

Decoding conformational polymorphism in a thiazete-1,1-dioxide
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Understanding and controlling polymorphism are very difficult tasks and, at the same time, very attractive research themes in the light of solving crucial chemical problems, because different polymorphs of the same substance show different intensive physicochemical properties such as solubility, conductivity, optical properties, and so on.

Aim of this work is to *quantitatively* compare and rationalize the electronic and crystallographic features of two conformational polymorphs as a function of temperature through the analysis of their non-covalent interaction (NCI) networks, highlighting possible correlations among their charge densities, conformations and interaction energetics. We focused on the known polymorphic forms of an isothiazole derivative, DTC(I) and (II)^[1,2]. They both crystallize in P2₁/n but differ in crucial packing aspects due to different orientations of a single terminal –OCH₃ group. The evolution of the crystal cohesive energy and charge density features was monitored through high-level periodic LCGTF calculations at fixed experimental geometries among $T = 100(2)$ K and RT. Quantum mechanical energy estimates were also complemented by empirical atom-atom potential sum calculations^[3] and real-space reduced density gradient^[4] analysis.

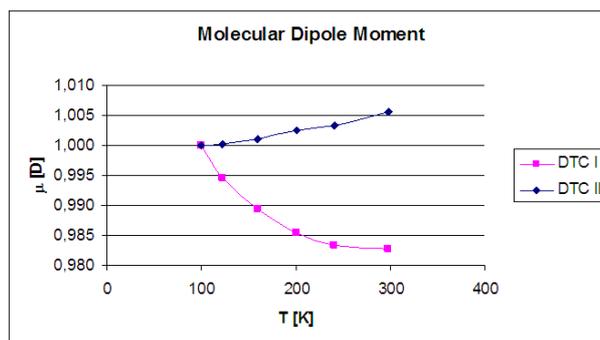


Fig. 1 : Relative changes of the in-crystal molecular dipole moments in DTC(I) (purple squares) and DTC(II) (blue rhombi). Structures at $T = 100$ K were taken as suitable references. The plotted curves serve just as eye guidelines.

As expected, we found that the cohesive energies of the two forms are very similar. Form (I) was always found to be metastable with respect to the denser (II) polymorph, implying that they are not enantiotropically related in the 100 K – RT range. Dispersive/repulsive and electrostatic NCIs dominate the crystal packing in both polymorphs, but in form (II) long-range electrostatic interactions are invariably stronger than in (I), as it can be inferred from the relative magnitudes of the corresponding molecular dipole moments (at $T = 100$ K, $|\mu|_{(I)} = 10.4$ D and $|\mu|_{(II)} = 11.0$ D). While in (I) a systematic $\approx 1.6\%$ large increment of $|\mu|$ is detected on going from RT down to 100 K, in (II) $|\mu|$ undergoes a slight ($\approx 0.5\%$) and considerably less steep reduction upon lowering T (Fig. 1). In (I), the energy dominant structure is a pair exhibiting a strong parallel head-to-tail arrangement of the molecular dipoles, so an increase in $|\mu|$ allows the crystal to gain stability as the cell shrinks upon lowering T . In (II), on the other hand, a molecular pair with head-to-head arranged dipoles occupies the same coordination shell. In this case, a strengthening of the dipole moment would eventually result in an unfavourable electrostatic contribution. Effects of the present findings on the molecular covalent bonds^[5] are also briefly discussed.

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