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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

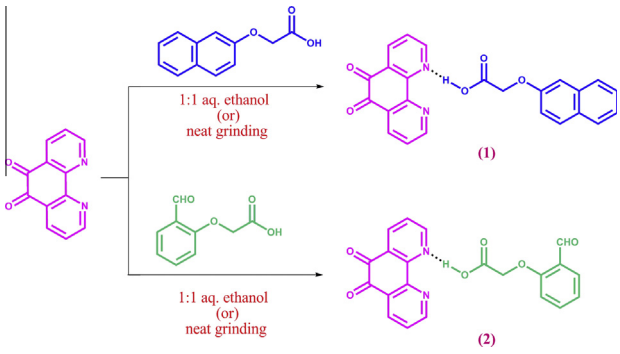
G.S. Suresh Kumar [a,*], A. Antony Muthu Prabhu [b], N. Bhuvanesh [c], X.A.V. Ronica [b], S. Kumaresan [d]

[a] Faculty of Chemistry, Department of Science and Humanities, Dr. Mahalingam College of Engineering and Technology (Dr. MCET), Udumalai Road, Pollachi 642 003, Tamil Nadu, India
[b] Department of Chemistry, Manonmaniam Sundaranar University, Tirunelveli 627 012, Tamil Nadu, India
[c] Department of Chemistry, Texas A & M University, College Station, TX 77842, USA
[d] Department of Chemistry, Noorul Islam University, Kumaracoil, Thuckalay 629 180, Tamil Nadu, India

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.

GRAPHICAL ABSTRACT



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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.

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

* Corresponding author. Tel.: +91 9003180667.
E-mail address: shunsureshkumar@gmail.com (G.S. Suresh Kumar).

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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 ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker (Avance) 400 MHz NMR instrument using TMS as internal standard and DMSO-d_6 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 $K_{\alpha1}$, Cu $K_{\alpha2}$, 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 $10° \leqslant 2\theta \leqslant 80°$. 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*

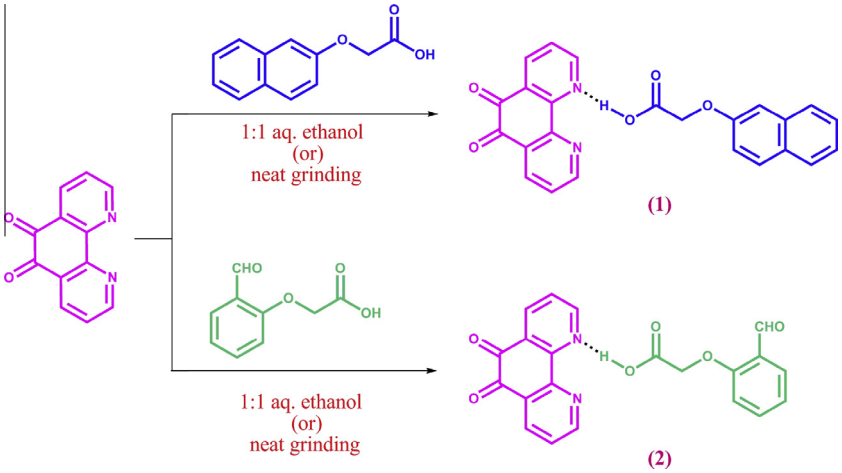
1,10-Phenanthroline-5,6-dione (1.0 mmol) and 2-naphthoxyacetic acid (1.0 mmol) or 2-formylphenoxyacetic acid (1.0 mmol) were dissolved individually in aqueous ethanol (1:1 v/v, 10 mL) in two Erelenmeyer flasks (25 mL) at room temperature. The mixtures were stirred and warmed until the starting materials 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**.