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Topochemical Ene-Azide Cycloaddition Reaction

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Abstract: Topochemical reactions, high-yielding solid-state reactions arising from the proximal alignment of reacting partners in the crystal lattice, do not require solvents, catalysts, and additives are of high demand in the context of green processes and environmental safety. However, the bottleneck is the limited number of reactions that can be done in the crystal medium. We present the topochemical ene-azide cycloaddition (TEAC) reaction, wherein alkene and azide groups undergo lattice-controlled cycloaddition reaction giving triazoline in crystals. A designed monomer that arranges in a head-to-tail manner in its crystals pre-organizing the reacting groups of adjacent molecules in proximity undergoes spontaneous cycloaddition reaction in a single-crystal-to-single-crystal fashion, yielding the triazoline-linked polymer. A unique advantage of this reaction is that the triazoline can be converted to aziridine by simple heating, which we exploited for the otherwise challenging post-synthetic backbone modification of the polymer. This reaction may revolutionize the field of polymer science.

Topochemical reactions, the reactions that occur in the crystal lattice due to the proximal alignment of reacting groups, attract much attention due to their high yield, regio/stereo-specificity, green reaction conditions, and ability to give products that are not conceivable by conventional solution-phase chemistry.[1] Since the discovery of light-induced topochemical [2+2] cycloaddition in the 1960s,[2] this field has been growing, and even today, it continues to elicit interest. A few more light-driven topochemical reactions such as [4+4] cycloaddition,[1d,1e,3] polymerization of diynes,[4] bisindenones,[5] dienes,[1a,1g,6] and quinodimethanes[1h,7] have been discovered (Figure 1a), but [2+2] cycloaddition continues to be the most commonly exploited topochemical reaction.[1i,8] One commonly encountered disadvantage of light-induced topochemical reactions is the low yield due to the poor phototransmittance through the initially formed product-phase, especially when it is not crystalline, leaving the inner part of the crystal unreacted.[1g,9] Though a few thermal topochemical reactions are known,[1h,10] they are seldom used for reaction designs. A real breakthrough came when we furtherance the topochemical alkyne-azide cycloaddition (TAAC) reaction (Figure 1a), [11] wherein proximally placed azide and alkyne groups undergo regiospecific 1,3-dipolar cycloaddition reaction under thermal conditions, leading to the formation of 1,2,3-triazoles in the crystal-state. We have exploited this thermal TAAC reaction for the synthesis of several polymers.[12]

The broad applicability and success of this thermal topochemical reaction and the advantages of topochemical reactions over solution-phase reactions, in general, prompts the discovery and development of novel thermal topochemical reactions. Here we report the topochemical ene-azide cycloaddition (TEAC) reaction as a novel thermal topochemical reaction that gives Δ^2-1,2,3-triazoline product, which, at will, can be modified to synthetically versatile aziridine product (Figure 1b). We illustrate this concept by the regio- and stereospecific polymerization of a dipeptide monomer to a triazoline-linked polymer in a single-crystal-to-single-crystal fashion and its post-synthetic backbone modification to an aziridine-linked polymer.

Thermal 1,3-dipolar alkyne-azide cycloaddition (AAC) reaction giving 1,2,3-triazoles (Huisgen reaction) and ene-azide cycloaddition (EAC) reaction giving Δ^2-1,2,3-triazolines are highly exothermic reactions with similar activation energies,[13] and both give a mixture of products in the absence of any catalyst.[14] While Cu(I) catalyzed AAC reaction (click chemistry) is regiospecific and occurs under mild conditions,[15] no catalyst has been developed so far for the EAC reaction to make it universal or regio-/stereospecific. Furthermore, the solution-phase EAC reaction is limited to only highly activated[16] or strained alkene.[17] Moreover, it yields a mixture of regioisomers, viz. 1,4-disubstituted and 1,5-disubstituted triazolines and other products.[18] Hence, solution-phase EAC reactions are neither widely applicable nor used for synthetic purposes. This prompted us to investigate the EAC reaction under topochemical conditions.

The major challenge in designing a topochemical reaction lies in the crystal engineering to place the reacting groups in the crystal lattice at a distance and geometry suitable for their reaction with minimal movement. Generally, small peptides showing hydrogen-bonded packing in their crystals align head-to-tail in a direction perpendicular to the H-bonding direction (Figure 1c).[19] Thus, a sheet-forming peptide terminally modified with two mutually complementary reacting groups (CRGs) would arrange in head-to-tail fashion in its crystal, placing the CRGs of adjacent molecules at proximity. Diphenylalanine-based peptides are known to adopt hydrogen-bonded packing in their crystals. [12g,20] We anticipated that the diphenylalanine-based peptide (monomer) **1** would exhibit an H-bonded packing in its crystal with proximally placed azide and ene groups between molecules of adjacent H-bonded arrays.

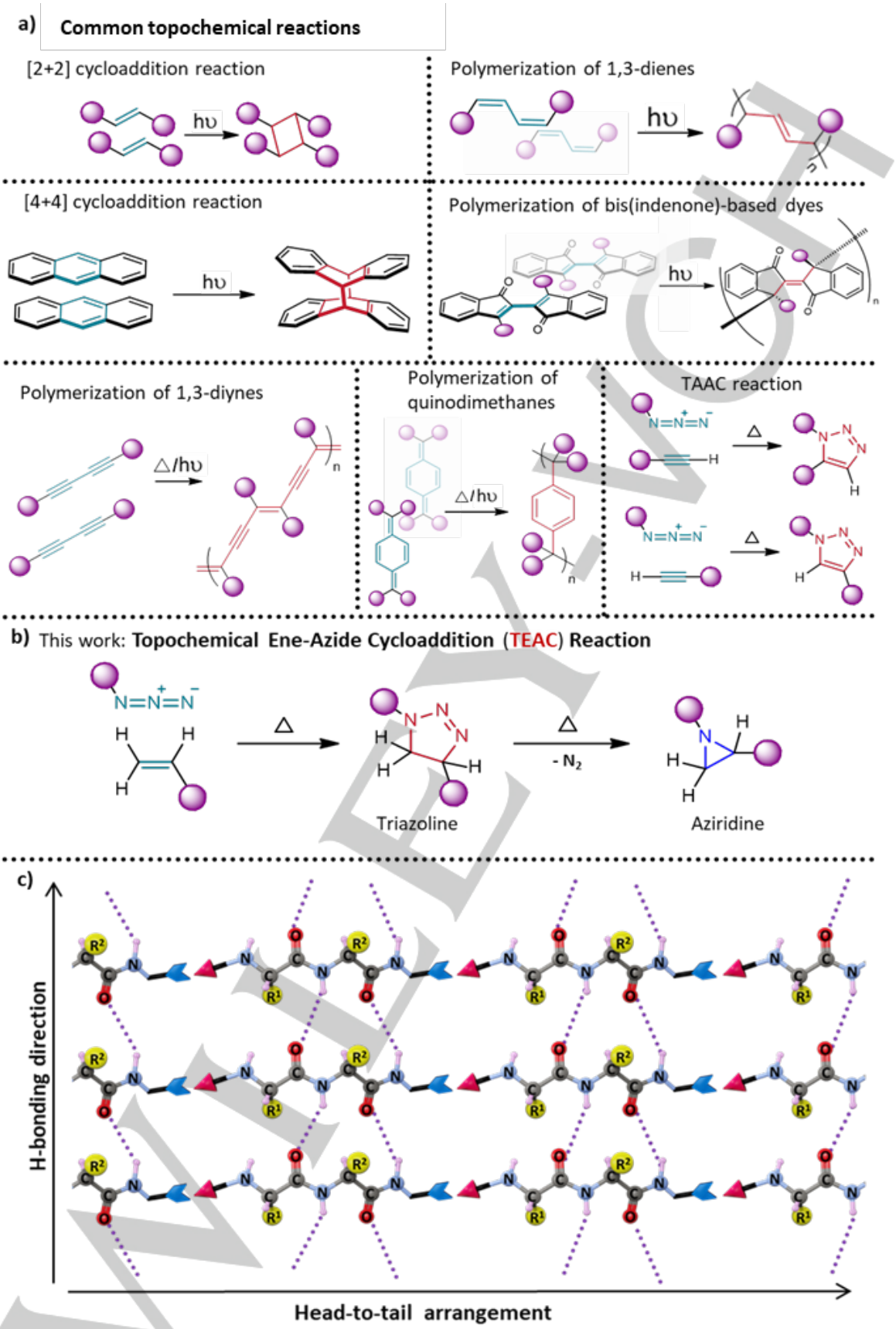

Figure 1. a) Common topochemical reactions. b) Topochemical ene-azide cycloaddition reaction. c) Schematic representation of the crystal packing of small peptides showing their head-to-tail arrangement perpendicular to the H-bonding direction.

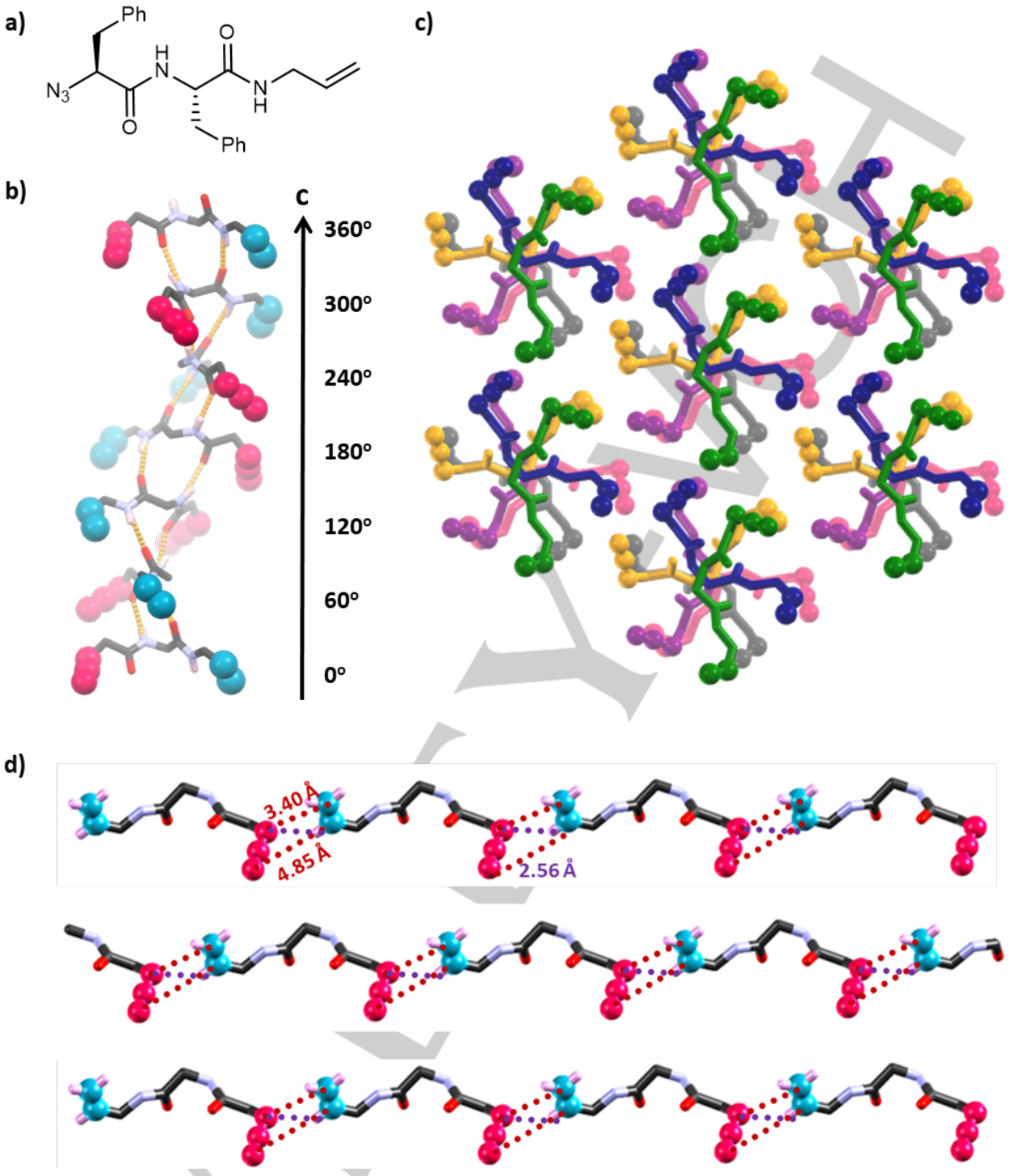

Figure 2. a) Chemical structure of monomer **1**. b) Twist-stacking of monomer **1** along the 'c' axis via NH…O hydrogen bonding. Orange dotted lines represent hydrogen bonding. c) View of the monomer **1** along the 'c' axis showing a twist-stacked packing. d) Parallelly arranged linear CH…N hydrogen-bonded chains of monomer **1** in the 'ab' plane showing the proximal arrangement of azide (magenta) and alkene (sky blue) units. Maroon dotted-line indicate the proximity of azide and alkene, and purple dotted-lines indicate the CH…N hydrogen bond. (Hydrogen atoms and phenyl rings are hidden for clarity)

We have synthesized monomer **1** (Figure 2a, Figure S1) and crystallized from a mixture of ethyl acetate and petroleum ether. Single-crystal X-ray diffraction (SCXRD) analysis revealed that monomer **1** adopts the hexagonal packing in the $P6_5$ space group (Table S1). NH…O Hydrogen bonds connect the molecules, forming a twisted sheet along the 'c' direction (Figure 2b). Adjacent H-bonded molecules are aligned at an angle of 60° along the six-fold screw axis and show a left-handed supramolecular helicity (Video S1). Perpendicular to the helix axis, molecules are head-to-tail arranged and are connected

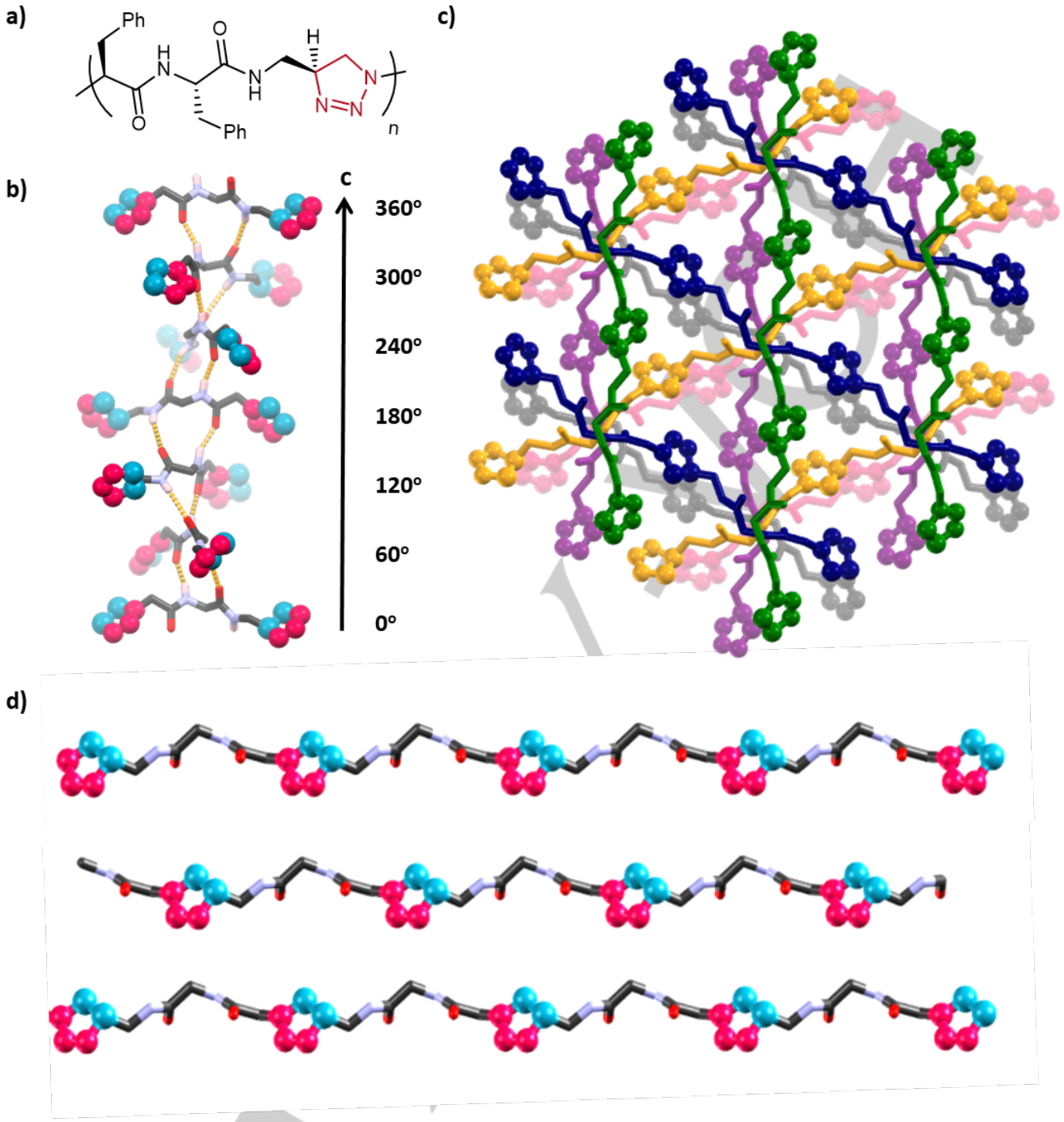

Figure 3. a) Chemical structure of polymer **2**. b) Twist-stacking of polymer **2** along 'c' axis via NH…O hydrogen bonding; Orange dotted lines represent hydrogen bonding. c) View of the polymer **2** along the 'c' axis showing a twist-stacked packing. d) Parallel arrangement of 1,4-triazoline linked polymer chains in 'ab'-plane. (Triazoline rings are highlighted in ball and stick model. Hydrogen atoms and phenyl rings are hidden for clarity).

through a CH…N hydrogen bond between the alkene-H and α-N of the azide (Figure 2d). Such CH…N hydrogen-bonded chains of molecules are parallelly arranged in the 'ab' plane, and by virtue of the six-fold screw axis, such parallelly arranged chains are twist-stacked (twist angle of 60°) along the 'c' direction (Figure 2c).

Though the molecules are arranged in a head-to-tail fashion in 'ab' planes, the azide and alkene of adjacent molecules are not in the parallel orientation required for their cycloaddition reaction (Fig 2d). However, the presence of voids around the azide and alkene groups and the flexible linkages connecting these groups in monomer **1** would allow rotation of these complementary reactive groups to reach a reactive parallel orientation (Figure S3). Hence, they could undergo topochemical cycloaddition reaction forming a triazoline-linked polymer (Figure 3a). Crystals of many molecules having an unfavorable arrangement of their reacting groups undergo topochemical reactions due to the

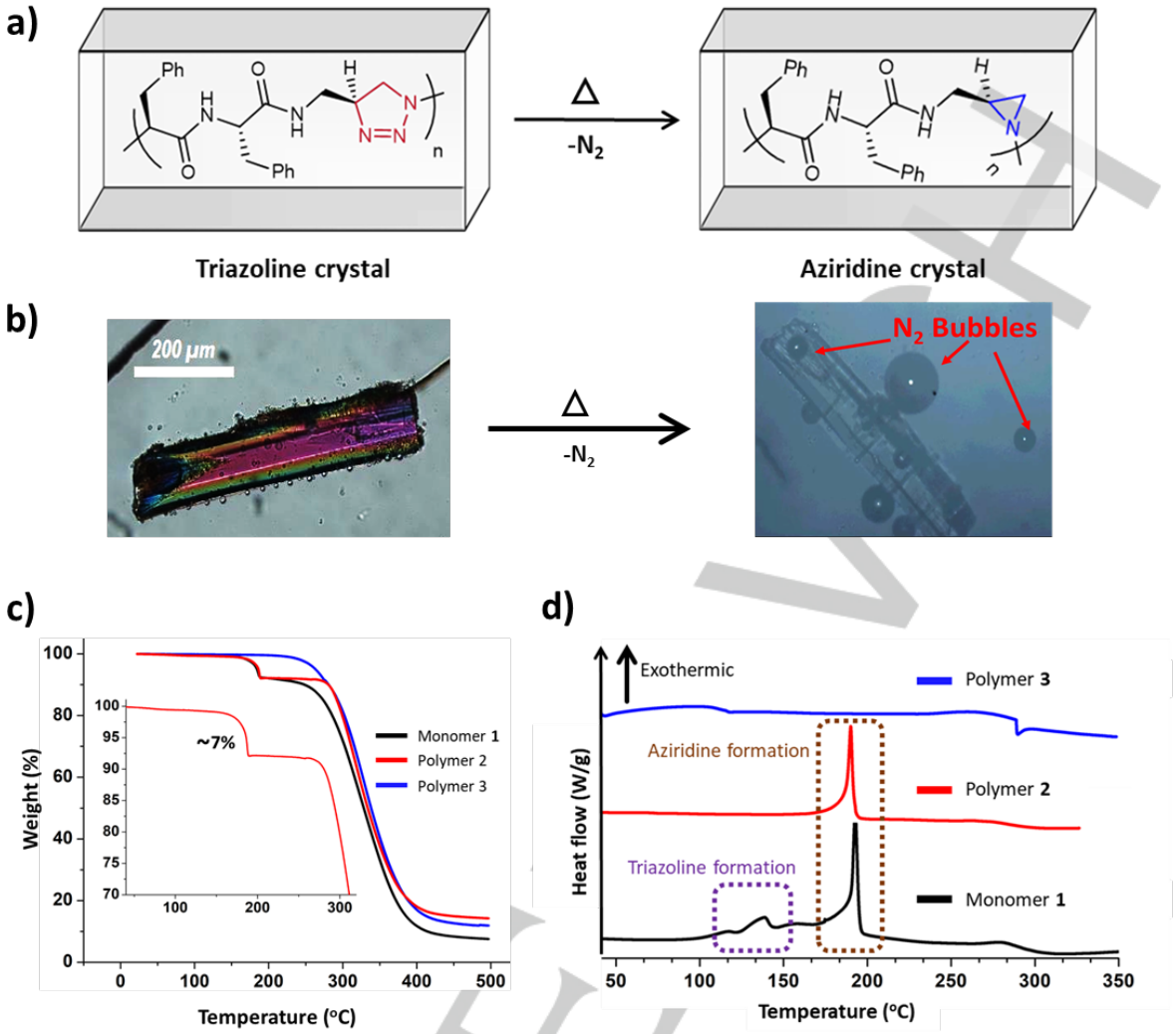

Figure 4. a) Chemical transformation of polymer **2** to polymer **3** upon heating. b) Crystal kept in the immersion oil on heating at the range of 175-190 °C releases N_2 as bubbles. c) TGA comparison of monomer **1**, polymer **2** and polymer **3** (Inset: ~7% weight loss corresponding to N2) d) DSC comparison of monomer **1**, polymer **2** and polymer **3**.

transient attainment of reactive orientation via molecular motion.[12g]

We found that the crystals react spontaneously at room temperature. We have systematically studied the reactivities of these crystals by various time-dependent analytical techniques. For this, we kept 100 mg of crystals at room temperature and withdrawn small portions at different intervals, and analyzed by using IR, NMR, and PXRD measurements. The time-dependent IR spectroscopy reveals that the peak corresponding to the azide stretching at ~2117 cm^{-1} diminishes progressively with time, suggesting the gradual consumption of azide presumably due to the ene-azide cycloaddition reaction (Figure S4). After 60d, the azide signal disappeared completely, suggesting the completion of the reaction. Similarly, the time-dependent ^1H NMR spectroscopy also proved the gradual progress of the reaction. The signals corresponding to the alkene protons at 5.72 and 5.06-5.01 ppm diminished with time and the new signal corresponding to the proton at the newly formed stereogenic center of the triazoline grew concomitantly (Figure S5). The presence of only one signal corresponding to the proton at the newly generated chiral center in the triazoline ring suggests that the observed spontaneous solid-state reaction is both regiospecific and stereospecific. Though this spontaneous reaction at room temperature takes about 60 days for completion, the reaction gets accelerated at higher temperatures; at 50 °C, the reaction completes within 64 h and at 100 °C, it completes in 4h. We recorded the PXRD profiles of the sample at different stages of the reaction. At all stages of the reaction, the PXRD profile exhibited sharp reflection peaks, suggesting the crystallinity of the sample throughout the reaction. As the reaction progressed, some peaks shifted, some peaks vanished, and some new peaks have appeared, suggesting a smooth transition from reactant crystal to product crystal. Thus, the time-dependent PXRD study revealed that the reaction is a crystal-to-crystal reaction (Figure S6).

As the morphology and the crystallinity of the sample were intact (Figure S7), we determined the crystal structure of a fully reacted crystal. As expected, ene-azide cycloaddition reaction happened in a single-crystal-to-single-crystal (SCSC) manner,

yielding triazoline-linked linear polymer without affecting the crystal symmetry. The cycloaddition reaction was both regiospecific and stereospecific to give 1,4-disubstituted triazoline having (S)-stereochemistry for the newly generated chiral center. The polymer chains are parallelly arranged in 'ab' planes (Figure 3d) and such layers are twist-stacked along the screw axis with a twist of 60° (Video S2, Figure 3b,c). Aligning polymers in such an interesting topology is not possible by conventional solution-phase polymerization. GPC analysis revealed the presence of polymers with a weight averaged molecular weight (Mw) of around 170 kDa (Figure S8).

One advantage of triazolines over triazoles is that they can be converted to other functional groups.[21] This allows the unique possibility of post-polymerization modification of the backbone linkage of the triazoline-linked polymers. Garcia-Garibay et al. have reported that the crystalline triazoline derivatives undergo denitrogenation upon photoirradiation or heating to yield aziridine derivatives.[22] Encouraged by this report, we heated the polymer crystals anticipating the conversion of triazoline-linked polymer to aziridine-linked polymer (Figure 4a). From 175 °C onwards, we observed the evolution of nitrogen as bubbles during the heating, and this bubbling continued till the complete melting (190 °C) of the polymer (Figure 4b, Video S3). The denitrogenation happens with retention of crystallinity. We inferred this from the birefringence pattern of the crystal when viewed through a polarising microscope (Figure S9, Video S4). Thermogravimetric analysis (TGA) of the polymer crystals indicated a weight loss of around 7%, in the temperature range 189-193 °C and this corresponds to the weight percentage of nitrogen (7.4%) that can be evolved as N_2 molecule in the denitrogenation of the triazoline-based polymer (Figure 4c). This suggests that denitrogenation is complete by 193 °C.

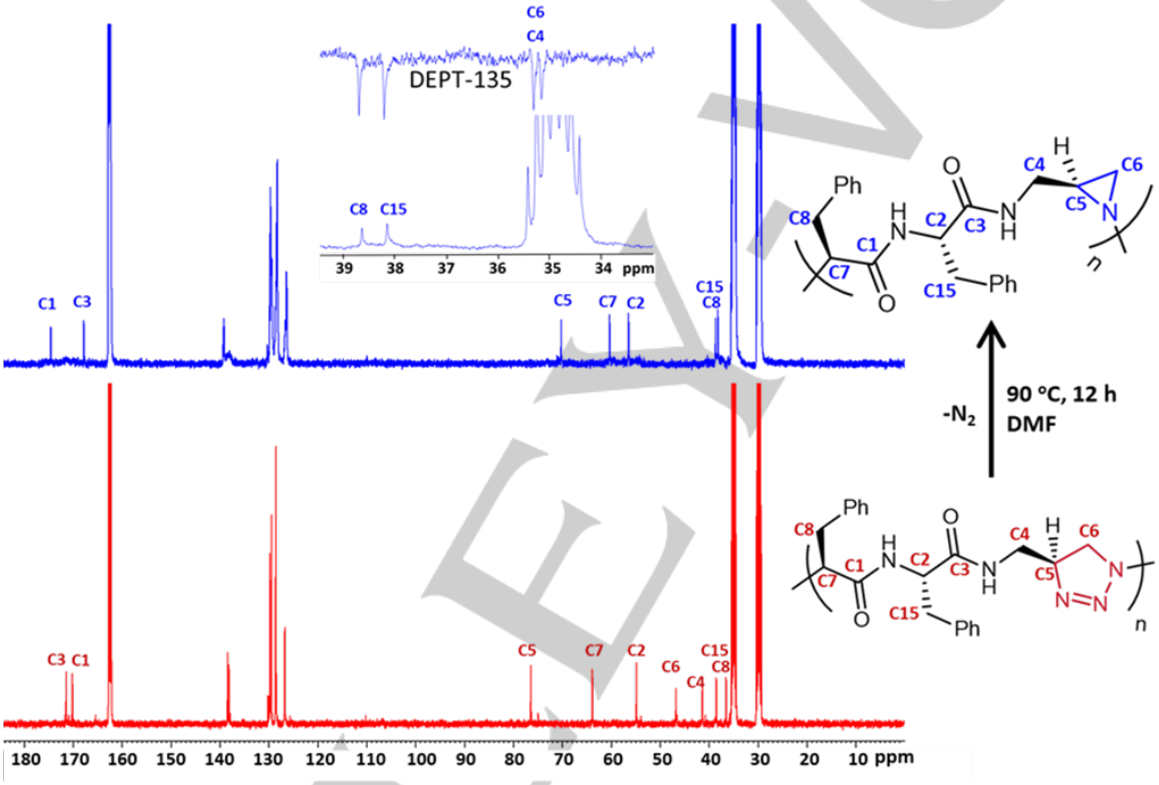

Figure 5. ^{13}C NMR spectra of polymers in DMF-d7 before (polymer **2**) and after (polymer **3**) heating.

The NMR analysis of polymer **2** heated till 193 °C confirmed its conversion to aziridine-linked polymer. Differential Scanning Calorimetry (DSC) analysis of the triazoline-linked polymer showed an exothermic peak at 191 °C (Figure 4d), which coincides with the denitrogenation temperature observed in TGA. The denitrogenation can also be done in solution. Thus, heating a solution of polymer **2** in DMF at 90 °C for 12 h resulted in its smooth denitrogenation to the aziridine-linked polymer **3**. This is evident from the shift of carbon signals in the ^{13}C NMR spectra of polymers in DMF-d7 before (polymer **2**) and after (polymer **3**) heating (Figure 5). Notably, the carbon signals corresponding to C5 (76.41 ppm) and C6 (46.69 ppm) in the triazoline ring of polymer **2** underwent an upfield shift to 70.21 ppm (C5) and 35.19 ppm (C6) respectively after it turned into an aziridine ring. This smooth conversion to aziridine opens up further possibilities of backbone modification to access a diverse range of functionalized polymers through the nucleophilic opening of the aziridine ring.[23] The GPC analysis of the aziridine-linked polymer showed a weight-average mass of 149 kDa (Figure S10).

In conclusion, we have developed a new topochemical cycloaddition reaction between ene and azide groups that leads to the regiospecific and stereospecific formation of substituted triazolines. When a monomer containing these complementary reacting groups pre-organizes in a ready-to-react head-to-tail arrangement in its crystals, it can undergo TEAC reaction to yield a triazoline-linked polymer. The crystal confinement ensures regiospecificity and stereospecificity for such a reaction. We have demonstrated the utility of TEAC reaction in

polymerization by an SCSC synthesis of a triazoline-linked pseudoprotein from a dipeptide monomer. We have also shown that the triazoline moieties in the polymer can undergo denitrogenation upon heating to yield aziridine-linked polymer; this is also a solvent-free and catalyst-free method for the synthesis of aziridine-linked polymers. This post-polymerization backbone alteration to aziridine offers several possibilities for further backbone functionalization by its nucleophilic ring-opening. We hope this report will pave the way for many researches exploiting this novel topochemical reaction.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Topochemical reaction• single-crystal-to-single-crystal • click chemistry • triazoline-linked polymer • aziridine-linked polymer

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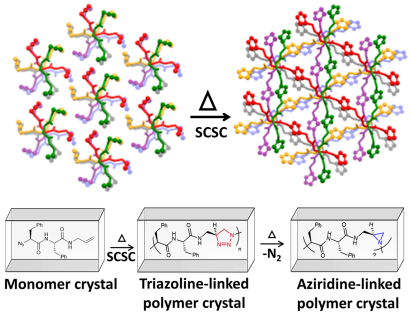

The rationally designed monomer having reactive groups, azide and alkene, adopt suitable crystal packing for a novel Topochemical Ene-Azide Cycloaddition reaction (TEAC). Spontaneously, the monomer undergoes polymerization to yield triazoline-linked polymer in a single-crystal-to-single-crystal fashion. The triazoline-linked polymer is transformed into a value-added aziridine-linked polymer by simple heating. This work may generate a new class of crystalline polymers with futuristic applications.