Journal Name

COMMUNICATION

Partial Rotation of isopropyl Group in the Solid State: Single-Crystal-to-Single-Crystal Phase Transformation in a Carvacrol Derivative

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A hitherto unseen rotation of isopropyl group in the solid state, predicted to be forbidden based on theoretical investigations, is reported. This C–C rotation observed during temperature dependant single-crystal-to-single-crystal transformation is attributed to the concomitant changes in molecular structure and intermolecular packing.

Rotation about C–C bond is a dynamic phenomenon commonly associated with methyl, ethyl, trifluoromethyl and *tert*-butyl groups. As the gas phase rotational energy barriers for these groups are easily achievable at room temperature (thermal energy, kT), many of these rotations are generally observed at RT.[1-4] These dynamic rotations are also commonly seen in liquid/solution states as well as in the solid state.[5-9] In crystals, due to the triumph of close packing and translational symmetry over 'intermolecular randomness' and also due to the preferred selection of smallest possible asymmetric unit,[10] these C–C rotations are typically manifested as orientational disorders, either static or dynamic.[11-20] In case of static orientational disorder (or positional disorder),[16-18] during crystallization, the group in question adopts different orientations giving rise to a crystal containing different rotamers. The relative orientations of the group in different rotamers present in the crystal are independent of the temperature of data collection. In dynamic orientational disorder,[19-20] the group in focus seems to be dynamically changing its orientation (inter-conversion of rotamers as in solution). The extent of dynamicity depends on the temperature of data collection and in many cases the disorder can be resolved at lower temperatures.

While the phenomenon of C–C rotation of several flexible groups such as methyl, trifluoromethyl and *tert*-butyl in the solid state is well established, the behavior of isopropyl group is still under debate. There are a few papers reporting the rotation of isopropyl group in gas and solution phase observed by NMR and other spectroscopic techniques,[21-27] however, to the best of our knowledge, no single report till date claims to have observed isopropyl rotation in the solid state. Moreover, recent experimental and theoretical studies on 3-isopropylchrysene carried out by Wang *et. al.* rules out the feasibility of rotation of isopropyl group in the solid state.[28] In this communication, we present a case of temperature dependant phase transformation in Thiourea Acetyl Carvacrol Hydrazide (IUPAC name: 1-(benzoyl)-3-[(5'-isopropyl-

2'-methylphenoxy)acetamino]thiourea; figure 1; hereafter TACH, see ESI for synthetic scheme and characterization data) wherein the crystalline forms before and after the transition depict two opposite orientations of the isopropyl group indicating the possibility of such a rotation in crystals.
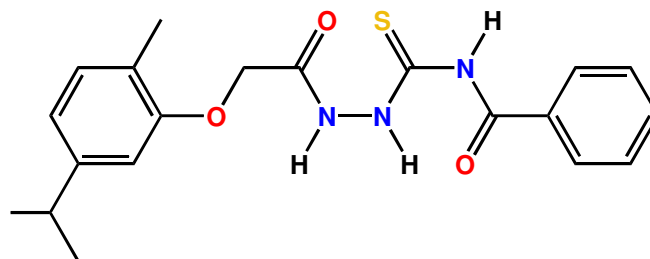

Figure 1. Molecular structure of TACH

A room temperature crystal structure of TACH belongs to the monoclinic centrosymmetric space group *C*2/*c* with one molecule in the asymmetric unit (Form I; Z=8)[29]. In other words, all molecules in the crystal lattice are identical and are related to each other by a group of symmetry operations in the space group. When cooled down to ~ 200 K and below, the crystal undergoes a phase transformation while still retaining its single crystallinity (single-crystal-to-single-crystal (SCSC) transformation). Crystal structure analysis at 200 K revealed that the transformed crystalline phase contains TACH molecules with two different conformations crystallising in the space group of lower symmetry (triclinic), namely *P*-1, with Z=4 (Form II)[29]. Figure 2 shows view of asymmetric units in forms I and II. The two conformers in Form II mainly differ in orientation of isopropyl groups with one of the conformers being similar to that in Form I. Table 1 provides some representative torsion angles distinguishing molecular structures in the two forms.
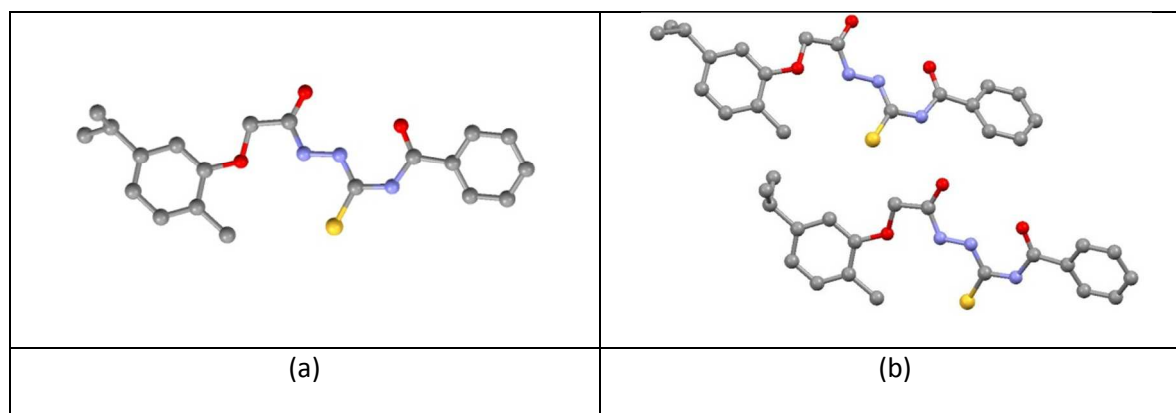
(a)	(b)

Figure 2. (a) TACH; Form I, *C*2/*c*; One symmetry independent molecule (Z'=1) with isopropyl group oriented outward (exo); (b) TACH; Form II, *P*-1; Two symmetry independent molecules (Z'=2) with isopropyl groups having different orientations (outward (exo) and inward (endo)) at 200 K. Colour codes, Gray: Carbon, Red: Oxygen, Blue: Nitrogen, Orange: Sulphur. Hydrogen atoms are omitted for clarity.

Table 1. Representative torsion angles in Form I [*C*2/*c*; one symmetry independent molecule (Z'=1)] and Form 2 [*P*-1; two symmetry independent molecules (Z'=2)].

Structure			
	Form I (*C*2/*c*) Mol 1 (exo)	**Form II (*P*-1)**	
		Mol 1 (exo)	Mol 2 (endo)
Interplanar angle between phenyl rings (°)	25.79	30.96	29.32
Orientation of isopropyl group, Torsion [H7-C7-C2-C1] (°)	15.98	28.64	178.55

Temperature dependent changes of crystal symmetry is a well studied phenomenon in organic crystals,[30-34] however the associated conformational changes, like that of isopropyl group in TACH, are quite uncommon. Two probable mechanisms for the orientational switching of isopropyl group between the two rotamers could be (1) flipping and (2) rotation of the (phenyl)C−C(isopropyl) bond. The possibility of flipping seems unlikely and could be completely ruled out by close packing considerations in the crystal and also due to unfavorable energetic requirements. The mechanism of C−C rotation appears to be more appropriate as the occurrences of such rotation in the gas and solution phases have been reported in the literature,[21-27] though it would contradict the report of Wang *et. al.*[28] claiming such solid state rotation as 'energetically forbidden'.

Systematic crystal packing analysis and *in-silico* investigations provide clear understanding of the observed phenomenon. In RT structure (Form I; C2/c), molecules are arranged in such a way that the isopropyl groups of all molecules face exactly opposite to each other [figure 3 (a) and (c)]. When the temperature is lowered, the combined effect of change in molecular conformation and contraction of unit cell makes the overall structure strained (molecules are relaxed at RT!). After a limit (~200K), this temperature induced strain results in a breakdown of the crystalline symmetry, due to major conformational changes and sliding over of the molecules synergistically, resulting in a new phase i.e. Form II (Figure 3 (b) and (d)). Higher value of Z' (2) along with the occurrence of complementary (endo vs. exo) packing of iso-propyl conformations appear to be major driving factors for the formation of Form II at low temperatures (Figure 3 (d)). Noteworthy enough, the transformed phase was found to be merohedrally twinned where the degree of twinning increases with decrease in temperature of data collection (see ESI). The density functional calculations based on the use of M06-2X functional[35,36] on the gas phase structures of TACH predicted the RT conformer (exo) to be nearly 3.2 kcal.mol^{-1} lower in energy than the other rotamer (endo), as obtained from the self-consistent reaction field theory.

Importantly, the SCSC phase transformation was found to be reversible with the lower symmetric triclinic phase (Form II; *P*-1) converting back to the higher symmetric monoclinic phase (Form I; *C*2/*c*) upon heating above 200 K. The concomitant changes in intra- and inter-molecular geometries of the two structures—with respect to temperature—appear to result in the reversal of relative stabilities of the two forms. In order to confirm this phase transformation as a bulk phenomenon, variable temperature powder X-ray diffraction (PXRD) was carried out on a fine ground powder.[37] Upon transition (≤ 200K), significant peak shifts were noted in the 2theta range 12–20 degrees with minimal differences in rest of the pattern (Figure 4).[38] These differences in the experimental PXRD patterns before and after the transformation correlate well with that of the respective simulated patterns obtained from Form I and Form II structures at respective temperatures (295K (RT), 250K, 200K and 110K; see ESI for structure details and PXRD overlay).

In summary, rotation of isopropyl group was observed during the temperature induced phase transformation of TACH. The rotational flexibility of bulkier groups in crystalline solids depends mainly upon the immediate supramolecular surroundings of the group and could be overcome by various stimuli such as temperature and/or pressure resulting in otherwise forbidden rotations in the solid state.
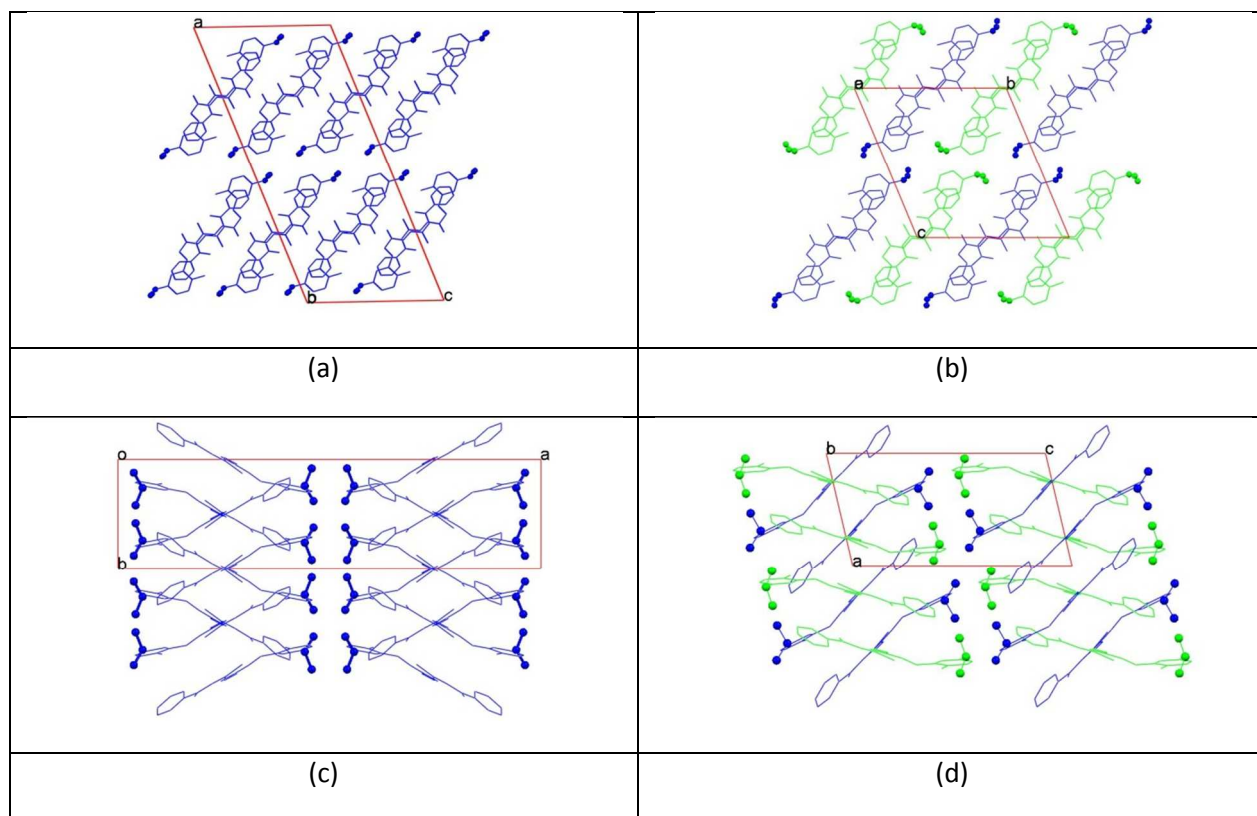
Figure 3. Packing diagrams showing different arrangement of isopropyl groups in Form I [figures (a) and (c)] and Form II [figures (b) and (d)] (Molecules are shown in wireframe style with the isopropyl group highlighted in ball and stick style. Symmetry independent molecules are colour coded). Hydrogen atoms are omitted for clarity.
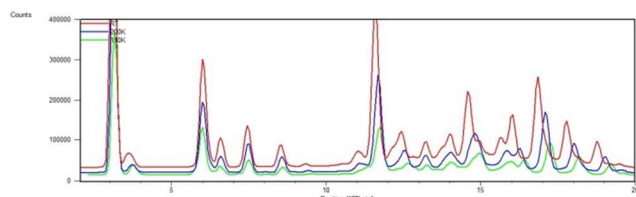

Figure 4. Comparison of experimental powder patterns (collected on powder sample filled in capillary with synchrotron radiation, $\lambda = 1$ Å) at RT ($\sim$295K) (red), 200K (blue) and 110K (green).

Notes and references

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10   Asymmetric unit: An asymmetric unit of a space group is a simply connected smallest closed part of space from which, by application of all symmetry operations of the space group, the whole space is filled. http://reference.iucr.org/dictionary/Asymmetric_unit.

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29   Crystal data: **Form I** CCDC 941953; MF: $C_{20}H_{23}N_3O_3S_1$; monoclinic; a = 33.842(3) Å; b = 8.1803(9) Å; c = 15.5183(15) Å; β = 111.285(11) °, V = 4002.9(8) Å^3; T = 293(2) K; space group, *C*2/*c*, Z = 8; ρ_{calcd} = 1.279 g/cc; reflns measured, 15199; unique reflns, 3533; no. of parameters = 259; R_{obs} = 0.0704; wR_{2obs} = 0.1893; $\Delta\rho_{min,max}$ = –0.264, 0.217 eÅ^{-3}; goof = 1.02. **Form II** CCDC 1060426; MF: $C_{20}H_{23}N_3O_3S_1$; triclinic; a = 8.1589(10) Å; b = 15.3909(13) Å; c = 16.8655(18) Å; 67.525(9); β = 78.145(10) °; 89.508(9), V = 1909.5(4) Å^3; T = 110(1) K; space group, *P*-1, Z = 4; ρ_{calcd} = 1.341 g/cc; reflns measured, 13175; unique reflns, 6719; no. of parameters = 494; R_{obs} = 0.0997; wR_{2obs} = 0.2765; $\Delta\rho_{min,max}$ = –0.657, 1.193 eÅ^{-3}; goof = 1.05.

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37   PXRD data were collected on fine ground powder in capillary mode using synchrotron radiation of wavelength 1 Å at Elletra, Italy.

38   It is to be noted that the reduced unit cell parameters of Form I (C-centered Monoclinic) are similar to the cell parameters of transformed phase, Form II (Primitive Triclinic). The major difference in the structures is in the orientation of isopropyl group with minor differences in intermolecular arrangement. As a result, the PXRD patterns (both simulated and experimental) of the two structures are not anticipated to be very different.

Graphical abstract:

Partial Rotation of isopropyl Group in the Solid State: Single-Crystal-to-Single-Crystal Phase Transformation in a Carvacrol Derivative

Iso-propyl group rotation observed in single crystal of TACH appears to be a result of counterbalance of molecular energetics and supramolecular packing in response to the thermal stimulus.