

# Solvent mediated centric/non-centric polymorph pairs of an indole derivative: Subtle variation of C–H···O hydrogen bonds and C–H··· $\pi$ interactions†

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Centric ( $P2_1/n$ ) and non-centric ( $P2_1$ ) polymorphic pairs of biologically active 1-(4-fluorophenyl)-6,6-dimethyl-2-phenyl-1,5,6,7-tetrahydro-4*H*-indol-4-one crystallized from different solvents have been elucidated *via* single crystal and powder X-ray diffraction studies, morphological observations and calorimetric measurements. C–H···O hydrogen bonding and weak intermolecular C–H··· $\pi$  interactions generate distinct packing features in the two forms.

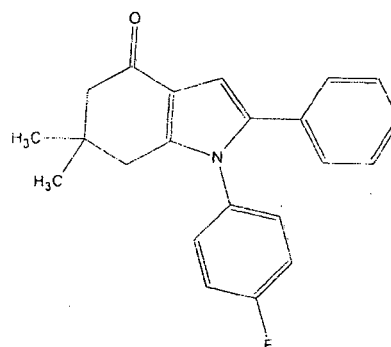
## Introduction

Polymorphism in crystalline materials has become a major area of intense activity in pharmaceutical research.<sup>1</sup> A large number of molecules exhibiting polymorphism is clearly seen from an analysis of the entries in the Cambridge Structural Database (CSD).<sup>2</sup> The occurrence of polymorphic modifications in molecular compounds is manifested not just as a consequence of minimum free energy of the crystalline phases but also by kinetics of crystal nucleation and growth.<sup>3</sup> Polymorphs are generally classified as conformational,<sup>4</sup> concomitant,<sup>5,6</sup> and solvates.<sup>1,7</sup> Formation of a particular polymorph with desired properties is of immense interest in the drug industry since the drug activity of a material can change abruptly from one form to another.<sup>8</sup> In recent years, organic crystals depicting non-linear optical (NLO) property have been extensively studied involving the design and synthesis of stable chromophore molecules to crystallize in non-centrosymmetric crystal forms.<sup>9–11</sup> In this work, we have investigated the appearance of solvent induced polymorphs by crystallizing the compound, 1-(4-fluorophenyl)-6,6-dimethyl-2-phenyl-1,5,6,7-tetrahydro-4*H*-indol-4-one, in 1 : 5 mixture of dichloromethane ( $\text{CH}_2\text{Cl}_2$ ) and hexane ( $\text{C}_6\text{H}_{14}$ ) resulting in a centrosymmetric ( $P2_1/n$ ) form (Form I) and in acetone ( $\text{CH}_3\text{COCH}_3$ ) generating a non centrosymmetric ( $P2_1$ ) form (Form II). The importance of the two crystal forms becomes significant in the context that the compound has been shown to have considerable anti-implantation activity in rats.<sup>13</sup>

## Experimental

The compound 1-(4-fluorophenyl)-6,6-dimethyl-2-phenyl-1,5,6,7-tetrahydro-4*H*-indol-4-one (Scheme 1) was synthesized in the early 1980s and reported in the literature by Nagarajan *et al.*<sup>12</sup> The crude material (colourless powder) was obtained from the old stock (~20 years from the synthesis) of KN (one of the authors) and used for crystallization without further purification.

A powder X-ray diffraction pattern (PXRD) [Fig. 1] of the crude material was recorded on a Siemens D5005 powder X-ray diffractometer with the generator power of 30KV/25mA and with Cu K $\alpha$  radiation to check the crystallinity of the material. Single crystals of the form I were consistently grown from a solution in dichloromethane and hexane (1 : 5) by slow evaporation process at 10 °C in a refrigerator and crystals of form II were similarly obtained from a solution in acetone also at 10 °C. Approximately 3–5 mg of the raw crystalline powdered material were dissolved in 2.5–3.5 ml of respective solvent(s) in 5 ml glass beakers. The beakers with the clear solution were covered with paraffin film and a couple of fine holes were made using a thin needle to allow slow evaporation. The beakers were kept undisturbed in a refrigerator at 10 °C for several days (7–14 d), till the solvents were evaporated



Scheme 1 1-(4-Fluorophenyl)-6,6-dimethyl-2-phenyl-1,5,6,7-tetrahydro-4*H*-indol-4-one.

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† Electronic supplementary information (ESI) available: Complete single crystal X-ray diffraction data for the two forms and a number of additional diagrams showing the intermolecular interactions. See DOI: 10.1039/b604118c

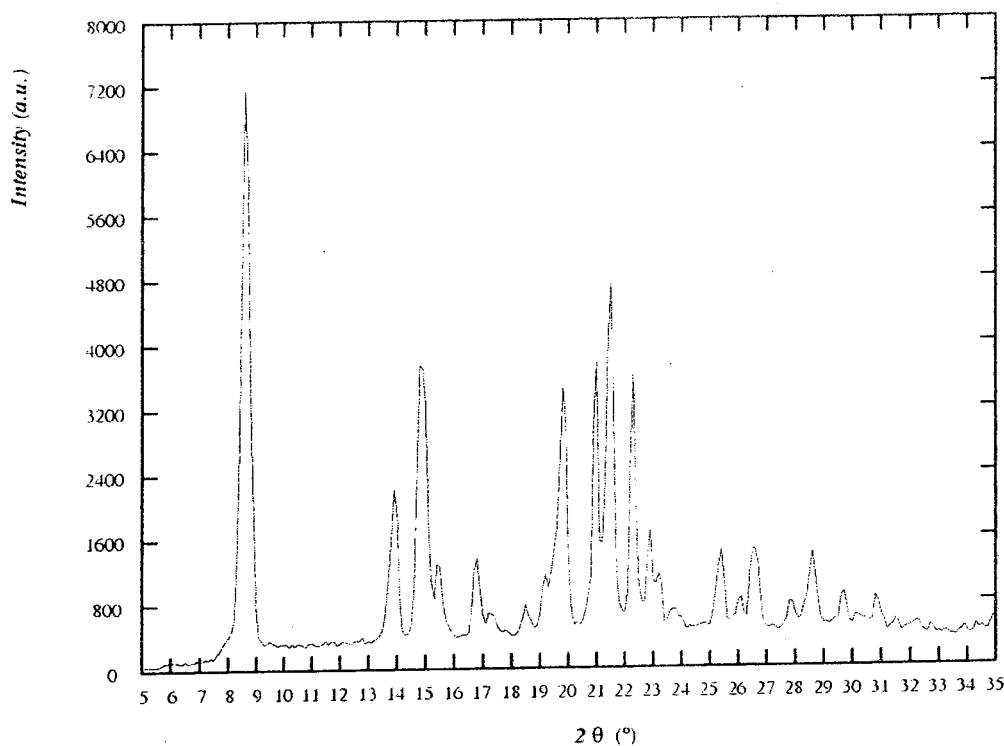


Fig. 1 Powder X-ray diffraction pattern of the crude material.

completely. Many other solvents and solvent mixtures were used to crystallize the compound but crystals grown from solvents like MeOH,  $\text{CHCl}_3$ , EtOAc and their mixtures with hexane did not yield crystals suitable for single crystal study.

The experimental PXRD patterns (Fig. 2a,b) of crushed crystals of both forms were recorded on the same instrument under similar conditions. These diffraction patterns provide an unambiguous proof for the existence of the two different forms. Further, these diffraction patterns clearly show unique phases with no indication of concomitant polymorphism. The PXRD of the raw material matches well with that of form I indicating that form I was generated in the bulk while purified after its synthesis in the early 1980s.

All the crystallization beakers were examined under an OLYMPUS SZX12 optical microscope equipped with an optical polarizer and an OLYMPUS DP11 digital camera to identify the different morphologies (Form I and Form II) as shown in Fig. 3a,b. The crystals of form I were grown as cluster of well-defined rectangular blocks, while those of form II were found to be individual big rhombohedral blocks.

The two forms were also characterized in a fairly straightforward manner by differential scanning calorimetric (DSC) studies. The DSC data (Fig. 4a,b) were recorded on a Mettler Toledo STAR<sup>®</sup> System with heating/cooling rates of  $5\text{ °C min}^{-1}$  from 50 to 210 °C. The material, recovered after heating until melting, when re-crystallized under the individual crystallization conditions, yielded the respective polymorphs, hence confirming no decomposition on melting.

The DSC data of form I (Fig. 4a) displays a melting endotherm between 203.6 and 205.6 °C ( $44.29\text{ kJ mol}^{-1}$ ) with

the sharp peak at 204.3 °C. The material was heated up to 210 °C to ensure complete melting of the solid. On cooling the melt from 210 °C, a pair of exothermic peaks, indicating solidification, between 186.4 and 183.0 °C ( $43.15\text{ kJ mol}^{-1}$ ) with peaks at 185.8 and 184.2 °C, respectively, are observed. The DSC data of form II (Fig. 4b) exhibits a small endothermic hump (unknown phase transition) between 163.1 and 177.1 °C ( $5.18\text{ kJ mol}^{-1}$ ) before melting between 203.6 and 206.7 °C ( $42.37\text{ kJ mol}^{-1}$ ) with a sharp peak at 204.7 °C (Fig. 4b). The material was heated up to 208 °C to ensure complete melting of the solid. Further, on cooling the melt from 210 °C, the solidification exotherm is observed between 118.4 and 115.8 °C ( $30.90\text{ kJ mol}^{-1}$ ) with a single peak at 117.9 °C, different from those observed in the case of form I.

The NLO activity of the crystals of both the forms were measured using Quanta Ray DCR3 LASER (1064 nm, 20 Hz, 10 ns) and a Photo Diode was used as detector; 1064 nm was cut off by a  $\text{CuSO}_4$  solution and BG38 filter. A freshly grown single crystal of urea was used as a standard for evaluating the SHG activity.

### Crystallography

The single crystal X-ray diffraction data<sup>13,14</sup> were collected on a Bruker AXS SMART APEX CCD diffractometer at 90.0(2) K using the OXFORD Cryosystem with  $\text{N}_2$  flow and Mo  $\text{K}\alpha$  radiation. Data were collected with a  $\omega$  scan width of  $0.3^\circ$  using SMART<sup>15</sup> in three different settings of  $\phi$  (0, 90 and  $180^\circ$ ) keeping the sample to detector distance of 6.062 cm and the  $2\theta$  value fixed at  $-25^\circ$ . The data were reduced

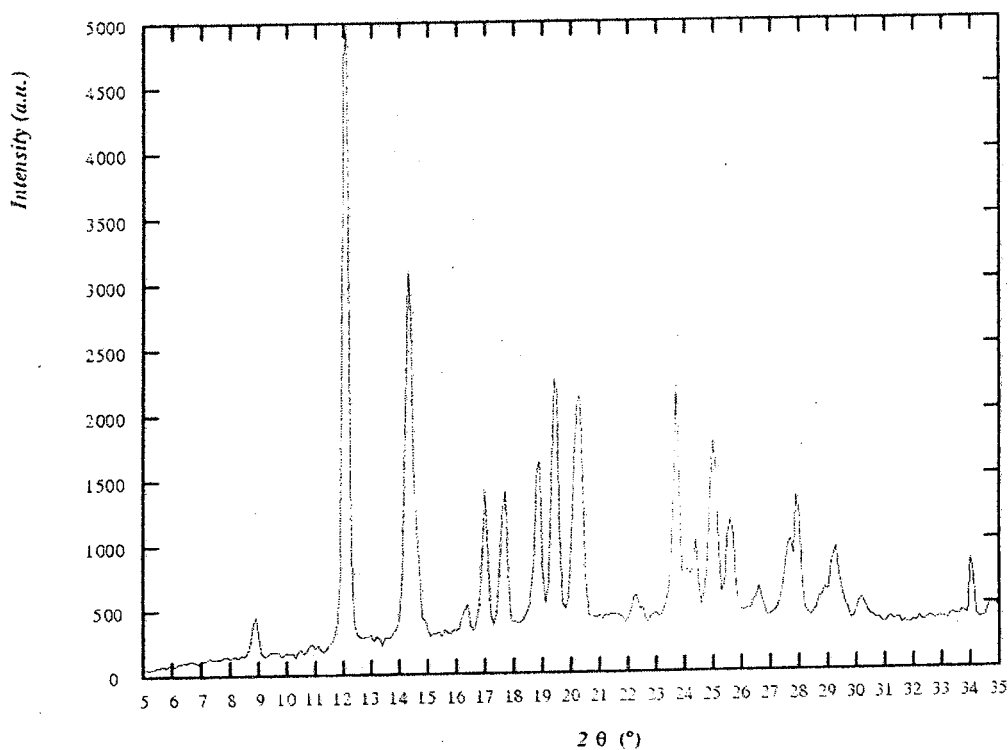
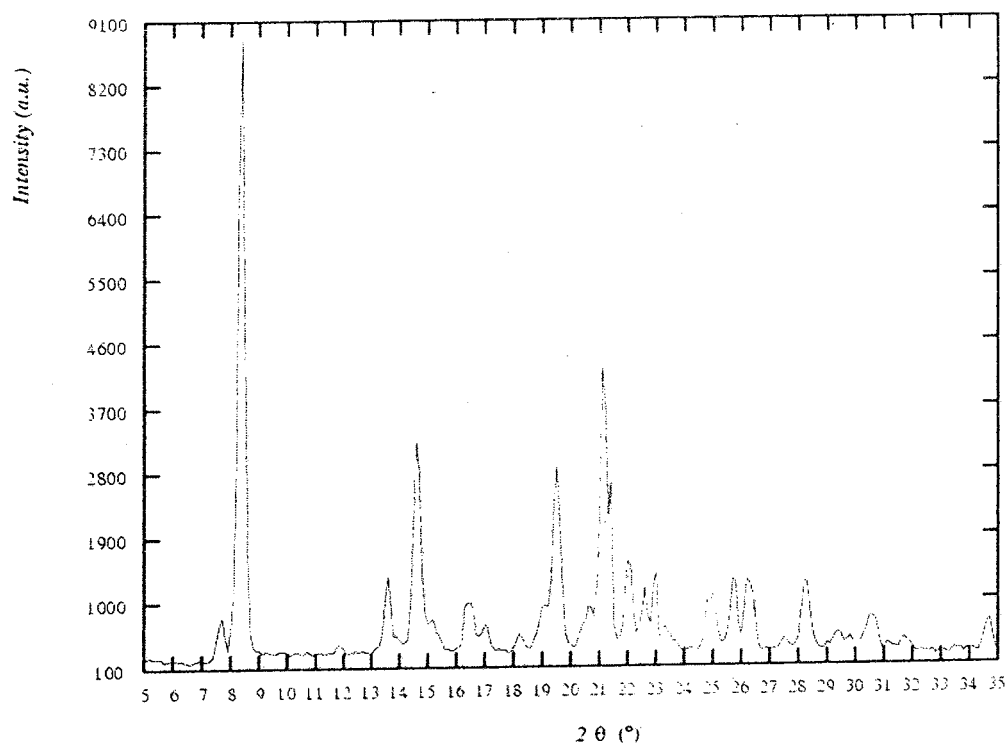


Fig. 2 Observed powder X-ray diffraction pattern of (a) form I; and (b) form II.

by SAINTPLUS,<sup>15</sup> an empirical absorption correction was applied using the package SADABS<sup>16</sup> and XPREP<sup>15</sup> was used to determine the space group and the structures were solved using SIR92<sup>17</sup> and refined using SHELXL97.<sup>18</sup> Molecular and packing diagrams were generated using ORTEP32<sup>19</sup> and

CAMERON<sup>20</sup> present in the WinGx<sup>21</sup> (Version 1.64.05) program suite. The geometric calculations were done by PARST95<sup>22</sup> and PLATON.<sup>23</sup> CCDC reference numbers 283793 and 283794. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b604118c

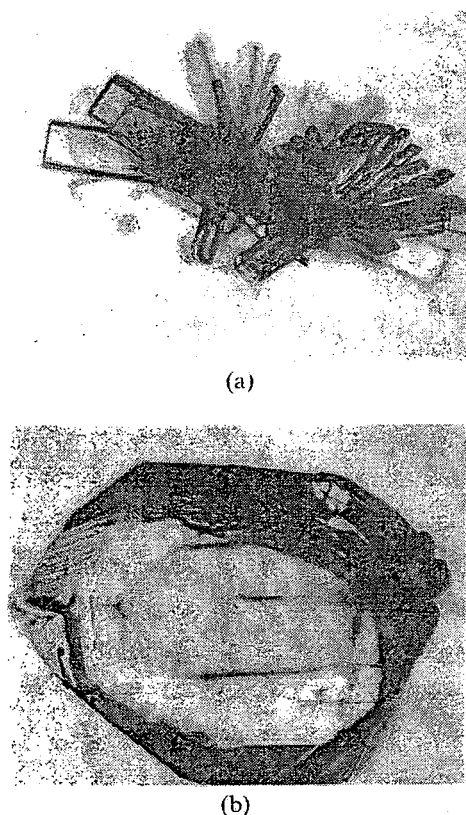


Fig. 3 Photographs of the crystal of the two polymorphs (a) form I; and (b) form II.

## Results and discussions

The crystal structure of the form I (Fig. 5a) was solved and refined in the monoclinic centrosymmetric space group  $P2_1/n$  with  $Z = 4$ . The saturated cyclohexane ring of the indole moiety has an envelope conformation with the atom C6 significantly away [ $-0.6189(3)$  Å] from the plane formed by C5, C4, C9, C8 and C7. The two phenyl rings are twisted out of plane [ $\angle C8-N1-C10-C11 = 112.8(2)^\circ$  and  $\angle N1-C2-C16-C17 = 157.7(1)^\circ$ ] of the indole moiety. Table 1 compares the relevant torsion angles of the two forms. The dihedral angle between the two planes passing through the *1-phenyl* and the *2-phenyl* rings, respectively, is  $68.82(1)^\circ$ . The molecules pack in the unit cell involving a pair of bifurcated intermolecular C-H $\cdots$ O hydrogen bonds across the center of symmetry resulting in a *head to tail* molecular dimer motif [Table 2, Fig. 5b (Fig. 2a of the ESI)†] involving H3, H17 and O1.

A pair of C-H $\cdots$  $\pi$  interactions has been identified between these molecules involving H5A and Cg1 (Cg1 denotes the center of the ring containing C16-C21) [Table 2, Fig. 5b (Fig. 2b of the ESI)†]. These dimer motifs are then linked to the neighboring ones *via* a couple of intermolecular C-H $\cdots$  $\pi$  interactions involving H12 and Cg1 generating a molecular chain along the 'a' direction [Fig. 5b (Fig. 2c of the ESI)†]. These particular packing interactions generate chains of molecular dimers in the crystal lattice in *b* direction. This form, being centrosymmetric, does not show any NLO activity. The PXRD simulated from the single crystal data using STOE

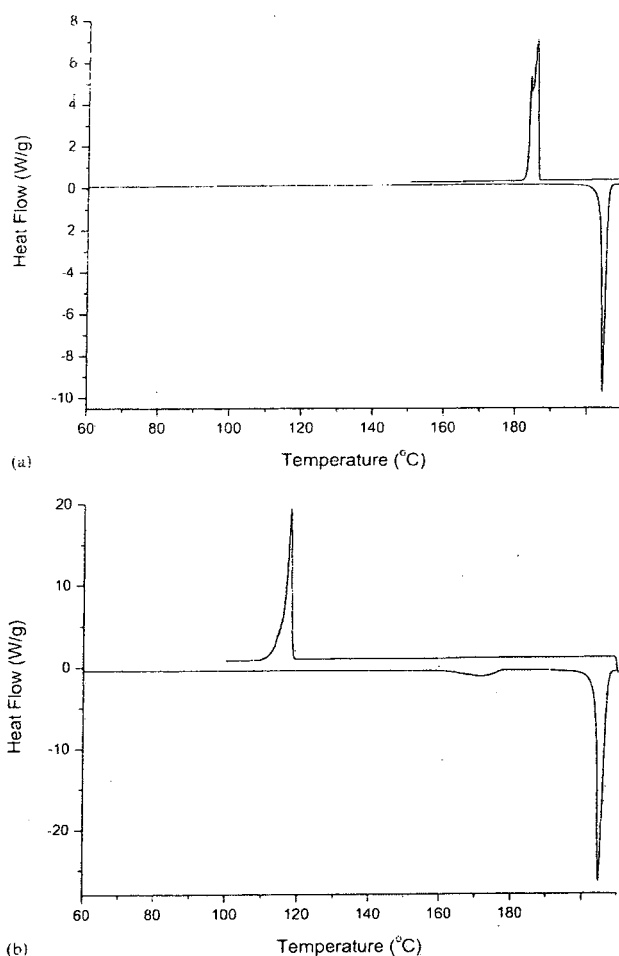
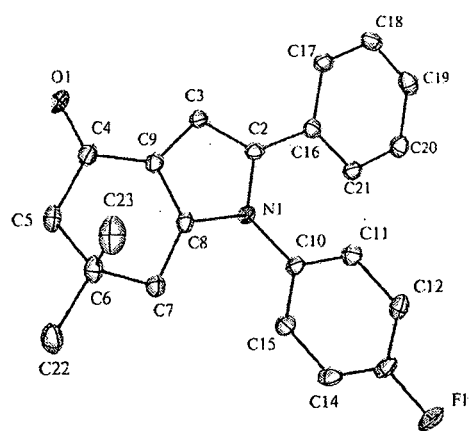


Fig. 4 DSC traces of (a) form I; and (b) form II.

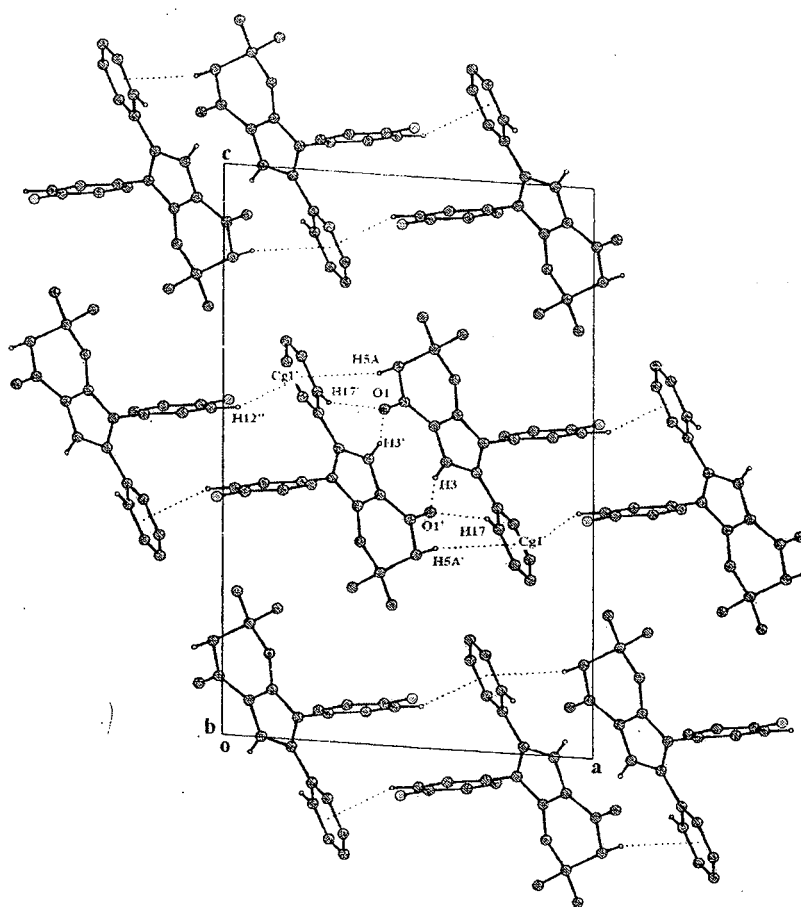
theoretical pattern simulation and Cu K $\alpha$  radiation. The one to one agreement of this pattern with experimentally observed PXRD for form I (Fig. 1a in the ESI)† proves that crystals of form I did not undergo any reaction or phase transition on crushing/mild grinding.

The crystal structure of form II (Fig. 6a) was solved and refined in the monoclinic non-centrosymmetric space group  $P2_1$  with  $Z = 2$ . The atom C6 in the saturated cyclohexane ring is away by  $0.6655(3)$  Å from the plane formed by C5, C4, C9, C8 and C7 resulting in an envelope conformation. The relative torsion angles of the phenyl rings from that of the indole moiety are  $\angle C8-N1-C10-C11 = 120.3(2)^\circ$  and  $\angle N1-C2-C16-C17 = 133.2(2)^\circ$ , respectively. The dihedral angle between the two planes passing through the *1-phenyl* and the *2-phenyl* rings is  $56.48(5)^\circ$ . The molecules pack in the unit cell *via* trifurcated C-H $\cdots$ O hydrogen bonds forming a 3-D network of molecular chains [Table 2, Fig. 6b (Fig. 3a and 3b of the ESI)†], and an intermolecular C-H $\cdots$  $\pi$  interaction [Table 2 (Cg1 denotes the center of the ring containing C16-C21), Fig. 6b (Fig. 3c of the ESI)†] has also been identified in the packing. As can be expected, this form shows a SHG signal of 2.2 mV, almost as strong as that of the standard urea crystal.

The PXRD simulated from the single crystal data using STOE theoretical pattern simulation and Cu K $\alpha$  radiation.



(a)



(b)

Fig. 5 (a) ORTEP of form I drawn with 50% ellipsoidal probability. (b) Packing of form I viewed down *b* axis, intermolecular interactions are shown as dotted lines.

Table 1 Relevant torsion angles

Torsion angle	Form I	Form II
C <sub>7</sub> -C <sub>6</sub> -C <sub>5</sub> -C <sub>4</sub>	54.4(2) <sup>o</sup>	58.5(2) <sup>o</sup>
C <sub>6</sub> -C <sub>5</sub> -C <sub>4</sub> -C <sub>9</sub>	-33.0(2) <sup>o</sup>	-35.9(2) <sup>o</sup>
C <sub>5</sub> -C <sub>4</sub> -C <sub>9</sub> -C <sub>8</sub>	5.3(2) <sup>o</sup>	4.6(2) <sup>o</sup>
C <sub>4</sub> -C <sub>9</sub> -C <sub>8</sub> -C <sub>7</sub>	-1.0(2) <sup>o</sup>	2.3(2) <sup>o</sup>
C <sub>9</sub> -C <sub>8</sub> -C <sub>7</sub> -C <sub>6</sub>	23.0(2) <sup>o</sup>	21.1(2) <sup>o</sup>
C <sub>8</sub> -C <sub>7</sub> -C <sub>6</sub> -C <sub>5</sub>	-46.5(2) <sup>o</sup>	-48.6(2) <sup>o</sup>
C <sub>9</sub> -C <sub>8</sub> -N <sub>1</sub> -C <sub>10</sub>	-174.4(2) <sup>o</sup>	-179.0(1) <sup>o</sup>
C <sub>8</sub> -N <sub>1</sub> -C <sub>10</sub> -C <sub>11</sub>	112.8(2) <sup>o</sup>	120.3(2) <sup>o</sup>
C <sub>10</sub> -N <sub>1</sub> -C <sub>2</sub> -C <sub>16</sub>	-9.5(2) <sup>o</sup>	-2.6(2) <sup>o</sup>
N <sub>1</sub> -C <sub>2</sub> -C <sub>16</sub> -C <sub>17</sub>	157.7(1) <sup>o</sup>	133.2(2) <sup>o</sup>
O <sub>1</sub> -C <sub>4</sub> -C <sub>5</sub> -C <sub>6</sub>	148.5(1) <sup>o</sup>	145.1(1) <sup>o</sup>

This pattern matches the experimentally observed PXRD for form II (Fig. 1b of the ESI)<sup>†</sup> and hence proves that crystals of form II, like those of form I, did not undergo any reaction or phase transition on crushing/mild grinding.

## Conclusion

The appearance of these two polymorphs has been observed to be extremely consistent with solvent variation. One form, say

form I, when dissolved and re-crystallized from a solution in acetone, yielded crystals of form II only, and *vice versa*. These observations point out that the generation of different forms from different solvent systems is solely dependent on solute-solvent interaction of the solute in different solvent environments. The DSC data for form I indicate that it is a thermodynamically stable form, while the DSC trace of form II suggests that it could be a kinetically controlled polymorph. Moreover, form II, on heating, gets transformed to a new phase which is different from form I as that solidifies at much lower temperature than that of form I. The differences in polarities (1 : 5 DCM/hexane is less polar than pure acetone) of the solvents used for the crystallization of the title compound have resulted in generating polymorphs without including the solvent molecules in the crystal structure. The tendency of these solvents to yield centrosymmetric or non-centrosymmetric forms depends on the kinetic factors in solution rather than structure based control. The growth of two different polymorphs from different solvent systems show that the solute-solvent interaction has a major role to play in crystal nucleation. It is of interest to note that organic NLO materials can be prepared by careful control of solvent-solute interactions. The presence of organic fluorine and its possible

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- 13 Crystal data-Form I: Chemical formula  $C_{22}H_{20}NOF$ , formula weight 333.4, monoclinic, space group  $P2_1/n$ ,  $a = 12.874(8)$ ,  $b = 6.713(4)$ ,  $c = 20.311(15)$  Å,  $\beta = 94.65(1)^\circ$ ,  $V = 1749.5(2)$  Å<sup>3</sup>,  $Z = 4$ ,  $\rho_{calc} = 1.27$  g cm<sup>-3</sup>,  $T = 90.0(2)$  K,  $\mu = 0.84$  mm<sup>-1</sup>, reflections measured 12157, unique 3196,  $R1_{obs} = 0.039$ ,  $wR2_{obs} = 0.039$ ,  $\delta\rho_{min,max} = -0.223, 0.260$ .
- 14 Crystal data-Form II: Chemical formula  $C_{22}H_{20}NOF$ , formula weight 333.4, monoclinic, space group  $P2_1$ ,  $a = 7.892(5)$ ,  $b = 10.861(6)$ ,  $c = 10.786(2)$  Å,  $\beta = 109.99(8)^\circ$ ,  $V = 868.9(3)$  Å<sup>3</sup>,  $Z = 2$ ,  $\rho_{calc} = 1.27$  g cm<sup>-3</sup>,  $T = 90.0(2)$  K,  $\mu = 0.83$  mm<sup>-1</sup>, flack  $x = -0.3(6)$ , reflections measured 6405, unique 3154,  $R1_{obs} = 0.027$ ,  $wR2_{obs} = 0.072$ ,  $\delta\rho_{min,max} = -0.174, 0.155$ .
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