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Molecular structure investigation of organic cocrystals of 1,10-phenanthroline-5,6-dione with aryloxyacetic acid: A combined experimental and theoretical study



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HIGHLIGHTS

- Cocrystals were synthesized *via* solvent mediated crystallization and neat grinding methods.
- Cocrystal **1** is stabilized through H-bonding as well as π - π interaction.
- Cocrystals **1** and **2** are stable up to 210 °C.
- Binding energy of cocrystal **2** is higher than that of cocrystal **1**.
- Formation of H-bonding in cocrystals 1 and 2 is confirmed by MEP and NBO analysis.

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G R A P H I C A L A B S T R A C T



ABSTRACT

Two organic cocrystals namely, 1,10-phenanthroline-5,6-dione:2-naphthoxyacetic acid [(phendione) (2-naa)] (1) and 1,10-phenanthroline-5,6-dione:2-formylphenoxyacetic acid [(phendione)(2-fpaa)] (2) were synthesized and studied by single crystal XRD, FT-IR, NMR, thermogravimetric, and powder X-ray diffraction analysis. The molecular properties of cocrystals were studied using density functional theory (DFT), basis set B3LYP/6-31G(d,p). Both cocrystals are stabilized through intermolecular hydrogen bonding (O-H...N). The total electron density and molecular electrostatic potential surfaces of the cocrystals were constructed by NBO analysis using B3LYP/6-31G(d,p) method to display the electrostatic potential (electron + nuclei) distribution. The energy gap between HOMO and LUMO was measured for both cocrystals.

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Introduction

Cocrystal technology has shown great promise in rectifying the undesirable properties of a drug substance. A pharmaceutical cocrystal is a single crystalline solid that incorporates two neutral molecules, one being an active pharmaceutical ingredient (API) and the other a cocrystal former [1]. Once an API has been selected for cocrystallization studies, non-toxic cocrystallizing agent should be chosen so as to result in a pharmaceutically acceptable product. In recent times, cocrystal formation using the crystal engineering approach has been shown to be effective for altering the

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physicochemical properties such as melting point [2], solubility [3], thermal [4], and photostability [5] as well as mechanical properties [6] of active pharmaceutical ingredients (APIs).

The recent progress in density functional theory (DFT) has provided a very useful tool for understanding molecular properties and for explaining the behavior of atoms in molecules. DFT methods have become very popular in the past decade due to their accuracy and less computational time [7]. The calculation of a wide range of molecular properties with DFT allows a close connection between theory and experiment, and often leads to important clues about the geometric, electronic, and spectroscopic properties of the systems being studied [7].

1,10-Phenanthroline-5,6-dione (phendione), displays significant anticancer activity, both with and without a coordinated metal [8]. It is also an excellent anti-*Candida* agent [9]. Phenoxyacetic acid moiety is associated with potent antimicrobial, antidiabetic, antibiotic, anti-obesity, antiplatelet aggregation activities, etc. [10a,b].

In continuation of our work in organic cocrystals [10], herein we report the syntheses of binary cocrystals of 1,10-phenanthroline-5,6-dione (phendione) with 2-naphthoxyacetic acid (2-naa) and 2-formylphenoxyacetic acid (2-fpaa) through solvent mediated crystallization as well as neat grinding methods (Scheme 1). The structure of the newly synthesized cocrystals were analyzed using FT-IR spectroscopy, powder X-ray diffraction (PXRD), NMR, and single crystal X-ray diffraction (SXRD). The molecular properties of the cocrystals [(phendione)(2-naa)] (1) and [(phendione) (2-fpaa)] (2) were studied using DFT method.

Experimental

General details

1,10-Phenanthroline-5,6-dione (phendione) [11], 2-naphthoxyacetic acid (2-naa) and 2-formylphenoxyacetic acid (2-fpaa) [12] were synthesized as per the literature methods. FT-IR spectra were recorded on a JASCO FT-IR-410 spectrometer in the range 4000– 400 cm⁻¹ on KBr discs. The ¹H NMR and ¹³C NMR spectra were recorded on a Bruker (Avance) 400 MHz NMR instrument using TMS as internal standard and DMSO-d₆ as solvent. Thermogravimetric analysis (TGA) experiments were performed on a Diamond Thermal Analyzer in the temperature range of 25–700 °C under nitrogen atmosphere at a heating rate of 10 °C/min. Powder X-ray diffraction data were collected using a XPERT-PRO diffractometer system with Cu K_{α1}, Cu K_{α2}, and Cu K_β with radiation of wavelength 1.54060, 1.54443, and 1.39225 Å respectively. Powder X-ray diffraction data were recorded in the range $10^{\circ} \leq 2\theta \leq 80^{\circ}$. The step size was 0.0170°. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer.

Syntheses of cocrystals [(phendione)(2-naa)] (1) and [(phendione) (2-fpaa)] (2) via solution crystallization method

1,10-Phenanthroline-5,6-dione (1.0 mmol) and 2-naphthoxyacetic acid (1.0 mmol) or 2-formylphenoxyacetic acid (1.0 mmol) were dissolved individually in aqueous ethanol (1:1 v/v, 10 mL) in two Erelenmeyer flasks (25 mL) at room temperature. The mixtures were stirred and warmed until the starting materials completely dissolved. These mixtures were filtered to avoid the inclusion of any undissolved starting materials. Slow evaporation of the filtrate under ambient conditions over 3–4 days yielded crystals of [(phendione)(2-naa)] (1) (yield: 80%) and [(phendione)(2-fpaa)] (2) (yield: 84%) suitable for X-ray diffraction. Anal. Calcd. for [(phendione)(2-naa)] (1) $C_{24}H_{16}N_2O_5$: C, 69.90; H, 3.91; N, 6.79%. Found: C, 69.84; H, 3.98; N, 6.72% and for [(phendione)(2-fpaa)] (2) $C_{21}H_{14}N_2O_6$: C, 64.62; H, 3.62; N, 7.18%. Found: C, 64.60; H, 3.66; N, 7.10%.

Solvent-free syntheses of [(phendione)(2-naa)] (1) and [(phendione)(2-fpaa)] (2) via neat grinding method

1,10-Phenanthroline-5,6-dione (1.0 mmol) and 2-naphthoxyacetic acid (1.0 mmol) or 2-formylphenoxyacetic acid (1.0 mmol) were ground well individually at 30 °C under dry condition. After 30 min, red/brown colored solids of [(phendione)(2-naa)] (1) and [(phendione)(2-fpaa)] (2) were found to have formed (PXRD, Figs. s1 and s2, vide Supporting information).

X-ray structure determination

A BRUKER APEX 2 X-ray (three-circle) diffractometer was employed for crystal screening, unit cell determination, and data collection. Integrated intensity information for each reflection was obtained by reduction of the data frames with the program APEX2 [13]. A solution was obtained readily using SHELXTL (XS) [14]. Absence of additional symmetry and subcell were verified using PLATON [15] and CELL_NOW respectively. Olex2 was employed for the final data presentation and structure plots [16].



Scheme 1. Syntheses of cocrystals 1 and 2.

Computational methodology

Theoretical studies on cocrystals 1 and 2 in gas phase were performed using the analytical gradient methods of DFT with Becke's three parameters (B3) exchange functional together with the Lee-Yang-Parr (LYP) non-local correlation functional, symbolized B3LYP [17] by means of 6-31G(d,p) basis set implemented in Gaussian 09 software package [18]. The optimized structural parameters in gas phase were used to calculate energies and thermodynamic properties of the compounds. The energies of the highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbital, and HOMO-LUMO energy gap have also been measured. Gauss-View 5.0.8 visualization program [19] was used to construct the molecular electrostatic potential (MEP) map and the shape of the frontier molecular orbitals. The natural charges of the atoms are determined by natural bond orbital (NBO) analysis using B3LYP/6-31G(d.p) method. Isoelectronic molecular electrostatic potential surfaces (MEP) and electron density surfaces [20] mapped with electrostatic potential were calculated.

Results and discussion

Crystal structure

The crystallographic data and structure refinement parameters of the cocrystals **1** and **2** are presented in Table 1. The bond lengths and angles are given in Table 2. The hydrogen bond geometry is shown in Table 3. Crystallographic data for the cocrystals **1** and **2** have been deposited with the Cambridge Crystallographic Data Centre (CCDC) (deposition numbers: 899820 and 899821 respectively).

Single crystal XRD of cocrystal 1

Fig. 1 shows the ORTEP diagram of cocrystal 1 along with the adopted atomic numbering scheme. The asymmetric unit of cocrystal 1 contains two molecules of 1,10-phenanthroline-5,6dione (phendione) and two molecules of 2-naphthoxyacetic acid (2-naa). The compound crystallizes in noncentrosymmetric space group *Cc*, with Z = 8 (Z' = 2). Absence of additional symmetry and smaller unit cell were verified using Platon and CELL_NOW respectively. The crystal structure shows that there is no proton transfer from the carboxyl group of 2-naa to phendione in the asymmetric unit. A predicted intermolecular hydrogen bonding motif O5-H5...N2 is observed between the carboxylic O-H of 2-naa and the nitrogen of phendione. From Table 2, the C-O bond lengths [C24-O4: 1.197(2), C24-O5: 1.328(2)] indicate that the acid moiety is present as -COOH. Each 2-naa combines with one unit of phendione through O5-H5...N2 (O5-H5...N2 distance is 2.834 Å) hydrogen bonding with Etter's [21] graph set designator D forming discrete molecules. O5-H5...N2 is essentially linear, with an angle 173.08° (Table 3).

The dihedral angle between the carboxyl group (O4-C24-O5) of 2-naa and the pyridyl ring of phendione is 20.84° . Phendione lies almost on the same plane of the naphthalene ring of 2-naa, since its dihedral angle is 5.55° . Two types of π - π stacking forces were observed (Fig. 2) between non-hydrogen bonded pyridyl ring of phendione and substituted phenyl ring of 2-naa (3.524 and 3.584 Å). Fig. 3 depicts the crystal packing arrangement of cocrystal **1** along *b*-axis.

Single crystal XRD of cocrystal 2

The ORTEP diagram of the cocrystal **2** is shown in Fig. 4. The geometrical parameters of **2** are listed in Table 2. The asymmetric unit of **2** contains one molecule of 1,10-phenanthroline-5,6-dione

Table 1

Crystal data and structure refinement parameters of cocrystals 1 and 2.

| | Cocrystal 1 | Cocrystal 2 |
|---------------------------------|----------------------------------|------------------------------------|
| | eoerystar I | |
| CCDC no. | 899820 | 899821 |
| Empirical formula | $C_{24}H_{16}N_2O_5$ | $C_{21}H_{14}N_2O_6$ |
| Formula weight | 412.39 | 390.34 |
| Appearance | Red block | Brown block |
| Crystal size | $0.19 \times 0.06 \times 0.06$ | $0.40 \times 0.40 \times 0.08$ |
| Wavelength (Å) | 0.71073 Å | 0.71073 Å |
| Crystal system | Monoclinic | Triclinic |
| Space group | Сс | P – 1 |
| Unit cell dimensions | a = 7.107(3) Å | a = 7.7654(3) Å |
| | b = 17.121(8) Å | b = 9.558(4) Å |
| | c = 30.825(13) Å | <i>c</i> = 12.757(5) Å |
| | $\alpha = \gamma = 90^{\circ}$ | $\alpha = 84.072(4)^{\circ}$ |
| | $\beta = 96.412(4)^{\circ}$ | $\beta = 85.611(4)^{\circ}$ |
| | | $\gamma = 71.416(4)^{\circ}$ |
| Volume | 3727(3) Å ³ | 878.9(6) Å ³ |
| Ζ | 8 | 2 |
| Density (calculated) | 1.470 mg/m ³ | 1.475 mg/m ³ |
| Absorption coefficient | 0.105 mm^{-1} | 0.110 mm^{-1} |
| F(000) | 1712 | 404 |
| Theta range for data collection | 2.38-27.50° | 1.61-27.50° |
| Index ranges | $-9 \leqslant h \leqslant 9$, | $-9 \leq h \leq 9$, |
| - | $-22 \leqslant k \leqslant 22$, | $-12 \leqslant k \leqslant 12$, |
| | $-40 \leqslant l \leqslant 39$ | $16 \leq l \leq 16$ |
| Reflections collected | 21,146 | 10,187 |
| Independent reflections | 8339 | 3954 [<i>R</i> (int) = 0.0223] |
| | [R(int) = 0.0215] | |
| Completeness to theta | 99.3% | 97.9% |
| Absorption correction | Semi-empirical | Semi-empirical from |
| | from equivalents | equivalents |
| Max. and min. transmission | 0.9937 and 0.9804 | 0.9912 and 0.9572 |
| Refinement method | Full-matrix least- | Full-matrix least- |
| | squares on F ² | squares on F ² |
| Data/restraints/parameters | 8339/2/561 | 3954/0/263 |
| Goodness-of-fit on F^2 | 1.030 | 1.068 |
| Final R indices [I > 2sigma(I)] | $R_1 = 0.0334$, | $R_1 = 0.0377$, |
| | $wR_2 = 0.0825$ | $wR_2 = 0.0970$ |
| R indices (all data) | R1 = 0.0367, | $R_1 = 0.0444$, |
| | wR2 = 0.0850 | $wR_2 = 0.1018$ |
| Largest diff. peak and hole | 0.232 and | 0.308 and -0.199 e Å ⁻³ |
| - * | -0.170 e Å ⁻³ | |

(phendione) and one molecule of 2-fpaa. The compound crystallizes in noncentrosymmetric space group P - 1 with Z = 2. In the asymmetric unit, the crystal structure shows that there is no proton transfer from the carboxyl group of 2-fpaa to the phendione. From the C–O bond lengths [C8–O3: 1.2115(16) Å, C8–O2: 1.3177(15) Å] of the carboxyl acid moiety (Table 2), the nondeprotonation of the –COOH group could be inferred. Each 2-fpaa (carbonyl O–H) combines with one unit of phendione (pyridyl N-atom) through O2–H2···N2 (O2–H2···N2 bond distance is 2.783 Å) hydrogen bonding with Etter's [21] graph set designator D forming discrete molecules.

The N2···H5 bond length of cocrystal **1** (1.999 and 1.981 Å) is longer than the N2···H2 bond length of cocrystal **2** (1.957 Å) (Table 3). This reveals that hydrogen bond of cocrystal **2** is stronger than cocrystal **1** and this gives extra stability to cocrystal **2**.

The dihedral angle between the carboxyl group (O3–C8–O2) of 2-fpaa and the phendione (hydrogen bonded pyridyl ring) is 38.07°, and that of phendione (hydrogen bonded pyridyl ring) and aryl ring of 2-fpaa is 63.17°. Extra stabilization through π – π interactions could not be visualized as the short contacts are more than 4.1 Å. Fig. 5 shows the crystal packing arrangement along a^* axis.

FT-IR spectra of cocrystals 1 and 2

The formation of a cocrystal could be confirmed by the changes in the carbonyl frequencies in the crystals. The change in carbonyl

| Table 2 | |
|--|---------------------|
| Selected bond lengths and bond angles of experimental and theoretical studies on | cocrystals 1 and 2. |

| Bond | Cocrystal 1 | | | | Bond | Cocrystal 2 | Cocrystal 2 | | | |
|------------------|-------------|--------|--------|--------|-------------|--------------------|--------------------|--------|--------|--|
| | SCXRD | PM3 | HF | DFT | | SCXRD | PM3 | HF | DFT | |
| Bond lengths (Å) | | | | | | | | | | |
| C13-03 | 1.378 (19) | 1.379 | 1.349 | 1.365 | C1-01 | 1.366 (15) | 1.385 | 1.346 | 1.360 | |
| C24-04 | 1.197 (2) | 1.220 | 1.187 | 1.214 | C8-03 | 1.211 (16) | 1.220 | 1.187 | 1.214 | |
| C24-05 | 1.328 (2) | 1.337 | 1.313 | 1.330 | C8-02 | 1.318 (15) | 1.341 | 1.310 | 1.328 | |
| 05—H5 | 0.840 | 0.974 | 0.961 | 0.999 | 02—H2 | 0.840 | 0.975 | 0.962 | 1.001 | |
| C10-N2 | 1.342 (2) | 1.354 | 1.316 | 1.333 | C21-N2 | 1.339 (17) | 1350 | 1.316 | 1.334 | |
| C5-N2 | 1.345 (2) | 1.361 | 1.320 | 1.339 | C18-N2 | 1.341 (16) | 1.357 | 1.320 | 1.339 | |
| C9-N2 | 1.333 | 1.350 | 1.319 | 1.343 | C10-N1 | 1.335 (17) | 1.354 | 1.319 | 1.339 | |
| C4—N2 | 1.347 (2) | 1.357 | 1.323 | 1.339 | C14—N1 | 1.341 (16) | 1.362 | 1.323 | 1.344 | |
| Bond angles (°) | | | | | | | | | | |
| C13-03-023 | 115.36 (12) | 116.70 | 119.47 | 118.02 | C1-01-C7 | 117.66 (9) | 117.11 | 120.82 | 119.48 | |
| C23-C24-04 | 125.40 (15) | 126.35 | 125.15 | 124.47 | C7–C8–O3 | 124.47 (11) | 128.52 | 124.73 | 123.97 | |
| 04–C24–O5 | 125.78 (15) | 118.71 | 125.43 | 126.26 | 03 | 125.27 (12) | 118.16 | 125.76 | 126.57 | |
| C24-05-H5 | 109.50 | 113.05 | 112.40 | 111.39 | C8-02-H2 | 109.50 | 113.02 | 112.59 | 111.48 | |
| C6-C1-C2 | 118.72 (14) | 114.19 | 117.50 | 117.47 | C17-C16-C15 | 118.02 (11) | 113.93 | 117.49 | 117.47 | |
| C3–C2–C1 | 117.22 (15) | 113.96 | 117.58 | 117.64 | C13-C15-C16 | 117.40 (11) | 114.18 | 117.59 | 117.64 | |

Table 3

Hydrogen bond geometries (Å and $^\circ)$ in the crystal structure of 1 and 2.

| | $d(H{\cdot}{\cdot}{\cdot}A)$ | d(D—H) | $d(D - H \cdots A)$ | $D \!\!-\!\!\!\!- \!$ |
|---|------------------------------|----------------|---------------------|---|
| Cocrystal 1 O5—H5…N2 O5a—H5a…N2a | 1.999 1.981 | 0.840 0.840 | 2.834 2.816 | 172.30 173.08 |
| Cocrystal 2 O2—H2····N2 | 1.957 | 0.840 | 2.783 | 167.06 |

A - acceptor, D - donor, and H - hydrogen atom.

frequencies in cocrystals is due to the involvement of carboxyl group in hydrogen bond formation because of the hydrogen bond interactions that disturb the electron distribution on carboxyl group [22]. The IR spectra of phendione, 2-naa, 2-fpaa, and cocrystals (**1** and **2**) are given in the Supporting information (*vide* Supporting information, Figs. s3–s7).

Table 4 shows the carbonyl stretching frequencies of starting materials and cocrystals (1 and 2). The carbonyl stretching frequency for cocrystals 1 and 2 is above 1600 cm^{-1} in the infrared

spectra confirming the presence of nonionized carboxylic acids [22]. Two intense carbonyl bands at 1755 and 1685 cm⁻¹ are displayed in the IR spectrum of cocrystal **1**. The band at 1755 cm⁻¹ is due to the carbonyl stretching frequency of 2-naa and 1685 cm⁻¹ is due to the carbonyl stretching frequency of the phendione in the cocrystal **1**.

In the IR spectrum of cocrystal **2**, two bands at 1724 and 1693 cm⁻¹ are due to the carbonyl stretching frequencies of 2-fpaa and 1682 cm⁻¹ is due to the carbonyl stretching frequency of phendione. Carbonyl stretching frequencies of phendione is not much affected in cocrystals **1** and **2** which confirm the noninvolvement of phendione carbonyl in hydrogen bonding. The change in carbonyl frequency (COOH) in cocrystals (**1** and **2**) is due to the involvement of carboxyl group in hydrogen bond formation.

From single crystal XRD data, the carbonyl (C=O) bond length of cocrystal **1** (1.197 Å) is lower than 2-naa (1.212 Å) [22e–f]. The decrease in bond length of carboxyl group decreases the carbonyl stretching frequency of cocrystal **1**. But in cocrystal **2** (1.211 Å), the carbonyl bond length is higher than that of 2-fpaa (1.203 Å) [22g]. The increase in bond length of carboxyl group increases the carbonyl stretching frequency of cocrystal **2**.



Fig. 1. ORTEP diagram of [(phendione)(2-naa)] (1) along with the adopted atomic numbering scheme.



Fig. 2. H-bonding and π - π stacking interactions in [(phendione)(2-naa)] (1).



Fig. 3. Packing arrangement of [(phendione)(2-naa)] (1) along *b* axis.



Fig. 4. ORTEP diagram of [(phendione)(2-fpaa)] (2) along with the adopted atomic numbering scheme.



Fig. 5. Packing arrangement of [(phendione)(2-fpaa)] (2) along a* axis.

Table 4 Carbonyl stretching frequencies y_{-1} (cm⁻¹

Carbonyl stretching frequencies $\nu_{C=O}\ (cm^{-1})$ of starting materials and cocrystals 1 and 2.

| Compounds | Stretching frequencies $v_{C=0}$ (cm ⁻¹) |
|--------------------|--|
| Phendione | 1686 |
| 2-naa | 1738 |
| 2-fpaa | 1760 (COOH) |
| | 1720 (CHO) |
| Cocrystal 1 | 1755 |
| | 1685 |
| Cocrystal 2 | 1724 |
| | 1693 |
| | 1682 |
| | |

¹H NMR and ¹³C NMR spectra of cocrystals **1** and **2**

Liquid ¹H NMR spectra of cocrystals are used to find out the stoichiometric ratio of individual molecules in cocrytal [10a,10b]. ¹H NMR (in DMSO-d₆) spectra of cocrystals **1** and **2** confirm that the 1:1 stoichiometric ratio of phendione with 2-naphthoxyacetic acid and 2-formylphenoxyacetic acid (*vide* Supporting information, ¹H NMR and ¹³C NMR spectra, Figs. s8–s11 and peak analysis of cocrystals (**1** and **2**), Table s1 and s2).

The chemical shift (δ ppm) of $-OCH_2$ protons of cocrystals **1** (H23A and H23B) and **2** (H7A and H7B) are observed at 4.81 and 4.90 ppm whereas $-OCH_2$ carbon of cocrystal **1** (C23) and cocrystal **2** (C7) resonate at 64.5 and 65.1 ppm respectively.

¹H NMR and ¹³C NMR spectra of cocrystals **1** and **2** show that proton and carbon atoms of phendione have similar chemical shift value in both cocrystals. This indicates that in liquid NMR spectra the cocrystals show the chemical shift of individual molecules.

TGA/DTA of cocrystals 1 and 2

Cocrystal **1** is stable up to 210 °C at which point it quickly suffers about 34.43% weight loss (calculated: 35.50%) which is

consistent with the elimination of one molecule of naphthol moiety. At higher temperatures, the weight loss is experienced at about 325 °C. The loss in mass at this point is about 14.55% (calculated: 13.90%) and may be attributed to the loss of one molecule of acetic acid. At still higher temperatures, the decomposition speeds up again and at about 380 °C, a weight loss of 50.92% (calculated: 50.60%) is observed, which may be due to the decomposition of the remaining phendione moiety (*vide* Supporting information, Fig. s12).

Cocrystal **2** is stable up to 210 °C at which point it loses about 41.02% (calculated: 40.5%) of its weight. This may be due to the elimination of one molecule of formaldehyde, one molecule of carbon dioxide, one molecule of methanol, and two molecules of carbon monoxide. At 270 °C, there is a weight loss of about 20% (calculated: 20.5%) which may be attributed to the loss of one molecule of phenyl unit. Further increase in temperature speeds up the decomposition and at about 370 °C, a weight loss of 38.97% (calculated: 39%) was noticed which may be due to the decomposition of the remaining phendione moiety (*vide* Supporting information, Fig. s13).

Powder XRD of cocrystals 1 and 2

Powder XRD is useful for the fast identification of the new phases of compounds. The cocrystal formed between phendione and 2-naa/2-fpaa at a molar ratio of 1:1 is further supported by powder XRD studies. Powder XRD pattern of the 1:1 ground mixture of the starting materials displayed similar pattern of the cocrystals of both **1** and **2** obtained from solution crystallization (*vide* Supporting information, Figs. s1 and s2).

Theoretical studies

Gas phase geometry optimizations were performed starting from the crystal structures of cocrystals **1** and **2** at the B3LYP/6-31G(d,p) level of theory using Gaussian 09W software [18]. In most theoretical studies, optimizing the geometry of the species under investigation is the first step. Gas phase geometrical parameters of the optimized structures of cocrystals **1** and **2** at the PM3, HF/ 3-21G(d), and DFT/6-31G(d,p) levels are listed in Table 2. The conformational analysis based on the geometrical parameters such as bond length, bond angle, and planarity of cocrystals **1** and **2** (Table 2) reveals that DFT method represents a good correlation between the calculated geometrical parameters and the single crystal XRD data. Fig. 6 shows the optimized structures of cocrystals **1** and **2**. The calculated geometrical parameter displays good correlation with experimental values that can lead to the calculation of other parameters for the cocrystals **1** and **2**.

The molecular properties of phendione, 2-naa, 2-fpaa, cocrystal **1**, and cocrystal **2** are summarized in Table 5. The total energy of both cocrystals is more negative in magnitude than that of individual molecules. The binding energy of the cocrystals is given as,

$$\Delta E = E_{\text{cocrystal}} - (E_{\text{phendione}} + E_{2-\text{naa or}2-\text{fpaa}}) \tag{1}$$

where $E_{\text{cocrystal}}$, $E_{\text{phendione}}$, and $E_{2-\text{naa}}$ or 2-fpaa represent the energy of the cocrystal, phendione, 2-naa, and 2-fpaa respectively. Cocrystal **1** has more negative binding energy than cocrystal **2**. The binding energies of cocrystals are negative, indicating that the cocrystals can be formed thermodynamically. Generally, the binding energies of the cocrystals increase with the increase in the number of the weak bonds (H-bonds, van der Waals, etc.) formed [23]. H-bonding, $\pi-\pi$, and C—H… π interactions are confirmed from both the theoretical binding energy and SCXRD studies of cocrystal **1**.

Theoretically calculated Gibbs free energy changes (ΔG) using DFT calculations is of a negative magnitude (Table 5) suggesting that the formation of cocrystals was a spontaneous and feasible



Fig. 6. Optimized structures of cocrystals (a) **1** and (b) **2**.

process. The higher ΔS values indicate that the cocrystal **2** has lower degree of randomness than the cocrystal **1** in gas phase.

Frontier molecular orbital (FMO) analysis

Molecular orbitals (HOMO and LUMO) and their properties are very useful for physicists, chemists, and biochemists; and are very important parameters for quantum chemistry. This is also used by the frontier electron density for predicting the most reactive position in π -electron systems [24]. The conjugated molecules are analyzed by the highest occupied molecular orbital-lowest unoccupied molecular orbital (HOMO-LUMO) separation, which is the result of a significant degree of intramolecular charge transfer from the end-capping electron-donor groups to the efficient electron-acceptor groups through π -conjugated path [25]. Both the highest occupied and lowest unoccupied molecular orbitals are the main factors taking part in chemical stability [26]. HOMO and LUMO energy of cocrystals 1 and 2 and their formers were calculated by B3LYP/6-31G(d,p) method (Table 5). This electronic absorption corresponds to the transition from the ground to the first excited state and is mainly described by one-electron excitation from HOMO to LUMO.

The energy of HOMO is directly related to the ionization potential while that of E_{LUMO} is directly related to the electron affinity. The energy gap between HOMO and LUMO is a critical parameter in determining molecular electrical transport properties [27]. The interaction between the two molecules leads to the extension of the conjugation system and decrease in the energy gaps. The efficient H-bonding causes the flow of electrons from the protondonor to the proton-acceptor, which intensifies the electron density on the proton-acceptor and widens the energy gap of the cocrystals [23].

It is clear from Fig. 7 that while HOMO is localized on the aromatic rings of 2-naa/2-fpaa, LUMO is localized on the whole molecule of phendione (*vide* Supporting information, HOMO and LUMO diagram for phendione, 2-naa, and 2-fpaa). The HOMO to LUMO transition implies an electron density transfer from the aromatic rings of 2-naa/2-fpaa to the electron deficient phendione. Cocrystals **1** and **2** possess lower ionization potential data than that of the phendione, and thus they are ready to lose electrons.

Absolute hardness and softness are important properties to measure the molecular stability and reactivity. A hard molecule has a large energy gap and a soft molecule has a narrow energy gap. Soft molecules are more reactive than hard ones because they could easily offer electrons to an acceptor. For the simplest transfer of electrons, adsorption could occur at the part of the molecule where softness has the highest magnitude and hardness has the lowest [28]. The thermal stabilities of cocrystals **1** and **2** display higher σ values than that of the phendione since several intermolecular interactions exist in the two cocrystals. These indicate that cocrystals **1** and **2** are more reactive than phendione and 2-naa/2-fpaa (Table 5).

Table 5

Theoretical studies on cocrystals 1 and 2.

| Parameters | Phendione | 2-naa | 2-fpaa | Cocrystal 1 | Cocrystal 2 |
|--|------------|------------|------------|-------------|--------------------|
| Total energy, E (kcal/mol) | -452434.79 | -432352.29 | -407150.88 | -884732.37 | -859396.66 |
| Binding energy, ΔE (kcal/mol) | - | - | - | -54.71 | -189.01 |
| $E_{\rm HOMO}~(\rm eV)$ | -7.8591 | -7.6517 | -6.8721 | -6.4537 | -6.3184 |
| E_{LUMO} (eV) | -3.5169 | -0.9588 | -1.8546 | -3.9329 | -3.6331 |
| $E_{\rm HOMO} - E_{\rm LUMO} (eV)$ | -4.3422 | -6.6929 | -5.0175 | -2.5208 | -2.6853 |
| Dipole moment (Debye) | 2.6879 | 2.1316 | 5.8165 | 2.5767 | 6.0968 |
| Ionization potential, I (eV) | 7.8591 | 7.6517 | 6.8721 | 6.4537 | 6.3184 |
| Electron affinity, A (eV) | 3.5169 | 0.9588 | 1.8546 | 3.9329 | 3.6331 |
| Electronegativity, χ (eV) | 5.6880 | 4.3052 | 4.3633 | 5.1933 | 4.9757 |
| Electrochemical potential, μ (eV) | -5.6880 | -4.3052 | -4.3633 | -5.1933 | -4.9757 |
| Absolute hardness, η (eV) | 2.1711 | 3.3464 | 2.5087 | 1.2604 | 1.2318 |
| Softness, σ (eV) | 0.4606 | 0.2988 | 0.3986 | 0.7934 | 0.8118 |
| Nucleophilicity, ω (eV) | 7.4509 | 2.7693 | 3.7945 | 10.6991 | 10.0493 |
| Enthalpy, H (kcal/mol) | -452330.12 | -432222.05 | -407044.78 | -884495.55 | -859183.68 |
| ΔH (kcal/mol) | - | - | - | 56.62 | 191.22 |
| Gibbs free energy, G (kcal/mol) | -452361.50 | -432255.48 | -407077.47 | -884550.27 | -859236.83 |
| ΔG (kcal/mol) | - | - | - | -66.71 | -202.14 |
| Entropy, S (cal/mol K) | 105.248 | 112.104 | 109.536 | 183.438 | 178.308 |
| (a) Electronic | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| (b) Translational | 41.930 | 41.815 | 41.471 | 43.939 | 43.776 |
| (c) Rotational | 32.025 | 32.349 | 31.661 | 37.461 | 36.944 |
| (d) Vibrational | 31.292 | 37.940 | 36.404 | 102.038 | 97.588 |
| ΔS (cal/mol K) | - | _ | - | -33.914 | -36.476 |
| Zero-point vibrational energy (kcal/mol) | 97.45065 | 122.31905 | 98.49396 | 220.35554 | 197.69819 |
| Rotational constant (GHz) | 0.85555 | 1.84669 | 1.36622 | 0.38751 | 0.39094 |
| | 0.53806 | 0.26013 | 0.46322 | 0.04281 | 0.05609 |
| | 0.33032 | 0.22834 | 0.34668 | 0.03856 | 0.04907 |
| Zero-point energy (kcal/mol) | -452337.68 | -432230.31 | -407052.70 | -884511.99 | -859199.68 |
| Mullikan charges | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |



Fig. 7. HOMO and LUMO energy diagrams of cocrystals (a) 1 and (b) 2.

The nucleophilicity measures the electrophilic power of a molecule. It has been reported that the lower the value of ω , the lower the capacity of the molecule to donate electrons [28]. Table 5 reveals that the 2-naa and 2-fpaa donate electron to phendione. The dipole moment in a molecule is mainly used to study the intermolecular interactions involving the non-bonded type dipole–dipole interactions, because higher dipole moment values indicate stronger intermolecular interactions [29]. Cocrystal **2** has





Fig. 8. Molecular electrostatic potential map of cocrystals (a) 1 and (b) 2.

higher dipole moment than its former-compounds and cocrystal **1** (Table 5).

Analysis of molecular electrostatic potential (MEP)

Molecular electrostatic potential (MEP) is related to the electronic density and is a very useful descriptor in understanding sites for electrophilic attack and nucleophilic reactions as well as hydrogen bonding interactions. This is correlated with dipole moments, electronegativity, partial charges, and chemical reactivity of the molecules [29,30].

MEP maps allow us to visualize variable charged regions of a molecule. Knowledge of the charge distributions can be used to determine how molecules interact with one another. Different values of the electrostatic potential are represented by different colours: red represents regions of most negative electrostatic potential, blue region represents regions of most positive electrostatic potential, and green represents regions of zero potential. Potential increases in the following order: red < orange < yellow < green < blue [31].

Fig. 8 shows the MEP maps of cocrystals **1** and **2** determined using DFT/B3LYP 6-31G(d,p) method. As can be seen in Fig. 8, the negative (red^{1}) region is localized on the carbonyl-oxygen atom

and pyridyl nitrogen atom of phendione with a minimum value of -0.06244 and -0.05883 a.u. for cocrystals **1** and **2** respectively. However, maximum positive (blue) region is localized on the carboxylic acid hydrogen atoms, with a maximum value of 0.06244 and 0.05883 a.u. respectively. The proton/electron donating/accepting behaviors are confirmed by the MEP map of their parent compounds (*vide* Supporting information).

Therefore, MEP maps of cocrystals 1 and 2 (Fig. 8) confirm the existence of an intermolecular O-H···N bonding. The pale blue and yellow regions reveal the presence of weak interactions. Hence it can be said these color differences give the information about the region from where the compounds can have π - π and C-H··· π intermolecular interactions in the gaseous phase. In cocrystal 1, the pale blue region is located on the aromatic ring of phendione and the yellow region is located on the aromatic ring of 2-naa. The pale blue region is localized on both the aromatic rings of phendione which confirms the formation of two types of π - π interactions in cocrystal 1. This was confirmed from the SCXRD studies (Fig. 2). For cocrystal **1**, H-bonding, π - π , and C-H- \cdots π interactions were confirmed from both theoretical and SCXRD studies. But in cocrystal **2**, the π - π interaction was not observed in SCXRD which is confirmed by theoretical studies. The MEP map of cocrystal 2 shows that the aromatic rings of both phendione and 2-fpaa have the pale blue region. SCXRD data confirmed the formation of C–H··· π interactions. H-bonding and C–H··· π interactions of cocrystal 2 are confirmed by both theoretical and SCXRD studies.

¹ For interpretation of color in 'Figs. 2 and 8', the reader is referred to the web version of this article.

| Table 6 | |
|---------|--|
|---------|--|

NBO results showing the formation of Lewis and non-Lewis orbitals of cocrystal 1 and 2.

| Bond orbital | Occupancy | Atoms | Contribution from parent NBO (%) | Atomic hybrid contributions (%) | Bond orbital | Occupancy | Atoms | Contribution from parent NBO (%) | Atomic hybrid contributions (%) |
|-----------------|-----------|------------|-------------------------------------|--|-----------------|-----------|------------|--|--|
| Cocrusta | 11 | | | | Dhendione | | | | |
| C1_01 | 1 00559 | C1 | 24.41 | $c(21.10) \pm p2.20(69.70)$ | C2_N1 | 1 09595 | C 2 | 40.42 | $c(21.25) \pm n2.10(69.59)$ |
| CI OI | 1.55556 | 01 | 65 50 | s(31.13) + p2.20(03.70) s(42.44) + p1.25(57.22) | C2 N1 | 1.56565 | C2 N1 | 50.57 | s(31.55) + p2.13(66.56) |
| $(2 - 0)^{2}$ | 1 00560 | C2 | 34.42 | s(42.44) + p1.55(57.22) s(31.21) + p2.20(68.69) | C2—N1 | 1 69657 | C2 | <i>J</i> J J J J J J J J J J J J J J J J J J | s(0.00) + p1.00(99.93) |
| C2-02 | 1.99500 | 02 | 55.58 | s(31.21) + p2.20(08.03) s(42.44) + p1.25(57.22) | C2-N1 | 1.09037 | C2 N1 | 59.02 | s(0.00) + p1.00(99.93) s(0.00) + p1.00(99.74) |
| C4 N1 | 1 09202 | 02 | 0J.J8 41.76 | s(42.44) + p1.55(57.22) | C12 N1 | 1 00212 | C12 | 50.52 | s(0.00) + p1.00(35.74) |
| C4-INI | 1.96505 | C4 N1 | 41.70 | s(30.98) + p2.25(68.97) s(25.77) + p1.70(64.05) | CI2-NI | 1.96512 | N1 | J0.15 /1 95 | s(33.72) + p1.79(64.09) s(21.08) + p2.22(68.87) |
| CE NO | 1 00/21 | IN I CE | J0.24 41.14 | s(33.77) + p1.79(64.03) | CF 01 | 1 00550 | IN I CE | 41.05 | s(31.08) + p2.22(68.87) s(21.14) + p2.21(68.75) |
| C5-112 | 1.96451 | ND ND | 41.14 50.0C | s(30.75) + p2.25(69.20) | 01-01 | 1.99559 | 01 | 54.41 | s(31.14) + p2.21(66.73) s(42.42) + p1.25(57.22) |
| C0 N1 | 1 09600 | 1NZ C0 | 40.15 | s(30.40) + p1.74(03.37) | CE 01 | 1 05217 | CE | 05.55 | s(42.43) + p1.33(37.23) |
| C9-INI | 1.98000 | C9 N1 | 40.15 | s(31.17) + p2.21(08.70) s(25.08) + p1.77(62.84) | CJ-01 | 1.93317 | 01 | 53.40 64.54 | s(0.00) + p1.00(99.87) s(0.00) + p1.00(99.87) |
| C0_N1 | 1 60005 | C0 | J9.8J 40.41 | $s(0.00) \pm p1.00(00.02)$ | C11_N10 | 1 09212 | C11 | 04.J4 /1 95 | s(0.00) + p1.00(33.07) s(21.08) + 2.22(68.87) |
| C9-INI | 1.099995 | N1 | 40.41 50.50 | s(0.00) + p1.00(39.92) s(0.00) + p1.00(99.76) | | 1.96512 | N10 | 58 15 | s(35.08)p + 2.22(08.87) s(35.72) + p1.79(64.09) |
| C10-N2 | 1 08603 | C10 | 30.38 | s(30.07) + p2.32(69.86) | 6-02 | 1 00550 | 6 | 34.41 | s(35.72) + p1.75(04.05) s(31.14) + p2.21(68.75) |
| | 1.56005 | N2 | 50.62 | s(36.24) + p1.76(63.60) | 0 02 | 1.555555 | 02 | 65 50 | s(J1.14) + p2.21(00.75) s(J2.43) + p1.35(57.23) |
| C10-N2 | 1 711/15 | C10 | 37.54 | s(0.00) + p1.00(99.91) | 6-02 | 1 05317 | 02 C6 | 35.46 | s(42.43) + p1.33(37.23) s(0.00) + p1.00(99.87) |
| | 1.71145 | N2 | 57.5 4 62.46 | s(0.00) + p1.00(99.91) | 0 02 | 1.55517 | 02 | 64 54 | s(0.00) + p1.00(99.87) |
| C13-03 | 1 08000 | C13 | 32.30 | s(24.77) + p3.03(75.02) | C0-N10 | 1 08585 | C0 | 59.57 | s(35.56) + p1.81(64.24) |
| C15 05 | 1.50555 | 03 | 67.61 | s(32.84) + p2.04(67.09) | C5 MIO | 1.50505 | N10 | 40.43 | s(31.35) + p2.19(68.58) |
| C23-03 | 1 98991 | C23 | 32 41 | s(21.32) + p3.68(78.43) | C9-N10 | 1 69657 | (9 | 58 92 | s(0.00) + p1.00(99.74) |
| 625 65 | 1.56551 | 03 | 67.59 | s(28.90) + p2.66(71.04) | C 5 1110 | 1.05057 | N10 | 41.08 | s(0.00) + p1.00(99.93) |
| C24—04 | 1 99794 | C24 | 34.02 | s(3428) + p191(6561) | 2-naa | | 1110 | 11.00 | S(0.00) * p1.00(00.00) |
| 621 01 | 1.55751 | 04 | 65.98 | s(41.65) + p1.39(57.97) | 2 1144 | | | | |
| C24—04 | 1 99237 | C24 | 29.78 | s(0.00) + p1.00(99.80) | C1 - 01 | 1 98954 | C1 | 32 20 | s(24.44) + p3.08(75.35) |
| 621 01 | 1.55257 | 04 | 70.22 | s(0.00) + p1.00(99.68) | 01 01 | 1.50551 | 01 | 67.80 | s(32.73) + p2.05(67.20) |
| C24-05 | 1 99613 | C24 | 32.03 | s(29.36) + p2.40(70.39) | 01-011 | 1 99003 | 01 | 66.81 | s(28.95) + p2.05(07.20) |
| 621 05 | 1.55015 | 05 | 67.90 | s(33.99) + p1.94(65.95) | or en | 1.55005 | C11 | 33.19 | $s(22,11) + p_3 51(77,66)$ |
| 05-H5 | 1 98454 | 05 | 79.45 | s(27.62) + p2.62(72.32) | C12 - 03 | 1 99606 | C12 | 34 14 | s(34.44) + p1.90(65.45) |
| 00 110 | 100101 | H5 | 20.55 | s(9973) + p0.00(0.27) | 012 00 | 1100000 | 03 | 65.86 | s(42,40) + p1,35(57,20) |
| | | 110 | 20100 | 5(00110) poloc(0121) | C12 - 03 | 1 99169 | C12 | 32.45 | s(0.00) + p1.00(99.82) |
| | | | | | 012 00 | 1100100 | 03 | 67 55 | s(0.00) + p1.00(99.64) |
| | | | | | C12 - 02 | 1 99593 | C12 | 31 15 | s(27.66) + p2.61(72.07) |
| | | | | | 012 02 | 100000 | 02 | 68.85 | s(33.64) + p1.97(66.29) |
| | | | | | 02—H2 | 1.98507 | 02 | 74.95 | s(21.67) + p3.61(78.25) |
| | | | | | | | H2 | 25.05 | s(99.78) + p0.00(0.22) |
| Cocrvsta | 12 | | | | 2-fpaa | | | | |
| C8-02 | 1.99606 | C8 | 32.12 | s(29.65) + p2.36(70.11) | C8-02 | 1.99603 | C8 | 31.22 | s(27.89) + p2.58(71.85) |
| | | 02 | 67.88 | s(33.06) + p2.02(66.88) | | | 02 | 68.78 | s(33.89) + p1.95(66.04) |
| C8-03 | 1.99792 | C8 | 34.04 | s(34.35) + p1.91(65.54) | C8-03 | 1.99812 | C8 | 34.12 | s(34.52) + p1.89(65.37) |
| | | 03 | 65.96 | s(41.60) + p1.39(58.02) | | | 03 | 65.88 | s(41.92) + p1.38(57.68) |
| C8-03 | 1.99226 | C8 | 29.83 | s(0.00) + p1.00(99.80) | C8-03 | 1.99255 | C8 | 31.40 | s(0.00) + p1.00(99.81) |
| | | 03 | 70.17 | s(0.00) + p1.00(99.67) | | | 03 | 68.60 | s(0.00) + p1.00(99.64) |
| C15-05 | 1.99560 | C15 | 34.42 | s(31.22) + p2.20(68.68) | 02-H2 | 1.98613 | 02 | 76.11 | s(21.41) + p3.67(78.52) |
| | | 05 | 65.58 | s(42.43) + p1.35(57.23) | | | H2 | 23.89 | s(99.77) + p0.00(0.23) |
| C15-05 | 1.95269 | C15 | 35.64 | s(0.00) + p1.00(99.87) | | | | | |
| | | 05 | 64.36 | s(0.00) + p1.00(99.67) | | | | | |
| C16-06 | 1.99558 | C16 | 34.42 | s(31.20) + p2.20(68.70) | | | | | |
| | | 06 | 65.58 | s(42.43) + p1.35(57.22) | | | | | |
| C16-06 | 1.95281 | C16 | 35.64 | s(0.00) + p1.00(99.87) | | | | | |
| | | 06 | 64.36 | s(0.00) + p1.00(99.67) | | | | | |
| C14N1 | 1.98303 | C14 | 41.75 | s(30.97) + p2.23(68.98) | | | | | |
| | | N1 | 58.25 | s(35.78) + p1.79(64.04) | | | | | |
| C10-N1 | 1.98600 | C10 | 40.14 | s(31.17) + p2.21(68.76) | | | | | |
| | | N1 | 59.86 | s(35.99) + p1.77(63.83) | | | | | |
| C10-N1 | 1.70077 | C10 | 40.39 | s(0.00) + p1.00(99.92) | | | | | |
| | | N1 | 59.61 | s(0.00) + p1.00(99.76) | | | | | |
| C18-N2 | 1.98432 | C18 | 41.11 | s(30.74) + p2.25(69.21) | | | | | |
| | | N2 | 58.89 | s(36.48) + p1.74(63.36) | | | | | |
| C18-N2 | 1.70249 | C18 | 39.20 | s(0.00) + p1.00(99.94) | | | | | |
| | | N2 | 60.80 | s(0.00) + p1.00(99.80) | | | | | |
| C21-N2 | 1.98605 | C21 | 39.35 | s(30.07) + p2.32(69.86) | | | | | |
| | | N2 | 60.65 | s(36.24) + p1.75(63.59) | | | | | |

Mulliken charge and natural atomic charge distribution

Mulliken and natural atomic charge distribution of atoms in cocrystals **1** and **2** are given in Supporting information (*vide* Supporting information, Tables s-3 and s-4). As can be seen from Tables s-3 and s-4, the positive charges on hydrogen (H5 for 2-naa and H2 for 2-fpaa) bound to the O-atoms of 2-naa (O5) and 2-fpaa (O2) are found to be much higher than those for other H-atoms in 2-naa and 2-fpaa. This shows that these acidic

protons (H5 and H2) have a tendency to accept electrons. In phendione, the strong negative charge is distributed on N-atoms, N1 and N2. This reveals that both N-atoms can act as electron donors. But in the cocrystals, one of the N-atoms (N2 for both 1 and 2) has a higher negative value than the other N-atom (N1 for both 1 and 2) in the phendione moiety. This confirmed that the hydrogen bonding is formed between the N-atom (N2 for both 1 and 2) of phendione moiety and acidic H-atom of 2-naa (H5) or 2-fpaa (H2) moiety.

Natural bond orbital (NBO) analysis

It is well-known that NBO analysis provides an efficient method for studying intra- and inter-molecular bonding and interactions among bonds and also provides a convenient basis for investigating charge transfer or conjugative interaction in molecular systems [32]. Delocalization of electron density between occupied Lewis type (bonded or lone pair) NBO orbitals and formally unoccupied (antibonded or Rydgberg) non-Lewis NBO orbitals correspond to a stabilizing donor–acceptor interaction (Table 6).

BD(1) C10—N2 orbital with 1.98603 electrons has 39.38% C10 character in an sp^{2.32} hybrid and 60.62% N2 character in an sp^{1.76} hybrid. The sp^{2.32} hybrid on C-atom has 69.86% p-character and the sp^{1.76} hybrid on N-atom has 63.60% p-character in cocrystal **1**. BD(1) O5—H5 orbital with 1.98454 electrons has 79.45% O5 character in an sp^{2.62} hybrid and 20.55% H5 character in an sp^{0.00} hybrid. The sp^{2.62} hybrid on O-atom has 72.32% p-character and the sp^{0.00} hybrid on H-atom has 0.27% p-character in cocrystal **1**. The selected C—N (phendione) and O—H (2-naa/2-fpaa) bond orbital, sp character, and occupancy values are slightly changed in cocrystals **1** and **2**. These results also indicate that the hydrogen bonding is formed between N-atom of phendione moiety and H-atom of 2-naa or 2-fpaa moiety.

In order to investigate the intermolecular interactions, the stabilization energies of cocrystals **1** and **2** were computed using second-order perturbation theory. For each donor NBO(i) and acceptor NBO(j), the stabilization energy $E^{(2)}$ associated with electron delocalization between donor and acceptor is estimated [33,34] as,

$$E^{(2)} = \Delta E_{ij} = q_i \frac{F(i,j)^2}{\varepsilon_i - \varepsilon_i}$$

where q_i is the donor orbital occupancy, ε_i and ε_j are diagonal elements (orbital energies), and F(i, j) is the off-diagonal NBO Fock Matrix element. The results of second-order perturbation theory analysis of the Fock Matrix at the B3LYP/6-31G(d,p) level of theory are presented in Table 7.

The most important interaction energy in cocrystal **1** is electron donation from N2 LP(1) to the antibonding (O5–H5) resulting in a

stabilization energy of 22.84 kJ/mol, whereas in cocrystal **2**, the electron donation from N2 LP(1) to O2—H2 results in a stabilization energy of 33.14 kJ/mol.

The larger the $E^{(2)}$ value, the more intensive is the interaction between electron donors and electron acceptors and greater the extent of conjugation of the whole system. Therefore, we conclude from the NBO analysis that the H-bond is formed strongly between N-atom of phendione and H-atom of 2-naa in cocrystal **2**.

Conclusion

Two new cocrystals, [(phendione)(2-naa)] (1) and [(phendione)(2-fpaa)] (2) have been synthesized using solvent mediated crystallization as well as neat grinding method. The single crystal X-ray diffraction data collection and refinement explored the complete molecular structure of the cocrystals stabilized through the hydrogen bonding. The O-H···N bond length of cocrystal 2 is lower than that of cocrystal 1 which shows cocrystal 2 is more stable than cocrystal 1. TGA results showed that cocrystals 1 and 2 were stabilized up to 210 °C. Binding energy, MEP, Mulliken charge, natural charge distribution, and NBO analysis confirmed the formation of intermolecular interactions in cocrystal 1 and 2, and the stability of cocrystal 2 is higher than that of the cocrystal 1. Dipole moment of cocrystal 2 is higher than those of its formers and hence cocrystal 2 is more polar and soluble in polar solvents.

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Appendix A. Supplementary material

CCDC 899820 and 899821 contain the supplementary crystallographic data for [(pnendione)(2-naa)] (1) and [(phendione) (2-fpaa)] (2) respectively. This can be obtained free of charge from

Table 7

| Second o | order pe | rturbation | theory | analysis | of Fock | Matrix o | of cocrystals | 1 and 2 | from NBO | analysis | using | B3LYP/ | 6-31G(d, | p) method | • |
|----------|----------|------------|--------|----------|---------|----------|---------------|-----------------------|----------|----------|-------|--------|----------|-----------|---|
|----------|----------|------------|--------|----------|---------|----------|---------------|-----------------------|----------|----------|-------|--------|----------|-----------|---|

| Donor (i) -acceptor (j) interaction | Cocrystal 1 | | | Donor (i) -acceptor (j) interaction | Cocrystal 2 | | | |
|---|--|----------------------------------|--------------------------------|---|--|----------------------------------|--------------------------------|--|
| | E ^{(2)a} (kJ mol ⁻¹) | E(j)-E(i) ^b (a.u.) | F(i, j) ^c (a.u.) | | E ^{(2)a} (kJ mol ⁻¹) | E(j)-E(i) ^b (a.u.) | F(i, j) ^c (a.u.) | |
| 1,10-Phenanthroline-5,6-dione | | | | 1,10-Phenanthroline-5,6-dione | | | | |
| $LP(1)N1 \rightarrow \pi^*(C3-C4)$ | 10.54 | 0.89 | 0.088 | LP(1)N1 $\rightarrow \pi^*(C28-C29)$ | 10.52 | 0.89 | 0.087 | |
| $LP(1)N2 \rightarrow \pi^*(C5-C6)$ | 9.63 | 0.90 | 0.085 | $LP(1)N2 \rightarrow \pi^*(C32-C33)$ | 9.58 | 0.90 | 0.085 | |
| $LP(1)O1 \rightarrow RY^{*}(1)C1$ | 14.30 | 1.55 | 0.133 | $LP(1)O5 \rightarrow RY^{*}(1)C15$ | 14.30 | 1.55 | 0.133 | |
| $LP(1)O1 \rightarrow \pi^*(C1-C2)$ | 23.85 | 0.62 | 0.109 | $LP(1)O5 \rightarrow \pi^*(C15C16)$ | 23.88 | 0.62 | 0.109 | |
| $LP(1)O1 \rightarrow \pi^*(C1-C6)$ | 19.48 | 0.71 | 0.106 | $LP(1)O5 \rightarrow \pi^*(C15C13)$ | 19.48 | 0.71 | 0.106 | |
| $LP(1)O2 \rightarrow RY^{*}(1)(C2)$ | 14.30 | 1.55 | 0.133 | $LP(1)O6 \rightarrow RY^{*}(1)(C16)$ | 14.30 | 1.55 | 0.133 | |
| $LP(1)O2 \rightarrow \pi^*(C1-C2)$ | 23.88 | 0.62 | 0.109 | $LP(1)O6 \rightarrow \pi^*(C16-C17)$ | 23.85 | 0.62 | 0.109 | |
| $LP(1)O2 \rightarrow \pi^*(C2C3)$ | 19.45 | 0.71 | 0.106 | $LP(1)O6 \rightarrow \pi^*(C16-C17)$ | 19.52 | 0.71 | 0.106 | |
| 2-Naphthoxyacetic acid | | | | 2-Formylphenoxyacetic acid | | | | |
| $LP(2)O3 \rightarrow \pi^*(C13-C14)$ | 31.54 | 0.35 | 0.097 | $LP(1)O2 \rightarrow LP^{*}(1)H2$ | 13.66 | 0.71 | 0.099 | |
| $LP(1)O4 \rightarrow RY^{*}(1)C24$ | 14.67 | 1.43 | 0.130 | $LP(3)O2 \rightarrow RY^{*}(1)H2$ | 18.62 | 1.71 | 0.178 | |
| $LP(1)O4 \rightarrow \sigma^{*}(C24-C23)$ | 22.04 | 0.62 | 0.107 | $LP^*(1)H2 \rightarrow RY^*(1)H2$ | 29.19 | 1.05 | 0.324 | |
| $LP(1)O4 \rightarrow \pi^*(C24 - O4)$ | 28.80 | 0.66 | 0.125 | $LP(1)N2 \rightarrow LP^{*}(1)H2$ | 33.14 | 0.53 | 0.130 | |
| $LP(2)05 \rightarrow \pi^*(C24 - 05)$ | 57.56 | 0.32 | 0.123 | | | | | |
| 1,10-Phenanthroline-5,6-dione to 2-nap | hthoxyacetic acid | | | 1.10-Phenanthroline-5.6-dione to 2-formylphenoxyacetic acid | | | | |
| $LP(1)N2 \to \pi^*(05-H5)$ | 22.84 | 0.80 | 0.122 | $LP(1)N2 \rightarrow \pi^*(02H2)$ | 33.14 | 0.53 | 0.130 | |

ED – Electron density. LP – Lone pair.

RY – Rydberg.

^a $E^{(2)}$ – Energy of hyper conjugative interactions.

^b Energy difference between donor and acceptor *i* and *j* NBO orbitals.

^c F(i, j) – Fock Matrix element between *i* and *j* NBO orbitals.

 $\Gamma(i, j) = \Gamma OCK$ Matrix element between i and j NDO of bitar

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