Supramolecular assembly in designing co-crystals of fumaric acid and pyrimidine/picolinate derivatives

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ABSTRACT

Two co-crystals possessing fumaric acid and 2-amino-4,6-dimethoxypyrimidine (1) and fumaric acid and ethyl 2-picolinate (2) were prepared. The structure of both compounds was determined using single-crystal X-ray crystallography. The asymmetric unit of cocrystal 1 formed in a triclinic system with space group P-1 consists of one 2-amino-4,6-dimethoxypyrimidine and one half of fumarate, whereas cocrystal of 2 formed in a monoclinic system with space group P21/c consists of an ethyl-2-picolinate and a half of fumarate. Co-crystal 1 exhibits intramolecular O–H···N and N–H···O hydrogen bonds as well as intermolecular N–H···O hydrogen bonds, whereas co-crystal 2 exhibits intermolecular C–H···O and O–H···N hydrogen bonds as well as weak π···π stacking interactions. Intermolecular interactions were investigated using Hirshfeld surface analyses. H···H (40.9%), O···H (32.9%), and C···H (8.2%) are the major interactions in 1 and H···H (41.6%), O···H (34.8%), and C···H (8.5%) are the most common in 2. Furthermore, density functional theory (DFT) was used to investigate the structural features of the molecules using the B3LYP-D3/6-311G(d,p) basis set. Molecular electrostatic potential (MEP) surface and global reactivity descriptors for molecules were determined to explain the reactivity of molecular behavior, structural activity, and hydrogen bonds.

Introduction

Crystal engineering, which is the application of the concepts of supramolecular chemistry to the solid state with the assumption that crystalline solids are in fact self-assembling systems, provides an excellent opportunity for studying and comprehending the hierarchy of intermolecular interactions between the various functional groups in order to construct new solid-state structures with desired physical and chemical characteristics (1–4). Over the years, organic supramolecular frameworks have attracted a lot of interest in supramolecular chemistry because of their ability to use hydrogen bonds (H-bonds) as a prominent driving force (1–5). Research on organic entities based on supramolecular synthons is rapidly progressing using crystal engineering techniques (6,7). Hydrogen bonds, halogen bonds, and stacking interactions have been used extensively in the construction of these synthons, with hydrogen bonding being the most common due to its strength, directionality, and...
predictability \((8,9)\). These synthons can be classified as homo-synthons or hetero-synthons depending on their structure \((8,9)\). Many studies suggest that supramolecular hetero-synthons are preferred over homo-synthons \((10–12)\). The hydrogen bond, which acts as a link between molecules, has the ability to form supramolecular assemblies of hydrogen donor and acceptor molecules due to its highly directed character \((1–5)\). Furthermore, the strength of noncovalent interactions varies from mild forces like van der Waals interactions between \(\text{C-H-}\) (\(X = \text{O, N}\)) molecules to strong forces like hydrogen bonds between \(\text{O-H-}\) molecules. In most cases, the visible solid-state structure is the result of a combination of strong and weak interactions \((13–17)\).

Crystal engineering with the use of carboxylic acid molecules has also been shown to be a useful method for investigating the hierarchy of intermolecular interactions among the various multifunctional groups \((18,19)\). Carboxylic acids also produce supramolecular hetero-synthons comprising various \(\text{N-substituted heterocyclic compounds, allowing them to form multicomponent crystals}\) \((18,19)\). In recent years, multicomponent crystals (binary salts and binary co-crystals) \((18–20)\), a particularly significant class of pharmaceutical materials among various solid-crystalline forms due to their ability to increase the solubility and dissolution of active pharmaceutical ingredients (APIs) or food additives \((21,22)\), have attracted a lot of attention for fine-tuning the properties of crystalline products without changing the target molecule \((21,22)\).

Fumaric acid, the trans isomer of butenedioic acid, is abundantly found in nature \((23)\) and acts as an essential intermediary in the formation of organic acids as an adduct with a wide range of amines, resulting in a variety of fascinating one-, two-, and three-dimensional supramolecular structures \((23)\). Moreover, fumaric acid is an essential part of the paper and food industries because of its role in the manufacture of polymeric materials and as an important component of cell culture medium \((24,25)\). Pyrimidines and their derivatives are biologically essential compounds that occur naturally as nucleic acid components and have a wide range of pharmacological properties, including antiviral, anti-inflammatory, anticancer, and antidepressant effects \((26–30)\). Meanwhile, pyridines and pyrimidines are commonly used in the field of crystal engineering due to their flexibility. The well-known synthons HT (heterotrimers) and LHT (linear hetero-tetramers) are formed in the presence of pyrimidines and carboxylic acids \((31–33)\).

Herein, we report the formation of two co-crystals containing fumaric acid and 2-amino-4,6-dimethoxypyrimidine \(1\), and fumaric acid and ethyl-2-picolinate \(2\) (Scheme 1). Single crystal X-ray crystallography was used to describe the structures of both co-crystals. In addition, computational studies were conducted to gain insight into the structure of these co-crystal. Hirshfeld surface analyses were also performed on the co-crystals in order to find different interactions.

### Experimental

#### Material

2-amino-4,6-dimethoxypyrimidine, ethyl 2-picolinate and fumaric acid were purchased from Sigma-Aldrich. Sodium hydroxide was procured from Loba Chemie.
**Synthesis of co-crystal 1 and 2**

2-amino-4,6-dimethoxypyrimidine (0.42 g) was added to fumaric acid (2.7 mmol; 0.30 g) dissolved in an aqueous solution of sodium hydroxide (0.022 mg) (pH 7.82) (20 ml), and the mixture was agitated for half an hour at 80 °C. The resultant solution was filtered out and, and then left to slowly evaporate at room temperature for a week, leading to the development of colorless prismatic crystals for 1.

To prepare cocrystal 2, ethyl 2-picolinate (0.41 g) was combined with fumaric acid (2.7 mmol; 0.30 g) dissolved in an aqueous sodium hydroxide (0.022 mg) (pH 7.82) (20 ml) at 80 °C for 30 min with magnetic stirring. After filtering out the reaction mixture, the solution was gradually allowed to evaporate at room temperature. Colorless prism-like crystals detached from the mother liquor within a week.

**X-ray crystallography**

X-ray intensity measurements were conducted on crystals with dimensions 0.78 × 0.67 × 0.48 mm³ of 1 and 0.67 × 0.58 × 0.44 mm³ of 2 at 296 K, using a STOE IPDS 2 (34) diffractometer with an X-ray generator running at 50 kV and 45 mA and used Mo-Kα radiation with wavelength 0.71073 Å. The three-dimensional structure was solved directly and refined with full-matrix least-squares on $F^2$ using the SHELXL software (35,36), which was implemented in WinGX (37). All atomic parameters except hydrogen were refined using the anisotropic approximation of atomic displacements in 1 and 2. All hydrogen atoms in the model were included using the riding model and isotropic thermal parameters. Table 1 lists the whole crystallographic details. CCDC reference numbers 1873032 for 1 and 2122233 for 2 refer to the deposit of crystallographic data with the Cambridge Crystallographic Data Centre, which is freely available at [www.ccdc.cam.ac.uk/data request/cif](http://www.ccdc.cam.ac.uk/data request/cif).

**Computational details**

DFT calculations were performed with Becke’s three-parameter Lee–Yang–Parr hybrid exchange–correlation (B3LYP) functions, including Grimme dispersion corrections (D3), using the Gaussian 09 package (38) to optimize the synthesized compounds (1 and 2). This approach was used in this study to optimize molecules in the gas phase using the B3LYP-D3/6-311G(d,p) basis set (39). To ensure that the cocrystal 1 and 2 were properly optimized, frequency calculations were performed at the same level of theory to confirm the global minima, with no imaginary vibrational frequencies. Chemical properties were calculated using frontier molecular orbitals (HOMO–LUMO) derived from optimized compounds utilizing the same level of theory. The properties of the molecular electrostatic potential (MEP) were determined using theoretical computations. GaussView, GaussSum, Multiwfn, and Chemcraft (40–43) programs were used for visualization.

### Table 1. Experimental details of 1 and 2.

|               | 1               | 2               |
|---------------|-----------------|-----------------|
| CCDC number   | 1873032         | 2122233         |
| Chemical formula | C10H11N3O6      | C10H11NO6       |
| Crystal system, space group | Triclinic, P–1 | Monoclinic, P21/c |
| M (g/mol)     | 213.20          | 209.20          |
| Z             | 2               | 4               |
| a (Å)         | 7.0295(9)       | 9.4090(16)      |
| b (Å)         | 7.9096(9)       | 13.9343(15)     |
| c (Å)         | 9.3538(11)      | 8.2977(16)      |
| α (deg)       | 86.606(9)       | 90.103633(15)   |
| β (deg)       | 89.20969(9)     | 103.633(15)     |
| γ (deg)       | 77.389(11)      | 90              |
| Volume (Å³)   | 492.55(11)      | 1057(3)         |
| Temperature (K)| 296            | 9.4090(16)      |
| Radiation; λ (Å) | MoKα; 0.71073  | 13.9343(15)     |
| μ (mm⁻¹)      | 0.12            | 9.4090(16)      |
| Crystal size (mm) | 0.78 × 0.67 × 0.48 | 0.67 × 0.58 × 0.44 |
| Diffractometer | Stoe IPDS 2     |                 |
| Absorption correction | Integration |                 |
| hmin, hmax    | –8, 8           | –11, 11         |
| kmin, kmax    | –9, 9           | –16, 17         |
| lmin, lmax    | –11, 11         | –8, 10          |
| Tmin, Tmax    | 0.473, 0.669    | 0.944, 0.970    |
| No. of measured, independent, observed [I > 2σ(I)] reflections | 5852, 1941, 1445 | 5382, 2026, 656 |
| Rint          | 0.055           | 0.026           |
| R1, wR2       | 0.617           | 0.615           |
| R1(F² > 2σ(F²), S | 0.051, 0.141, 1.01 | 0.044, 0.120, 0.71 |
| Refinement method | Full matrix least squares on F² |                 |
| No. of reflections | 1941           | 2026            |
| No. of parameters | 140            | 142             |
| Δρmin, Δρmax (e Å⁻³) | –0.23, 0.31 | –0.15, 0.14 |
and presentation in this study. The CrystalExplorer21 software was used to generate Hirshfeld surface analyses and fingerprint plots from the crystal data in order to investigate the different interactions (44,45).

Results and discussion

Crystal structures of 1 and 2

Cocrystal 1, which is crystallized in the triclinic space group P−1, consists of half a fumarate, and one 2-amino-4,6-dimethoxypyrimidine in the asymmetric unit (Figure 1(a)). Two typical intramolecular hydrogen bonds, N3−H3B···O4 and O3−H3C···N2, connect 2-amino-4,6-dimethoxypyrimidine and the fumaric acid, with H···O distances of 1.98 and 1.80 Å for H···N, and angles of 173 and 179° for N3−H3B···O4 and O3−H3C···N2, respectively. Furthermore, these two molecules are linked together by forming one of the most common hydrogen-bonded R2_2(8) graph sets in cocrystal 1. As shown in Figure 2(a) and Table 2, these molecules are linked to each other as dimers via N3−H3A···O4` bonding, in which the NH of the amino group of the pyrimidine ring acts as the donor and the O-atom is from the carbonyl group of fumaric acid, forming R2_2(8) loop (symmetry code: (i) −x + 1, −y + 2, −z and (i) −x + 2, −y, −z + 2, for 1 and 2, respectively.

The asymmetric unit of cocrystal 2 consists of an ethyl-2-picolinate and a half of fumarate (Figure 1(b)). The molecules in the extended structure of 2 (Figure 2b) are connected by numerous C1−H1···O4′, C2−H2···O2′, C4−H4···O4″, and O3−H3B···N1″ interactions
Molecules in co-crystal 2 are linked to each other by C−H···O and O−H···N bonding, forming an R\textsubscript{2}(7) graph set. Furthermore, there are very weak π···π stacking interactions between two pyridine rings of ethyl-2-picolinate molecules, which link the molecules into a three-dimensional network. The C−N bond lengths in 1 are 1.341(2), 1.350(2), and 1.324(2) Å. These results suggest a single bond character for the C−N bonds. In 2, C−N1 and C5−N1 bond lengths are 1.329(3) and 1.339(3) Å, respectively. The bond lengths involving C and O [C−O = 1.336(2), C6−O1 = 1.436(2), C4−O2 = 1.335(2), C5−O2 = 1.431(2), C7−O3 = 1.270(2), C7−O4 = 1.225(2) Å in 1 and C6−O1 = 1.323(3), C6−O2 = 1.196(3), C7−O1 = 1.447(3), C9−O3 = 1.306(3), C9−O4 = 1.192(3) Å in 2] show some slight variations between 1 and 2 (Table 3). In 2, the C9−O3 bond is longer than in 1 (C7−O3) which is probably due to the O···H contacts.

**Hirshfeld surface analysis**

Hirshfeld surface analysis is used to investigate the effect of intermolecular interaction on the surface visualized with color codes. In addition, information on the percentage contribution of atom interactions with two-dimensional fingerprint representation is also obtained. Normalized contact distance \(d_{\text{norm}}\) depends on the van der Waals (vdW) radii, \(d_e\) and \(d_i\). \(d_{\text{norm}}\) enables the identification of regions of importance for intermolecular hydrogen bonds. The \(d_{\text{norm}}\) consists of red, white, and blue colors. A red dot appears on the surface when atoms form intermolecular bonds that are closer than the sum of their van der Waals radii.

The intermolecular interaction of the structure may be observed in the red regions. It is also represented in blue if it is distant from the sum of the vdW radii. In

| Table 2. Hydrogen bonding geometries of 1 and 2 (Å, deg). |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| D−H−A | \(d_e\) | \(d_i\) | \(d_{\text{norm}}\) | Symmetry code |
| 1 | O3−H3C−N2 | 0.83 | 1.80 | 2.635 | 179 |
| N3−H3B−O4 | 0.86 | 1.98 | 2.840 (2) | 173 |
| N3−H3A−O4 | 0.86 | 2.05 | 2.854 (2) | 155 |
| 2 | C1−H1−O4 | 0.93 | 2.54 | 3.242 (4) | 132 |
| C2−H2−O2 | 0.93 | 2.59 | 3.370 (4) | 142 |
| C4−H4−O4 | 0.93 | 2.66 | 3.276 (4) | 125 |
| O3 | 0.82 | 1.89 | 2.705 (3) | 177 |

**Figure 2.** View of a portion of the sheet in co-crystal 1 and 2, showing the O−H···N, N−H···O, and C−H···O hydrogen bonds.
addition, shape index and curvedness maps are used to investigate whether \( \pi \cdots \pi \) interactions play a role in crystal structure packing. The red and blue triangles appearing in the shape indices are attributed to \( \pi \cdots \pi \) interactions between aromatic rings. The planar large green surfaces on the rings represent the existence of \( \pi \)-stacking in the curvedness map. The curvature of the planar regions is shown by blue stripes that divide them.

The CrystalExplorer21 software, which included TONTO, was used to generate Hirshfeld surface analyses and fingerprint plots from the crystal data in order to investigate the different interactions in the crystal structure of compounds 1 and 2 (44,45). \( \pi \cdots \pi \) interactions between pyrimidine–pyrimidine aromatic rings in the structure are ascribed to the neighboring red and blue triangles visible in the shape index of cocrystal 1. However, these red and blue triangles are not seen in the shape index of cocrystal 2. Curvedness maps of cocrystal are given in Figure 3. The planarity of the pyrimidine and pyridine rings is represented by the large green surfaces seen in the curvedness maps. The existence of \( \pi \cdots \pi \) stacking is responsible for these surfaces. These large and green planar regions on the curvature surface reveal the presence of \( \pi \cdots \pi \) interactions (46). As moving away from the rings, the planar regions are separated from each other by blue stripes. The Hirshfeld surface of crystal 1 has four complementary bright red regions, but the surface of crystal 2 has two large red regions and a few small faint red dots.

The Hirshfeld surface was mapped on \( d_{\text{norm}} \) with values ranging from \(-0.7601\) to \(1.1939\) Å in 1 and \(-0.7063\) to \(1.1805\) Å in 2. The contribution percentages of the dominant intermolecular interactions of co-crystals 1 and 2 are shown in two-dimensional fingerprint plots in Figure 4.

H–H interactions contribute the most to the molecular surfaces due to the presence of hydrogen in the structure of both cocrystals. The contributions of these interactions to the Hirshfeld surface are 40.9% and 41.6% for cocrystal 1 and 2, respectively. While O–H interactions account for the second-largest proportion of interactions for both cocrystal, N–H interactions account for the third-largest contribution (Figures 4 and 5). The existence of intermolecular O–H and N–H interactions is indicated by the development of these points near the respective donor and acceptor atoms. The hydrogen bonds in the structures of both cocrystal, N–H–O (for 1) and C–H–O (for 2), cause O–H interactions. Similarly, N–H interactions result from the presence of O–H–N hydrogen bonds. Weak C–H and C–H–\( \pi \) interactions result in symmetrical wings in the fingerprint plot of the C–H contacts. C–H interactions (8.2% and 8.5%, for 1 and 2, respectively) contributed significantly to the stability of crystal structures in cocrystals 1 and 2. C–C interactions, which are also related to \( \pi \)–\( \pi \) stacking, are one of the interaction contributions of cocrystals. The amount of these contributions is 2.2% (for 1) and 2.5% (for 2), respectively. In conclusion, our findings reveal that the C–H and C–H–\( \pi \) intermolecular contacts play an important role in the packing arrangement of crystal structures as well as the overall stability of molecular structures.

**Optimized geometry of the synthesized cocrystal 1 and 2**

As seen in Figure 1, the optimization energy analysis approach yields optimum step numbers for co-crystal 1 and 2 utilizing the B3LYP-D3/6-311G(d,p) basis set. Table 4 shows the bond lengths and bond angles calculated using the DFT method with an optimized structural

| Bond   | X-ray 1 | Angle | X-ray 1 | Bond   | X-ray 2 | Angle | X-ray 2 |
|--------|---------|-------|---------|--------|---------|-------|---------|
| C2–O1  | 1.336(2) | C2–O2–C6 | 117.9(2) | C6–O1  | 1.323(3) | O1–O2–C6 | 123.7(3) |
| C6–O1  | 1.436(2) | C4–O2–C5 | 117.2(2) | C6–O2  | 1.196(3) | C5–C6–O1 | 112.5(2) |
| C4–O2  | 1.335(2) | O3–C7–O4 | 124.7(2) | C7–O1  | 1.447(3) | C5–C6–O2 | 123.8(3) |
| C5–O2  | 1.431(2) | N1–C1–N2 | 124.9(2) | C9–O3  | 1.306(3) | C4–C9–O3 | 124.1(3) |
| C7–O3  | 1.270(2) | N1–C1–N3 | 117.6(2) | C9–O4  | 1.192(3) | C10–C9–O3 | 113.4(3) |
| C7–O4  | 1.225(2) | N2–C1–N3 | 117.6(2) | C1–N1  | 1.329(3) | C10–C9–O4 | 122.5(2) |
| C1–N1  | 1.341(2) | C8–C7–O3 | 115.0(2) | C5–N1  | 1.339(3) | C1–N1–C5 | 116.2(2) |
| C1–N2  | 1.350(2) | C8–C7–O4 | 120.3(2) | C5–C6  | 1.498(4) | C8–C7–O1 | 107.6(2) |
| C1–N3  | 1.324(2) | N2–C4–O2 | 112.2(2) | C7–C8  | 1.486(4) | C6–O1–C7 | 116.4(2) |

**Figure 3.** Hirshfeld surfaces \( d_{\text{norm}} \), shape index, and curvedness for 1 and 2.
basis set of B3LYP-D3/6-311G(d,p). The predicted C–C bonds in cocrystal 1 and 2, such as C24-C30 (for 1), C4-C5, C5-C11, C13-C19, C22-C27 and C19-C31 (for 2), were mildly modified in the optimized structure to 1.33 Å (for 1), 1.48, 1.33, 1.34, 1.51, and 1.39 Å, respectively, compared to bond distance obtained from single-crystal X-ray diffraction method, as mentioned in Table 4. The C–O bond lengths in C23-O22, C29-O28 (for compound 1), C4-O3, and C16-O15 (for 2) were determined to be 1.22, 1.20 Å (for 1), 1.21 Å (for 2), respectively. These bond lengths are in good conformity with experimental results. The bond angles in C28-C29-O27 (122.9°), C30-C29-O28 (126.1°), O1-C8-N3 (112.6°) (for 1), C5-C11-C10 (124.3°), O1-C4-O2 (122.2°), N13-C19-C16 (118.4°), and C19-C16-O15 (123.1°) (for 2) were found to be slightly altered in the optimized structures of compounds when compared to XRD studies, as shown in Table 4. The observed differences in bond lengths and angles may, however, be due to the XRD data being for a molecule in contact with many molecules, while the DFT findings are for an isolated compound.

**Frontier molecular orbitals (FMOs) and global reactivity descriptors**

The highest occupied molecular orbital is referred to as HOMO, and the lowest empty molecular orbital is

| Bond             | Bond length (Å) | Bond angle (°) |
|------------------|-----------------|----------------|
| C10-O2           | 1.34            | 117.6          |
| C8-O1            | 1.34            | 118.7          |
| C9-N5            | 1.34            | 117.2          |
| C23-O21          | 1.32            | 125.3          |
| C23-O22          | 1.22            | 117.7          |
| O1-C17           | 1.42            | 114.9          |
| O2-C13           | 1.43            | 119.4          |
| C24-C30          | 1.33            | 124.6          |
| C29-O28          | 1.20            | 112.6          |
| C29-O27          | 1.35            | 126.1          |
| C4-O3            | 1.21            | 122.2          |
| C4-C5            | 1.48            | 124.3          |
| C5-C11           | 1.33            | 123.2          |
| C13-C19          | 1.34            | 118.4          |
| C19-C16          | 1.50            | 123.85         |
| C16-O15          | 1.21            | 123.1          |
| C16-O14          | 1.34            | 123.5          |
| O14-C22          | 1.45            | 115.8          |
| C19-C31          | 1.39            | 106.9          |
| N13-C17          | 1.33            | 107.6          |

**Table 4.** Optimized geometrical parameters of compounds 1 and 2 obtained by B3LYP-D3/6-311G level theory.
referred to as LUMO. The HOMO and LUMO energies are well known to be important parameters in quantum chemistry. The HOMO and LUMO orbitals, known collectively as frontier molecular orbitals (FMOs), are important in chemical reactions and in determining the stability of chemical species. The chemical reactivity and kinetic stability of a molecule were determined by the HOMO and LUMO eigenvalues, as well as the HOMO–LUMO energy gap. The narrowing of the HOMO and LUMO energy gaps elucidates the intramolecular charge transfer (ICT) interaction within the molecule, which is responsible for its activity. The HOMO and LUMO spatial plots for optimized molecules 1 and 2 are shown in Figure 6.

Figure 6. Spatial plots of HOMO and LUMO bonds and associated energy gaps (Eg) for compounds 1 and 2.

Table 4 illustrates the energy Eigenvalues for HOMO and LUMO, as well as the HOMO–LUMO energy gap and several global reactivity descriptions at B3LYP-D3/6-311G(d,p) levels of theory.

Table 5. Calculated quantum chemical parameters of cocrystals 1 and 2 using DFT/B3LYP-D3 method.

| Parameters                      | Compound 1 | Compound 2 |
|--------------------------------|------------|------------|
| $E_{\text{LUMO}}$              | -2.29      | -2.51      |
| $E_{\text{HOMO}}$              | -6.26      | -7.08      |
| $\Delta E_{\text{g}}$ (E_{\text{LUMO}}-E_{\text{HOMO}})$ (eV) | 3.97 | 4.57 |
| Minimum SCF energy (eV)        | -27342.45  | -26435.65  |
| Dipole moment (Debye)          | 3.21       | 1.65       |
| Ionization potential (l)       | 6.26       | 7.08       |
| Electron affinity (A)          | 2.29       | 2.51       |
| Chemical hardness (q)          | 1.985      | 2.285      |
| Chemical softness (S)          | 0.251      | 0.218      |
| Electronegativity (χ)          | 4.275      | 4.795      |
| Electronic chemical potential (μ) | -4.275 | -4.795 |
| Electrophilicity index (ω)     | 4.60       | 5.03       |
and 2 is calculated from the HOMO and LUMO energies as 1.985 and 2.285 eV, respectively (Table 5). Table 5 shows the other global descriptors based on frontier molecular orbitals obtained using the B3LYP-D3/6-311G(d,p) basis level of theory.

Molecular electrostatic potential surface (MEP) and a projection of the localized orbital locator (LOL)

Molecular electrostatic potential (MEP) of a molecule can be used to evaluate its relative polarity and reactivity, as well as to identify molecules and interactions. MEP are generated using the optimized structures of compounds 1 and 2 at the B3LYP-D3/6-311G(d,p) level theory (Figure 7). The MEP surface is color-coded as follows: red represents an electron-rich region (electrophilic reactive center), blue represents an electron-deficient region (nucleophilic reactive center), and yellow represents a somewhat electron-rich region, and green represents neutral. The potential builds in the following order: red < orange < yellow < green < blue. Compounds 1 and 2 have a positive density around the hydrogen atoms, which are part of the carboxylic acid (-COOH). Therefore, nucleophilic reactivity is linked to these regions. The electron density on the surface of the oxygen atoms involved

Figure 7. The molecular electrostatic potentials of (a) cocrystal 1 and (b) cocrystal 2 are mapped, along with the electron distribution on the surface.

Figure 8. A shaded surface map with electron localization function (ELF) projection effect in (a) cocrystal 1 and (b) cocrystal 2. The z-axis in this diagram represents the Localised Orbital Locator (LOL).
in the construction of hydrogen bonds between two fragments of the compounds decreases, and the atoms turn light red (yellow color) on the surface. Similarly, a hydrogen attached to the oxygen atom of carboxylic (fumaric acid) participated in the formation of hydrogen bonds with the nitrogen atom of 4,6-dimethoxypyrimidin-2-amine experienced decreasing electron density on the surface. The region with the highest electronegative potential is located on the oxygen atom (ester oxygen) of ethyl 2-picolinate fragment of 2, which is not involved in any bond or non-bond interaction (Figure 7b), and it will be the parim-inary target of electrophilic reactivity. To observe localized electron density on atom surfaces, the visualized electron density maps for 1 and 2 were developed based on the LOL equation \( \text{LOL}(r) = \frac{\tau(r)}{1 + \tau(r)} \), which is a function for high localization regions defined by Schmider and Becke (50,51). The larger the LOL in a particular area, the more electron transport is likely to be restricted inside it. As illustrated in Figure 7(a) and (b), the shaded surface map served as an evaluation tool with the projected localized orbital locator (LOL) for the studied compounds. As shown in Figure 8, the blue colour in carbon atoms demonstrates depleted electron zones, while the red colour represents highly localized electron regions. Furthermore, all carbons have electron-depleted zones, whereas aromatic hydrogen atoms have highly confined electron regions. To maintain stability, it is preferable for electrons to con-gregate on the rings’ outer edges (52).

Conclusions

Two novel co-crystals, (1) and (2) were explored using the single Crystal X-ray crystallography and Hirshfeld surface analysis. Strong intramolecular \( \mathcal{O} \mathcal{H}--\mathcal{N} \) and intermolecular \( \mathcal{N} \mathcal{H}--\mathcal{O} \) hydrogen bonds stabilize the crystal packing of 1, whereas weak \( \mathcal{C} \mathcal{H}--\mathcal{O} \) and strong \( \mathcal{O} \mathcal{H}--\mathcal{N} \) intermolecular hydrogen bonds stabilize the crystal packing of 2. There are also weak \( \pi--\pi \) stacking interactions in the crystal structures of both 1 and 2, forming a three-dimensional supramolecular architecture. DFT calculations were performed to study the molecular geometry and other molecular parameters of the asymmetric unit of molecules using the B3LYP-D3/6–311G (d, p) level of theory, and the results showed a good correlation with experimental data. The HOMO–LUMO gap indicates that 1 is less kinetically stable than 2, which sugestts that 1 has a medium level of chemical reactivity in comparison to 2. The intermolecular interactions of in the crystal structures 1 and 2 were investigated using Hirshfeld surface and fingerprint analysis. For both 1 and 2, the results are found to be consistent with single-crystal structure studies.

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Disclosure statement

There are no conflicts of interests to disclose.

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