Research Article

Synthesis, Crystal Structure, and Hirshfeld Surface Analysis of Ciprofloxacin-Salicylic Acid Molecular Salt

Ravikumar Nagalapalli and Shankar Yaga Bheem

Department of Chemistry, BABA Institute of Technology & Sciences, Visakhapatnam 530048, India

Correspondence should be addressed to Ravikumar Nagalapalli; ravikumar.n@bitsvizag.com

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In the present study, ciprofloxacin-salicylic acid molecular salt has been synthesized and preliminarily characterized by FT-IR spectroscopy. The single crystal X-ray diffraction (SCXRD) reveals the proton transfer from carboxylic acid group of salicylic acid to piperazine moiety in ciprofloxacin confirming the formation of new molecular salt. The molecular packing of the molecular salt is mainly supported by $N^+-H\cdots O^-$, $O-H\cdots O$, $C-H\cdots F$, $C-H\cdots \pi$, and $\pi-\pi$ interactions. The 3D Hirshfeld surfaces and the associated 2D fingerprint plots were investigated for intermolecular hydrogen bonding interactions.

1. Introduction

In the pharmaceutical industry salt formation is a widely used method to modulate the physicochemical properties of active pharmaceutical ingredients (APIs) [1]. Salts have been shown to modulate the solubility and bioavailability of APIs [2–4]. An active pharmaceutical salt is a combination of an API with the GRAS (generally regarded as safe by US FDA) listed coformer [5]. A crystal engineering approach in the selection of acid or base for a given drug molecule to make salts or cocrystals is reported in the literature [6, 7]. Hydrochloride salts are the most preferred method to improve the solubility and stability of APIs [1], but hygroscopicity is a drawback for the hydrochloride salts [8]. Ciprofloxacin (CPF) is a synthetic antibacterial fluoroquinolone related to nalidixic acid having a fluorine atom and piperazine ring at the positions 6 and 7 of quinolone-3-carboxylic acid. It is one of the most active fluoroquinolones with a wide spectrum of biological activity, which is active against both Gram-positive [9] and Gram-negative bacteria [10]. In recent years, CPF has drawn great interest from crystal engineers, due to its tendency to form robust supramolecular architectures with compounds having carboxylic acid functional groups, and also various salts of ciprofloxacin are reported in [11–16]. Our endeavours in the present study are synthesis of CPF

molecular salt with GRAS listed salicylic acid, determination of crystal structure by SCXRD, and investigation of various intra- and intermolecular hydrogen bonding by Hirshfeld surface analysis. The molecular structures of CPF and SA are shown in Figure 1.

2. Materials and Methods

2.1. Materials. Ciprofloxacin (purity 98%) and salicylic acid (purity 99%) were purchased from Alfa Aesar, India. Methanol with HPLC grade purity was obtained from Rankem, India, and used without further purification. Distilled water was used for crystallization.

2.2. Synthesis of CPF-SA Molecular Salt. A 1:1 stoichiometric ratio of CPF (33 mg, 0.1 mmol) and SA (13.8 mg, 0.1 mmol) was dissolved in methanol (5 mL) and water (5 mL) mixture at 60°C for 10 minutes, and the resulting solution is filtered, cooled, and left for slow evaporation at room temperature. Colorless prism shape crystals of CPF-SA salt, suitable for single crystal X-ray analysis, were obtained after 2 days.

2.3. Infrared Spectroscopy (FT-IR). A Bruker Alpha-T Fourier transform infrared spectrophotometer in the spectral range 4000 to 600 cm^{-1} with resolution of 2 cm^{-1} was used to

FIGURE 1: Chemical diagrams of ciprofloxacin (a) and salicylic acid (b).

record the infrared spectra of the samples with the KBr pellet making technique.

2.4. Single Crystal X-Ray Diffraction (SCXRD). Single crystal X-ray diffraction data was collected at 298 (1) K on Rigaku Mercury diffractometer using a single wavelength Enhance X-ray source with Mo K_{α} radiation ($\lambda = 0.71070 \text{ \AA}$). The Crystal Clear [17] program was used for data collection and cell refinement. The Crystal Structure [17] program was used for data reduction. The structure was solved by SIR92 [18] program and CRYSTALS [19] program was used for structure refinement. The ORTEP [20] program was used for molecular graphics. All the H positions bound to C atoms were calculated after each cycle of refinement using a riding model $C-H = 0.95 \text{ \AA}$ and $U_{iso}(H) = 1.2U_{eq}(C)$. All the H atoms bound to N and O atoms were located in different Fourier maps and freely refined. The crystallographic details were summarized in Table 1.

2.5. Theoretical Calculation. Molecular Hirshfeld surfaces are generated by CrystalExplorer [21] computer program.

3. Results and Discussion

The CPF-SA molecular salt crystallizes in triclinic space group $P-1$. The crystal structure of CPF-SA molecular salt has one ciprofloxacin cation, one salicylate, and one-half O_2 (Figure 2). The carboxylic acid group of CPF is in unionized state because the C–O and C=O bond distances differ by greater than $0.1 \text{ \AA}$ and are involved in intramolecular hydrogen bonding with the quinolone carbonyl oxygen atom. The carboxylate moiety C–O bond distances are about near equal (difference $< 0.03 \text{ \AA}$). The carboxylic acid group in CPF is planar to the quinolone ring, as evidenced by the torsion angle ($C5-C6-C10-O1 = 175.8^\circ$). A carboxylic acid group in salicylic acid transfers proton to the nitrogen atom of the piperazine moiety in CPF, thereby forming a salicylate anion and CPF cation. Proton transfer is evidenced by the difference between the C–O bond distances $C(18)-O(5) = 1.264(2) \text{ \AA}$ and $C(18)-O(4) = 1.249(2) \text{ \AA}$ of the carboxylate group in salicylate moiety with the ΔD_{C-O} value of $0.015 \text{ \AA}$. The relatively small ΔD_{C-O} value confirmed the formation of carboxylate group [22]. The piperazinium moiety in CPF adopts chair conformation. The CPF aromatic molecular core is π -stacked infinitely along the crystallographic b -axis at

TABLE 1: The crystal and experimental data.

Empirical formula	$C_{24}H_{24}FN_3O_7$
Formula weight	485.46
Crystal system	Triclinic
Space group	$P-1$
T (K)	298(1)
λ (Å)	0.71070
a (Å)	6.9532(10)
b (Å)	9.8979(11)
c (Å)	17.212(2)
α (°)	79.397(19)
β (°)	85.53(2)
γ (°)	83.09(2)
V (Å ³)	1154.0(3)
Z	2
D_{cal} (g cm ⁻³)	1.397
μ (mm ⁻¹)	0.109
$F(0\ 0\ 0)$	508
Crystal size (mm)	$0.20 \times 0.20 \times 0.20$
Crystal shape and color	Prism, colorless
θ_{range} (°)	2.4 to 27.4
h	$-8 \rightarrow 7$
k	$-12 \rightarrow 12$
l	$-21 \rightarrow 21$
Reflections collected	4623
Reflections unique	$4575/R_{int} = 0.039$
Absorption correction	Multi-scan
Goodness-of-fit on F^2	1.18
R_1 and wR_2 indices (all data)	0.055, 0.057
$\Delta\rho_{max}, \Delta\rho_{min}$ (e·Å ⁻³)	0.26 and -0.29
CCDC	968489

$3.58 \text{ \AA}$ distance. The CPF cations reside in the ab -plane and the salicylate anions are perpendicular to it (along the c -axis). The molecular packing of the crystal is also stabilized by C–H $\cdots$ F interactions. The overall crystal packing of the molecular salt is shown in Figure 3. Selected bond lengths, bond angles, torsion angles, and possible hydrogen bonding interactions are given in Table 2.

FT-IR spectroscopy is a widely used technique in the characterization of the formation of new solid phases. The infrared peaks of the $-\text{COOH}$ group of CPF resonate at 1696 and 1262 cm^{-1} due to C=O and C–O stretch, respectively. The broad peak at 2424 cm^{-1} is attributed to the protonated piperazine nitrogen atom (NH_2^+) [23]. Moreover, the appearance of two characteristic carboxylate IR absorption vibrations at 1574 and 1337 cm^{-1} due to asymmetric and symmetric O–C–O stretch, respectively, confirmed the proton transfer from the $-\text{COOH}$ group in SA.

The 3D Hirshfeld surfaces and 2D fingerprint maps are unique for each molecule in the asymmetric unit of a given crystal. Hirshfeld surfaces provide a three-dimensional picture of intermolecular interactions in a crystal [24]. For CPF-SA molecular salt, N–H $\cdots$ O and O–H $\cdots$ O hydrogen

FIGURE 2: ORTEP diagram of CPF-SA molecular salt, showing 50% probability ellipsoids.

FIGURE 3: Crystal packing diagram of CPF-SA molecular salt.

TABLE 2: Geometrical parameters.

(a) Selected bond lengths (Å), bond angles (°), and torsion angles (°)			
F1–C2	1.3619(13)	N1–C16	1.488(2)
O1–C10	1.215(2)	N1–C15	1.483(2)
O2–C10	1.3318(19)	N2–C1	1.3857(16)
O3–C5	1.2635(16)	N2–C14	1.4645(18)
O4–C18	1.249(2)	N2–C17	1.4786(19)
O5–C18	1.264(2)	N3–C11	1.4589(17)
O6–C24	1.346(2)	N3–C7	1.3484(17)
O7–O8	1.045(4)	N3–C8	1.4085(16)
C15–N1–C16	110.77(11)	N3–C8–C9	120.21(11)
C14–N2–C17	111.31(11)	O2–C10–C6	115.56(13)
C1–N2–C14	118.30(11)	O1–C10–C6	123.16(13)
C1–N2–C17	120.91(11)	O1–C10–O2	121.28(13)
C7–N3–C11	120.32(11)	N3–C11–C13	118.98(12)
C7–N3–C8	119.30(11)	N3–C11–C12	118.65(12)
C8–N3–C11	120.29(10)	N2–C14–C15	111.16(12)
N2–C1–C9	122.20(12)	N1–C15–C14	111.17(12)
N2–C1–C2	121.91(12)	N1–C16–C17	109.93(13)
F1–C2–C1	119.16(11)	N2–C17–C16	109.68(12)
F1–C2–C3	117.41(12)	O4–C18–C19	118.77(15)
O3–C5–C4	121.59(12)	O5–C18–C19	119.49(13)
O3–C5–C6	123.06(12)	O4–C18–O5	121.72(16)
N3–C7–C6	124.37(13)	O6–C24–C23	118.18(18)
N3–C8–C4	118.97(11)	O6–C24–C19	121.39(17)
C1–N2–C14–C15	157.17(12)	C7–N3–C8–C9	178.24(11)
C10–C6–C7–N3	179.51(12)	N3–C8–C9–C1	176.34(11)

(b) Hydrogen bonding interactions				
Interaction	D–H/Å	H···A/Å	D···A/Å	<D–H···A/°
O6–H60···O4	0.96(2)	1.64(2)	2.357(3)	152.5(19)
N1–H100···O4 ⁱ	0.976(14)	2.473(15)	3.105(2)	122.2(11)
N1–H100···O5 ⁱ	0.976(14)	1.755(14)	2.722(18)	170.8(13)
N1–H101···O7 ⁱⁱ	0.943(15)	1.873(15)	2.803(3)	168.1(15)
N1–H101···O8 ⁱⁱ	0.943(15)	1.849(15)	2.740(3)	156.5(15)
O2–H201···O3	0.93	1.67(2)	2.562(16)	161.6(19)
C7–H7···O1	0.95	2.480	2.811(18)	101.0
C12–H121···O1 ⁱⁱⁱ	0.95	2.530	3.479(2)	174.0
C15–H121···O2 ^{iv}	0.95	2.590	3.395(18)	143.0
C16–H162···O6 ^v	0.95	2.490	3.371(2)	154.0
C17–H171···F1	0.95	2.170	2.862(2)	129.0

Symmetry codes: (i) $-x + 2, -y + 1, -z + 1$ (ii) $-x + 1, -y + 1, -z + 1$ (iii) $-x + 1, -y + 2, -z + 2$ (iv) $-x + 2, -y + 1, -z + 2$ (v) $x, y - 1, z$.

bonding intermolecular interactions appear as two small spikes (upper left spike is sharp and lower right spike is broad) in the 2D fingerprint map, which have the most significant contribution to the total Hirshfeld surfaces of 1, comprised of 36.6%. The H–H interactions, which appeared in the middle of scattered points in the 2D fingerprint map, are comprised of 34.0% of the total Hirshfeld surfaces. The C–H···F interactions also have a relatively significant contribution to the

FIGURE 4: Hirshfeld surface (a) and 2D fingerprint map (b).

total Hirshfeld surfaces of CPF-SA molecular salt, comprised of 6.0%. Apart from those above interactions, the other $\pi \cdots \pi$ (C–C), lone-pair··· π (O–C), and lone-pair···lone-pair (O–O) interactions are also observed. The 3D Hirshfeld surfaces and 2D fingerprint maps of CPF-SA molecular salt are shown in Figure 4.

4. Conclusions

To summarize, we have reported synthesis, X-ray crystal structure analysis, and the Hirshfeld surfaces analyses of ciprofloxacin-salicylic acid molecular salt. The formation of the molecular salt was further characterized and confirmed by FT-IR analysis. The crystal structure of the salt is mainly stabilized by $N^+H \cdots O^-$, $O-H \cdots O$, $C-H \cdots F$, and $\pi \cdots \pi$ interactions. The 3D Hirshfeld surface analysis and 2D fingerprint maps analysis revealed that $N-H \cdots O$ and $O-H \cdots O$ hydrogen bonding intermolecular interactions are more prominent in the salt.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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