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Supramolecular Cocrystal of 2-Amino-4-Chloro-6-Methylpyrimidine with 4-Methylbenzoic Acid: Synthesis, Structural Determinations and Quantum Chemical Investigations

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***Abstract*—**The 1:1 cocrystal of 2-amino-4-chloro-6-methylpyrimidine (2A4C6MP) with 4-methylbenzoic acid (4MBA) (I) has been prepared by slow evaporation method in methanol, which was crystallized in monoclinic *C*2/*c* space group, $Z = 8$, and $a = 28.431$ (2) Å, $b = 7.3098$ (5) Å, $c = 14.2622$ (10) Å and $\beta = 109.618$ (3)°. The presence of unionized –COOH functional group in cocrystal I was identified both by spectral methods (^{1}H and ^{13}C NMR, FTIR) and X-ray diffraction structural analysis. The 2A4C6MP molecule interact with the carboxylic group of the respective 4MBA molecule through N—H···O and O—H···N hydrogen bonds, forming a cyclic hydrogen–bonded motif $R^2_2(8)$. The crystal structure was stabilized by $N_{pyrimidine}$—H···O=C and C=O—H···$N_{pyrimidine}$ types hydrogen bonding interactions. Theoretical investigations have been computed by HF and density function (B3LYP) method with 6–311+G (d,p)basis set. The vibrational frequencies together with ^{1}H and ^{13}C NMR chemical shifts have been calculated on the fully optimized geometry of cocrystal I. Theoretical calculations are in good agreement with the experimental results. Solvent–free formation of this cocrystal I is confirmed by powder X-ray diffraction analysis.

***Keywords*—**Supramolecular Cocrystal, 2-amino-4-chloro-6-methylpyrimidine, Hartree-Fock and DFT Studies, Spectroscopic Analysis.

I. Introduction

SUPRAMOLECULAR interactions have involved significant attentions for the last several years since the usage of the intermolecular non-covalent interactions is based on the design and development of functional materials [1], [2]. Intermolecular interactions can be used as a key molecular recognition element in the designing of crystalline multiple component system especially for cocrystals structures. Recently, active pharmaceutical ingredient (APIs) was reported to exist in cocrystal formation [3], [4]. A cocrystals formation is often used in order to modify the properties of the compounds in pharmaceuticals fields such as improving the stability, solubility, melting point and reducing the hygroscopicity of the drug product [5].

Pyrimidine and aminopyrimidine derivatives are biologically important compounds and they apparent themselves in nature as components of nucleic acid and drug [6], [7]. Their interactions with carboxylic acids are of greatest consequence since they are involved in protein-nucleic acid recognition and drug-protein recognition processes where the pyrimidine moiety of a drug forms hydrogen bonding with the carboxyl group of the protein [8], [9].

Several cocrystals of 2-amino-4-chloro-6-methylpyrimidine (2A4C6MP) with several of carboxylic acid have been reported from [6]. In addition, methylbenzoic acid is used as an intermediate for polymer stabilizers, pesticides and light sensitive compound [10]. The crystal structure of 4-methylbenzoic acid (4MBA) [11] has been reported.

The use of computational and theoretical studies using Ab-initio (HF) and density functional theory (DFT) has provided a very useful tool for understanding molecular properties and for explaining the behavior of atoms in molecules. The calculation of a broad range of molecular properties with HF and DFT enables a close connection between theory and experimental, and often leads the important clues about geometric, electronic, and spectroscopic properties of the system being studied [12].

In the present study, preparation, structural and characterization of cocrystal **I** were reported by using PXRD, FTIR, ^{1}H and ^{13}C NMR spectroscopes. The structural optimized calculation using hatree-fock (HF) and density functional theory (DFT) method at the basis set levels of 6–311+G (d,p) provide the results of geometrical parameters, fundamental frequencies, GIAO ^{1}H and ^{13}C NMR chemical shift values.

II. Experimental

A. General Remarks

All chemicals are reagent grade and used as commercially purchased without further purification. FTIR spectra were recorded on a PerkinElmer 2000 Spectrum in the form of KBr pellets. 1H-NMR and 13C-NMR spectra were recorded at 500 MHz, in DMSO-d6, on Bruker 500MHz Avance III spectrometer. The chemical shifts are reported in parts per million (ppm) downfield from internal tetramethylsilane (TMS) (chemical shift in δ values). PXRD diffractogram at 25˚C provided another piece of information for the identification and crystallinity of starting materials and cocrystal. PXRD diffractogram was collected by BRUKER

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D8 ADVANCE DIFFRACTOMETER. The source of PXRD was CuKα (1.542 Å) and the diffractometer was operated at 40 kV and 30 mA. The X-ray was passed through a 1mm slit and the signal a 1mm slit, a nickel filter, and another 0.1mm slit. The detector type was a scintillation counter. The scanning rate was set at 0.05˚ ranging from 5˚ to 45˚. The quantity of sample used was around 20-30 mg.

B. Synthesis

Both of the starting materials 2-amino-4-chloro-6-methylpyrimidine and 4-methylbenzoic acid were obtained from Sigma–Aldrich chemical suppliers. Analytical grade solvent was used for preparation of the cocrystal I. The 1:1 mixture of 2A4C6MP (72 mg, 1 mmol) and 4-methylbenzoic acid (68 mg, 1 mmol) was dissolved in 20 mL of 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 cocrystal I appeared after a few days (Fig. 1).

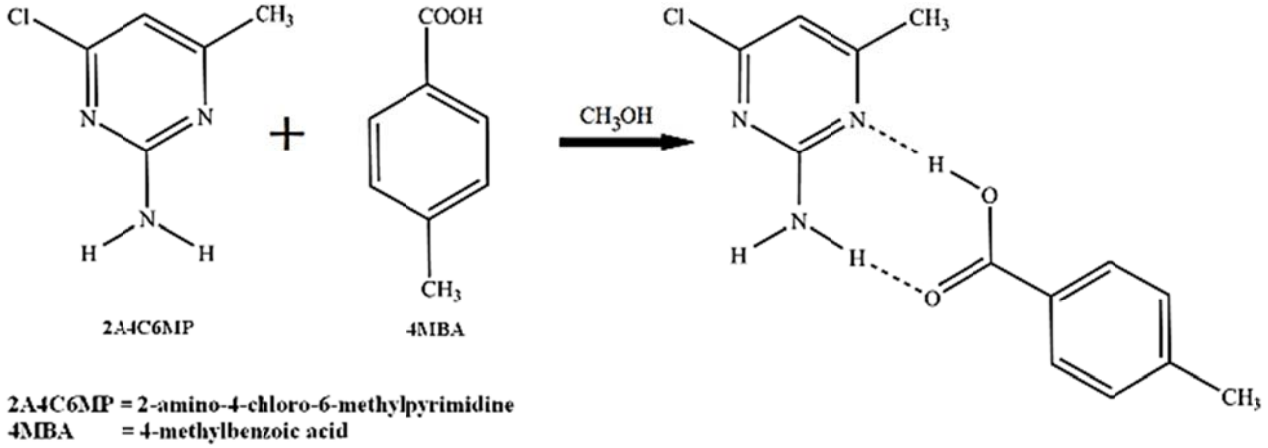


Fig. 1 Supramolecular heterosynthons that can be formed between carboxylic acid and 2-aminopyrimidine: carboxylate supramolecular heterosynthon I

C. Instrumentation Details

Single crystal suitable for X-ray analysis was performed on Bruker SMART APEXII CCD diffractometer using MoKα radiation (λ = 0.71073 Å). Data Collection was performed by using the APEX2 software [13], whereas the cell refinement and data reduction were performed under the SAINT software [13]. The complete crystallographic data were collected at room temperature 294 K and the crystallographic data are shown in Table I. The crystal structure was solved by direct methods using the program SHELXTL and refined by full-matrix least squares technique on F^2 using anisotropic displacement parameters using SHELXTL [14] program. Absorption correction was applied to the final crystal data by using the SADABS software [13]. All geometrical calculations were carried out using the program PLATON [15]. The molecular graphics were drawn using SHELXTL program. Anisotropic thermal factors were assigned to all non-hydrogen atoms.

The O- and N-bound hydrogen atoms were located in a difference Fourier map. Atom H1O1 was refined freely while atoms H1N2 and H2N2 were refined with a bond restraint N—H=0.87 (1) Å [refined distances O1—H1O1 = 0.85(3) Å, N2—H1N2= 0.860(10) Å and N2—H2N2 = 0.855 (10) Å]. The remaining hydrogen atoms were positioned geometrically (C—H = 0.95—0.98 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.

D. Theoretical Calculations

The theoretical calculations were performed by the Hartree–Fock (HF) and Density Functional Theory (Becke's non-local three parameter exchange and the Lee, Young and Parr; B3LYP) methods by the Gaussian 09 [16] program package in 6–311+G (d,p) basis set.

The molecular geometries were optimized to standard convergence criteria and further used to calculate the vibrational wave numbers and isotropic chemical shifts. The calculated vibrational frequencies are corresponded to potential energy minima which no imaginary frequency was found. Due to neglect of the anharmonicity in the real system, the scaling factors of 0.9668 at B3LYP level and of 0.9059 at HF level [17] were used to suit the calculated vibrational wavenumbers with experimental data. The gauge-invariant atomic orbital (GIAO) method was used to calculate the 1H and 13C NMR chemical shifts in ppm relative to TMS as internal standard. The GIAO approach allows the computation of the absolute chemical shielding due to the electronic environment of the individual nuclei and this method is often more accurate than those calculated with other approaches for the same basis set [18]. Gauss View molecular visualization program have been used for animation of vibrational band assignments and preparation of the spectrum [19].

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III. Structural Studies

Cocrystal **I** of the composition [(2A4C6MP) (4MBA)] was prepared by reacting equal mol of 2-amino-4-chloro-6-methylpyrimidine and 4-methylbenzoic acid in 1:1 ratio, which crystallizes as monoclinic colourless crystals in the centrosymmetric space group *C*2/*c*. The structure of cocrystal I with the atom numbering is shown in Fig. 2. Crystallographic data for the cocrystal I was deposited with the Cambridge Crystallographic Data Centre (CCDC) (deposition number 1027071).

A search in the Cambridge Structural Database (CSD, Version 5.35 of May 2014; Allen, 2002) [20] for organic compounds including only the elements C, H, O, N and Cl was conducted, and revealed 10 cocrystal structures containing both 2-amino-4-chloro-6-methylpyrimidine and aromatic carboxylic acid, with such a supramolecular heterosynthon observed in all of them.

In the structures with code of EXEYIQ, EXEYOW, EXEYUC, EXEZAJ, EXEZEN, EXEZIR, EXEZOX, EXEZUD, EXIBAP and EXIBET [6] the 2-aminopyrimidine is a neutral molecule forming a cocrystal. Table II shows a comparison between the experimental, calculated structural parameters with the similar 2-aminopyrimidine crystal structure (CSD refcode: EXEZIR and EXEZOX [6]). In general, the experimental [(2A4C6MP) (4MBA)] bond lengths and bond angles values are comparable with the corresponding values obtained by similar crystal structures [6].

The N1—C1—N3 bond angles in pyrimidine ring is 124.56 (18)°. This bond angle value of 124.74 (18)° and 124.87 (17)° are also observed in the cocrystal of EXEZIR and EXEZOX [6]. This value is in good agreement with the N—C—N bond angle in the free aromatic nitrogen atom of pyrimidine ring encountered in with an average value of 124–128° [21].

The C–O distances for COOH [C6—O1 and C6—O2] group of the 4MBA are 1.308(3) and 1.210(3) Å, respectively. Meanwhile, the similar range of bond length distances of 1.313 (3) Å and 1.206 (3) Å in EXEZIR and 1.311 (2) Å and 1.206 (2) Å in EXEZOX are also observed. These values emphasize the fact that cocrystal **I** is formed only via a strong hydrogen bond between the proton–donor and proton–acceptor compounds; no proton transfer occurs.

TABLE I
Crystallographic Parameters for Cocrystal I

Empirical formula	$C_{13}H_{14}N_3O_2Cl_1$
CCDC deposition No.	1027017
Formula mass	279.72
Temperature (K)	294(2)
Crystal system	Monoclinic
Space group	*C*2/*c*
Unit Cell dimensions	
a (Å)	28.431 (2)
b (Å)	7.3098 (5)
c (Å)	14.2622 (10)
α (°)	90
β (°)	109.618 (3)
γ (°)	90
V (Å^3)	2791.9 (3)
Z	8
Dc (g cm^{-3})	1.331
μ (mm^{-1})	0.28
F (000)	1168
θ range (°)	2.9–30.1
Measured reflections	21196
Unique reflections	2742
Observed reflections (I>2σ(I))	2239
No. of parameters	186
R[(a)]	0.041
wR[(b)]	0.157
GOF[(c)]	1.08
Residual peaks (e·Å^{-3})	0.32, –0.33
Crystal size (mm^3)	0.59 × 0.44 × 0.08
Colour and shape	colourless, plate

For I, $w = 1/[\sigma^2(F_o^2) + (0.0898P)^2 + 1.4962P]$, where $P = (F_o^2 + 2F_c^2)/3$; [a] $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, [b] $R_w = \{w\Sigma(|F_o| - |F_c|)^2/\Sigma w|F_o|^2\}\}^{1/2}$, [c] $GOF = \{\Sigma w(|F_o| - |F_c|)^2/(n-p)\}^{1/2}$, where n is the number of reflections and p the total number of parameters refined.

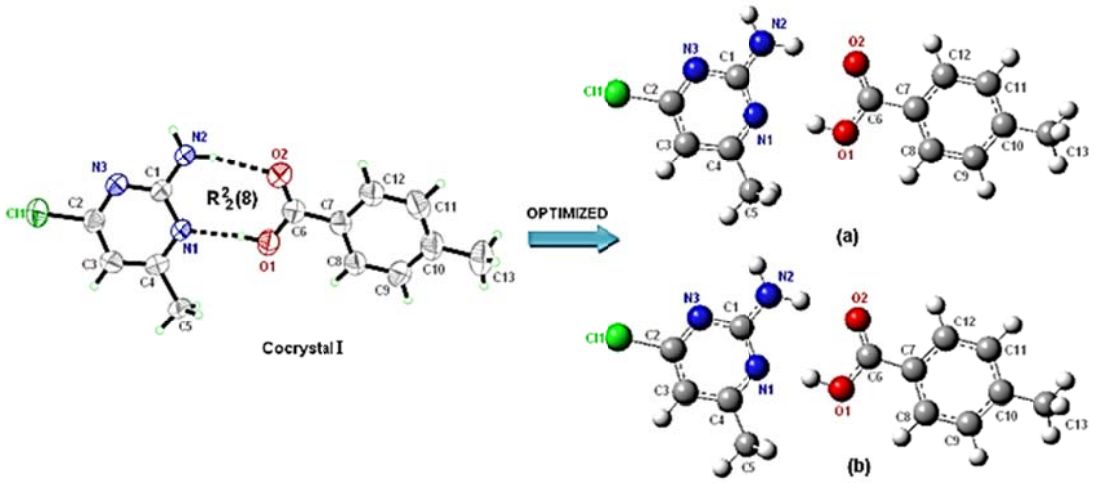


Fig. 2 An ORTEP view of the title cocrystal **I** showing the atom-numbering. Displacement ellipsoids are drawn at the 50% probability level. The optimized structure at basis set of (a) HF/6-311+G(d,p) and (b) B3LYP/6-311+G(d,p)

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The non-hydrogen atoms of the 2A4C6MP molecule is essentially planar, with maximum deviation of 0.012 (2) Å for atom C1. The dihedral angle between the pyridine (N1/C1/N3/C2–C5) and benzene (C7–C12) rings is 19.21 (11)°. The acid molecule is essentially planar, with a dihedral angle of 5.4 (3)° between the benzene (C7–C12) ring and carboxylic (O1/O2/C6) group. All the bond lengths and angles are in the normal ranges [22]. In this cocrystal I, the carboxylic acid group interacts with the corresponding 2-aminopyrimidine moiety through N2—H1N2···O2 and O1—H1O1···N1 (Fig. 2) hydrogen bonds to form a cyclic hydrogen–bonded ring motif, $R_2^2(8)$ [23]. This motif has already been recognized as a robust synthon and it is one of the top five ring motifs among the 24 most frequently observed hydrogen-bonded cyclic bimolecular motifs (supramolecular synthons) [24]. These motifs are linked by N2—H2N2···O2 hydrogen bonds (symmetry code in Table III), forming a ring spanning the centre of symmetry at (−x+1, y, −z+3/2) to produce a DADA array (Where D is a hydrogen–bond donor and A is a hydrogen–bond acceptor) of four hydrogen bonds. This set of fused rings can be represented by the graph–set notations $R^2_2(8)$ heterosynthon, $R^2_2(8)$homosynthon and $R^2_2(8)$ heterosynthon arrangement forming a cyclic heterotetrameric synthon as shown in Fig. 3 (a). This type of motif has been reported in the crystal structures of 4-chloro-6-methoxypyrimidine-2-amine-succinic acid (2/1) [25] and 2,6-diamino-4-chloropyrimidine-benzoic acid (1/1) [26]. The crystal structure is stabilized by a π-π stacking interaction between two aminopyrimidine groups (at x, y, z and 1–x, 2–y, 1–z), with a perpendicular separation of 3.4651 (8) Å and a centroid-centroid distance of 3.8570 (11) Å, which stacks heterotetramers into infinite one-dimensional chains along *c*-axis in Fig. 3 (b).

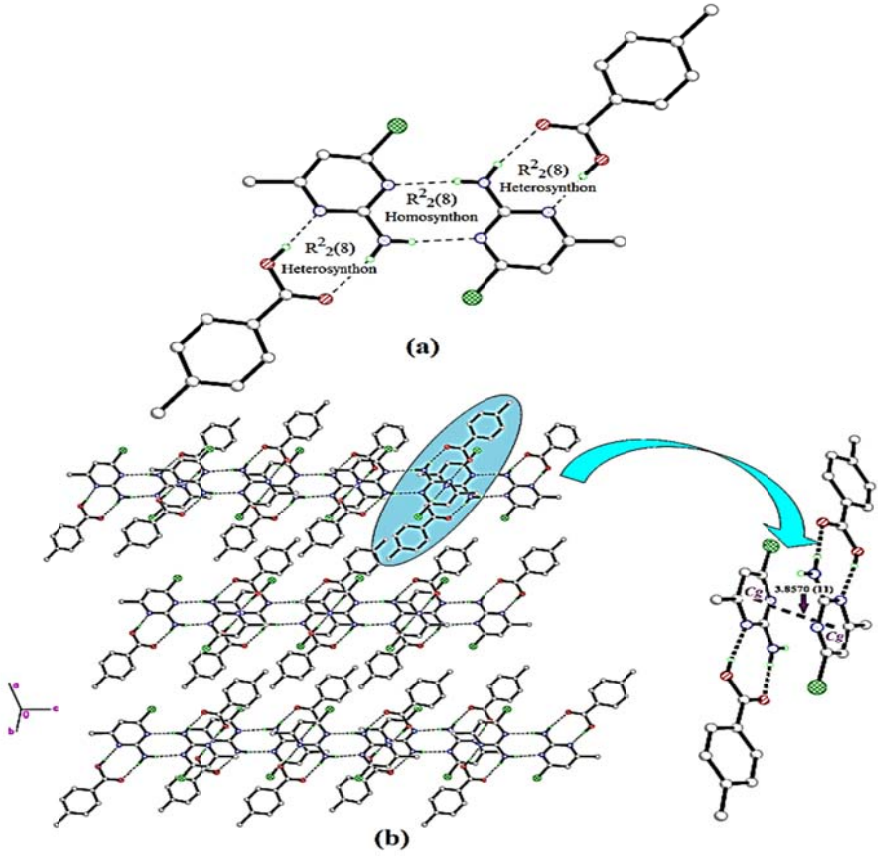


Fig. 3 Hydrogen bonding interactions in the cocrystal I: (a) heterotetrameric synthon; (b) π-π stacking interaction stacks heterotetramers into infinite one-dimensional chains along *c*-axis

IV. Optimized Structural Studies

The labeling of optimized structure in cocrystal I is presented in Figs. 2 (a) and (b). The optimized geometrical parameters (bond length and bond angles) of the title compound were obtained using by HF and B3LYP with the 6–311+G (d,p) basis sets. Some selected geometric parameters experimentally obtained and theoretically calculated are listed at Table II. As can be seen from Table II, most of the optimized bond lengths are slightly longer than the experimental values and the bond angles are slightly different from the experimental values. We note that the experimental results are for the solid phase and the theoretical calculations are for the gas phase.

The C—O bond lengths of the COOH group are slightly different in X-ray [C6—O1 = 1.308 (3) Å and C6—O2 = 1.210 (3) Å], while these bond lengths have been calculated at

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1.312 Å and 1.196 Å for HF and 1.329 Å and 1.224 Å for B3LYP method using 6–311+G (d,p) basis set, respectively. The experimental C—O bond lengths in the carboxylic acid group are intermediate between single Csp^2—O (1.308–1.320 Å) and double Csp^2=O bond values (1.214–1.224 Å) [22] which clearly distinguishes the neutral molecule of the acid. The theoretical B3LYP method values correlate well compared with the experimental results.

In the 2A4C6MP ring, the bond angles of N1—C1—N3 was obtained to be 124.56 (18)°in X–ray while these bond angles have been calculated at 125.05° and 124.62° with HF and B3LYP method using 6–311+G (d,p) basis set, respectively.

Notable conformational differences and observed in the orientation of the carboxylic group of the 4MBA molecule, when the x–ray structure is compared with the optimized structure. The orientation of the carboxylic group from the experimental data is defined by torsion angles of O1—C6—C7—C12 [−174.2 (2)°], O2—C6—C7—C12 [4.5 (4)°], O1—C6—C7—C8 [3.1(3)°] and O2—C6—C7—C8 [−178.3 (2)°]. The corresponding torsion angles have been calculated at 179.93624°, −0.08193°, 0.09031° and −179.92786° for HF and 179.99208°, −0.05859°, 0.14675° and −179.90392° for B3LYP method using 6–311+G (d,p) basis set, respectively. The angle differences of 2–6° are due to the effect of the involvement of the carboxylic group in intermolecular interactions observed in the crystal structure.

V. Vibrational Analysis

The harmonic vibrational frequencies were calculated for [(2A4C6MP) (4MBA)] at HF and B3LYP levels using the triple split valence basis set along with diffuse and polarization function, 6–311+G (d,p). The selected experimental and theoretical vibrational frequencies with probable vibrational assignments are given in Table IV. The bands observed in the measured region 4000–400 cm^{-1} arise from the internal vibrations of the amino groups, pyrimidine ring and 4-methylbenzoic acid. The calculated (HF and DFT) and experimental vibrational frequencies are comparable to each other where the correlation values of 0.98 for HF and 0.99 for DFT are obtained. According to these results, there is a good correlation between the theoretical and experimental vibrational frequencies.

The band observed in the 1700–1800 cm^{-1} region due to the C=O stretching vibration is one of the characteristic features of the carboxylic group. The band appears at 1700 cm^{-1} is assigned as C=O stretching vibration in FTIR spectrum. Meanwhile, the calculated C=O frequencies are found at 1672 cm^{-1} from HF method and 1746 cm^{-1} with B3LYP method. The change in carbonyl frequencies is due to the carbonyl group involvement in the hydrogen bond formation and is also an indicator of the formation of a cocrystal [27].

The hydroxyl vibrations are likely to be the most sensitive to the environment, so they show pronounced shifts in the spectra of the hydrogen–bonded species. The non–hydrogen bonded or a free hydroxyl group absorb strongly in the 3550 – 3700 cm^{-1} region [28]. The O—H stretching vibration is observed at 3128 cm^{-1}, while it is calculated at 2875 cm^{-1} for HF and 3383 cm^{-1} for DFT, respectively. The reduction in the O—H stretching indicates the presence of hydrogen bonding within the cocrystal.

The molecule under investigation possesses one NH_2 group and hence one can be expect one being asymmetric and other is symmetric N—H vibrations. It is stated that in N—H stretching vibrations (amines group) occur in the region 3500–3300 cm^{-1} [29]. The FTIR spectrum of the title aminopyrimidine compound contains intense broad bands in the range of the νN—H vibrations. The NH_2 asymmetric and symmetric stretching vibration in FTIR experimental spectrum found at 3334 and 3206 cm^{-1}. These stretching have been calculated at 3579 and 3289 cm^{-1} with HF method and 3574 and 3411 cm^{-1} with B3LYP method using 6–311+G (d,p) basis set. These amino vibrations values in good agreement for both experimental and theoretical methods.

The aliphatic C—Cl bands absorb at range 830–560 cm^{-1} and the substitution more than one chlorine on a carbon atom raises the C—Cl wavenumber [30]. In this cocrystal **I**, the C—Cl stretching frequency appears in FTIR at 474 cm^{-1}. It shows good correlation when compared with calculations frequencies which is the HF calculations gives 409 cm^{-1} and the DFT calculations gives 471 cm^{-1}.

For the aromatic benzene ring, in our title molecule the C=C stretching appears at 1605 and 1454 cm^{-1} while the calculations values are observed at 1556 and 1535 cm^{-1} for HF and 1585 and 1582 cm^{-1} for B3LYP methods respectively. It shows that these values are comparable with the ranges at 1600 cm^{-1} and 1475 cm^{-1} for aromatic ring vibrations [29]. Primary aromatic amines with nitrogen directly on the ring absorb at 1430-1575 cm^{-1} due to stretching of the phenyl carbon nitrogen bond [31]. For our title molecule, the *ν*C—N appears at 1562.5 cm^{-1}, while the HF calculations give the *ν*C—N at 1564 cm^{-1} and 1596 cm^{-1} for DFT calculations.

The title cocrystal **I** [(2A4C6MP) (4MBA)] possesses a CH_3 group in the sixth position of aminopyrimidine and in the forth position of carboxylic acid. The methyl stretching vibrations is expected around 2980 cm^{-1} and 2870 cm^{-1} [32]. In the present studies, the stretching aromatic C–CH_3 group vibrations was noted at 2973 and 2818 cm^{-1} which are in comparable with theoretical results of 3030 and 3008 cm^{-1} for HF and 2961 and 2942 cm^{-1} for B3LYP method using 6–311+G (d,p) basis set. The slight differences of the vibration frequencies between experimental and calculated values may be due to the hydrogen atom of the methyl group of 4MBA and the oxygen atom of 2A4C6MP.

VI. NMR Analysis

The ^1H and ^{13}C NMR spectra of cocrystal were carried out in DMSO–d_6 at room temperature using TMS as internal standard. The optimized structure of [(2A4C6MP) (4MBA)] is used to calculate the NMR spectra at the HF and DFT (B3LYP) methods with 6–311+G (d,p) level using the GIAO method. The results of the calculated values shifted to higher values of chemical shift and further corrected with the TMS isotropic chemical shift values. The theoretical ^1H and ^{13}C

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NMR chemical shifts of [(2A4C6MP) (4MBA)] have been compared with the experimental data as shown in Table V.

In the experimental ^{1}H NMR spectrum, the hydrogen of the carboxylic acid (COOH) is observed at 12.796 ppm (11.467 ppm in HF and 14.47 in DFT spectrum) and indicates that a hydrogen bond is confirmed the formation of cocrystal **I**. The ^{1}H NMR spectra show a broad singlet peak at 7.013 ppm which due to protons in NH_2 (aminopyrimidine) group attached to carbon atom while this signal is observed computationally at 7.8549 (H1N2), 4.7557 (H2N2) ppm with HF and 9.6058 (H1N2), 4.8957 (H2N2) ppm with B3LYP method. The discrepancies between the experimental and theoretical values are due to the formation of intermolecular N2—H2N2···O2 hydrogen bonding (Table III) observed in the crystal packing. The signals at 6.565−7.851 ppm range are typical for hydrogen atoms attached to aromatic ring. The presence of the methyl group in 2A4C6MP and 4MBA gave single peaks at δ values of 2.37 and 2.22 ppm and the values of the calculated chemical shift of methyl group were also in same range of 2.72–2.01 ppm for HF and 2.86–1.91 ppm for B3LYP method using 6–311+G (d,p) basis set.

The ^{13}C NMR spectrum given in Table V clearly shows the cocrystal of [(2A4C6MP) (4MBA)]. 4MBA gives a single signal at 167.276 ppm for COOH (C6) carbon atom. This signals has been calculated at 171.682 ppm for HF method and 176.55 ppm with B3LYP method using 6–311+G (d,p) basis set, respectively. The C atoms (C5 and C13) of methyl groups are observed at 23.18 and 21.08 ppm. These peaks theoretically calculated at 23.806 and 21.735 ppm with HF and at 24.563 and 23.875 ppm with B3LYP method using 6–311+G (d,p) basis set. As can be seen from Table V, the theoretical ^{1}H and ^{13}C NMR chemical shift values for the title compound were in the normal range and in a good agreement with the experimental ^{1}H and ^{13}C NMR chemical shift data.

VII. Powder XRD Analysis

Powder XRD is a useful method for fast identification of the new phases [33]. A different PXRD pattern for the cocrystal from those of the individual components confirms the formation of a new phase.

The PXRD pattern of 2A4C6MP shows some characteristics peaks at 9.1°, 12.1°, 16.9°, 18.3°, 24.3°, 24.7°, 25.4°, 27.6°, 28.9°, 29.7°, 33.6°, 34.9°, 35.5°, 36.9°, 39.0°, 40.0°, 42.3° and 43.0° and 43.8° (2θ) while the PXRD pattern of 4MBA shows characteristics peaks at 12.5°, 13.7°, 14.5°, 15.4°, 17.2°, 22.6°, 24.9°, 26.5°, 27.8°, 29.4°, 30.6°, 31.3°, 32.4°, 33.0°, 35.0°, 36.4°, 36.8°, 39.9°, 40.8°and 42.4° (2θ).

The PXRD pattern of cocrystal I shows appearance of new peaks at 6.6°, 12.5°, 13.6°, 14.6°, 15.2°, 15.7°, 17.3°, 18.2°, 18.9°, 19.8°, 20.5°, 21.2°, 21.6°, 22.2°, 23.7°, 24.3°, 25.2°, 26.4°, 27.5°, 28.3°, 29.5°, 30.7°, 31.5°, 32.4°, 32.9°, 33.9°, 38.9°, 41.0° and 41.9° (2θ). Besides this, characteristics peaks of 2A4C6MP at (9.1°, 16.9°, 28.9°, 34.9°, 35.5°, 36.6°, 43.0° and 43.8°) and of (4MBA) at (24.9°, 26.5°, 35.0°, 36.4°, 36.8° and 42.4°) have disappeared in the PXRD pattern of cocrystal I. From the above results, it is clear that there is transformation in the crystalline lattices of [(2A4C6MP) (4MBA)] and new phases of cocrystal I have been formed.

VIII. Prediction of Cocrystals/Salts by Pka Values

The significant of pKa can act as a predictor either cocrystals or salts for carboxylic acids and pyrimidines [34]. ΔpKa of carboxylic acid vs. N_{arom} moieties can be used to predict whether or not proton–transfer will occur [ΔpKa = pKa 2A4C6MP – pKa (4MBA)]. Generally, a sufficiently large ΔpKa value (i.e. greater than 3) should result in a salt [35]. With less ΔpKa values, a cocrystal can be predicted, but this argument seems inadequate prediction salt or cocrystal formation in a solid state if $0< \Delta pKa < 3$ [36]. In this study, the pKa values for 2A4C6MP and 4MBA are 4.16 and 4.26, respectively, while ΔpKa values for this acid–base complex are –0.1 (Table VI) and noted in the formation of cocrystal.

IX. Conclusion

In this study, we have synthesized a [(2A4C6MP) (4MBA)] cocrystal and characterized by PXRD, spectroscopy (FTIR, ^{1}H and ^{13}C NMR) and structural determination (single–crystal X–ray diffraction) techniques. To support the solid state structure, the geometric parameters, vibrational frequencies and ^{1}H and ^{13}C NMR chemical shifts of the title cocrystal **I** have been calculated using the HF and B3LYP method with 6–311+G (d,p) basis sets and compared with the experimental findings. The experimental geometric parameters, vibrational frequencies and chemical shift values are in a comparable and in a good agreement with the experimental findings. The discrepancies between the experimental and theoretical geometric parameters, IR frequencies, and chemical shift values are mainly due to the hydrogen bonding interactions since all the hydrogen bound to the nitrogen and oxygen atoms are involved in hydrogen bonding in the crystal structure. It should be noted that the theoretical calculations refer to the molecules and their dimers in their vacuum (gas phases). While, the experimental results referring to molecules in chemical environment (solid state). Thus, these results have differed because the states of the molecules are different.

Supplementary Materials

This data (CCDC: 1027017) can be obtained free of charge at www.ccdc.cam.ac.uk.conts/retrieving.html/ or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 IEZ, UK; fax: +44(0) 1223-336033; e-mail: deposit@ccdc.cam.ac.uk.

TABLE II
THE EXPERIMENTAL AND OPTIMIZED GEOMETRICAL PARAMETERS OF THE TITLE COCRYSTAL I

Parameters	Experimental	Calculated		EXEZIR	EXEZOX
		HF 6−311+G(d,p)	DFT B3LYP 6−311+G(d,p)	[6]	[6]
Bond lengths (Å)					
Cl1—C2	1.725 (2)	1.736	1.758	1.728 (2)	1.729 (2)
O1—C6	1.308 (3)	1.312	1.329	1.313 (3)	1.311 (2)
O2—C6	1.210 (3)	1.196	1.224	1.206 (3)	1.206 (2)
N1—C1	1.352 (2)	1.331	1.352	1.354 (2)	1.350 (2)
N1—C4	1.335 (3)	1.328	1.343	1.331 (3)	1.334 (2)
N2—C1	1.328 (3)	1.334	1.343	1.330 (3)	1.328 (2)
N3—C2	1.314 (3)	1.294	1.308	1.311 (3)	1.313 (2)
N3—C1	1.349 (2)	1.338	1.354	1.347 (2)	1.351 (2)
C4—C5	1.534 (3)	1.502	1.503	1.536 (3)	1.518 (3)
C6—C7	1.482 (3)	1.486	1.487	1.489 (3)	1.492 (3)
C10—C13	1.511 (3)	1.590	1.508	-	-
Bond angles (°)					
C2—N3—C1	115.35 (16)	116.00	116.03	115.44 (16)	115.08 (17)
C1—N1—C4	117.49 (17)	117.42	117.63	117.22 (17)	117.47 (16)
N2—C1—N3	117.33 (16)	116.55	117.14	117.65 (17)	117.22 (17)
N2—C1—N1	118.11 (17)	118.39	118.24	117.61 (18)	117.91 (16)
N3—C1—N1	124.56 (18)	125.05	124.62	124.74 (18)	124.87 (17)
N3—C2—C3	124.96 (18)	124.70	124.70	125.07 (19)	125.20 (17)
N3—C2—Cl1	115.27 (15)	116.48	116.60	115.58 (15)	115.34 (15)
C3—C2—Cl1	119.77 (16)	118.82	118.69	119.35 (16)	119.46 (15)
C2—C3—C4	115.96 (19)	114.93	115.54	115.66 (18)	116.09 (18)
N1—C4—C3	121.63 (18)	121.89	121.47	121.85 (18)	121.26 (18)
N1—C4—C5	116.96 (18)	116.67	116.96	116.99 (18)	117.38 (17)
C3—C4—C5	121.41 (19)	121.44	121.57	121.16 (18)	121.36 (18)
O2—C6—O1	123.3 (2)	122.71	123.19	122.7 (2)	123.42 (18)
O2—C6—C7	122.5 (2)	123.20	122.76	124.42 (19)	122.98 (17)
O1—C6—C7	114.19 (19)	114.08	114.06	112.89 (18)	113.59 (16)
C11—C10—C13	120.8 (2)	120.47	120.79	-	-
C9—C10—C13	121.4 (2)	121.06	120.98	-	-
Torsion angles (°)					
C2—N3—C1—N2	−178.26 (19)	179.99940	179.99135	-	-
C2—N3—C1—N1	2.1 (3)	−0.00116	−0.00210	-	-
C4—N1—C1—N2	178.46 (19)	−179.99876	−179.98827	-	-
C4—N1—C1—N3	−2.0 (3)	0.00181	0.00511	-	-
C1—N3—C2—C3	−0.5 (3)	0.0000	−0.00150	-	-
C1—N3—C2—Cl1	179.52 (15)	180.000	179.99626	-	-
N3—C2—C3—C4	−1.1 (3)	0.00054	0.00181	-	-
Cl1—C2—C3—C4	178.84 (16)	−179.99952	−179.99590	-	-
C1—N1—C4—C3	0.1 (3)	−0.00123	−0.00459	-	-
C1—N1—C4—C5	−179.18 (18)	179.9973	179.99215	-	-
C2—C3—C4—N1	1.3 (3)	0.000	0.00141	-	-
C2—C3—C4—C5	−179.45 (19)	−179.99876	−179.99519	-	-
O2—C6—C7—C12	4.5 (4)	−0.08193	−0.05859	-	-
O1—C6—C7—C12	−174.2 (2)	179.93624	179.99208	-	-
O2—C6—C7—C8	−178.3 (2)	−179.92786	−179.90392	-	-
O1—C6—C7—C8	3.1 (3)	0.09031	0.14675	-	-
C8—C9—C10—C13	179.1 (2)	178.86037	178.53684	-	-
C8—C9—C10—C11	−1.1 (4)	−0.20813	−0.31171	-	-
C12—C11—C10—C13	−179.2 (3)	−178.85728	−178.53662	-	-
C12—C11—C10—C9	0.9 (5)	0.21695	0.31412	-	-

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TABLE III
THE HYDROGEN BONDING GEOMETRY FOR TITLE COCRYSTAL I

D—H···*A*	D—H (Å)	H···A(Å)	D···A(Å)	D—H···A(°)
N2—H2*N*2···N3^{i}	0.86 (2)	2.19 (2)	3.045 (2)	173 (3)
N2—H1*N*2···O2	0.86 (2)	2.07 (2)	2.919 (3)	168 (2)
O1—H1*O*1···N1	0.85 (3)	1.85 (3)	2.694 (2)	169 (3)

Symmetry codes: (i) −x+1, y, −z+3/2.

TABLE IV
SELECTED EXPERIMENTAL AND CALCULATED VIBRATIONAL FREQUENCIES OF THE TITLE COCRYSTAL I

Experimental (cm^{-1})	Calculated IR (km mol^{-1})				Assignment[a]
	HF 6-311+G (d,p)		DFT B3LYP 6-311+G (d,p)		
	Unscaled	Scaled	Unscaled	Scaled	
3334	3694.75	3579.47	3945.26	3574.01	*ν* NH_2
3206	3395.78	3289.83	3766.10	3411.71	*ν* NH_2
3182	2967.99	2875.39	3734.76	3383.32	*ν* OH
2973.2	3127.74	3030.15	3268.71	2961.12	*ν* CH_3
2818.5	3105.4	3008.51	3247.3	2941.73	*ν* CH_3
1700.8	1726.05	1672.20	1927.91	1746.49	*ν* C=O
1562.5	1614.86	1564.48	1762.23	1596.40	*ν* C-N
1605.9	1607.12	1556.98	1749.75	1585.10	*ν* Ar C=C
1454	1585.05	1535.60	1746.36	1582.03	*ν* Ar C=C
474.6	422.32	409.14	460.65	417.30	*ν* C-Cl

[a] Vibrational assignment: *ν*, stretching

TABLE V
THE EXPERIMENTAL AND THEORETICAL NMR CHEMICALS SHIFTS

Chemical Shift, (ppm)[a]	**Experimental**	**Calculated**	
		HF 6−311+G (d,p)[b]	**B3LYP 6−311+G (d,p)[c]**
^{1}H NMR			
O1-H1O1	12.796	11.4673	14.4703
N2-H1N2	7.013	7.8549	9.6058
N2-H2N2	-	4.7557	4.8957
Aromatic proton	7.851−6.565	8.8596, 8.6502	8.4747, 8.4072
		7.600, 7.4792	7.5273, 7.442
		6.2137	6.2909
Methyl group	2.22−2.52	2.7201, 2.5545 2.5536, 2.5233 2.2684, 2.0141	2.8637, 2.5282 2.5258, 2.4312 2.2685, 1.9102
^{13}C NMR			
C2	169.805	179.663	177.978
C6	167.276	171.682	176.55
C4	163.221	182.8	175.412
C1	159.851	170.469	168.72
C10	142.987	154.694	151.634
C12	129.294	142.342	137.999
C8	-	141.459	137.186
C11	129.078	132.5	134.394
C9	-	131.463	133.933
C7	127.980	130.607	134.121
C3	107.99	105.06	112.942
C5	23.18	23.8058	24.5625
C13	21.08	21.735	23.8748

[a] The atoms numbering are referred to the X-ray molecular diagram in Fig. 2
[b] The isotropic chemical shift with respect to Tetramethysilane (TMS) in HF 6-311+G (d,p) are 32.4495 ppm for ^{1}H NMR and 195.8342 ppm for ^{13}C NMR.
[c] The isotropic chemical shift with respect to Tetramethysilane (TMS) in B3LYP 6-311+G (d,p) are 31.9844 ppm for ^{1}H NMR and 184.0085 ppm for ^{13}C NMR.

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TABLE VI
ACIDITY OF COMPLEXES OF 2A4C6MP BASES AND CARBOXYLIC ACID

Compounds	pKa	ΔpKab	Crystalline form	References
2-methylbenzoic acid	3.96	0.2	Cocrystal	[6]
3-methylbenzoic acid	4.08	0.08	Cocrystal	[6]
4-methylbenzoic acid	4.26	-0.1	Cocrystal	This work
2-chlorobenzoic acid	3.07	1.09	Cocrystal	[6]
4-chlorobenzoic acid	4.07	0.09	Cocrystal	[6]
Benzoic acid	4.08	0.08	Cocrystal	[6]
3-nitrobenzoic acid	3.48	0.68	Cocrystal	[6]
4-nitrobenzoic acid	3.16	1.00	Cocrystal	[6]
4-methoxybenzoic acid	4.37	-0.21	Cocrystal	[6]
Phthalic acid	5.49	-1.33	Cocrystal	[6]
Cinnamic acid	4.51	-0.35	Cocrystal	[6]

[b] The pKa value of 2-amino-4-chloro-6-methylpyrimidine (2A4C6MP) is 4.16.

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