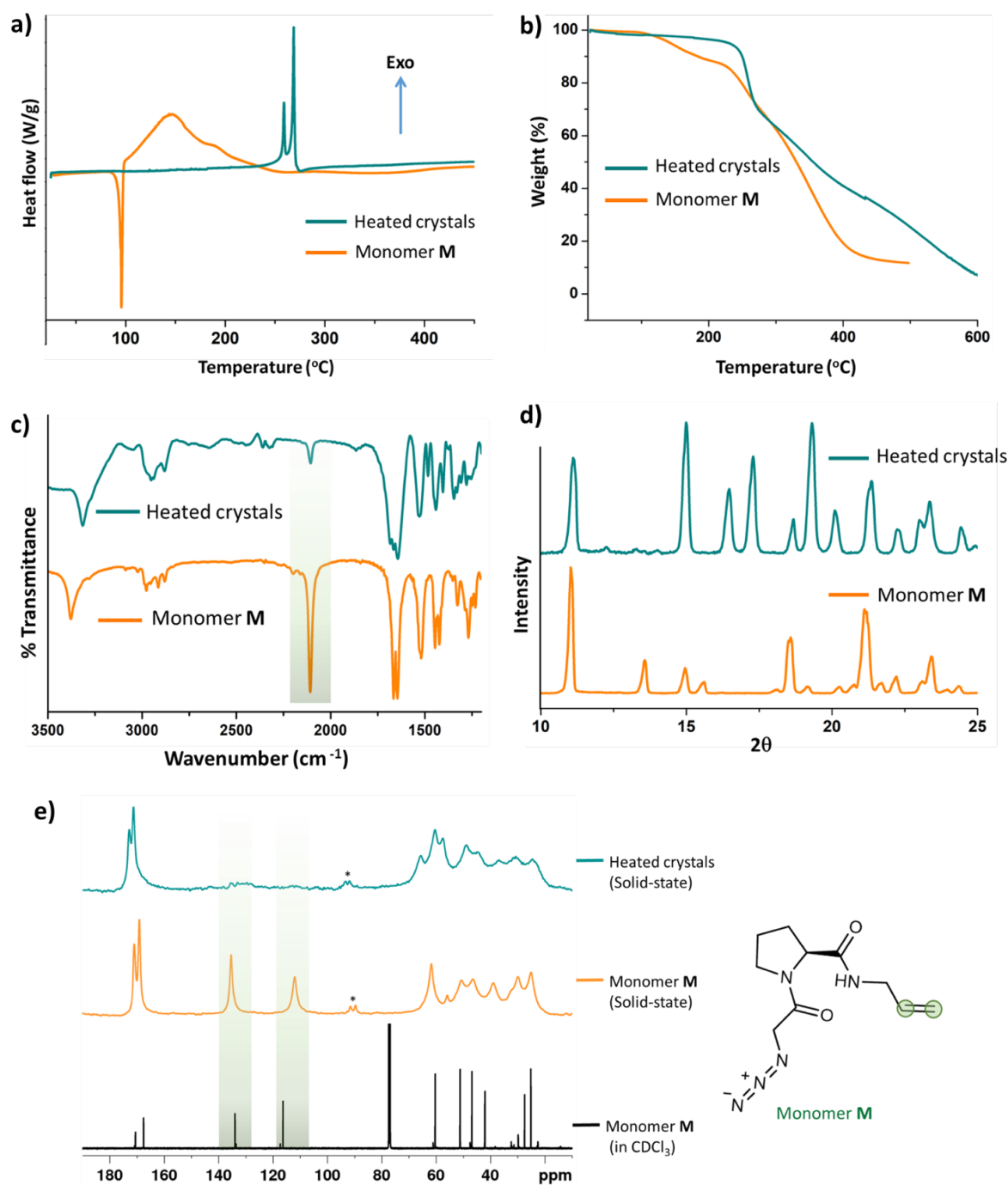


Figure 3. a) Comparison of DSC profiles of monomer **M** and heated crystals. b) Comparison of TGA profiles of monomer **M** and heated crystals. c) Comparison of IR spectra of monomer **M** and heated crystals. d) Comparison of PXRD diffractograms of monomer **M** and heated crystals. e) Overlay of ¹³C NMR spectra of monomer **M** in CDCl₃, monomer **M** in solid-state and heated crystals in solid-state. (* denotes side bands)

to N₂ (11.8%, theoretical amount) that can be evolved from the triazoline-linked polymer formed in the molten state. On the other hand, the heated crystals showed a weight loss due to denitrogenation after 250 °C, immediately followed by decomposition (Fig. 3b).

A comparison of the IR spectra of the monomer **M** and the heated sample showed a diminished intensity of the peak corresponding to the asymmetric stretching of the azide group at 2108 cm⁻¹ in the heated sample, suggesting the consumption of the azide group in the TEAC reaction (Fig. 3c). Similarly, consumption of the complimentary reactive group, alkene, is understood from the solid-state-NMR analysis. Comparison of ¹³C NMR cross-polarization magic angle spinning (CP-MAS) spectra of the monomer and heated sample exhibited prominent differences in the carbon signals. Notably, the peaks corresponding to the alkene carbons at 135 and 112 ppm disappeared in the heated sample, hinting at the quantitative consumption of the alkene in the TEAC reaction (Fig. 3e). The MALDI-TOF analysis of the heated sample showed products of mass up to 3kDa, suggesting that the TEAC reaction is indeed a polymerization reaction. A comparison of the PXRD patterns of the monomer and heated sample illustrated a clear difference in the diffraction signals. The sharp signals indicated retention of the crystallinity of the sample even after the TEAC reaction (Fig. 3d). Optical polarizing microscopy imaging of the heated crystals showed birefringence patterns that conveyed their single-crystalline nature (Fig. 4a). It is noteworthy that the polymerization completes in 48 h when the crystals are heated at 80 °C. However, polymerization at 60 °C yielded better-quality single crystals. While these experiments established the TEAC reaction of the monomer **M** crystals, we could not establish the regio- and stereochemistry of the cycloaddition product unambiguously from these experiments.

Though the monomer crystal structure predicted the formation of a 1,4-triazoline-linked wave-like polymer, in order to ensure regiochemistry and stereochemistry of the reaction and the conformation of the polymer, we determined its crystal structure by SCXRD analysis of the

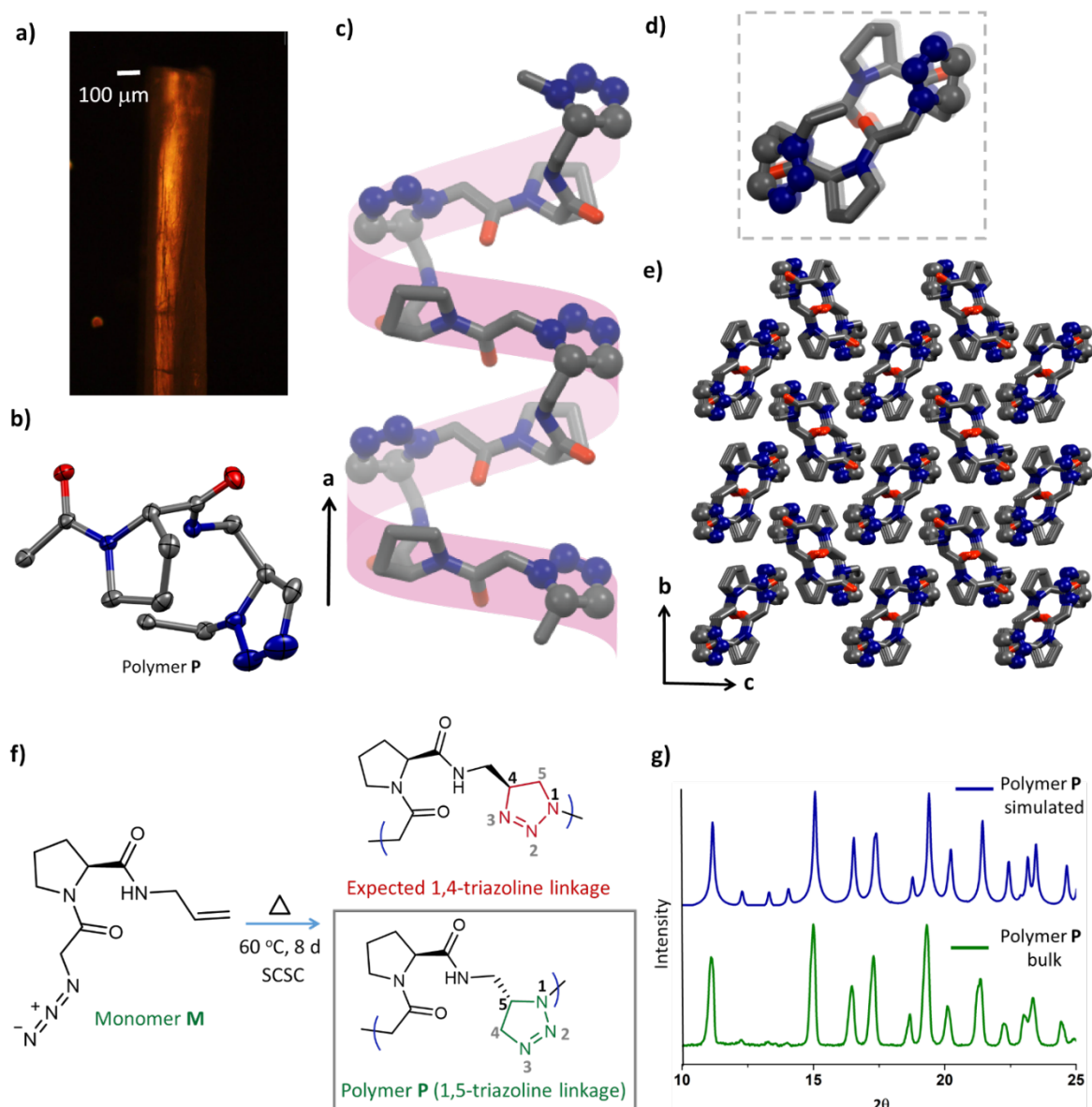


Figure 4. a) Polarizing microscope image of a heated crystal. b) ORTEP diagrams of polymer **P** (ellipsoids at 50% probability level). c) TEAC polymerization proceeded along ‘a’ axis results in a covalent helical polymer. d) View of a covalent helical polymer along its axis. e) Crystal packing showing hexagonal arrangement of helical polymers. Triazoline units are highlighted in the ball and stick model. f) Chemical structures of the expected 1,4-triazoline-linked polymer and the obtained product, 1,5-triazoline-linked polymer. g) Comparison of polymer **P** bulk and simulated PXRD.

heated crystal (Fig. 4b, Table S1, S2). The polymer crystal retained the $P2_12_12_1$ space group of the monomer. While unit cell parameters ' a ' and ' b ' were elongated by 0.34% and 4.41%, respectively, ' c ' was shortened by 9.61%, leading to an overall 5% reduction in the unit cell volume (Table S1). Surprisingly, the polymerization proceeded within the supramolecular helices along ' a ' axis but not along ' c ' axis as anticipated from the monomer packing (Fig. 4c,d,e). Furthermore, the reaction occurred regiospecifically but gave the unexpected 1,5-triazoline-linked polymer than the expected 1,4-triazoline-linked polymer (Fig. 4f). It is noteworthy that this is the first report on the regiospecific formation of a 1,5-disubstituted triazoline product from an ene-azide cycloaddition reaction. Interestingly, the TEAC reaction demonstrated here is also stereospecific; the newly generated chiral center in the triazoline ring has an absolute configuration (S). As the polymerization covalently connects the molecules within a supramolecular helix, the polymer formed is a left-handed covalent helical polymer (CHP). Such CHPs characterized in an atomic resolution are rare.^{76,78}

The degree of polymerization (DP) in topochemical polymerization depends on the dimension of the crystal, and hence the molecular weight (MW) and DP are usually determined per unit length of the crystal.^{42,76,78} The MW and DP of polymer **P** are estimated to be 541 kDa and 2280 per micrometer, respectively (Supplementary information section 4). We heated the powder obtained by simple evaporation of a solution of monomer. The PXRD pattern of these heated powder matches with the PXRD profile simulated from the polymer **P** crystal, suggesting that they are the same form of the polymer (Fig. 4g).

The single-crystal-to-single-crystal process of this polymerization is helpful to analyze this anomalous reaction and to map the reaction path (Fig. 5a). In order to understand the changes and the molecular motion that occurred in the polymerization, we have overlaid the crystal structures of the supramolecular helical polymer (monomer **M**) and the covalent helical polymer (polymer **P**) (Fig 5b). While the azide group has slightly moved, the alkene group has

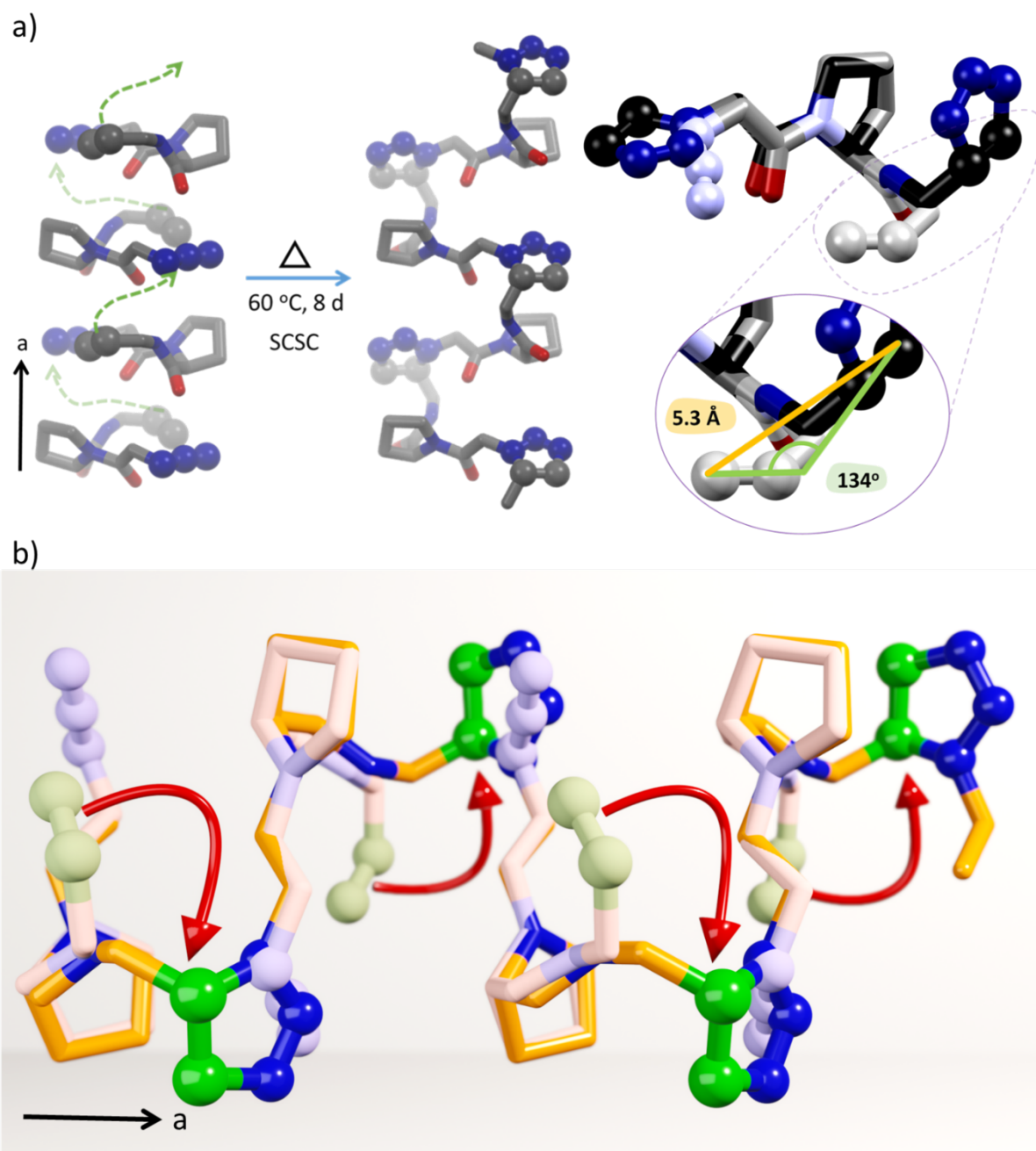


Figure 5. a) TEAC polymerization proceeds along ‘a’ axis with the massive alkene motion. b) Overlay of the supramolecular helical polymer/monomer **M** (faded colors) and covalent helical polymer/polymer **P** (darker colors). Red arrows denote the massive motion of the alkene units.

undergone a massive rotation prior to the TEAC polymerization. To reach a parallel orientation for the formation of 1,5-disubstituted triazoline, the alkene group has to rotate $\sim 134^\circ$ in the crystal lattice (Fig. 5a). Notably, the terminal carbon of the alkene must travel a distance of 5.3 Å for the reaction. Void analysis revealed that considerable voids (probe radius 0.8 Å) are present around the alkene groups, and this might have prompted the alkene groups to rotate before the TEAC reaction (Fig. S2). It is clear that the molecule has chosen a difficult path that involves a huge rotation followed by a topochemical reaction by avoiding an easy topochemical reaction exploiting the pre-organized ready-to-react orientation.

In conclusion, we have shown a reversal of the expected regiochemistry in a topochemical cycloaddition reaction. Though the crystal structure of a monomer for TEAC reaction had a packing suitable for facile and regiospecific topochemical cycloaddition reaction to give 1,4-triazoline-linked polymer, it underwent regiospecific topochemical cycloaddition polymerization to yield 1,5-triazoline-linked polymer. This is the first report on ene-azide cycloaddition leading to the regiospecific formation of 1,5-disubstituted triazoline. Despite the molecule had a ready-to-react arrangement that obeys Schmidt's topochemical criteria, upon heating, instead of reacting, part of the molecule underwent huge rotation to reach another reactive orientation transiently and reacted from the latter to yield a totally unexpected product. This study cautions that the crystals are no longer a mere static ensemble of molecules; If there is flexibility and space for molecular motion, molecules can undergo large motion in crystals, especially upon heating, and react in a totally unexpected way, even avoiding a pre-existing ready-to-react arrangement. While the topochemical postulates are largely helpful for the successful prediction of light-induced topochemical reactions, one has to be cautious in predicting the reaction pathway, based on crystal packing, in a heat-induced reaction.

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Author Contributions

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Notes

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