Click Polymerization

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Topochemical Click Reaction: Spontaneous Self-Stitching of a Monosaccharide to Linear Oligomers through Lattice-Controlled Azide–Alkyne Cycloaddition**

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Dedicated to Professor Yutaka Watanabe

The copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) click reaction is unarguably the most simple, efficient, and general technique for linking two molecules with the highest regiospecificity and atom economy.[1] The power of CuAAC to make tailor-made functional materials or conjugates has not only revolutionized chemistry and other branches of science, such as life sciences and materials science, but also continues to offer practicable solutions to exciting problems in various disciplines of science.[2] Concerns regarding the toxicity of copper in biological systems motivated researchers to develop elegant catalyst-free azide–alkyne click reactions.[3] However, a perfectly green click system would be one which reacts regiospecifically without catalyst, solvent, or other modes of activation. We now report lattice-controlled spontaneous topochemical azide–alkyne click oligomerization of a sugar derivative with azide and alkyne functionalities to give linear polymers (pseudostarches) in a regiospecific manner in the crystal, which are otherwise difficult to synthesize by conventional solution-state chemistry. This report on a "perfectly green" click reaction in the crystal will pave the way for research towards other topochemical click reactions.

"Click chemistry" refers to high-yielding modular chemical reactions of wide scope and high regiospecificity, giving inoffensive byproducts under simple reaction conditions.[4] The copper(I)-catalyzed regiospecific 1,3-dipolar cycloaddition of a terminal alkyne and an azide to give the 1,4-substituted triazole in high yield[5] is recognized as "the cream of the crop" among click reactions. Ru-catalyzed azide–alkyne cycloaddition (RuAAC) is an important complementary method to CuAAC for regiospecific synthesis of 1,5-substituted triazoles.[6] Though azide and alkyne are spring-loaded, high-energy compounds and their cycloaddition is thermodynamically favorable with relatively large driving force ($\Delta G° \approx -61$ kcal mol^{-1}), they do not react spontaneously simply by mixing due to the high energy barrier (activation energy $\Delta G \approx +26$ kcal mol^{-1}).[7] Catalysts essentially facilitate the formation of a transition state either by reducing the activation energy through electronic reorganization and/or by bringing the reactants into close proximity. Encapsulation in a constrained space[8] or cavity can also facilitate proximity and transition-state-like arrangement. Entrapping azide and alkyne partners in a host cavity is known to turn an otherwise nonspecific uncatalyzed cycloaddition into a regiospecific one.[9] Similarly, co-localization of pharmacophore fragments with azide and alkyne functionalities in enzyme cavities has been exploited for target-guided synthesis of high affinity inhibitors of these enzymes.[10]

In our attempt to synthesize D-galactose-based triazole-linked cyclodextrin analogues, freshly prepared monomer **1** (Figure 1A, see Supporting Information Scheme S1) under standard CuAAC conditions gave a mixture of cyclodimer, cyclotrimer, cyclotetramer, and higher cyclic oligomers. However an aged crystalline sample of **1** did not give any of these products and was also found to be insoluble in the reaction solvent (THF) and other common organic solvents (chloroform, ethyl acetate, acetonitrile, toluene). Interestingly, a freshly prepared and crystallized sample and aged crystals were morphologically indistinguishable (Figure 1B and C). Comparison of a freshly made sample with an aged sample by TLC revealed that the aged sample is chemically inhomogeneous, containing several polar compounds (Figure 1D). Identical morphology but chemical inhomogeneity is suggestive of some spontaneous topochemical reaction, that is, chemical transformation controlled by the crystal lattice.[11]

Chromatographic separation of the aged sample (15 d at room temperature) gave dimer **2** (≈30%), trimer **3** (≈7%), and an inseparable mixture of higher oligomers (≈60%). HRMS and IR spectral analyses of major product **2** (see Supporting Information Figure S1 and Figure 1F) suggested that it is a linear dimer of **1** with at least one free alkyne and one free azide group. A detailed structural analysis by

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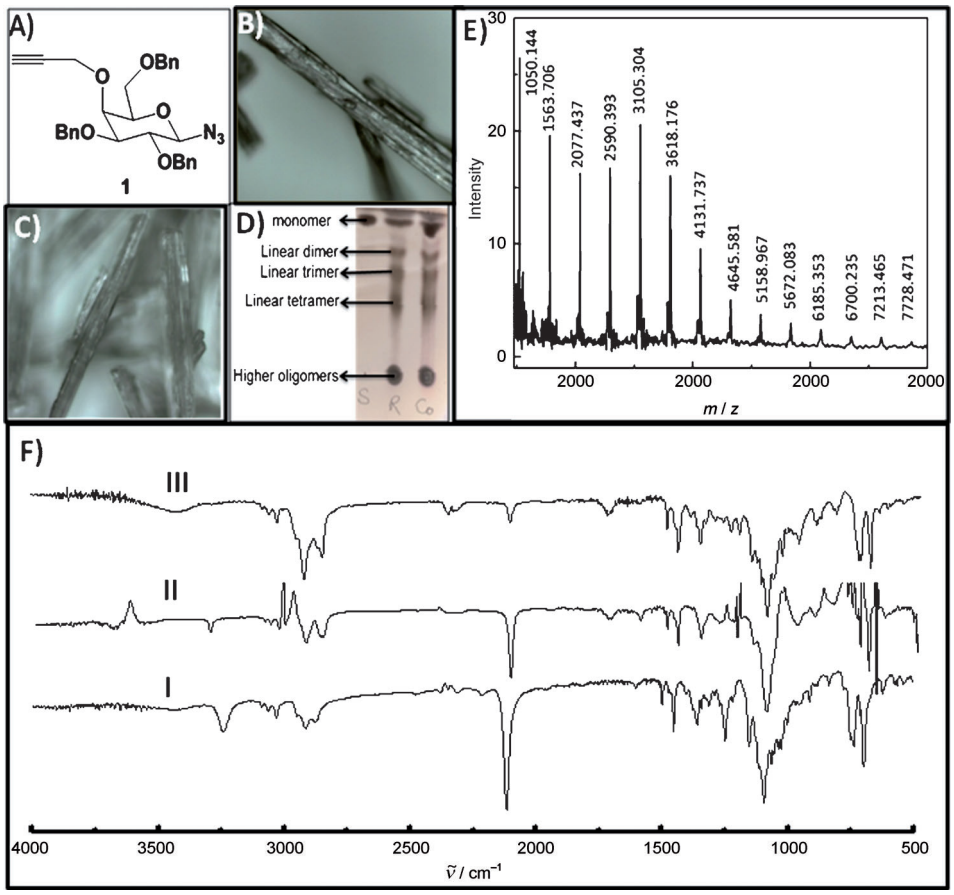

Figure 1. A) Structure of **1**. B) Photograph of a freshly made and crystallized sample of **1**. C) Photograph of crystals of **1** aged for 40 d. D) TLC comparison of freshly made and aged samples of **1**. E) MALDI-TOF spectrum of an aged crystalline sample of **1** showing *m/z* peaks due to dimer to pentadecamer. F) IR spectral comparison of freshly made **1** (I), linear dimer (II), and aged sample of **1** (III).

^{1}H NMR, ^{13}C NMR, DEPT, COSY, NOESY, HMQC, and HMBC spectroscopy revealed that **2** has a 1,5-triazolyl linkage, as shown in Figure 2 A (see Supporting Information Section 7 for details).

The MALDI-TOF MS of an aged crystalline sample (Figure 1 E) showed a mixture of oligomers ranging from dimer to pentadecamer, suggestive of click polymerization in the crystalline state. Despite the presence of many oligomers in an aged crystalline sample, its ^{1}H NMR spectrum was surprisingly simple, clear, and well resolved (see Supporting Information Figure S7). This suggests that the triazole linkage is isomerically uniform (only 1,5 isomer) in all oligomers and at each triazolyl unit in a given oligomer. This is due to highly regiospecific cycloaddition controlled by the crystal lattice. A similar uniform pattern was observed when a fresh sample of **1** was heated at 70 °C (below its melting point) for 24 h (see Supporting Information Figure S8). However, sudden melting of a pure sample of **1** followed by continued heating of the melt resulted in formation of heterogeneous oligomers showing very broad and unresolved peaks (see Supporting Information Figure S9) in the ^{1}H NMR spectrum. This could be due to the uncontrolled and nonspecific thermal cycloaddition in the molten state giving rise to heterogeneous oligomers (both cyclic and linear oligomers) with nonuniform (both 1,4- and 1,5-) triazole linkages.

Interestingly solutions of **1** in common organic solvents (DMF, THF, DCM, $CHCl_3$, ethyl acetate) were stable for months, and chemically homogeneous **1** could be obtained by evaporation. Usually the crystalline state is considered to be more stable, and crystallization is a method of purification. However, crystalline **1** is unstable and hence reacts spontaneously in a topochemical manner to give products in the crystal. This suggests that the reacting alkyne and azide groups are probably trapped in a local "transition-state-like" arrangement in the crystal, which facilitates regiospecific cycloaddition.

Interestingly, the Cu-catalyzed solution-phase reaction of **1** gives cyclic products with 1,4-triazolyl linkage, while the uncatalyzed spontaneous reaction in the crystal gives linear oligomers with 1,5-triazolyl linkage in a highly regiospecific manner (Figure 2). Though several triazole-linked cyclodextrin analogues have been synthesized by CuAAC reaction of monomers in solution, formation of linear polymer was not reported in any of these cases.[12] Formation of linear oligomers in the crystals of **1** suggests that the monomers are arranged in head-to-tail fashion in the crystal and, since the molecular motion is restricted in the crystal, they polymerize linearly in a topochemical manner to give linear polymers (Figure 2 B).

Differential scanning calorimetric (DSC) analysis of a freshly crystallized sample of **1** showed a melting point of 85.4 °C, in accordance with that determined with a melting point apparatus. Continued heating of this molten sample up to 250 °C resulted in a broad exothermic peak between 100 and 220 °C, suggestive of the uncontrolled thermal cycloaddition reaction in the melt (Figure 3 A). This explains the very broad and unresolved signals in the ^{1}H NMR spectrum of a sample kept at a temperature above its melting point (vide supra). The DSC analyses of crystalline samples of **1** kept at room temperature for different time periods revealed gradual reaction in the crystals. As time progressed the melting point shifted to lower temperatures, presumably due to depression of the melting point by the presence of increasing amounts of oligomers. FTIR monitoring of this topochemical reaction

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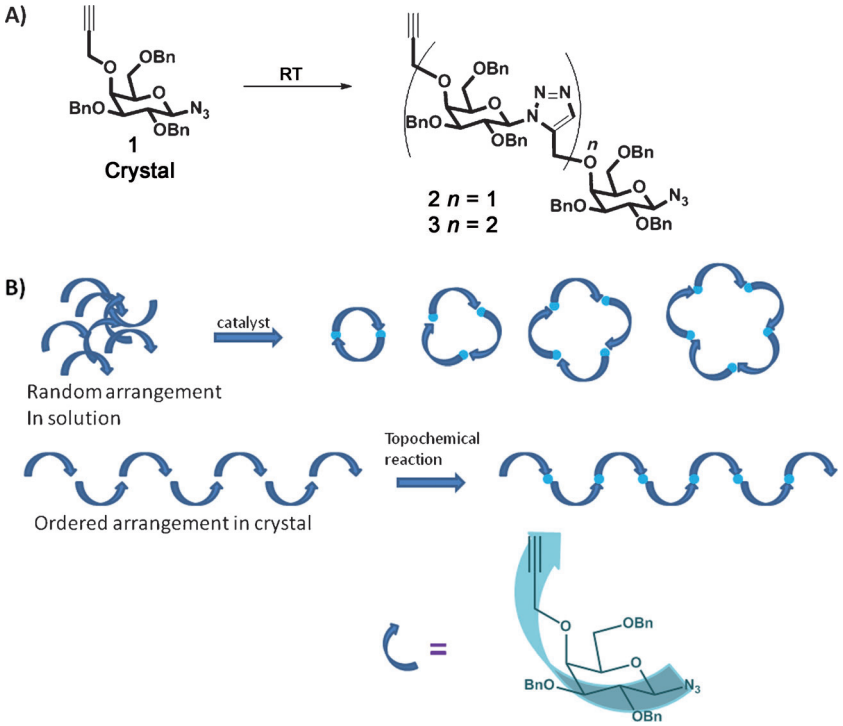

Figure 2. A) Spontaneous regiospecific oligomerization of **1** in the crystal. B) Schematic representation of the reactions in solution and in the crystal.

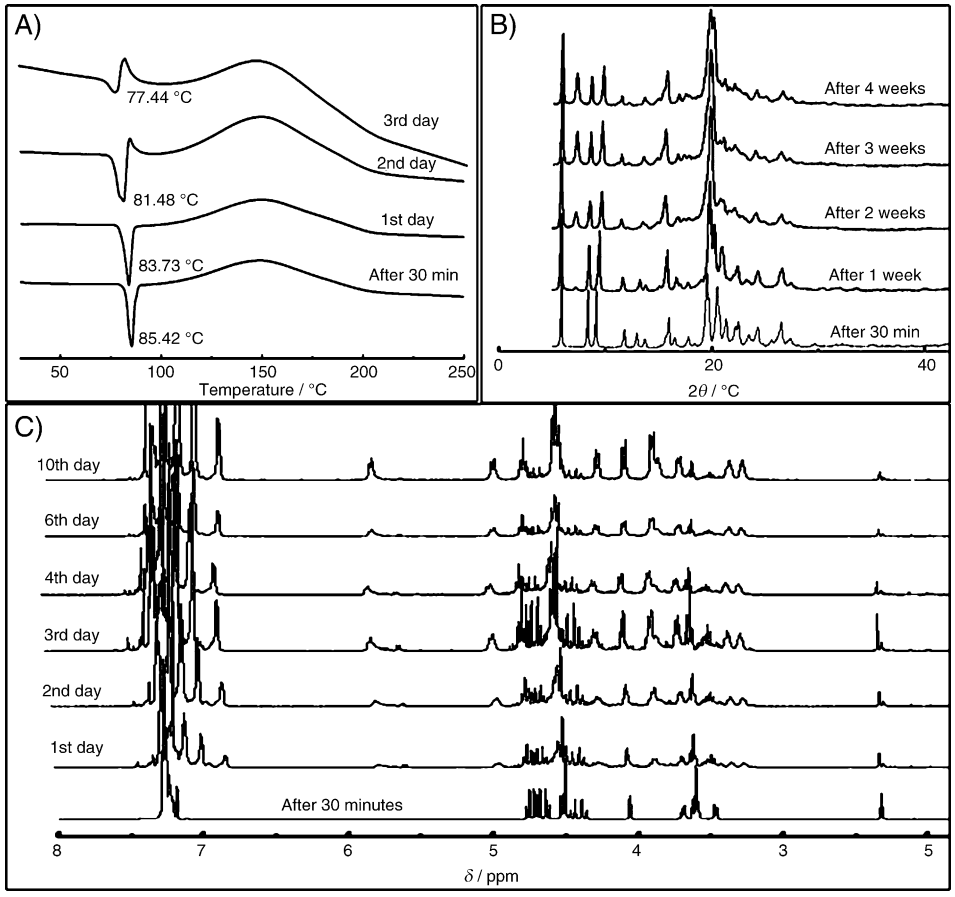

Figure 3. A) DSC plot of **1** at 30 min (I), 24 h (II), 48 h (III), and 78 h (IV). B) PXRD monitoring of the topochemical reaction at room temperature, showing sharp peaks even after the reaction. C) ^{1}H NMR monitoring of topochemical click reaction at 50 °C.

showed gradual disappearance of alkynic hydrogen and azide signals with time, as expected.

To establish the topochemical nature of this reaction, it was followed by powder (P) XRD at regular intervals (Figure 3 B and Supporting Information Section 10). A ground crystalline sample of **1** was made and kept at room temperature, and its PXRD pattern recorded at regular intervals for four weeks, by which time most of the starting material was converted to oligomers. Well-resolved sharp peaks were seen throughout this time period with gradual appearance of new peaks and disappearance/shift of some of the peaks of the starting material. This confirms preservation of the crystalline state even after the reaction, an important criterion for topochemical reaction.

To correlate the solid-state reactivity with the molecular arrangement, crystal structure analysis of monomer **1** was carried out (Figure 4). Molecules in crystals of **1** assemble in a head-to-tail fashion to form a helix around the crystallographic two-fold screw axis (*b* axis) through weak C–H···O, C–H···N, and C–H···π hydrogen bonds. This assembly brings the reactive alkyne and azide groups of adjacent molecules in a helix into close proximity with a preorganized transition-state-like geometry in a cavity in the crystal matrix (Figure 4 A), as anticipated. Interestingly, both of these motifs are held in this parallel orientation by two weak hydrogen bonds (one CH···N and one CH···O) from another neighboring molecule of an adjacent helix (Figure 4 B). While C6H6A···N3A holds the azide, C9H9···O6 holds the alkyne group. These weak hydrogen bonds connect helices together to provide a well-guided "reaction channel" throughout the crystal lattice. The involvement of these two weak hydrogen bonds in driving the reaction by preorganizing the two reacting groups tightly in a transition-state-like orientation is very interesting. The approach of the terminal alkyne carbon atom to the terminal azide nitrogen atom in the

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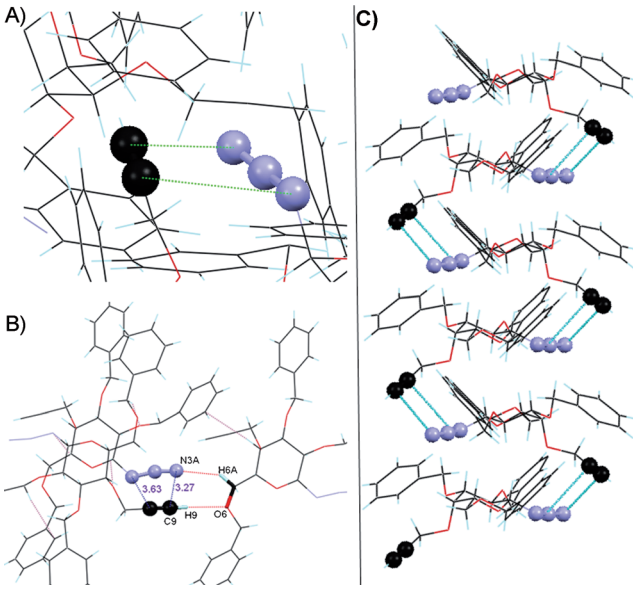

Figure 4. A) Crystal packing of **1** showing alkyne and azide motifs located in a cavity. B) Stabilization of the transition-state-like arrangement in the crystal by weak hydrogen bonds. C) Crystal packing showing infinite head-to-tail assembly of monomers along the screw axis with properly oriented azide and alkyne motifs for spontaneous reaction.

crystal explains the regiospecific formation of the 1,5 isomer. As the monomers are arranged in head-to-tail fashion along the helical axis (Figure 4C), the reaction proceeds along this axis and leads to formation of linear oligomers.

We monitored the kinetics of this topochemical reaction using ^{1}H NMR spectroscopy. A bulk sample of crystals was kept at room temperature, and small fractions were withdrawn at regular intervals and analyzed by ^{1}H NMR spectroscopy after dissolving in $CDCl_3$ (Figure 3C). From the first day onwards, oligomerization was observed, as judged from a gradual increase in intensity of triazole-connected anomeric protons and a concomitant decrease in intensity of alkynyl protons. The reaction followed sigmoidal kinetics at room temperature, as expected of a topochemical reaction. Similar reaction pattern and kinetics were observed when the reaction was carried out at higher or lower temperature. Interestingly, this topochemical click reaction is even facile at −10 °C, albeit with a reduced rate.

In conclusion, we have reported a spontaneous regiospecific topochemical azide–alkyne cycloaddition of a monosaccharide analogue to provide 1,5-triazolyl-linked linear oligosaccharide analogues, which are otherwise difficult to synthesize by conventional solution-state chemistry due to preferential formation of cyclic oligomers. The crystal lattice forms a reaction nanovessel, wherein the reactant motifs (alkyne and azide) are entrapped; their transition-state-like arrangement facilitates the reaction, their relative orientation in the nanovessel dictates the regiospecificity, and the crystal packing dictates the linearity. Unarguably, click chemistry has received enormous attention from chemistry and other fields of science ranging from material science to biology due to its simple and practical utility for various applications. Though the philosophy of click chemistry overlaps with green chemistry principles, a perfectly green click reaction will be the one that avoids the use of catalysts, solvents, or other means of activation. In this context, a topochemical click reaction is even more attractive as it is also simple and proceeds spontaneously. We hope this report will allure researchers to explore design of topochemical click reactions.

Experimental Section

Crystal data of **1**: CCDC 860868 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. $C_{30}H_{31}N_3O_5$, $M = 513.58$, colorless needle, $0.19 \times 0.04 \times 0.02$ mm, monoclinic, space group $P2_1$, $a = 10.514(5)$, $b = 8.482(4)$, $c = 15.238(7)$ Å, $\beta = 101.595(8)°$, $V = 1331.1(10)$ Å^3, $Z = 2$, $T = 100(2)$ K, $2\theta_{max} = 50.00°$, $\rho_{calcd} = 1.281$ g cm^{-3}, $F(000) = 544$, $\mu = 0.088$ mm^{-1}, 9356 reflections collected, 4580 unique reflections ($R_{int} = 0.0356$), multiscan absorption correction, $T_{min} = 0.983$, $T_{max} = 0.998$, 394 parameters, 184 restraints, GoF = 1.147, $R1 = 0.0938$, $wR2 = 0.2102$, R indices based on 3851 reflections with $I > 2\sigma(I)$ (refinement on F^2), $\Delta\rho_{max} = 0.48$, $\Delta\rho_{min} = -0.27$ e Å^{-3}.

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