A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201914164
Angew. Chem. 10.1002/ange.201914164

Link to VoR: http://dx.doi.org/10.1002/anie.201914164
http://dx.doi.org/10.1002/ange.201914164

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10.1002/anie.201914164

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Crystal-to-crystal synthesis of helically ordered polymers of trehalose *via* topochemical polymerization

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Abstract: We describe the synthesis of crystalline helical polymers of trehalose *via* topochemical azide-alkyne cycloaddition (TAAC) of a trehalose-based monomer. An unsymmetrical trehalose derivative having azide and alkyne crystallizes in two different forms having almost similar packing; Form **I**, from ethyl acetate/n-hexane and form **II**, from chloroform/n-hexane. In form **I**, the alkyne group is disordered over two distant positions; **A** and **B**. When the alkyne is at position **B**, molecules form a head-to-tail arrangement with an orientation suitable for their TAAC reaction to yield the polymer. However, in form **II** the chloroform molecules occupy the position **B** and thus block the reactive orientation. Upon heating, both the crystals undergo TAAC reaction to form crystalline polymers. Various studies revealed that form **II** releases the chloroform molecules upon heating, which makes the position **B** accessible for the alkyne and thus to react. Powder X-ray diffraction (PXRD) studies revealed that the monomers in both the crystals polymerize in a crystal-to-crystal fashion and Circular Dichroism (CD) studies of the product crystals revealed that the formed polymer is helically ordered. This solvent-free, catalyst-free polymerization method that eliminates the tedious purification of the polymeric product exemplifies the advantage of topochemical polymerization reaction over traditional solution-phase polymerization.

Introduction

Monosaccharides are structurally unique molecules possessing a pro-electrophilic hemiacetal group and several nucleophilic hydroxyl groups. Due to the presence of these mutually complimentary functionalities, monosaccharides can undergo enzymatic homopolymerization *via* iterative glycosylation to form specific polysaccharides possessing wide-ranging biological functions and interesting material properties.[1] The glycosylation connects two monosaccharides through a glycosidic bond between the anomeric carbon and another carbon and the disaccharide thus formed undergoes further sequential glycosylation to form the polysaccharide. However, when the monosaccharides are connected through two anomeric carbons, there is no possibility of chain growth beyond dimer. α,α-Trehalose is such a symmetrical disaccharide found in nature and is known to possess remarkable properties.[2] For instance, α,α-trehalose is known to prevent aggregation, fusion, and lysis of lipid membranes and proteins.[3] Hence there is much interest in the synthesis of trehalose-based polymers.[4-9] Several polymers having pendant trehalose units have been synthesized (Figure 1a) and these trehalosylated polymers have been shown to stabilize proteins against various stresses[4] and prevent aggregation of amyloid beta.[5] Co-polymers containing trehalose units in the backbone have also been synthesized (Figure 1b) by the copolymerization of a symmetrically functionalized trehalose-based monomer with a co-monomer having complimentary reacting group and these trehalose copolymers have been used for nucleic acid delivery.[6-8] However, there is no report on polymerization of a single trehalose-derived monomer unsymmetrically substituted with two complimentary reactive groups to give trehalose-backbone polymers. Here we report a crystal-to-crystal synthesis of a trehalose-based polymer *via* the topochemical polymerization of a trehalose-derived monomer unsymmetrically substituted with two complementary reacting motifs (Figure 1c).

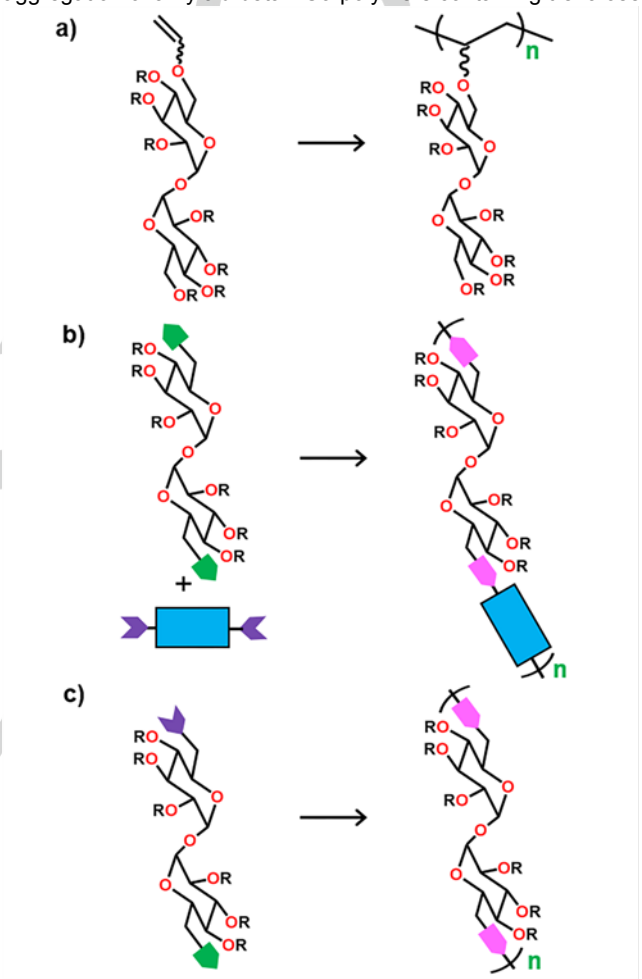

Figure 1. Different categories of trehalose-containing polymers. a) Polymers having pendant trehalose units. b) Co-polymers of trehalose and another co-monomer. c) Trehalose-main chain polymer from an unsymmetrical monomer.

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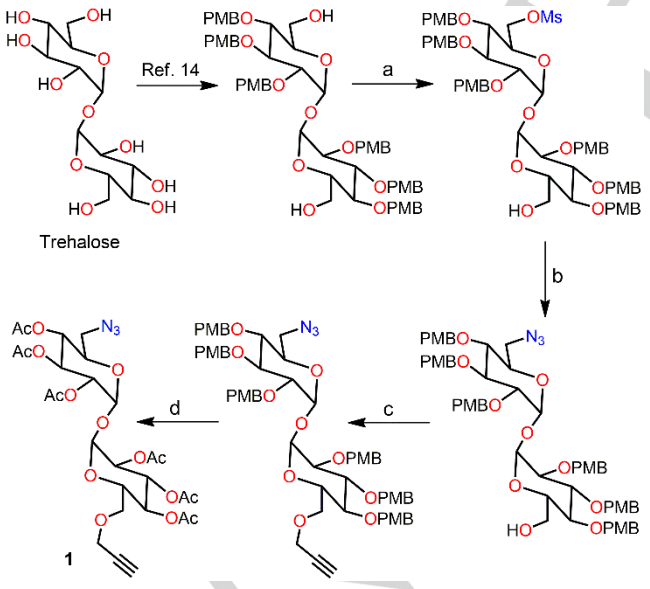
The main issues associated with the chemical synthesis of glycopolymers are (i) the difficult purification of the product from byproducts and other impurities, (ii) tedious removal of metal-based catalysts due to their complexation or entrapment in the polymer matrix, (iii) premature cessation of polymerization due to precipitation (iv) requirement of large amount of solvents for reaction and purification.[10] Topochemical reactions, the crystal-state reaction between two proximally-placed reacting groups, have received much attention due to their high yield, regiospecificity, ability to yield products that are not attainable by solution-phase synthesis and non-requirement of catalysts, solvents, purification etc.[11] There are several examples of topochemical polymerization, wherein a monomer has been converted to the polymer in the crystal state.[12] We have developed topochemical azide-alkyne cycloaddition (TAAC) polymerization for the synthesis of various biopolymer mimics.[13] When monomers substituted with azide and alkyne motifs are aligned, in their crystals, in head-to-tail fashion and with proximal placement of the azide and alkyne groups, they undergo 1,3-dipolar cycloaddition reaction to form triazole-linked polymers. We planned to use this strategy for the synthesis of trehalose-based polymers (Figure 1c).

Results and Discussion

We have synthesized an unsymmetrically substituted trehalose-derivative (**1**; Scheme 1) from trehalose,[14] wherein the primary hydroxyl positions were modified with alkyne and azide functionalities, for TAAC polymerization (Scheme S1, SI). Compound **1** gave crystals of different morphologies when crystallized from different solvent systems (Figure 2b). While crystallization from a solution of mixture of ethyl acetate and n-hexane (2:1; v/v) yielded long rod-shaped crystals (form **I**), crystallization from a mixture of chloroform and n-hexane (2:1; v/v) gave rectangular blocks (form **II**). As their morphologies were different, we made a comparative analysis by recording their melting points, differential scanning calorimetry (DSC) profiles, powder X-ray diffraction (PXRD) and thermogravimetric analysis (TGA). While form **I** showed a m.p. of 119-120 °C, form **II** melted in the range 123-125 °C. The DSC profiles of each of these two crystals showed an endothermic peak ascribable to the heat of melting followed by broad exothermic peak presumably due to the heat liberated in the azide-alkyne cycloaddition reaction in the molten state (Figure 2c). The endothermic peaks at 119 °C and 125 °C in the case of form **I** and form **II** respectively matched with their melting points determined using a melting point apparatus. PXRD patterns of both the crystals were found to be different, confirming that these two crystals are two different crystal forms (Figure 2d).



Scheme 1. Synthesis of the monomer **1**. a) MsCl, pyr, 0 °C, 67%; b) NaN_3, DMF, 80 °C, 87%; c) Propargyl bromide, NaH, DMF, 0 °C, 85%; d) i. CAN, acetonitrile: H_2O (4:1); ii. Ac_2O, pyr, 82%.

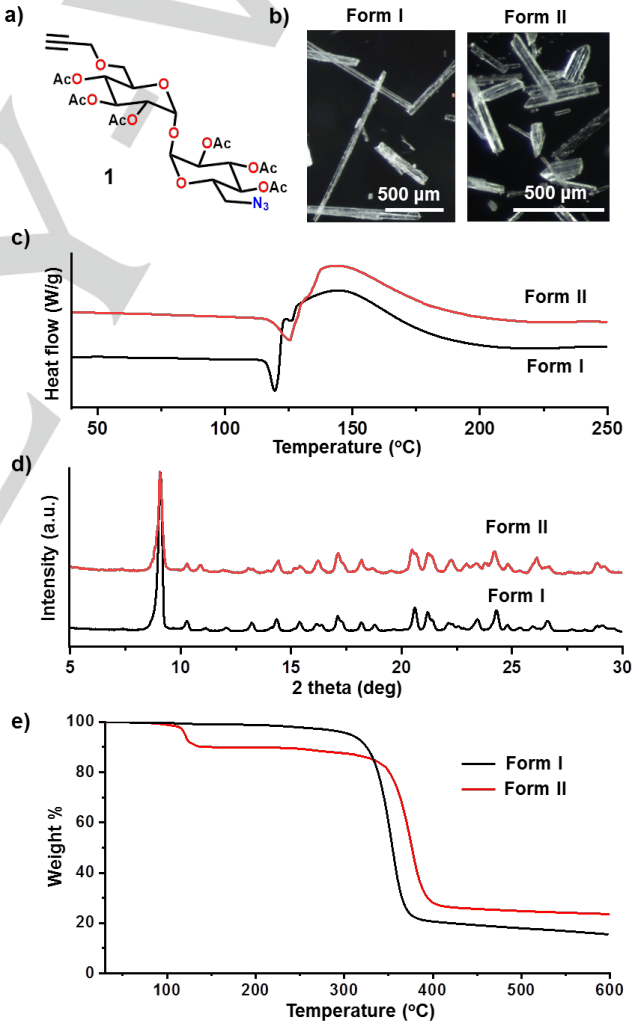


Figure 2. a) Chemical structure of the unsymmetrically substituted trehalose-derivative **1**. b) Photographs of the crystals obtained from ethyl acetate/n-hexane (form **I**) and chloroform/n-hexane (form **II**). Comparison of: c) DSC; d) PXRD and e) TGA profiles of form **I** (black) and form **II** (red).

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Interestingly, the TGA of form **II** exhibited a weight loss of 12% in the temperature of window 100-125 °C while that of form **I** did not show any weight loss until 300 °C (Figure 2e). The ^{1}H NMR spectrum of crystals of form **II** (obtained from chloroform and n-hexane) taken in DMSO-d_6 displayed the peak corresponding to chloroform at 8.32 ppm implying the presence of chloroform in these crystals (Figure S1, SI).

To get further structural insights, single crystal X-ray analyses were carried out for these crystals. Both the crystals adopted orthorhombic $P2_12_12_1$ space group (Table S1, SI). While the asymmetric unit of form **I** showed a single molecule of **1**, the asymmetric unit of form **II** contained one molecule of chloroform along with a molecule of **1**. Careful analysis of these crystal structures revealed that the molecular packing is similar except for the presence of chloroform in one of the crystals (Figure 3). Thus form **II** is a solvate of form **I**. Several non-covalent interactions such as C-H…O, C-H…N and C-H…π hydrogen bondings were found to stabilize the molecular packing in both the forms (Table S2, SI).

In both the forms, both the azide and alkyne groups exhibited positional disorders (Figure S3, SI). However, in form **I**, the propargyl group switched between two distant positions; position **A** and position **B** with an occupancy ratio of 0.65:0.35 (Figure 3a). Interestingly, when the propargyl group is in position **A**, there is no probability for the TAAC reaction to happen. When it is in position **B**, the reactive alkyne and azide groups are proximal (showed in dashed lines, Figure 3a) and are parallel to each other for the TAAC reaction to proceed along a-direction connecting the disaccharide molecules in zig-zag fashion (along the pink arrow, Figure 3a). In form **II**, a molecule of chloroform occupies the position **B** (Figure 3b) and this prevents the attainment of proximal arrangement of azide and alkyne groups for the TAAC reaction to proceed. We have previously observed that many crystals having azide and alkyne groups at proximity and in reactive orientation can undergo spontaneous TAAC reaction even at room temperature.[15,13e] In this context, the temporary prevention of attaining the reactive arrangement by the guest (chloroform) molecules is beneficial for long-time storage of the crystals in the unreactive state.

The crystals of both the forms were stable at room temperature (35 °C) for several months. In order to investigate the thermal reactivity of these crystals at higher temperatures, we have heated them at 90 °C, far below their melting points. To monitor the progress of the reactions, small fractions of these crystals were withdrawn at different intervals and analyzed by ^{1}H NMR spectroscopy after dissolving in $CDCl_3$ (Figure 4a and Figure 4b). From 24 h onwards, we observed the gradual appearance of new peaks corresponding to the triazole-linked products in the ^{1}H NMR spectra of both the forms. This time-dependent ^{1}H NMR spectroscopy analyses revealed the gradual disappearance of the alkyne C-*H* signal (2.34 ppm) and concomitant amplification of triazole C-*H* signals (7.50-7.69 ppm) suggesting gradual azide-alkyne cycloaddition in the crystals.

We have determined the melting points of the crystals kept at 90 °C for different durations. The melting points of both the crystal forms gradually reduced with time for the first 36 h (Figure 4c) and crystals heated for more than 36h did not melt but charred at very high temperatures. This gradual decrease in the melting point is due to the gradual formation of oligomeric products in the parent monomer crystal. Small amounts of products initially formed act as impurity in the parent crystal and hence shows this colligative property (depression in melting point). As the time progresses, larger and larger polymers are formed and this is the reason for the non-melting of crystals kept at 90 °C for more than 36h.

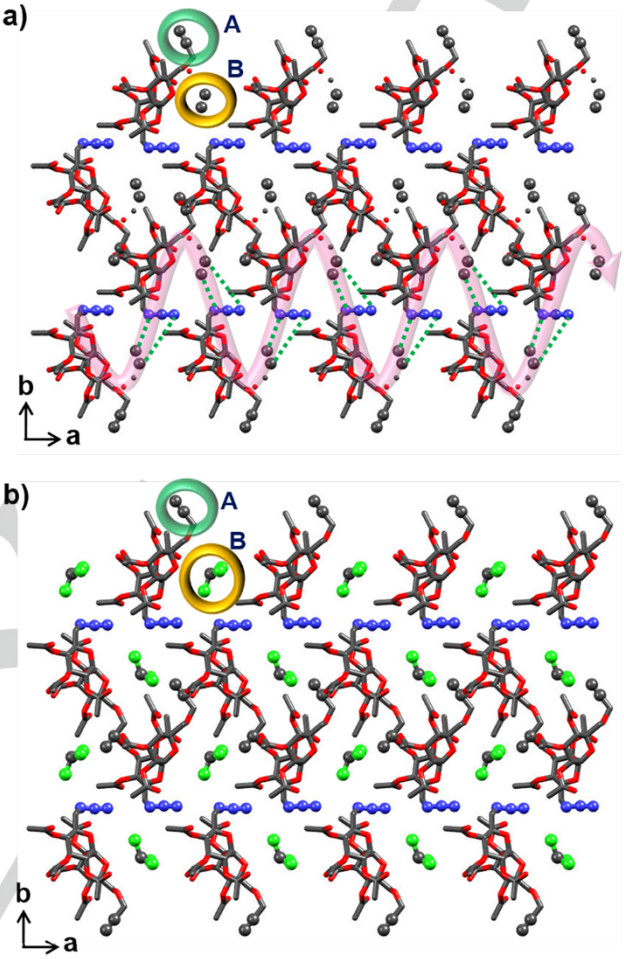

Figure 3. Crystal packing shows similar molecular arrangements in form **I** and form **II**. The azide and alkyne groups are represented in ball and stick model. a) Crystal packing of form **I** showing the partial occupancy of alkyne at positions A and B; when alkyne is at position B, the crystal is in a reactive configuration. Plausible TAAC polymerization path, along a-direction, is shown in pink arrow. b) Molecular packing in form **II** showing chloroform trapped in position **B**.

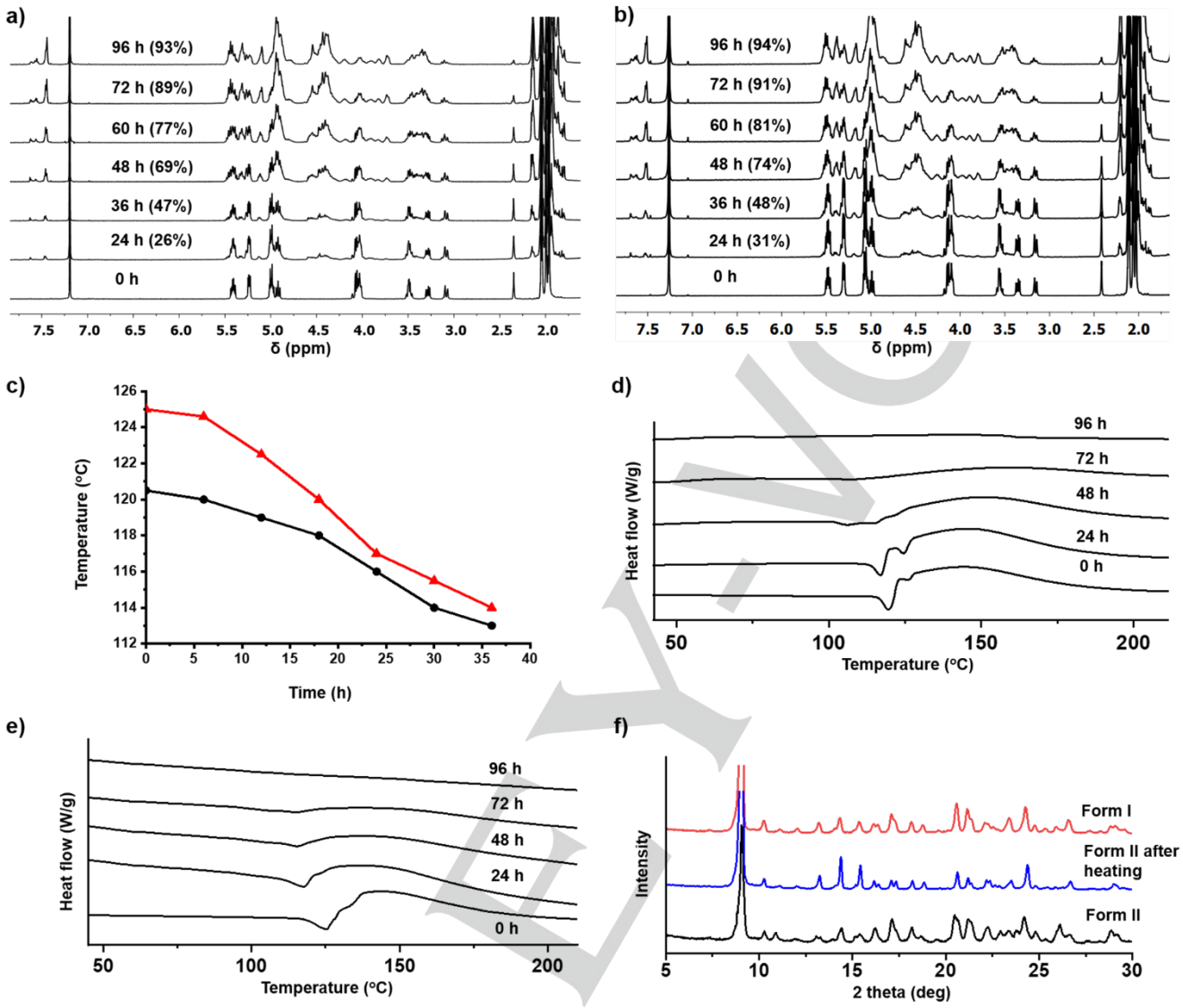

Figure 4. (a, b) Time-dependent ^{1}H NMR ($CDCl_3$) showing TAAC reaction in the crystals of form **I** (a) and form **II** (b). c) Decrease in the melting points of crystals of form **I** (black) and form **II** (red). (d, e) Time-dependent DSC during TAAC reaction of form **I** (d) and form **II** (e). f) Comparison of PXRD profiles of form **I**, form **II** and crystals of form **II** after heating at 75 °C.

Solid-state FTIR spectra of both form **I** and form **II** showed the azide stretching signal at 2108 cm^{-1}. Time-dependent FTIR spectroscopy revealed the gradual reduction in the intensity of this signal with time suggesting the gradual consumption of azide groups due to its participation in the cycloaddition reaction (Figure S4, SI). Furthermore, time-dependent DSC analyses of both form **I** and form **II**, showed gradual decrease in the intensity of exothermic peak due to the azide-alkyne cycloaddition reaction in the melt (Figure 4d and Figure 4e). This indicates the gradual depletion of free azide and alkyne groups with progress of time, which in turn implies the progress of azide-alkyne cycloaddition reaction in the crystals with time.

The complete conversion of both forms of the monomer **1** to the corresponding polymers took place within 96 h of heating (Figure 4). These solid-state reactions clearly followed sigmoidal kinetics as expected of a topochemical reaction (Figure S5, SI). The topochemical reaction of form **II** implies that, upon heating, chloroform escapes from the crystals providing free space for the propargyl group to reach position **B**. Accordingly, the TGA analysis of the form **II** crystals heated for 36 h at 90 °C showed no weight loss confirming the escape of chloroform (Figure S6, SI). Additionally, we have heated the crystals of form **II** at 75 °C for 24 h, by which time the chloroform molecules escaped completely as was evident from its ^{1}H NMR spectrum. The heated single crystal undergoes cracking along with the desolvation, which makes it unsuitable for SCXRD analysis. However, unit cell determination of a small piece of this cracked crystal revealed cell parameters identical to that of form-**I** (SI, section 19). In addition, the PXRD profile of these heated

crystals matched with that of form **I** implying the conversion of form **II** to form **I** upon loss of chloroform (Figure 4f).

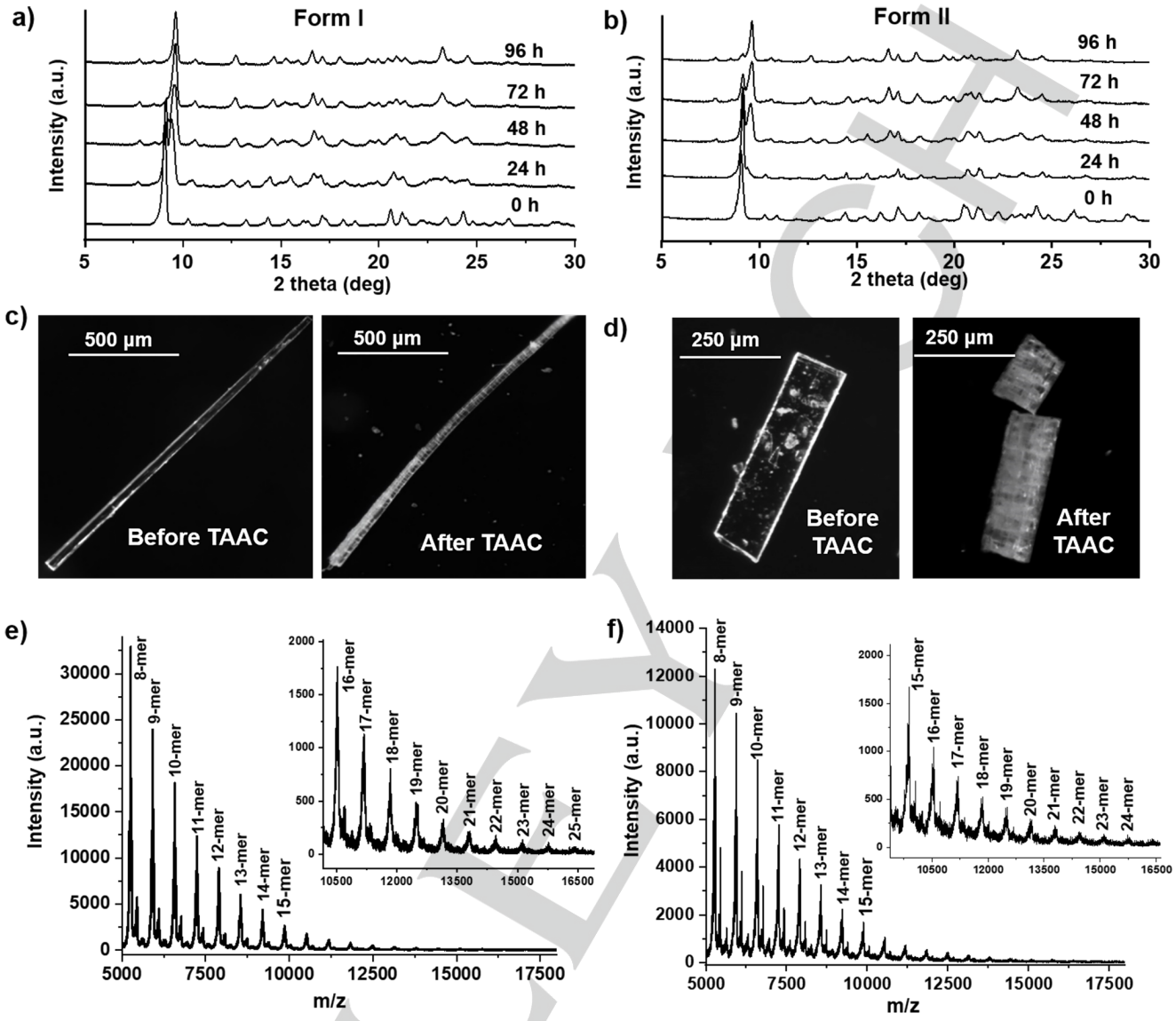

Figure 5. (a, b) Time-dependent PXRD profiles of form **I** (a) and form **II** (b). (c, d) Photographs of crystals before and after TAAC reaction of form **I** (c) and form **II** (d). (e, f) MALDI-TOF mass spectra of the polymers obtained from form **I** (e) and form **II** (f).

Furthermore, we probed the crystallinity of form **I** and form **II** during the course of the solid-state reaction by using time-dependent PXRD. The gradual conversion of monomer crystal to product crystal was evident from the gradual disappearance of peaks due to monomers (especially the major peak) and the concomittant appearance and growth of new peaks. We observed that at every stage of the reaction, the crystallinity was maintained in both the forms proving that the reactions happened under topochemical control (Figure 5a and Figure 5b) and are crystal-to-crystal reactions. However, crystals of both form **I** and form **II** developed cracks during the TAAC reaction and were unsuitable for the SCXRD analysis (Figure 5c and Figure 5d). However, the transparency of the crystals was unaffected. The excessive movement of the reactive groups to undergo TAAC reaction could be the reason for the cracking of crystals.

The polymers obtained were found to be soluble in several organic solvents such as chloroform, ethylacetate, acetone, DMF, DMSO and acetonitrile. MALDI-TOF analyses of the products obtained from form **I** and form **II** revealed the presence of large oligomers upto 25-mers (Figure 5e and Figure 5f). Gel permeation chromatography (GPC) analysis showed average molecular weights of 7,327 g/mol and 6,870 g/mol for polymers formed from form **I** and form **II** respectively (Figure S11, SI). The solid state CD spectrum of TAAC products (in KBr, Figure 6) obtained from both form **I** and form **II** showed the signatures for the presence of helicity. Solid-state CD spectra of polymers, obtained from form **I** and form **II,** showed negative cotton effect

at around 220 nm with shoulder at 215 nm. This implies that both the TAAC products adopt helical orientation in the solid-states. However, the random polymer made by dissolving the TAAC product in dichloromethane followed by evaporation showed no regular shape (Figure S13, SI). This clearly shows the importance of topochemical reaction in dictating the packing of the polymers. The polymers have been found to have helical nature in solution (Figure S14, SI).

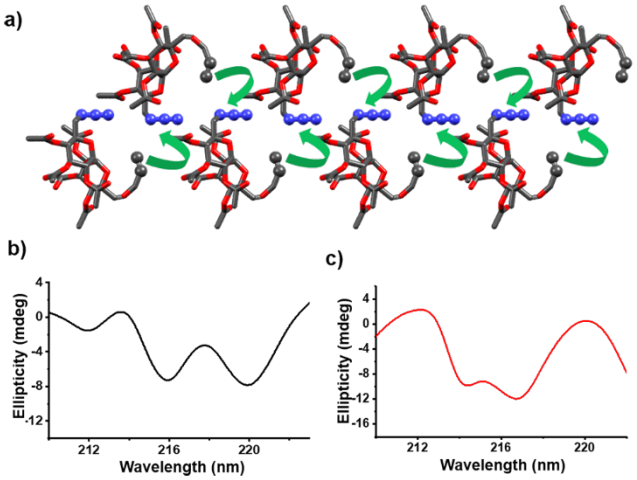

Figure 6. A) TAAC-reaction path showing the probable formation of helical polymers (hydrogen atoms are removed for clarity). (b, c) CD spectra (KBr pellet method) of the polymers obtained from form **I** (b) and form **II** (c) showing helical orientation in solid state.

Conclusion

In summary, we have synthesized an unsymmetrical α,α-trehalose derivative decorated with alkyne and azide as a monomer for TAAC polymerization. The monomer crystallized in two different forms *viz.*, form **I** and form **II** having similar packing except for the presence of chloroform in the crystal lattice in the latter. While Form **I** showed a reactive arrangement, the chloroform molecules blocked the attainment of reactive conformation in form **II**. However, upon heating, both the forms underwent TAAC polymerization to give helically ordered triazole-linked linear trehalose polymers. This is the first report on the polymerization of an unsymmetrically substituted trehalose monomer by topochemical polymerization. Solution-phase polymerization of sugar-based monomers poses several difficulties such as incomplete polymerization, necessity of metal catalysts which are difficult to remove, difficult purification, poor yield etc. This study demonstrates that topochemical reactions can be exploited for circumventing such problems associated with solution-phase synthesis.

Acknowledgements

KMS thank the Department of Science and Technology (DST) for a SwarnaJayanti Fellowship.

Keywords: Click reaction • Helical polymer • Polysaccharide • Topochemical reaction • Trehalose

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10.1002/anie.201914164

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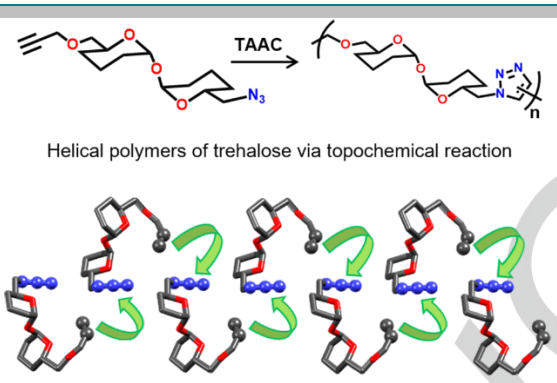
RESEARCH ARTICLE

Crystal-to-crystal synthesis of helical polymers of trehalose via topochemical azide-alkyne cycloaddition (TAAC) reaction of a monomer is discussed. This solvent-free, catalyst-free polymerization method that eliminates the tedious purification steps exemplifies the elegance of topochemical polymerization reaction over traditional solution-phase polymerization.



Helical polymers of trehalose via topochemical reaction

*Kutrapakam Hema, Rajesh G. Gonnade, Kana M. Sureshan**

Crystal-to-crystal synthesis of helically ordered polymers of trehalose *via* topochemical polymerization