

Topochemical Transketalization Reaction Driven by Hydrogen Bonding

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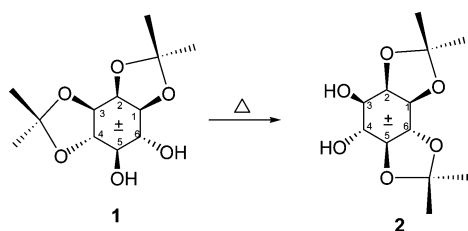
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Topochemical reactions, the solid-state reactions controlled by lattice interactions, have been a subject of scientific curiosity and extensive investigations.¹ As the molecular mobility is restricted in the crystalline state, bimolecular topochemical reactions depend on the proximity and proper orientation of the reacting groups in the crystal lattice. Since such a reaction depends on how a molecule crystallizes rather than its mere chemical structure, the prediction of a bimolecular topochemical reaction on the basis of the chemical structure is rather an unattained goal. Most of the known non-unimolecular² topochemical reactions involve cycloaddition³ or polymerization⁴ of the double-bond-containing molecules, presumably due to the higher chance of their parallel orientation (via π - π stacking) favorable for the reaction. On the contrary, other types of reactions observed in the crystalline state are very rare. A few S_N2 reactions,⁵ racemization,⁶ transesterification,⁷ and oligopeptide formation from the *N*-carboxyanhydride of an α -amino acid⁸ are some of the known examples in this category. We herein report the first topochemical transketalization reaction of a *myo*-inositol derivative.

During our ongoing program to synthesize different phospho-inositols, we required (\pm)-1,2:3,4-di-*O*-isopropylidene-*myo*-inositol, **1** (Scheme 1). While characterizing the diol **1**, it was observed that

Scheme 1



the crystals of **1** failed to show a consistent melting point and it varied greatly from trial to trial. For instance, crystals of **1** showed melting points of 137, 145, 149, and 155 °C in four different trials. Surprisingly, other analytical methods, including combustion analysis and mass spectral analysis, were consistent with the diketal **1**'s structure and sample homogeneity. On the basis of the fact that powders of a single crystal showed different melting points with different trials, any polymorphism being responsible for the observed anomaly was ruled out. Why, then, does it not show a sharp and consistent melting point, a criterion for purity? Is there any decomposition occurring while heating? To address this issue, ¹H NMR spectra of the sample before and after melting were compared. Surprisingly, the ¹H NMR spectrum of the molten sample revealed that it contains a mixture of **1** and (\pm)-1,2:5,6-di-*O*-isopropylidene-*myo*-inositol, **2**.⁹ Hence, it was inferred that isomerization rather than decomposition is responsible for the anomalous behavior. The variation of the melting point can be rationalized assuming the formation of different amount of **2** in different trials, presumably due to different rates and durations of heating. A systematic study revealed that the reaction is very fast and adopts

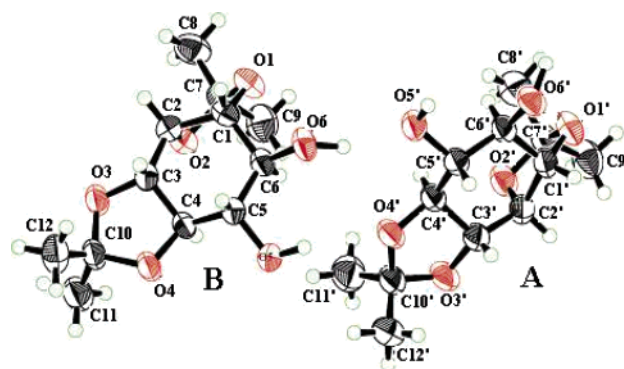


Figure 1. ORTEP diagram of an asymmetric unit of **1**.

a sigmoidal kinetics (see Supporting Information) with an induction period of about 6 min. Thus, just heating the crystals of **1** at 110 °C for 10 min effects a 92–95% isomerization. It is interesting not only because this is the first solid-state transketalization reaction but also because transketalization occurs without any acidic catalyst. The melting point determination as a function of reaction time revealed that the minimum temperature at which the system melts (partially) is 135 °C. That this ketal migration occurs much before the melting point suggests that it could be a topochemical reaction.¹⁰ DSC analysis of **1** further revealed that no phase transition occurs before the reaction temperature. Equilibrating DMF or benzene solution of **1** with PTSA resulted in the formation of a mixture of four ketals. The high degree of selectivity in the solid-state reaction is attributable to its topochemical nature. Out of curiosity, the X-ray crystal structure analysis of **1** was carried out.

Each asymmetric unit contains two types of molecules, type A and type B (Figure 1), and they are associated with strong intermolecular hydrogen bonding. The C6–OH of each type A molecule is in intermolecular hydrogen bonding with C5–OH of two adjacent type B molecules (O...O 2.72 Å, OHO 154.3°; O...O 2.72 Å, OHO 151°). Similarly, C5–OH of each type B molecule is in strong intermolecular hydrogen bonding with C6–OH of two neighboring type A molecules. This hydrogen-bonding pattern is very interesting in that each of the hydroxyl oxygens involved in this complementary H-bonding acts as a donor and acceptor simultaneously. In addition, C5–OH of type A and C6–OH of type B make complementary hydrogen bonds with each other (O...O 2.92 Å, OHO 169.2°). Also notably, the ketal oxygen, O4 (B), act as an acceptor of a H-bond from C5–OH and C6–OH of type A (O4...O5' 3.24 Å, O4...H–O5' 119.1°; O4...O6' 3.33 Å, O4...H–O6' 126.6°), which could be facilitating the reaction.

The C5–OH of each molecule is facing the *trans*-ketal carbon of a neighboring molecule (opposite enantiomer) from a close distance, and the angle between this hydroxyl oxygen (O5)–ketal carbon (neighbor) and O3 (neighbor) is very close to linearity, making a pseudo-trigonal-bipyramidal arrangement. The O5' (A) is only 3.715 Å away from the *trans*-ketal carbon (C10) of an adjacent type B molecule, and the angle between O5' (A), C10

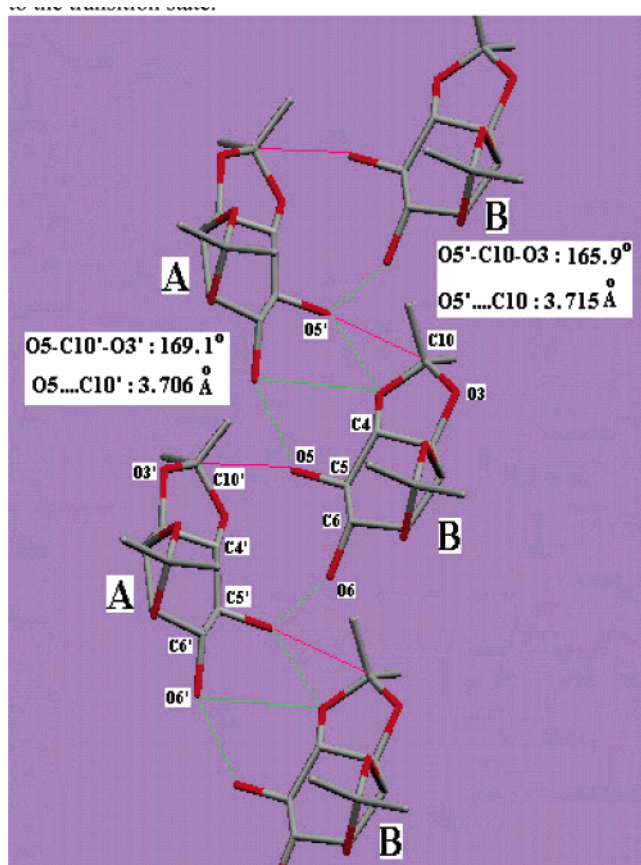


Figure 2. Packing diagram showing the properly disposed ketal and hydroxyl (in trigonal-bipyramidal arrangement) for ketal transfer. Green line represents the intermolecular hydrogen bonding.

(B), and O3 (B) is 165.9° . Similarly, O5 (B) is only 3.706 \AA away from *trans*-ketal (C10') of an adjacent type A molecule, and the angle between O5 (B), C10' (A), and O3' (A) is 169.1° (Figure 2). On the basis of this crystal packing, it is reasonable to expect the observed transketalization via initial nucleophilic attack¹¹ of C5–OH to the transketal carbon of a neighboring molecule to form a ketal-bridged polymeric intermediate (see Supporting Information), followed by the attack of C6–OH to the bridged ketal carbon to form **2**. Thus, each molecule acts as a ketal donor and acceptor at the same time. This accounts for the quantitative isomerization of **1** to **2** in the solid state without the intermediacy of a monoketal or triketal. Although there is no prominent attractive force between the reacting groups (OH and ketal carbon), the strong intermolecular hydrogen bonds on other parts of the molecule maintain the right geometry ideal for the reaction such that reacting groups are favorably disposed in an arrangement similar to the transition state.

Usually in the solution state, for the transketalization reaction, an acid catalyst is required and is believed to react via a carbonium ion intermediate. Although transketalization without an acid catalyst is interesting, based on the crystal structure the observed transketalization without catalyst is not so surprising. Since reacting groups are already preorganized in a transition-state-like arrangement, the feasibility of this topochemical reaction without a catalyst

can be rationalized. Thus, when the situation warrants it, the course of a topochemical reaction might take a different path from that in solution state.

In conclusion, we have presented a topochemical transketalization reaction for the first time. Crystal structure analysis revealed that strong intermolecular hydrogen bonding helps in predisposing the reacting functionalities in close proximity and at a suitable angle for the reaction. This is the first report on a ketal migration in the solid state.

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Supporting Information Available: Crystallographic data for **1** in CIF format; ¹H NMR, powder XRD spectra, DSC data, kinetic study, and control experiments. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (10) Powder XRD studies were also in agreement with a crystal-to-crystal transformation (see Supporting Information).
- (11) The distance and angle in other known topochemical S_N2 reactions are $3.42 \text{ \AA}/147^\circ$,^{5a} $2.9 \text{ \AA}/164^\circ$,^{5b} $3.20 \text{ \AA}/173^\circ$,^{5c} and $4.61 \text{ \AA}/168^\circ$.^{5d}

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