# Five benzoic acid derivatives: Crystallographic study using X-ray powder diffraction, electronic structure and molecular electrostatic potential calculation

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## ABSTRACT

Crystal structures of five ortho-, meta-, and para-substituted benzoic acid derivatives, 2-fluoro-4-hydroxymethyl benzoic acid (**1**), 4-chloro-3 nitrobenzoic acid (**2**), 5-bromo-2-methyl benzoic acid (**3**), 4-bromo-2 nitrobenzoic acid (**4**) and 4-chloro-2-iodobenzoic acid (**5**) have been determined using X-ray powder diffraction. DFT optimized molecular geometries of **1**—**5** agree closely with those obtained from the crystallographic study. The nature of intermolecular interactions in **1**—**5** has been analyzed through Hirshfeld surfaces and 2D fingerprint plots, and compared with that of unsubstituted benzoic acid compound. The crystal packing of **1**—**5** exhibits an interplay of intermolecular O—H···O, C—H···O and C—H … X (X = F, Cl, Br) hydrogen bonds, and C-X (X = Cl, Br, I)···O halogen bonds, which assemble molecules into a supramolecular framework. Hydrogen- and halogen-bond based interactions in **1**—**5** have been complemented by the molecular electrostatic potential (MEP) surface calculation. The electronic structure of compounds (**1**—**5**) reveals that the estimated band gap in **4**, with the nitro and bromo groups at the ortho and para positions with respect to the COOH group, is the lowest (2.72 eV) among the molecules; the corresponding value in the unsubstituted benzoic is 3.95 eV.

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## 1. Introduction

Noncovalent intermolecular interactions, especially the hydrogen bonds (HBs), have been extensively studied due to their importance across many scientific disciplines ranging from supramolecular chemistry to molecular recognition process in biological systems [1—4]. In recent years, halogen bonds (XBs) have also received significant attention because of their similarity to hydrogen bonds (HBs) in terms of strength and directionality [5—7]. From a crystal engineering prospective, both HB and XB play an important role for the assembly and organization of organic and inorganic building blocks using the concept of motifs and synthons [8,9]. A large fraction of drugs used both in clinics and pre-clinical studies are halogenated and due to the presence of many functional groups as well as halogen atoms in their structure, active pharmaceutical ingredients (APIs) typically have a multifaceted profile

in crystal engineering [10—12]. In structural crystallography, single crystal X-ray diffraction (SXRD) is the most widely used technique for determining crystal structures of molecular compounds, and the geometrical criteria such as, D (donor) … A (acceptor) distance and D-H/X … A angle, X = halogen atom, of specific HB and XB have been generally used in describing the crystal packing of molecular solids [13—15]. As many important materials are available only as microcrystalline powder and growing single crystals suitable for X-ray structure analysis is not always possible within a specified time frame, structure determination directly from powder X-ray diffraction (PXRD) is highly desirable. It should, however, be noted that crystal structure determination using PXRD is a far more difficult task than that of its single-crystal counterpart [16].

With recent advances in the direct space approaches for structure solution [17—20], ab-initio crystal structure analysis using PXRD has become a viable alternative [21—23]. Since PXRD based structure determination cannot establish the positions of hydrogen atoms unambiguously, consideration of geometrical criteria alone as obtained from the PXRD analysis without any supplementary evidence is unlikely to be reliable for assessing the intermolecular

interactions. Molecular electrostatic potential (MEP), a physically-based means for identifying and ranking the HB and XB ability provides a reliable and practical tool for studying the nature of intermolecular interactions [24–26]. This approach utilizes the calculated MEP surface around the molecule, in which the potential maxima and minima correspond to HB/XB donor and acceptor sites, respectively. Several studies correlating the MEP values with overall crystal packing directed intermolecular interactions have been reported [27–30]. In this context, benzoic acid (BA), the simplest aromatic carboxylic acid, is an important structural motif occurring frequently in crystal engineering and biology [31,32]. Several benzoic acid derivatives have been also reported to possess significant antimicrobial, antiviral, antioxidant, antiinflammatory, cytoprotective and antitumor activity [33–35]. In the crystalline state, carboxylic acids usually form cyclic hydrogen-bonded dimers generating an $R^2_2$ (8) graph-set motif [36] through head-to-head carboxyl O–H⋯O hydrogen bonds [37,38].

To study the effect of electron withdrawing substitution on the resulting solid state structures, particularly the role of the hydrogen and halogen bonds in building supramolecular assemblies, we have undertaken structural characterization of five benzoic acid derivatives, 2-fluoro-4-hydroxymethyl benzoic acid (**1**), 4-chloro-3 nitrobenzoic acid (**2**), 5-bromo-2-methyl benzoic acid (**3**), 4-bromo-2 nitrobenzoic acid (**4**) and 4-chloro-2-iodobenzoic acid (**5**) using PXRD. Crystal structure of **2** has been, however, reported earlier using SXRD [39]. The results of crystallographic analysis of **1**–**5** are reported here along with the DFT calculations to study their electronic structures. Intermolecular interactions in **1**–**5** have been correlated with the molecular electrostatic potential (MEP) surface analysis.

## 2. Experimental

### 2.1. Materials and X-ray data collection

The compounds 2-fluoro-4-hydroxymethyl benzoic acid (**1**), 4-chloro-3 nitrobenzoic acid (**2**), 5-bromo-2-methyl benzoic acid (**3**), 4-bromo-2 nitrobenzoic acid (**4**) and 4-chloro-2-iodobenzoic acid (**5**) were purchased from Sigma Aldrich, NY, USA and used without further purification. Powder X-ray diffraction (PXRD) data of compounds **1**–**5** were collected at 293(2) K using a Bruker D8 Advance diffractometer operating in the Bragg-Brentano geometry, with CuK$_\alpha$ radiation ($\lambda = 1.5418$ Å).

### 2.2. Indexing and structure analysis

The PXRD patterns of **1**–**5** were indexed using EXPO 2014 [40] into monoclinic unit cells. Given the volume of the unit cell and consideration of density, the number of formula units in the unit cell of **1**–**5** turned out as 4. Statistical analysis of PXRD data using the FINDSPACE module of EXPO 2014 [40] indicated the most probable space group as P2$_1$ for **1** and P2$_1$/a (or its variant) for **2**–**5**. The unit cell parameters and space group assignments were validated by a Le-Bail fit of PXRD data using a Pseudo-Voigt peak profile function [41] with the program FOX [42]. Structure solution of **1**–**5** was carried out by global optimization of structural models in direct space, based on a Monte-Carlo search using the simulated annealing technique (in parallel tempering mode), as implemented in FOX [42]. The optimization of isolated molecules was performed using the energy gradient method as incorporated in MOPAC 9.0 [43].

The best solution (i.e., the structure with lowest R$_{wp}$) was used as the initial structural model of **1**–**5** for Rietveld refinement [44], which was carried out using the GSAS program [45]. A pseudo-Voigt peak profile function was used during refinement and the

background of PXRD patterns in **1**–**5** was modeled by a shifted Chebyshev function of first kind with 20 points regularly distributed over the entire 2θ range. Initially, the lattice parameters, background coefficients and profile parameters were refined followed by the positional coordinates of all non-hydrogen atoms. Standard restraints were applied to bond lengths and bond angles, and planar restraints were used for the phenyl rings. Isotropic displacement parameter of halogen atoms in **1**–**5** was refined. For other non-hydrogen atoms, common isotropic displacement parameters were refined separately for C, N and O atoms. In the final stages of refinements, a preferred orientation correction (generalized spherical harmonic model) was applied. The final Rietveld plots of **1**–**5** (Fig. 1) showed good agreement between the observed PXRD profile and the calculated X-ray powder diffraction pattern. The molecular views of **1**–**5** with atom labeling scheme are shown in Fig. 2. A summary of crystal data and relevant refinement parameters for **1**–**5** is listed in Table 1.

### 2.3. Hirshfeld surface analysis

The Hirshfeld surfaces [46] and associated 2D fingerprint plots [47] were calculated using Crystal Explorer [48]. Bond lengths to hydrogen atoms were set to typical neutron values (C–H = 1.083 Å and N–H = 1.009 Å). For each point on the Hirshfeld isosurface, two distances d$_e$, the distance from the point to the nearest nucleus external to the surface, and d$_i$, the distance to the nearest nucleus internal to the surface, are defined. The normalized contact distance (d$_{norm}$) based on d$_e$ and d$_i$ is given by

$$d_{norm} \frac{d_i - r_i^{vdw}}{r_i^{vdw}} + \frac{d_e - r_e^{vdw}}{r_e^{vdw}} \tag{1}$$

where r$_i^{vdW}$ and r$_e^{vdW}$ are the van der Waals radii of the atoms. The value of d$_{norm}$ can be negative or positive depending on whether the intermolecular contacts are shorter or longer than the van der Waals separations. The parameter d$_{norm}$ displays a surface with a red-white-blue color scheme, where the bright red spots highlight shorter contacts, the white areas represent contacts around the van der Waals separation, and the blue regions are devoid of close contacts.

### 2.4. Computational study

Density functional theory (DFT) calculations were performed in the solid state (periodic) for **1**–**5** with the DMol$^3$ code [49] in the framework of a generalized gradient approximation (GGA) [50]. The geometry optimization was carried out using BLYP correlation functional [51,52] with a double numeric plus polarization (DNP) basis set. The starting atomic coordinates were taken from the final X-ray refinement cycle, and geometry optimization was carried out without any structural constraints.

The electrostatic potential at any point $\vec{r}$ in the space surrounding a molecule can be expressed as

$$V(\vec{r}) = \sum_A \frac{Z_A}{\left|\vec{R_A} - \vec{r}\right|} - \int \frac{\rho\left(\vec{r'}\right)}{\left|\vec{r} - \vec{r'}\right|} dr' \tag{2}$$

where Z$_A$ is the charge of the nucleus A located at $\vec{R_A}$ and ρ ($\vec{r}$) is the molecular electron density function. The sign of V ($\vec{r}$) at a particular region depends upon whether the effect of the nucleus or the electrons is dominant there. The molecular electrostatic potential (MEP) surfaces of **1**–**5** were generated, and the electron