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Quantitative Analysis of Weak Intermolecular Interactions in Polymorphs of N-(3-chlorophenyl) benzamide.

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ABSTRACT

In order to understand the stability of polymorphs of organic crystals it is important to study the nature of its intermolecular interactions. By calculating the energetic associated with these interactions it becomes possible to understand the nature of these interactions and their influence on the crystal packing that results in various polymorphic forms. In this regard, we have identified from the literature polymorphs of N-(3-chlorophenyl) benzamide and extracted molecular pairs from the crystal packing providing maximum stability to the crystal structure. The lattice energy of the compounds have been calculated by using PIXELC module in Coulomb-London-Pauli (CLP) package and is partitioned into corresponding coulombic, polarization, dispersion and repulsion contributions. It is found that the weak intermolecular interactions like N-H…O, C-H…π plays an important role in the stabilization of the crystal packing of these polymorphs. The lattice energy calculated using PIXEL reveals energetically more stable packing form.

Keywords: Intermolecular interactions; Polymorphs; Crystal Packing; PIXEL

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INTRODUCTION

The protean nature of an organic crystal, reflected in its ability to crystallize in more than one structural arrangements (phenomenon referred to as polymorphism), has since its discovery been a subject of attraction as well as a challenge for several research investigations relevant to different fields, such as pharmaceuticals, organic semiconductors, pigments, food, and explosives. The widespread occurrence of polymorphism in organic crystals makes the packing of organic molecules especially difficult to rationalize and predict. [1] Truly rational solid-state design will not be possible until polymorphism is understood and controlled. [2] The occurrence of polymorphs often reflects the kinetic factors that determine the rates of nucleation and growth of crystals and is even more difficult to understand than the thermodynamics of the most stable crystals. [3] Since the crystal that forms in some circumstances is not necessarily the most stable crystal, it is especially difficult to work out structure-stability relations of the sort on which physical-organic chemistry is based. [4] Complicating this issue is the fact that many polymorphs differ in energy only slightly (for example, by less than 10 or 12 kJ/mol, according to compilations of heats of transition between polymorphs. [5-6] However, the study of polymorphism can be valuable for several reasons. For example, it can yield information about the interplay molecular conformations and intermolecular interactions, will contribute to the determination of the stable thermodynamic form of a molecular crystal, etc. [1] In this regard the present work is subjected to the theoretical calculation of the lattice energies of two polymorphic forms of N-(3-chlorophenyl)benzamide [$C_{13}H_{10}ClNO$]. Polymorph 1 [7] crystallizes in the orthorhombic space group Pbca (Z = 8), whereas the polymorph 2 [8] crystallizes in the monoclinic space group P21/c (Z = 4). Crystallographic details of both these polymorphs have been represented in Table 1. These calculations results in the interaction energies responsible for the packing thus consequently predict the energetically more stable polymorphic form.

Table 1: Crystal data for the Polymorphs of N-(3-chlorophenyl)benzamide

Crystal data	Polymorph 1	Polymorph 2
Chemical Formula	$C_{13}H_{10}ClNO$	$C_{13}H_{10}ClNO$
Crystal system	Orthorhombic	Monoclinic
Space Group	Pbca	P21 /c
a	9.3585 (2) Å	12.5598 (17) A˚
b	9.7851 (2)	10.2782 (14) A˚
c	25.1419 (6)	9.0788 (13) A˚
α	90˚	90˚
β	90˚	109.421 (5) ˚
γ	90˚	90˚
Z	8	4

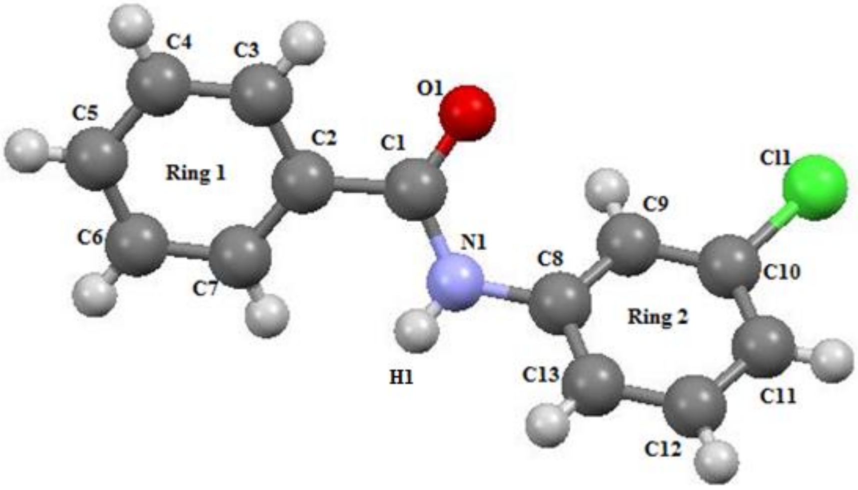

Figure 1: Molecular structure of N-(3-chlorophenyl)benzamide and the numbering scheme

MATERIAL AND METHOD

The Crystallographic Information File (CIF) for both polymorphs has been obtained from Cambridge Crystallographic Data Centre. All the molecular pairs involved in the crystal packing were extracted and their energies were determined using PIXEL.[9] PIXEL calculations were performed in order to estimate the nature and energies associated with the intermolecular interactions which will enable us to explore the role of these interactions in the stabilization of the crystal lattice. A representative illustration of the N-(3-chlorophenyl)benzamide indicating the atomic numbering scheme used for the present work is shown in Figure1.

Experimental

The lattice energies of both the compounds were calculated by PIXELC module in Couloumb-London-Pauli (CLP) computer program package (version 12.5.2014). [9] The total lattice energy is partitioned into its columbic, polarization, dispersion and repulsion contributions (Table 2). In CLP, the coulombic terms are handled by Coulomb's law while the polarization terms are calculated in the linear dipole approximation, with the incoming electric field acting on local polarizabilities and generating a dipole with its associated dipole separation energy; dispersion terms are simulated in London's inverse sixth power approximation, involving ionization potentials and polarizabilities; repulsion is presented as a modulated function of wave function overlap. All the stabilizing molecular pairs involved in crystal packing were selected from the mlc output file, which is generated after PIXEL energy calculations and were analysed with their interaction energies. The symmetry operator and centroid–centroid distance along with coulombic, polarization, dispersion, repulsion and total interaction energies between the molecular pairs are presented in Table 3. The molecular pairs are arranged in decreasing order of their stabilization energies. The PIXEL method has been preferred for the quantification of intermolecular interactions, primarily because of the following reasons: (i) It is computationally less demanding. [9] (ii) It allows partitioning of total interaction energy into corresponding coulombic, polarization, dispersion, and repulsion contribution which facilitates a better understanding of the nature of intermolecular interactions contributing towards the crystal packing.[10-11] (iii) The energies obtained from PIXEL calculation are generally comparable with high level quantum mechanical calculations.[12-13]

Table 2: Lattice energy from CLP (in kcal mol^{-1}) for both the polymorphs

Molecule	$E_{columbic}$	$E_{polarization}$	$E_{dispersion}$	$E_{repulsion}$	E_{total}
Polymorph 1	-66.2	-31.2	-132.5	94.6	-135.4
Polymorph 2	-70.8	-32.1	-148.6	121.8	-129.7

RESULTS AND DISCUSSION

Most stable molecular pairs of **Polymorph 1** extracted from crystal structure are shown in Figure 2(a-c). The symmetry operator and centroid–centroid distance along with columbic, polarization, dispersion, repulsion and total interaction energies between the molecular pairs of Polymorph 1 are presented in Table 3.

Table 3: PIXEL interaction energies (I.E.) (kcal/mol) between molecular pairs related by a symmetry operation and the associated intermolecular interactions in the crystal for Polymorph1

Motif	Interaction	Centroid distance (Å)	$E_{columbic}$	$E_{polarization}$	$E_{dispersion}$	$E_{repulsion}$	E_{total}	Symmetry
a	N-H…O	4.915	-42.8	-17.8	-39.3	52.6	-47.4	1/2-x,-1/2+y,z
b	C-H…Cl	8.241	-5.9	-3.6	-18.5	12.7	-15.2	-1/2+x,1.5-y,-z
c	C-H…π	8.250	-2.8	-2.3	-18.4	9.4	-14.0	-1/2+x,y,1/2-z

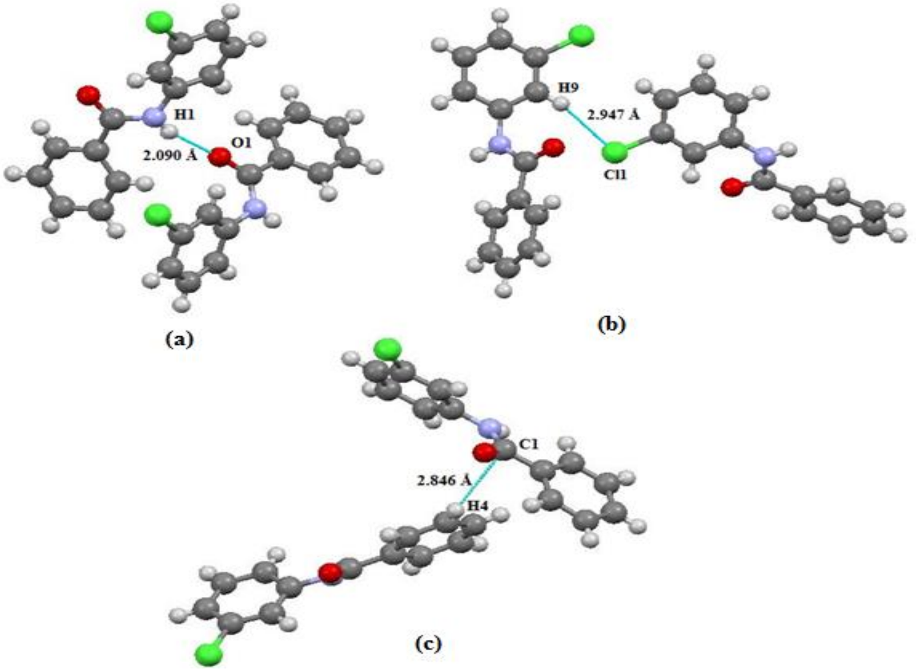

Figure 2: Molecular pairs (a-c in Table 3) extracted using Pixel that stabilizes the crystal packing of Polymorph 1.

The maximum stabilization to the crystal structure comes from N-H…O strong hydrogen bond involving H1, O1 and N1 atoms. The stabilization energy of the pair is -47.4 kcal mol^{-1} (Figure 2a) obtained using PIXEL. The main contribution is due to the columbic interaction. One more stabilized molecular pair shows the presence of strong hydrogen bonding C-H…Cl (Fig. 2b) involves C10, Cl1 and H9 atoms. The donor acceptor distance is 2.947Å. It provides the stabilization of 15.2 kcal mol^{-1}. Columbic interaction is the main contributor to the stabilization energy for this pair. Motif 3 (Fig. 2c) shows the presence of C–H…π (involving H4 and C1 of Centre of gravity [Cg1] of ring1) and provides stabilization of -14.0 kcal mol^{-1}.

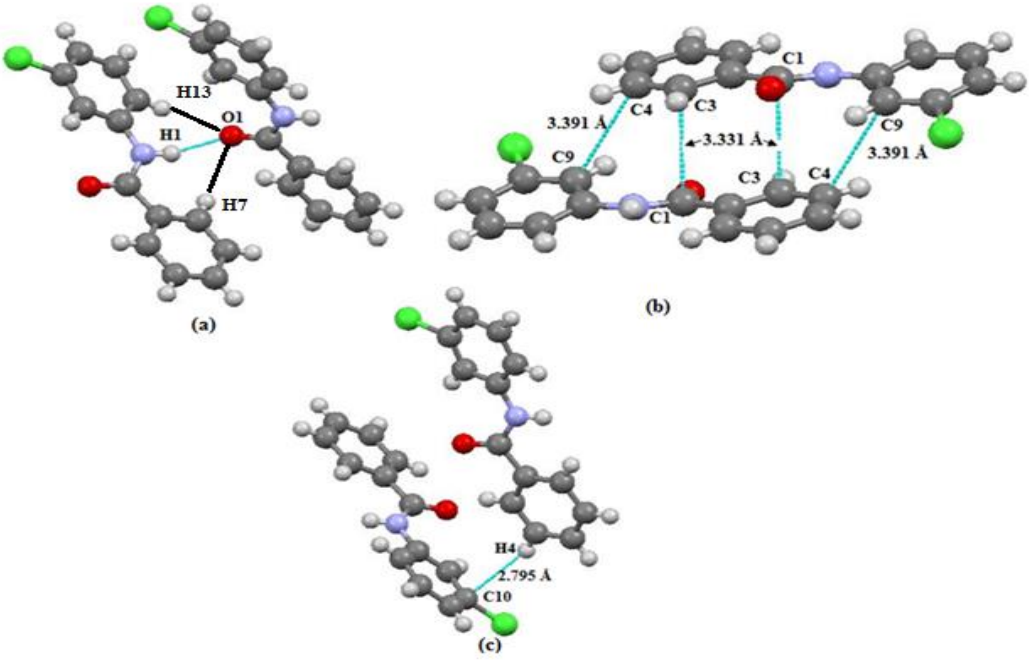

Figure 3: Molecular pairs (a-c in Table 4) extracted using Pixel that stabilizes the crystal packing of Polymorph 2.

Figure 3(a-c) represents molecular pairs of **Polymorph 2** that were extracted from crystal structure and plays major role in its stabilization. The symmetry operator and centroid-centroid distance along with columbic, polarization, dispersion, repulsion and total interaction energies between the molecular pairs for Polymorph 2 are summarized in Table 4.

Table 4: PIXEL interaction energies (I.E.) (kcal/mol) between molecular pairs related by a symmetry operation and the associated intermolecular interactions in the crystal for Polymorph 2

Motif	Interaction		Centroid distance (Å)	$E_{columbic}$	$E_{polarization}$	$E_{dispersion}$	$E_{repulsion}$	E_{total}	Symmetry
a	N-H…O		4.540	-47.6	-20.0	-48.9	68.2	-48.3	x,1/2-y,-1/2+z
b	π–π	C1-C3	5.945	-10.1	-4.6	-46.4	33.6	-27.6	1-x,1-y,1-z
		C4-C9	11.017	-7.1	-2.7	-17.9	11.3	-16.4	1-x,1-y,1-z
c	C-H…π		6.632	-6.4	-2.7	-17.2	10.3	-16.0	1-x,-1/2+y,1.5-z

The most stabilized molecular pair in Polymorph 2 shows the presence of trifurcated hydrogen bonding comprises of two acceptor C-H…O hydrogen bonding (involving O1 with H7 and H13 atoms) along with N-H…O strong hydrogen bond (involving H1, O1 and N1 atoms) with an interaction energy of -48.3 kcal mol^{-1} (Fig. 3a). The donor acceptor distance for N-H…O hydrogen bond is 1.937Å. The main contribution to the interaction energy comes from Dispersion and columbic interactions. Second most stabilized pair shows the presence of π…π interaction, a packing feature that is not observed in Polymorph 1. Molecules are arranged in anti-parallel manner and show the presence of double ring stacking (Cg1-Cg2). Cg1 and Cg2 represent the centre of gravity of two rings of the structure. One more stabilized molecular pair shows the presence of C–H…π interaction (involving H4 and C10 of Cg2 ring) with centroid-centroid distance 6.632 Å. It provides the stabilization of stabilization of -16.0 kcal mol^{-1} and the main contribution comes from the dispersion interaction energy.

CONCLUSIONS

Analysis of different structural motifs which aid in the stabilization of crystal packing for the two Polymorphic forms of N-(3-chlorophenyl)benzamide shows that for both of these forms N-H…O and C-H…π intermolecular interactions are the major contributors that stabilizes the crystal packing. In addition the stabilization of the Polymorph 1 also involves a strong C-H…Cl hydrogen bond that gives extra stability to its crystal packing. However Polymorph 2 involves additional π…π interaction. The Lattice energy for the Polymorph 1 from CLP calculations comes out to be -135.4 kcal mol^{-1} whereas its value comes out to be -129.7 kcal mol^{-1} for the Polymorph 2. These values suggest that the crystal packing of Polymorph 1 is energetically more stable than the Polymorph 2.

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