Hydrogen-bonded Supramolecular Association in Organic Acid-base Pyrimidine Salt and Hirshfeld Surface Analysis

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Abstract. The present study deals with the crystal structure of organic salt, namely, 2-amino-4-methoxy-6-methylpyrimidinium 2-chlorobenzoate, synthesized by slow evaporation technique. The structure of the grown crystal was elucidated by using single crystal X-ray diffraction technique. The colourless crystal structure of salt belongs to the monoclinic crystallographic system with space group $P_{2_1}/c$, $Z = 4$, and $a = 7.3269$ (3) Å, $b = 25.2003$ (10) Å, $c = 7.9743$ (3) Å, $\beta = 112.795$ (2) °. The pyrimidine moieties are protonated at one of the nitrogen atoms of the pyrimidine rings. The carboxylate group of the anions (hydrogen 2-chlorobenzoate) interacts with the protonated pyrimidine moiety through a pair of N−H···O hydrogen bonds resulting the complementary DDAA (D = donor and A = acceptor in hydrogen bonds) arrays of quadruple hydrogen-bonding patterns. The -COO- acceptor consistently seeks out the -N-H+ donor generating the most important intermolecular interaction by comparison with similar structures in the Cambridge Structural Database (CSD). The combination of the strong hydrogen bonding (N−H···O and C−H···O) and weak hydrogen bonding (π−π stacking) associations in the crystal packing led to the formation of the 3-Dimensional network structures. A detailed analysis of Hirshfeld surfaces and 2-D fingerprint plots facilitate a comparison of intermolecular interactions in the supramolecular architecture. An evaluation of the Hirshfeld surfaces confirm the importance of intermolecular interactions involving oxygen atoms as well as the π—π stacking interactions.

1. Introduction

Supramolecular interactions have gained a lot of attentions for several past years since it involved the usage of intermolecular non-covalent interactions include classical/ non-classical hydrogen bond, stacking, electrostatic, hydrophobic and charge-transfer interactions [1–4]. Hydrogen bonding interaction plays a vital role in molecular recognition for design a new materials with highly specific features. With hydrogen bond interactions, cocrystals and organic salts can be generated [4]. In pharmaceuticals field, salt formation generally used to modify the properties of the compound such as solubility, stability, and hygroscopicity of the drug product [4, 5]. In this regard, the most frequently used moieties with hydrogen bonding capability is carboxylic acid with N-containing compound, such as pyridine and pyrimidine [6, 7]. Pyrimidine and aminopyrimidine derivatives are biologically very...
important compounds since they occur in nature as components of nucleic acids, such as cytosine, uracil and thymine. Pyrimidine derivatives are very important molecules in biology and have many applications in the areas of pesticide and pharmaceutical agents [8] and also developed as antiviral agent (AZT), which is the most widely used as anti-AIDS drug [9]. The synthesis, crystal structure with hydrogen bonding and Hirshfeld surface analysis of the aminopyrimidine-carboxylate salt have been undertaken and are presented herein.

2. Synthesis
Both of the starting materials 2-amino-4-methoxy-6-methylpyrimidine and 2-chlorobenzoic acid were obtained from Sigma–Aldrich chemical suppliers. Analytical grade solvent was used for preparation of the salt. The 1:1 mixture of 2-amino-4-methoxy-6-methylpyrimidine (70 mg, 1 mmol) and 2-chlorobenzoic acid (78 mg, 1 mmol) was dissolved in 20 mL of hot methanol by heating magnetic stirrer hotplate for a few minutes. The resulting solution was allowed to cool slowly at room temperature and crystals of the title salt (I) appeared after a few days (Scheme 1).

3. Experimental detailed
3.1. X-ray Crystallography and Data Collection
Single crystal suitable for X-ray analysis was performed on Bruker SMART APEX II CCD diffractometer using MoKα radiation (λ = 0.71073 Å) with φ and ω scans. The SAINT [10] software was used to integrate the raw files to obtain useful data crystal, which was further solved and refined by the SHELXTL [11] software. Lastly, the data was enhanced by applying the absorption correction process through SADABS [10]. The molecular graphics were drawn using SHELXTL [11] program. Anisotropic thermal factors were assigned to all non-hydrogen atoms. The N-bound hydrogen atoms were located in a difference Fourier map and refined freely [refined N—H distances 0.95 (2), 0.92 (2) and 0.86 (2) Å] and were refined using a riding model, with $U_{iso}(H) = 1.2U_{eq}(C)$ or $1.5U_{eq}(methyl\ C)$. A rotating group model was applied to the methyl groups.

3.2. Hirshfeld Surface Analysis
The Hirshfeld surface analysis [12, 13] of salt I was generated by CrystalExplorer 3.1 [14], which can be summarized with fingerprint plots mapped over $d_{norm}$. The contact distances to the closest atom inside ($d_i$) and outside ($d_e$) of the Hirshfeld surface analyzed the intermolecular interaction through the mapping of $d_{norm}$.
Table 1: Crystal Structure Parameters of salt I.

| Compound          | Salt I |
|-------------------|--------|
| CCDC              | 1024221|
| Empirical Formula | (C₆H₁₀N₃O)⁺·(C₇H₄ClO₂)⁻ |
| Formula Mass      | 295.72 |
| Crystal System and Space group | Monoclinic, P₂₁/c |
| a (Å), b (Å), c (Å) | 7.3269 (3), 25.2003 (10), 7.9743 (3) |
| α (°), β (°), γ (°) | 90, 112.795 (2), 90 |
| V (Å³)            | 1357.38 (9) |
| Z, Dc (g cm⁻³), μ (mm⁻¹) | 4, 1.447, 0.29 |
| F(000), θ range (°) | 616, 2.90–30.0 |
| Measured reflections | 21861 |
| Unique reflections | 2650 |
| Observed reflections (I>2σ(I)) | 2279 |
| No. of parameters | 195 |
| R(a), wR(b), GOF(c) | 0.041, 0.085, 1.05 |
| Residual peaks (e·Å⁻³) | 0.24, −0.28 |
| Colour, shape and Crystal size (mm) | Colourless, needle, 0.72 x 0.18 x 0.009 |

For I, w = 1/[σ²(F₀)² + (0.0262P)² + 1.219P] where P = (F₀² + 2Fₑ²)/3. [a] R = Σ||F₀| – |Fₑ||/Σ||F₀||, [b] R ≡ Σw(|F₀| – |Fₑ|²)²/(Σw|F₀|²)¹/², [c] GOF = {Σw(|F₀| – |Fₑ|²)²/(n–p)}¹/², where n is the number of reflections and p the total number of parameters refined.

4. Results and Discussion

4.1. Molecular Features

Salt (I) of the composition 2-amino-4-methoxy-6-methylpyrimidine and 2-chlorobenzoic acid was prepared by reacting equal mole in 1:1 ratio, which crystallizes as monoclinic colourless needle crystals in the centrosymmetric space group P₂₁/c. The structure of I with the atom numbering scheme is shown in Figure 1.

![Figure 1](image)

A search in the Cambridge Structural Database (CSD V5.38), updated October 2017; [15] revealed 9 crystal structures containing both 2-amino-4-methoxy-6-methyl pyrimidine and aromatic/aliphatic carboxylic acid, with such a supramolecular heterosynthon observed in all of them. In the structures with code of EMUMAC [16], EQAVOJ [17], NUQTOJ [18], VAQRUB [19], VAQSAI [19], VAQSEM [19], VAQSIO [19], VAQSIQ [19], VAQSOW [19] and VACSUC [19], the 2-aminopyrimidine is a cation forming salts.
Table 2: Selected parameters (Å, °) of I with the similar 2-aminopyrimidine crystal structures.

| Compounds | Selected parameters | Bond Length (Å) | Selected parameters | Angles (°) |
|-----------|---------------------|----------------|---------------------|-----------|
| I         | N1—C1               | 1.363 (2)      | C4—N1—C1           | 120.63 (16) |
|           | C1—N2               | 1.326 (2)      | N1—C1—N2           | 117.90 (17) |
|           | O2—C13              | 1.262 (2)      | N2—C1—N3           | 119.61 (16) |
|           | O3—C13              | 1.254 (2)      | O3—C13—O2          | 125.04 (17) |
| VAQSAI [19] | N1—C1          | 1.356           | C4—N1—C1           | 120.06    |
|           | C1—N2               | 1.320           | N1—C1—N2           | 117.53    |
|           | C13—O2              | 1.270           | N2—C1—N3           | 119.68    |
|           | C13—O3              | 1.247           | O3—C13—O2          | 124.59    |
| VAQSIQ [19] | N1—C1          | 1.347           | C4—N1—C1           | 120.49    |
|           | C1—N2               | 1.315           | N1—C1—N2           | 118.04    |
|           | C13—O2              | 1.258           | N2—C1—N3           | 119.10    |
|           | C13—O3              | 1.245           | O3—C13—O2          | 124.55    |

Table 3: Hydrogen bonding geometry (Å, °) for I.

| D—H···A | D—H | H···A | D···A | D—H···A |
|---------|-----|------|------|--------|
| N1—H1N1···O1 | 0.95 (2) | 1.71 (2) | 2.662 (2) | 176 (3) |
| N2—H1N2···O3 | 0.92 (2) | 1.82 (2) | 2.741 (2) | 175 (2) |
| N2—H2N2···O3i | 0.86 (2) | 2.04 (2) | 2.775 (2) | 144 (2) |
| C9—H9A···O2ii | 0.95 | 2.49 | 3.423 (2) | 168 |

Symmetry Code: (i) −x+1, −y+1, −z+1; (ii) x, −y+3/2, z+1/2. Cg1: C7–C12; Cg2: N1/C1/N3/C2–C4

The asymmetric unit organic salt I (Figure 1) comprises one 2-chlorobenzoate anion and one 2-amino-4-methoxy-6-methylpyrimidinium cation. The hydroxyl group of the 2-chlorobenzoic acid is deprotonated and proton-transferred to the nitrogen atoms of 2-aminopyrimidine moieties. This is confirmed by the bond length of O2—C13 being 1.262 (2) Å suggesting shortened bond length as compared to the neutral 2-chlorobenzoic acid [20]. In the cation, the protonated N1 atom leads to a slight widening in the C1—N1—C4 angle of the pyrimidine ring [Table 2: 120.63 (16) °], compared to the corresponding angle of 116.01 (18) ° in neutral 2-amino-4-methoxy-6-methylpyrimidinum [21].

Table 2 also shows a comparison between the selected experimental structural parameters with the similar 2-aminopyrimidine crystal structures (CSD reference codes: VAQSAI [19] and VAQSIQ [19]). In general, the experimental bond length and bond angle values of the title salt I are comparable with the corresponding values obtained by similar crystal structures [19].

In the crystal packing of I, the protonated N1 atom and the 2-amino group (N2) are hydrogen-bonded to carboxylate oxygen atoms (O2 and O3) via a pair of intermolecular N1—H1N1···O2 and N2—H2N2···O3 hydrogen bonds forming a cyclic hydrogen-bonded motif (supramolecular heterosynthon) designated by the graph-set notation $R_2^2(8)$ [22]. The $R_2^2(8)$ motifs are centrosymmetrically paired via N2—H2N2···O3 (−x+1, −y+1, −z+1) (Table 3) hydrogen bonds resulting DDAA array (where D is a hydrogen-bond donor and A is a hydrogen-bond acceptor) of quadruple hydrogen bonds represented the graph-set notations of $R_2^2(8)$, $R_2^2(8)$ and $R_2^2(8)$ (Figure 2a). This type of motif has been reported in the crystal structures of and 2-amino-4-methoxy-6-methylpyrimidinum-1-ium trifluoroacetate [17], 2-amino-4-methoxy-6-methylpyrimidinum 2-fluorobenzoate, 2-amino-4-methoxy-6-methylpyrimidinum 3-chlorobenzoate, 2-amino-4-methoxy-6-methylpyrimidinum 3-nitrobenzoate and 2-amino-4-methoxy-6-methylpyrimidinum benzoate [19]. The quadruple hydrogen-bonding motifs are further extended through a C9—H9A···O2 (x, −y+3/2, z+1/2) hydrogen bonds, leading to the formation of hydrogen-bonded supramolecular chain structure along bc plane. The crystal structure of I is further stabilized by π–π interactions between the
pyrimidine (Cg2; N1/N3/C1–C4) rings (Cg2···Cg2 = 3.5392 (12) Å; 1–x, 1–y, –z) (Figure 2b) and resulting 3-Dimensional network.

Figure 2: The packing diagram for salt I (a) DDAA array of quadruple hydrogen bonds (b) supramolecular chain and π—π interactions.

4.2. Hirshfeld Surface Analysis
The intermolecular interactions of the title salt I is using the Hirshfeld surfaces analysis. This analysis shows surfaces mapped over dnorm, shape index with the 2-D fingerprint plot showing the contributions of different kind of intermolecular contacts. In I, the N2—H2N2···O3 and C9—H9A···O2 interactions are shown on the Hirshfeld surfaces marked with bright red spot for short contacts (Figure 3a). The largest region of H···H interactions appear with high concentration in the middle region of the fingerprint plot, shown in light blue minimum at d_e=d_i ~1.5 Å (Figure 3ii) with the overall Hirshfeld surfaces of 38.3%. The O···H/H···O contacts (Figure 3iii) which comprise 16.3% of the total Hirshfeld surfaces are made up of N2—H2N2···O3 and C9—H9A···O2 interactions. The N2—H2N2···O3 interactions are represented by two symmetrical narrow pointed spikes with d_e+d_i ~ 1.95 Å, while the C9—H9A···O2 interactions are shown by the light blue spikes with d_e+d_i ~ 2.4Å. The C···C contacts assigned to π—π stacking interactions appear as a distinct triangle in the fingerprint plot, seen in figure 3(iv) at around d_e=d_i ~1.8 Å having 1.9% contribution. The presence of the π—π stacking interactions is also indicated by the appearance of red and blue triangles on the shape-indexed surfaces, identified with red circle in Figure 3b.
Figure 3: The Hirshfeld surface mapped on (a) dnorm, (b) shape index and (i-iv) fingerprint plot of the title salt I.

5. Conclusion
Supramolecular networks of salt I was investigated by single-crystal X-ray diffractions analysis. The bond lengths and angles of moieties which involved in proton transfer are differ from their corresponding neutral co-former or related molecule. In I, the 2-chlorobenzoate anion was hydrogen-bonded to the protonated pyrimidine ring to form supramolecular heterosynthons via N⁺—H···O- interactions. Bright red spots observed on the Hirshfeld surfaces visualized the intermolecular interactions of salt I. From the fingerprint plots, the close contacts contribution in salt I are dominated by H···H and O···H/H···O contacts and also π—π stacking interactions have clear signatures in the fingerprint plots. These interactions play a key role towards the stabilization of salt I structure in the solid state.

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