Reversible Single Crystal-to-Single Crystal Phase Transition with Low-Temperature Induced Twinning of Diphenhydramine Citrate Salt

Polymorphism, single crystal phase change, twinning, API characterization

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A reversible single crystal-to-single crystal phase transformation of an antihistamine drug Diphenhydramine-Citrate (DPH-CIT)[1] salt provides an excellent opportunity for probing molecular mechanisms involved in solid-state phase changes. The single crystal structure of DPH-CIT solved at 218 K (Form I) belonged to the Monoclinic $P2_1/c$ space group, whereas the structure solved at 123K using the same crystal belonged to the Triclinic P-1 space group (Form II). The temperature cycling test on a Differential Scanning Calorimeter (DSC) using a DPH-CIT single crystal revealed a sharp phase transition at 146 K with little hysteresis. During both cooling and heating between room temperature and 100 K, unit cell volume of the DPH-CIT crystal exhibited a sharp volume enlargement at temperatures coinciding with the transition temperatures observed from DSC. Two additional single crystal structures were determined at 148K and 100K to provide more structural information. An analysis of molecular positions at the four temperatures showed that the phase change involved rotations of benzene rings on DPH molecules, which aligned along the unit cell c-axis. The formation of 2 to 3 weak C-H…O hydrogen bonds in Form II likely stabilized the Form II below 146 K. This work affirms the notion that volume expansion is a pre-requisite for solid-state phase change to occur.

1. Wang, C.; Paul, S.; Wang, K.; Hu, S.; Sun, C. C., Relationships among Crystal Structures, Mechanical Properties, and Tableting Performance Probed Using Four Salts of Diphenhydramine. *Crystal Growth & Design* **2017,** *17* (11), 6030-6040.