Communication

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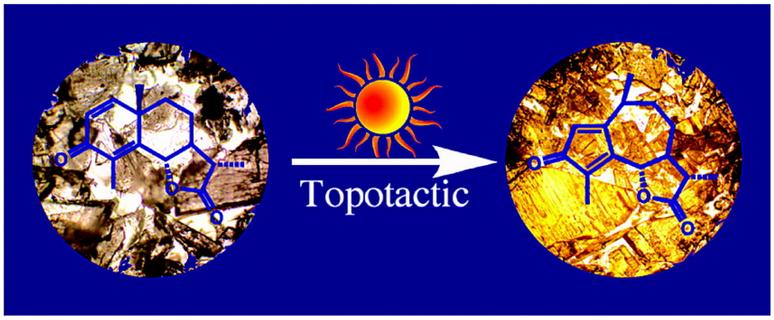

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The Photoarrangement of α-Santonin is a Single-Crystal-to-Single-Crystal Reaction: A Long Kept Secret in Solid-State Organic Chemistry Revealed

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The first organic photochemical reaction was reported by Trommsdorff in 1834 when he described how crystals of α-santonin **1** turn yellow and "burst" when exposed to sunlight.[1] Only 15 years later, Pfizer and Erhart mixed **1** with almond toffee to create the first drug ever formulated in the USA.[2] Solution studies through the 1960s revealed the formation of lumisantonin (**5**) and mazdasantonin (**6**), as primary and secondary photoproducts, respectively, but gave no insight into the crystal transformation.[3,4] It was not until 1968 that Matsuura et al. identified cage dimer **4** and suggested sequential Diels−Alder and 2 + 2 photodimerization reactions from the unstable cyclopentadienone **2** (Scheme 1).[5] The topochemical (lattice-controlled) nature of the Diels−Alder reaction was subsequently confirmed by Reish et al. using single-crystal X-ray diffraction analysis.[6] Given the historic interest of the reaction, that intermediate **2** has not been characterized, and the remarkable occurrence of three consecutive reactions within a crystal, we reinvestigated the reaction with polarizing microscopy, X-ray diffraction, spectroscopic methods, chemical trapping, and product analysis.

α-Santonin crystallized as previously reported, with molecules occupying two distinct crystallographic sites.[6] While irradiated single crystals grown from ether showed the expected yellow coloration, in situ polarized microscopy and videomicroscopy (Supporting Information, SI) revealed that their translucency and birefringence remain intact to conversion values of up to ca. 20−30%. We also noted that the crystals develop a very intense green emission when illuminated with UV light (vide infra). Recognizing the possibility of a single-crystal-to-single-crystal, or topotactic reaction involving a continuous and concomitant transformation that maintains the crystallinity of the medium,[7,8] we analyzed a single crystalline specimen before and after UV irradiation ($\lambda > 300$ nm) for periods 24, 50, and 200 h. Analysis of the X-ray data revealed that the reaction takes place at one of the two sites (the more reactive, or MR site) with conversion values of 7, 18, and 30%, respectively. The topotactic nature of the intramolecular reaction is consistent with the small atomic and molecular displacement required in going from **1** to **2** (Figure 1, rms = 0.79 Å).[9] While the molecule in the less reactive (LR) site appeared unchanged at low conversion values, clear molecular displacement was detected after 200 h (Figure 1). Further irradiation led to the decay of the diffraction data.

Clues to the differences in reactivity between the two sites were obtained by analyzing the partially reacted crystal (Figures 1 and 2). The product requires a significant displacement of the axial methyl group, as indicated by the arrow in Figure 2a, and a conformational change of the central ring that expands from six to seven carbons. When analyzing the packing environment at the two sites, the most notable difference is the disposition of two neighboring molecules shown in space filling models in Figure 2. While they form a groove that accommodates the displacement of the methyl group at the MR site (Figure 2a), there is no space for a similar displacement in the LR site (Figure 2b).

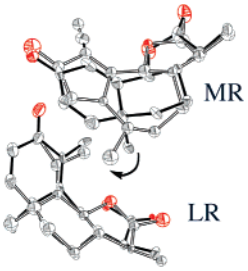


Figure 1. Structures of α-santonin **1** (dark bonds) and cyclopentadienone **2** (light bonds) in the crystal lattice of the former after a 30% topotactic rearrangement at the more reactive (MR) site. The structures at the less reactive (LR) site illustrate the corresponding position of **1** before (filled bonds) and after (light bonds). The greatest change from reactant to product is the displacement of the axial methyl group (illustrated by an arrow) and the ring flip of the seven-membered ring.

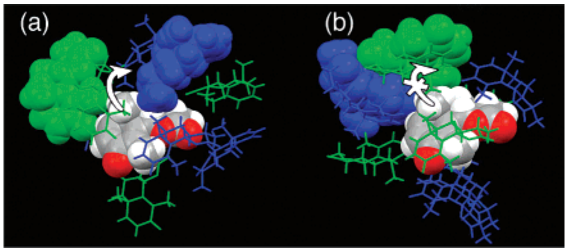
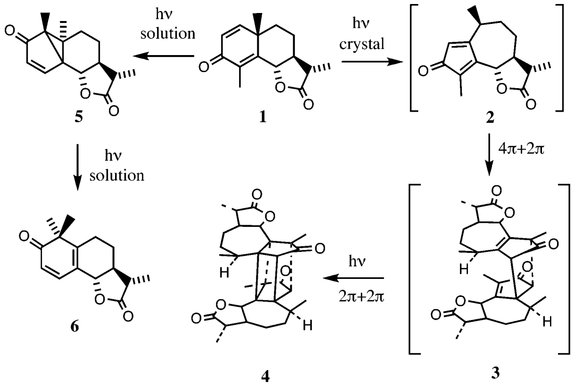


Figure 2. Packing environments of α-santonin **1** at the (a) more reactive (MR) and (b) less reactive (LR) sites with neighboring molecules in green and blue. The reacting molecule and two neighbors are shown in space filling models to illustrate how they form (a) a "groove" and (b) a "wall" that affect the motion of the methyl group, as indicated by the arrows.

Scheme 1



Spectroscopic analysis of the bright yellow crystals showed a new absorption at 380−550 nm and a strong green emission in the 530−650 nm range (Figure 3). A new carbonyl stretching band at 1707 cm^{-1} in the solid-state FTIR (SI) is consistent with that of

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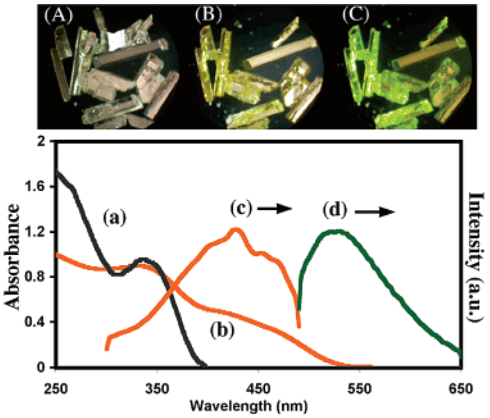
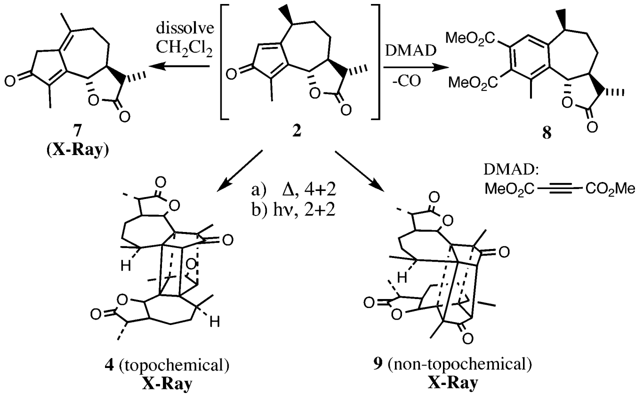


Figure 3. Top: Crystals of α-santonin between cross polarizers (A) before reaction, and after 1 h of UV irradiation illuminated with (B) visible and (C) UV light. Bottom: Absorption spectra of α-santonin crystals (a) before and (b) after 1 h reaction and, emission (c) excitation, and (d) emission of the reacted crystals. The yellow color and green emission are assigned to cyclopentadienone **2**.

Scheme 2



the formally antiaromatic[10] and highly unstable parent cyclopentadienone, previously documented by matrix isolation.[11] Dissolution of samples containing **2** led to the immediate disappearance of the yellow color and formation of known photosantoic acid **7** (ν_{CO} = 1678 cm^{-1}).[3] However, an interfacial reaction of a powdered sample with neat dimethyl acetylenedicarboxylate (DMAD) resulted in formation of diester **8** by sequential Diels−Alder and chelotropic decarbonylation reactions (Scheme 2).[12] Analysis of 0.1 g of **1** after irradiation times varying from 1 h to 1 week (168 h) revealed that the formation of dimer **4** has an induction period of several hours. Lumisantonin **5**, mazdasantonin **6**, photosantoic acid **7**, and the non-topochemical dimer **9**, which was previously reported by Matsuura,[5] were obtained in small amounts (Scheme 2 and SI). A detailed mechanistic interpretation of the formation of **2**, **5**, and **6** is presented in the SI.[3,5] In addition to characterizing these compounds by conventional spectroscopic methods in solution, the structures of photosantoic acid **7** and dimers **4** and **9** were confirmed by single-crystal X-ray diffraction (SI).

Our findings account for the induction period needed for dimer (**4**) formation. While two neighbors of **1** are well-disposed for a lattice-controlled dimerization after having being transformed into cyclopentadienone **2** (Figure 4),[13] the reaction is delayed by the slower reaction at the LR site, which appears to require a certain degree of lattice relaxation. The conversion-limited X-ray diffraction suggests that the Diels−Alder reaction occurs soon after the second molecule of **2** becomes available. This process is consistent with the difference in the packing arrangements of MR and LR sites as depicted in Figure 2. It is likely that the ensuing structural changes, which require large changes in shape and volume (Figure 4), are responsible for the crystal bursting. We ascribe the formation of **7**, which has not been reported thus far in the solid-state photoreaction of **1**,[5,6] to an isolation artifact resulting from a rapid tautomerization of **2**.[14,15] In conclusion, α-santonin provides a remarkable example of an efficient but limiting toptactic rearrangement and highlights the importance of lattice relaxation in solid-state reactions.

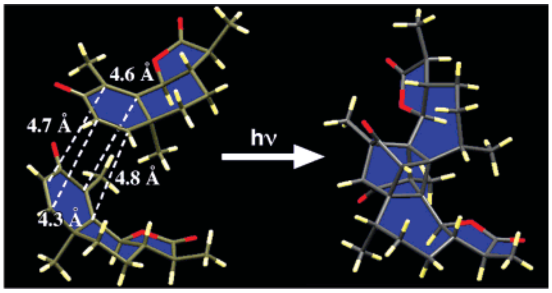


Figure 4. X-ray structural correlation between the reacting α-santonin neighbors, with the reacting carbons and their distances indicated, and topochemical dimer **4**. A large change in the shape and volume from two reactants to the product account for the crystal bursting.

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Supporting Information Available: Characterization of **4**, **5**, **6**, **7**, **8**, and **9**, in situ videomicrograph, and crystallographic information (cif) for compounds **1**, **4**, **7**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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