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A Spontaneous Single-Crystal-to-Single-Crystal Polymorphic Transition Involving Major Packing Changes

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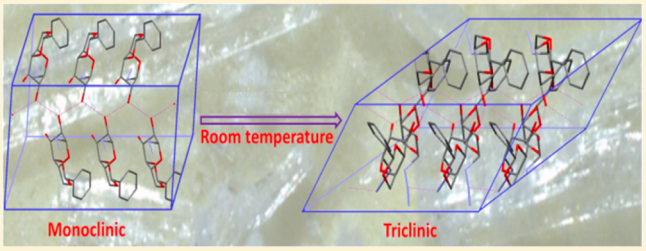
Supporting Information

ABSTRACT: 4,6-*O*-Benzylidene-α-D-galactosyl azide crystallizes into two morphologically distinct polymorphs depending on the solvent. While the α form appeared as thick rods and crystallized in $P2_1$ space group (monoclinic) with a single molecule in the asymmetric unit, the β form appeared as thin fibers and crystallized in *P*1 space group (triclinic) with six molecules in the asymmetric unit. Both the polymorphs appeared to melt at the same temperature. Differential scanning calorimetry analysis revealed that polymorph α irreversibly undergoes endothermic transition to polymorph β much before its melting point, which accounts for their apparently same melting points. Variable temperature powder X-ray diffraction (PXRD) experiments provided additional proof for the polymorphic transition. Single-crystal XRD analyses revealed that α to β transition occurs in a single-crystal-to-single-crystal (SCSC) fashion not only under thermal activation but also spontaneously at room temperature. The SCSC nature of this transition is surprising in light of the large structural differences between these polymorphs. Polarized light microscopy experiments not only proved the SCSC nature of the transition but also suggested nucleation and growth mechanism for the transition.



INTRODUCTION

Polymorphism, the phenomenon of existence of a particular compound in two or more crystalline states, is of great scientific[1] and commercial[2] interest. Polymorphism arises from different conformation or packing arrangement in the crystal lattice.[3] Though molecules in crystals have limited mobility, often part or whole molecules undergo conformational change or slight translational motion spontaneously or under activation by heat, pressure, light, and so forth. Such motion leads to either chemical reactions within the crystal (topochemical reactions[4]) or rearrangement to another polymorph of the same compound (polymorphic transition[5]). Polymorphic transitions occur mainly through (i) reconstructive mechanism (nucleation and crystal growth) or (ii) topotactic/epitactic mechanism.[6] Most polymorphic transitions occur via reconstructive mechanism leading to the disruption of packing continuity, rendering the resulting polymorphs unsuitable for single crystal XRD (SCXRD) analysis.[7] Single-crystal-to-single-crystal (SCSC) polymorphic transitions[5a,b,8] occur mainly via topotactic or epitactic mechanism, and usually in such cases both the polymorphs (parent and daughter crystals) have close structural relationship.[9] SCSC polymorphic transition between two different polymorphs having large structural difference is one of the rarest phenomena.[8m,10] Herein, we report a spontaneous SCSC polymorphic transition involving large packing changes from a $Z' = 1$ polymorph to $Z' = 6$ polymorph.

RESULTS AND DISCUSSION

During our ongoing project of synthesizing various sugar containing triazoles, we have observed that 4,6-*O*-benzylidene-α-D-galactosyl azide (**1**, Figure 1A) crystallizes in different solvents to morphologically distinct crystals. For instance, crystals formed from dichloromethane (DCM) solution

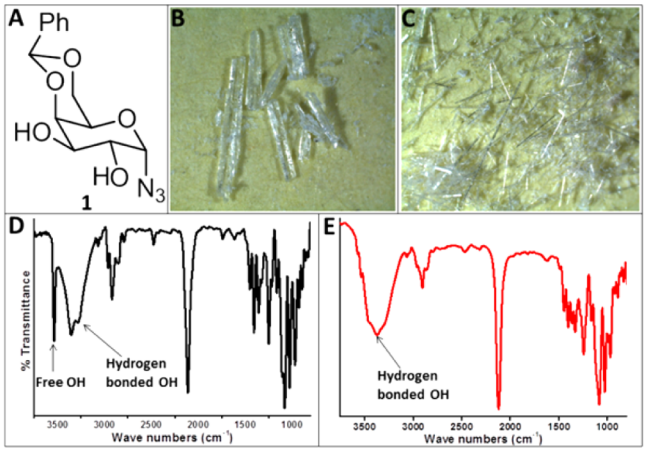


Figure 1. Chemical structure of compound **1** (A). Photographs of polymorphs α (B) and β (C). FTIR spectra of polymorphs α (D) and β (E).

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showed thick rodlike morphology (form α, Figure 1B), whereas the crystals obtained from benzene or ethyl acetate showed thin fibrillar morphology (form β, Figure 1C). NMR characterization and combustion analyses of these crystals revealed the sample homogeneity and absence of any solvent in the crystal lattice of both forms, suggesting that these two forms are polymorphs of **1**. Interestingly, Fourier transform infrared (FTIR) spectra of the two crystal forms were very distinct. The α form showed two distinct OH stretching bands: a broad signal at frequency 3084−3493 cm^{-1} suggestive of the presence of hydrogen-bonded OH groups and a sharp signal at 3540 cm^{-1} indicative of the presence of non-hydrogen-bonded OH groups too (Figure 1D). The β form showed only a broad OH stretching band at frequency 3023−3633 cm^{-1}, suggesting that only hydrogen-bonded OHs are present in this form (Figure 1E). Thus, FTIR studies suggest that in α form only one of the two hydroxyl groups is involved in hydrogen bonding and in β form both the hydroxyl groups are involved in hydrogen bonding.

Single crystal XRD (SCXRD) analysis of both forms revealed they are polymorphs of **1**. While the α form crystallized in the space group $P2_1$ (monoclinic) with a single molecule in the asymmetric unit (Figure 2A), the β form crystallized in the space group $P1$ (triclinic) with six molecules (conformers A−F) in the asymmetric unit (Figure 2B and Table S1 in the Supporting Information). There are significant differences in the H-bonding patterns of these two polymorphs. As expected from the IR data, only one of the two hydroxyl groups is involved in hydrogen bonding (O2−H2′···O2) in the crystal structure of polymorph α forming a hydrogen bonded zigzag chain along the "b" direction (Figure 2C). The other hydroxyl group is involved in two relatively weaker interactions: an OH···π hydrogen bond and a C−H···O hydrogen bond (Table S2 in the Supporting Information). In polymorph β, all the hydroxyl groups of all six conformers are involved in intermolecular hydrogen bonding, as was expected based on the IR studies, forming interlinked hydrogen bonded chains along the "a" direction (Figure 2D). In addition to these strong hydrogen bonds, the polymorph β is further stabilized by several C−H···O, CH···N, and CH···π interactions (Table S3 in the Supporting Information). Hirshfeld analysis also gave additional proof for the presence of these interactions (Supporting Information).[11] It is apparent from the crystal structures that the β form having more hydrogen bonding interactions is more stable than the α form.

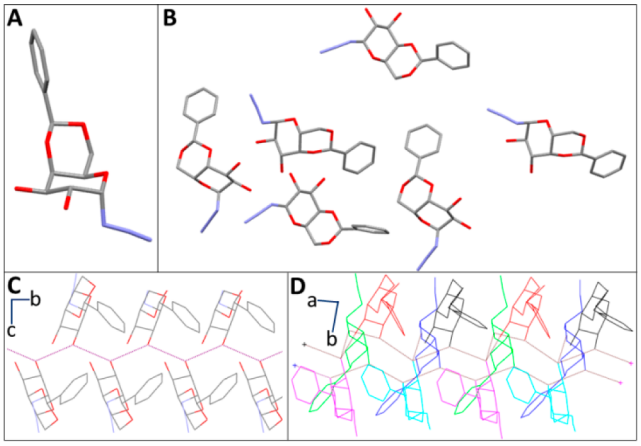

Figure 2. Asymmetric unit of polymorphs α (A) and β (B). Hydrogen atoms are omitted for clarity. Packing arrangement of α viewed along the "a" direction (C) and β viewed along the "c" direction. Six conformers are color-coded as red, green, black, pink, cyan, and blue (D).

Though morphologically and structurally different, both the polymorphs showed apparently same melting point (T_m = 165 °C). However, the differential scanning calorimetry (DSC) curve of the α form showed an endothermic peak at 140 °C (ΔH = 2.21 kJ/mol), well before its melting point, suggestive of some chemical or physical change in the solid state (Figure 3A). The TGA profile of the α form did not show any weight loss at 140 °C, ruling out any possible loss of its fragments (Figure 3B). The ^{1}H NMR spectrum of a sample of the α form heated to 145 °C was indistinguishable from the ^{1}H NMR spectrum of a fresh sample of **1**, ruling out the possibility of any chemical change being responsible for the endothermic peak at 140 °C (Figure S16 in the Supporting Information). These results suggest that some possible phase change occurs prior to the melting, possibly a polymorphic transition. However, no

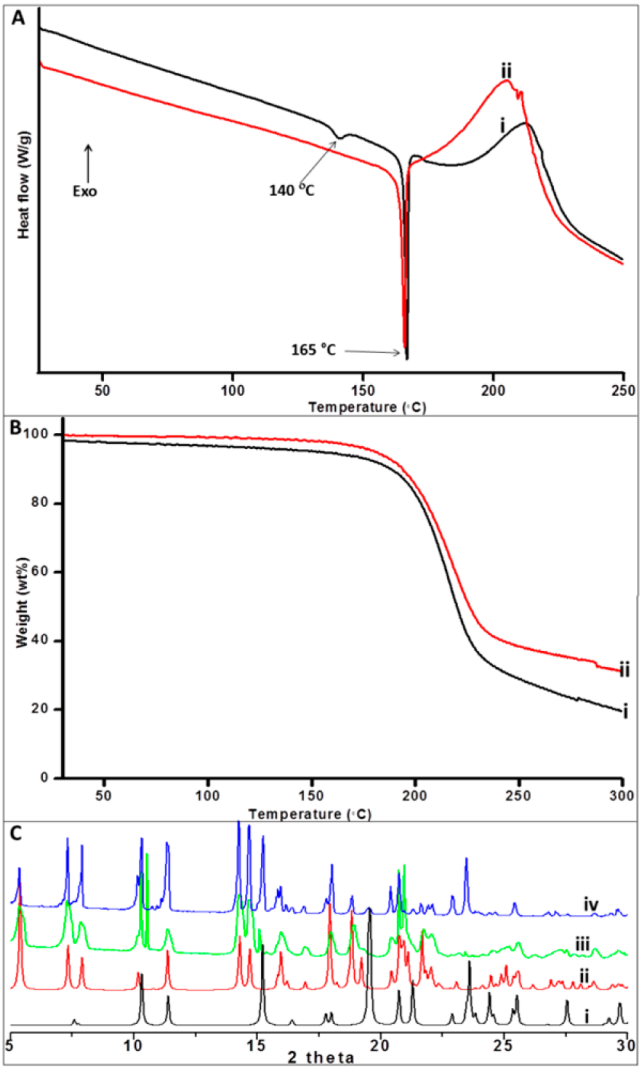

Figure 3. (A) DSC curves of polymorphs α (i) and β (ii). (B) TGA curves of polymorphs α (i) and β (ii). (C) Comparison of PXRD patterns of polymorph α (i), polymorph β (ii), form α preheated to 140 °C (iii), and polymorph α aged at room temperature (iv).

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polymorphic transition was observed when the preheated (to 145 °C) crystals of the α form were cooled to −70 °C (Figure S17 in the Supporting Information) or even after keeping the preheated crystals at liquid nitrogen temperature for 4 h, suggesting that the transition is irreversible.

Powder XRD (PXRD) of both the polymorphs were very distinct as anticipated (Figure 3C, i and ii). Interestingly, the polymorph α upon heating transforms to the polymorph β as evident from the PXRD pattern of a sample of polymorph α heated to 140 °C (Figure 3C, iii). FTIR spectrum of this heated sample was also indistinguishable from that of polymorph β, suggesting that the non-hydrogen-bonded OH group become hydrogen-bonded after transition (Figure S18 in the Supporting Information). This also suggests that a more stable form is being formed after the transition. Variable temperature PXRD of polymorph α also suggested its transition to polymorph β (Figure 4A). In light of this polymorphic transition before the melting point, it is not surprising that both the polymorphs showed apparently same melting point.

The crystals of polymorph α heated to 145 °C, which underwent transition to polymorph β, were transparent and morphologically indistinguishable from fresh unheated crystals. This suggests that the polymorphic transition from polymorph α to polymorph β could be a SCSC transition. In order to probe this, we have carried out SCXRD analysis of same crystal of polymorph α before and after the transition. We have mounted a single crystal of polymorph α on a glass fiber and collected its X-ray data (and solved as polymorph α) and then took it out of the goniometer along with the glass fiber and heated it in a test tube kept at a constant temperature bath (140 °C) for 5 min. Again, the X-ray data was collected for this heated sample and its structure solved, which showed that the crystal had undergone polymorphic transition to the β form. This clearly supports that it is a SCSC transition (Figure S20 in the Supporting Information). In order to understand the structural changes during transition from polymorph α to β, we have compared their crystal packing.

From an analysis of crystal packing, it is clear that polymorph β has a twofold modulation arising from minor conformational changes; A/A′, B/B′, and C/C′ are nearly superimposable pairs (Figure 4D). For a comparison of packing, this can be simplified as three conformers, A, B, and C (Figure 4E). Figure 4F shows a comparison of packing of polymorph α viewed along the "b" direction and polymorph β along the "a" direction. In polymorph α, molecules in the alternate columns are color coded as red and blue and the molecules below the blue are coded in green for convenience. Due to the zigzag hydrogen bonded assembly along the "b" direction, molecules in alternate columns fall on the same plane (red molecules on any two different columns) and molecules on adjacent columns are out of plane (red and blue molecules on adjacent columns) as shown in Figure 4G. The representative A, B, and C conformers of polymorph β are color coded as green, blue, and red, respectively. It is clear that both green and blue molecules of α, which are H-bonded to red molecules, have to undergo considerable rotation (green by 55° clockwise about the "a" axis, and blue by 90° clockwise about "a" and 180° clockwise about "c") to transform into β (Figure 4F).

It is surprising that, despite having major structural changes, the polymorphic transition is happening in an SCSC fashion. Rarely occurring SCSC transitions between polymorphs having large structural difference[8m,10] are known to occur via nucleation and growth mechanism and can easily be distinguished by polarized light microscopy. In order to see whether the transition from α to β occurs via such a mechanism, the crystals of polymorph α were heated on a

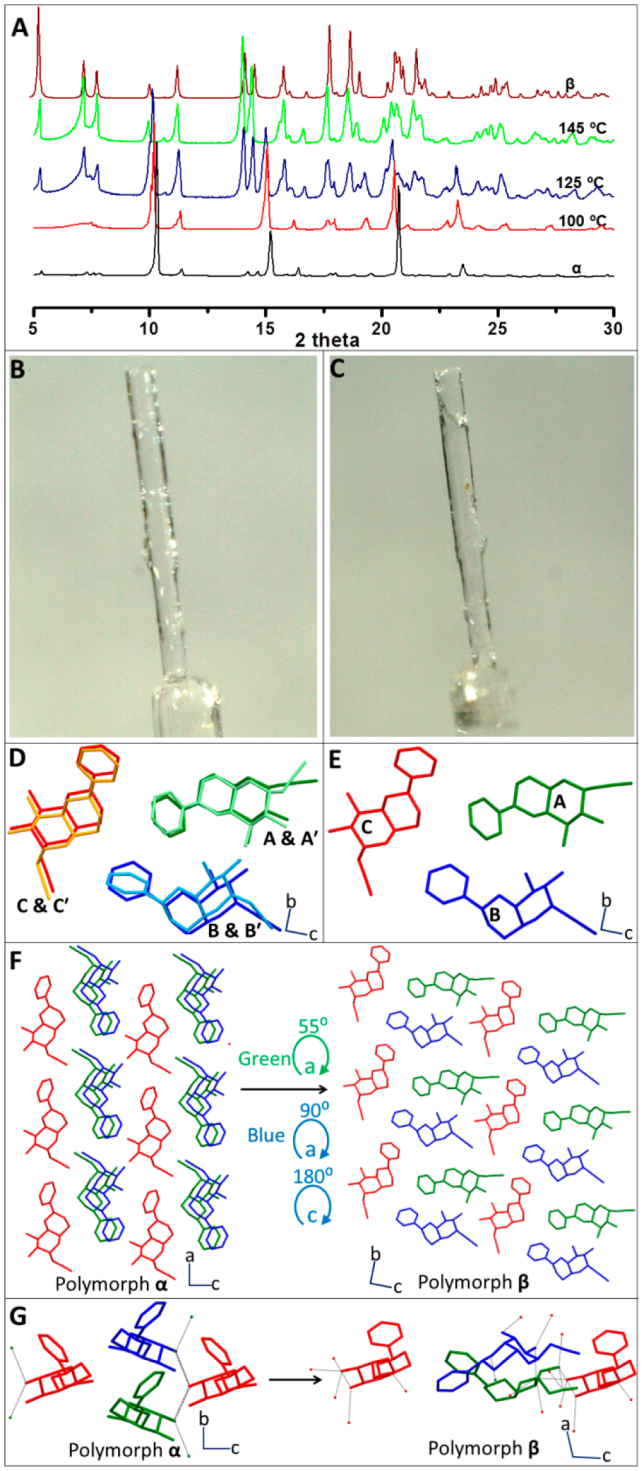

Figure 4. (A) Variable temperature PXRD patterns of polymorph α. Photographs of single crystal of polymorph α (B) before and (C) after heating at 140 °C for 5 min. (D) Twofold modulation of polymorph β viewed along the "a" direction. (E) Three representative conformers of polymorph β in the "bc" plane. (F) Comparison of packing of polymorphs α ("ac" plane) and β ("bc" plane). (G) Comparison of packing arrangements of polymorph α ("bc" plane) with that of polymorph β ("ac" plane) showing the gain in number of hydrogen bonds after transition.

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hot-stage polarizing microscope until melting. The color of the birefringence of the crystal changed during transition, and the growth of the new phase could be seen from a nucleation point (Figure 5A). At the melting point (165 °C), the interference

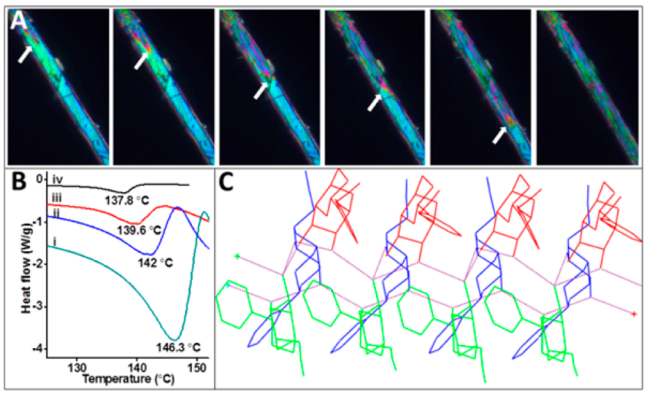

Figure 5. (A) Hot-stage polarizing microscopy images of polymorph α showing nucleation and growth. (B) DSC profiles of polymorph α carried out at different heating rates of 25 °C/min (i), 15 °C/min (ii), 10 °C/min (iii), and 5 °C/min (iv). (C) Crystal packing arrangement of an aged sample (kept at rt for 2 months) of polymorph α.

pattern disappeared as expected (Supporting Information). Thus, the hot-stage polarizing microscopy (HSM) experiments provide additional proof for the SCSC nature of the transition and for the nucleation and growth (reconstructive) mechanism.

According to the heat of transition rule,[12] if endothermic phase transition is involved, the polymorphs are related enantiotropically and such polymorphic transitions are reversible and their thermodynamic transition temperature lies below the experimental transition temperature. There are cases where the enantiotropes are not reversible because of kinetic factors,[13] and in such cases, the experimental transition temperature varies with the heating rate.[14] The endothermic and unidirectional polymorphic transition from α to β form suggests that this is a kinetically irreversible enantiotropic transition. DSC analyses with different scan rates revealed that the transition temperature varied with the heating rate as anticipated (Figure 5B), proving that it is indeed a case of kinetically irreversible enantiotropic transition.

Interestingly, we have observed a slow conversion of polymorph α into polymorph β even at ambient temperature. The PXRD pattern of an aged sample of polymorph α (stored at room temperature for 3 weeks) showed the presence of both the polymorphs, α and β (Figure 3C:iv). Single-crystal X-ray analysis of an aged crystal of polymorph α kept at rt for 1 month revealed that it underwent spontaneous SCSC transformation to polymorph β (Figure 5C). The spontaneous formation of polymorph β from polymorph α at room temperature suggests that the actual transition temperature must be below room temperature. It is clear that polymorph β ($Z' = 6$) is thermodynamically more stable than polymorph α ($Z' = 1$). It is noteworthy that the high Z' polymorphs are generally considered as thermodynamically less stable or metastable kinetic polymorphs.[15] A Cambridge Structural Database (CSD) analysis of polymorphic pairs with different Z' revealed that the low Z' forms are stable in the majority of the cases (Supporting Information).[16] High Z' structures and the factors that determine their formation are of current interest.[17]

To understand the reason for the spontaneity, we have calculated the thermodynamic parameters of the transition at ambient temperature (30 °C) from solubility experiments as reported (Supporting Information).[18] We have observed that the polymorph β is the less soluble polymorph among the two. It is known that, at any given temperature, the less soluble polymorph has lower free energy.[19] ΔG for the transition from polymorph α to polymorph β should be negative and therefore expected to occur at ambient temperature. As expected, the experimental results gave a negative value for the free energy change of the transition ($\Delta G = -0.459$ kJ mol^{-1} at room temperature), justifying the spontaneity of polymorphic transition. However, the ΔH of the transition ($\Delta H = 1.879$ kJmol^{-1}) was found to be positive even at room temperature. This suggests that the positive $T\Delta S$ term offsets the positive ΔH term to make the process spontaneous.

CONCLUSION

In summary, we report a pair of polymorphs of a sugar derived molecule, obtainable by crystallization from different solvents. The metastable polymorph irreversibly transforms into the thermodynamically stable polymorph not only under thermal activation but also spontaneously at ambient temperature. Notably, this transition happens in an SCSC fashion even though they do not have very similar orientation relationship. SCSC polymorphic transitions usually occur when both the polymorphs have close structural relationship. Polymorphic transition between polymorphs having large structural differences usually proceeds through nucleation and growth, leading to the loss of single-crystalline nature. Polarized light microscopy studies show that this SCSC polymorphic transition from polymorph α to polymorph β occurs through nucleation and crystal growth. To the best of our knowledge, this is the first report on the spontaneous SCSC polymorphic transition from a $Z' = 1$ structure to a $Z' = 6$ structure which are not closely related in their packing. Our results suggest that polymorphic transitions involving large structural changes can occur in an SCSC fashion.

ASSOCIATED CONTENT

Supporting Information

Details of synthesis and characterization of **1**, DSC, PXRD, single-crystal XRD, IR, NMR, and thermodynamic parameters determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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