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Intermolecular Interactions of 3,5-bis(4-Methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide in a Cocrystal with 1,3-bis(4-Methoxyphenyl)prop-2-en-1-one and Dimethylformamide Solvate

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Abstract: Two new multicomponent crystals consisting of 3,5-bis(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**1**) with 1,3-bis(4-methoxyphenyl)prop-2-en-1-one (**2**) and with dimethylformamide (DMF), both in 1:1 ratio, prepared and structurally characterized. The occurrence of **1** in different crystal structures enabled a comparison of hydrogen bonding contacts between the two structures as well as with the known structure of pure **1**. The backbone of molecule **1** was similar in the structures but the orientation of the methoxy groups varied. Molecule **1** was involved in various combinations of the possible hydrogen bonding contacts, including N–H ... O=C, N–H ... OMe, and N–H ... S. Both N–H hydrogens in the cocrystal (**1–2**) and the solvate (**1**-DMF) participated in hydrogen bonding but only one hydrogen atom took part in the structure of pure **1**. The S atom accepted contacts in both the structures of pure **1** and cocrystal **1–2** but not in that of the **1**-DMF solvate. The oxygen atoms of both methoxy groups acted as acceptors in the structure of pure **1**, whereas one oxygen was involved in the **1**-DMF solvate and none in cocrystal **1–2**.

Keywords: synthesis; heterocycles; crystal structure; crystallization; multicomponent crystals; 1H-pyrazole-1-carbothioamide; bis(4-methoxyphenyl)prop-2-en-1-one



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1. Introduction

The generation of crystalline materials with predictable molecular assembly is an important aim of crystal engineering [1,2]. Thus, materials with desired physical and chemical properties can be produced for beneficial application. In the organic solid state, crystal engineering is dependent on the ability to predict and control the assembly of molecules into the crystalline state. The mode of molecular packing is determined by the synergy between a variety of factors which include the need for efficient packing and optimization of electrostatic interactions. In addition, the structure can be influenced by directional interactions, of which a well-characterized example is hydrogen bonding.

The control of molecular assembly requires a detailed understanding of the complex relationships between intermolecular interactions in the crystalline state. A significant amount of knowledge can be gained by analysis of accumulated empirical data. The study of polymorphism [3,4], where a molecule or molecules crystallize in different crystal structures, is an example. It has contributed significantly toward the accumulation of the information required for the rationalization of intermolecular interactions [5].

Where crystallization of a molecule does not produce polymorphs but can form one or more multicomponent crystals, more detailed information about its packing preferences

can be derived by analysis and comparison of the pure and/or co-crystalline forms. This is a broadening of the information landscape that is beneficial to crystal engineering. More generally, the formation of multicomponent molecular systems is a topic of continued interest in solid state chemistry and materials science [6–11]. A particularly active area currently is the potential application of cocrystallization in the modification of physical properties of pharmaceuticals [12–18].

This paper reports an investigation of multicomponent crystals containing 3,5-bis(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**1**; Figure 1). The material was obtained based on a reported procedure [19] as a precursor in the synthesis of novel heterocycles as part of our ongoing research [20–25]. Molecule **1** contained hydrogen bonding donors (N–H) and acceptors (S, O) as well as phenyl groups that could be involved in $\pi \dots \pi$ and X–H $\dots \pi$ interactions. It was therefore a suitable candidate for investigation of the intermolecular contacts preferred in different crystal structures. Formation of multicomponent molecular crystals of **1** with 1,3-bis(4-methoxyphenyl)prop-2-en-1-one (**2**) and with dimethylformamide (DMF) solvent are reported. Figure 1 shows the chemical structures of molecules **1** and **2**. Both DMF and molecule **2** contained carbonyl groups which are strong hydrogen bond acceptors, and additionally, **2** contained methoxy groups which can also accept hydrogen bonds. While recognizing the ambiguity in the term ‘cocrystal’ [10], materials **1–2** are referred to as cocrystals and material **1–DMF** as a solvate for ease of discussion.

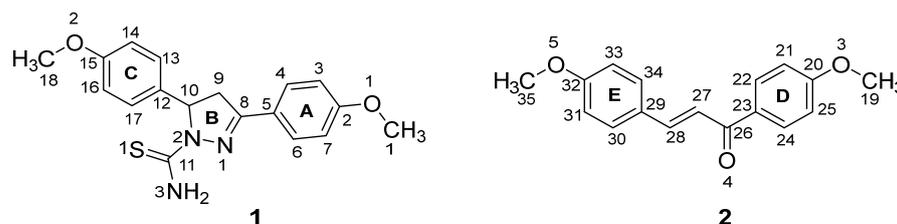


Figure 1. The molecules **1** and **2** showing the atom numbering scheme used in the discussion.

2. Materials and Methods

2.1. Synthesis and Crystallization

A mixture of chalcone **2** (0.54 g, 2.0 mmol) and thiosemicarbazide (0.32 g, 3.5 mmol) in ethanolic sodium hydroxide (0.22 g, 5.5 mmol; 20 mL) was refluxed for 12 h. The mixture was poured into ice water (100 mL) with continuous stirring for an hour and left at 20 °C overnight. The solid produced was filtered, washed with ethanol, and dried to give a mixture of **1** and **2**. Cocrystallization of the mixture produced 1:1 cocrystals of **1** and **2**. The mixture was purified by column chromatography using a mixture of ethyl acetate and petroleum ether 40–60 °C (5:1 by volume) followed by crystallization from DMF to give **1** and **2** in pure forms. Compound **1**. Mp 164–165 °C (lit. 165.2 °C [19]). ¹H NMR (500 MHz, DMSO-*d*₆): 3.40 (m, 2H, pyrazoline-H), 3.71 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 5.80 (d, *J* = 11.5 Hz, 1H, pyrazoline-H), 6.82 (d, *J* = 8.6 Hz, 2H, Ar), 6.92–7.00 (m, 4H, Ar), 7.70 (d, *J* = 8.6 Hz, 2H, Ar), and 7.91 (s, exch., 2H, NH₂). ¹³C NMR (125 MHz, DMSO-*d*₆): 40.4, 55.6, 55.9, 62.8, 114.3, 114.7, 123.9, 127.2, 129.4, 135.6, 155.5, 158.7, 161.8, and 176.3. Compound **2**. Mp 102–103 °C (lit. 99–103 °C [26]). ¹H NMR (500 MHz, DMSO-*d*₆): 3.78 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 6.98 (d, *J* = 8.6 Hz, 2H, Ar), 7.04 (d, *J* = 9.6 Hz, 2H, Ar), 7.65 (d, *J* = 16.2 Hz, 1H), 7.79 (d, *J* = 16.2, 1H), 7.81 (d, *J* = 8.6 Hz, 2H, Ar), and 8.12 (d, *J* = 9.6 Hz, 2H, Ar). ¹³C NMR (125 MHz, DMSO-*d*₆): 55.9, 56.1, 114.5, 114.9, 120.1, 128.0, 131.1, 131.3, 131.7, 143.6, 161.8, 163.6, and 187.8.

2.2. Crystal Structure Determination

Data for cocrystal **1–2** and **1–DMF** solvate were recorded at 296 K on an Agilent SuperNova Dual Atlas single crystal diffractometer with mirror monochromated Mo radiation. Structure solution calculations were performed using SHELXS [27] and refinement by SHELXL [28]. Anisotropic displacement parameters were used for non-hydrogen atoms

during refinement. A riding model was used for hydrogen atoms with idealized geometry and U_{iso} set to 1.2 or 1.5 times the value of U_{eq} for the atom to which they are bonded. HFIX 43 was used for hydrogens bonded to sp^2 hybridized carbon atoms and HFIX 137 for methyl hydrogens. HFIX 93 was used for N–H hydrogens. The dataset for 1-DMF was noticeably weak particularly at high angles and the DMF solvent molecule was disordered. The DMF site was refined with two components with occupancies 0.854(3) and 0.146(3). The crystal structures of 1-DMF and 1-2 were deposited in the CSD with reference numbers CCDC 2167760 and 2167761 (Supplementary Material).

2.3. Electrostatic Potentials and Hirshfeld Surface Calculations

The input files for electrostatic potential calculation were prepared using Avogadro [29]. The calculation was performed using RHF/631G(dp) basis set in Gamess [30] and analyzed using Macmolplot [31]. The Hirshfeld surface was generated using CrystalExplorer17 [32].

3. Results and Discussion

The crystal structure of pure 1 was previously reported (monoclinic, C2/c) [19]. This, along with cocrystal 1-2 and 1-DMF solvate, enabled a comparison of the intermolecular interactions of 1 in different crystal environments. The structures of two polymorphs of 2 have also been reported (orthorhombic, P2₁2₁2₁ [33,34] and Pc [35]).

3.1. Crystal Structure of Cocrystal 1-2

The crystal structure of cocrystal 1-2 was triclinic, P $\bar{1}$ (Table 1). The material was a 1:1 cocrystal of molecules of 1 and 2 (Figure 2a). Molecule 1 comprised two phenyl rings A (C2–C7) and C (C12–C17) as well as a pyrazolyl ring B (N1, N2, C8, C9, and C10). In cocrystal 1-2, rings A and B were essentially coplanar as shown by the small twist angle (3.38(21)) between them (Table 2). In the molecule, both methoxy groups (C1, O1) and (C18, O2) were essentially coplanar with the phenyl rings they were bonded to (the torsion angles were below 8°, Table 1). The pyrazolyl ring was in envelop conformation with C10 out of the least squares plane of the rest of the atoms by 0.278 (4) Å. The methane-thioamide group (S1, C11, and N2) was coplanar with the pyrazolyl ring (torsion angle N3-C11-N2-N1 = 3.0(3))°.

Table 1. Crystal and structure refinement data for 1-2 and 1-DMF.

	1-2	1-DMF
Molecular formula	C ₁₈ H ₁₉ N ₃ O ₂ S, C ₁₇ H ₁₆ O ₃	C ₁₈ H ₁₉ N ₃ O ₂ S, C ₃ H ₇ NO
T (K)	293(2)	293(2)
λ (Å)	0.71073	0.71073
Crystal system	Triclinic	Triclinic
Space group	P $\bar{1}$	P $\bar{1}$
a (Å)	9.6162(6)	9.3300(10)
b (Å)	13.2978(11)	9.4551(11)
c (Å)	14.2415(11)	13.6082(13)
α (°)	70.629(7)	91.915(9)
β (°)	74.519(6)	94.146(9)
γ (°)	72.199(7)	115.268(11)
V (Å ³)	1607.8(2)	1080.0(2)
Z	2	2
Calculated density (Mg m ⁻³)	1.259	1.275
Absorption coefficient (mm ⁻¹)	0.146	0.179
F(000)	644	440
Crystal size (mm ³)	0.389 × 0.105 × 0.079	0.431 × 0.179 × 0.155
Reflections collected	15,540	9197
Independent reflections	7698	5143
R(int)	0.0451	0.0206
Goodness-of-fit on F ²	1.028	1.061
R1 (I > 2 σ (I))	0.0633	0.0517
wR2 (I > 2 σ (I))	0.1369	0.1189
R1 (all data)	0.1434	0.0785
wR2 (all data)	0.1817	0.1392
Max/Min residual densities (e Å ⁻³)	0.17/−0.25	0.19/−0.24

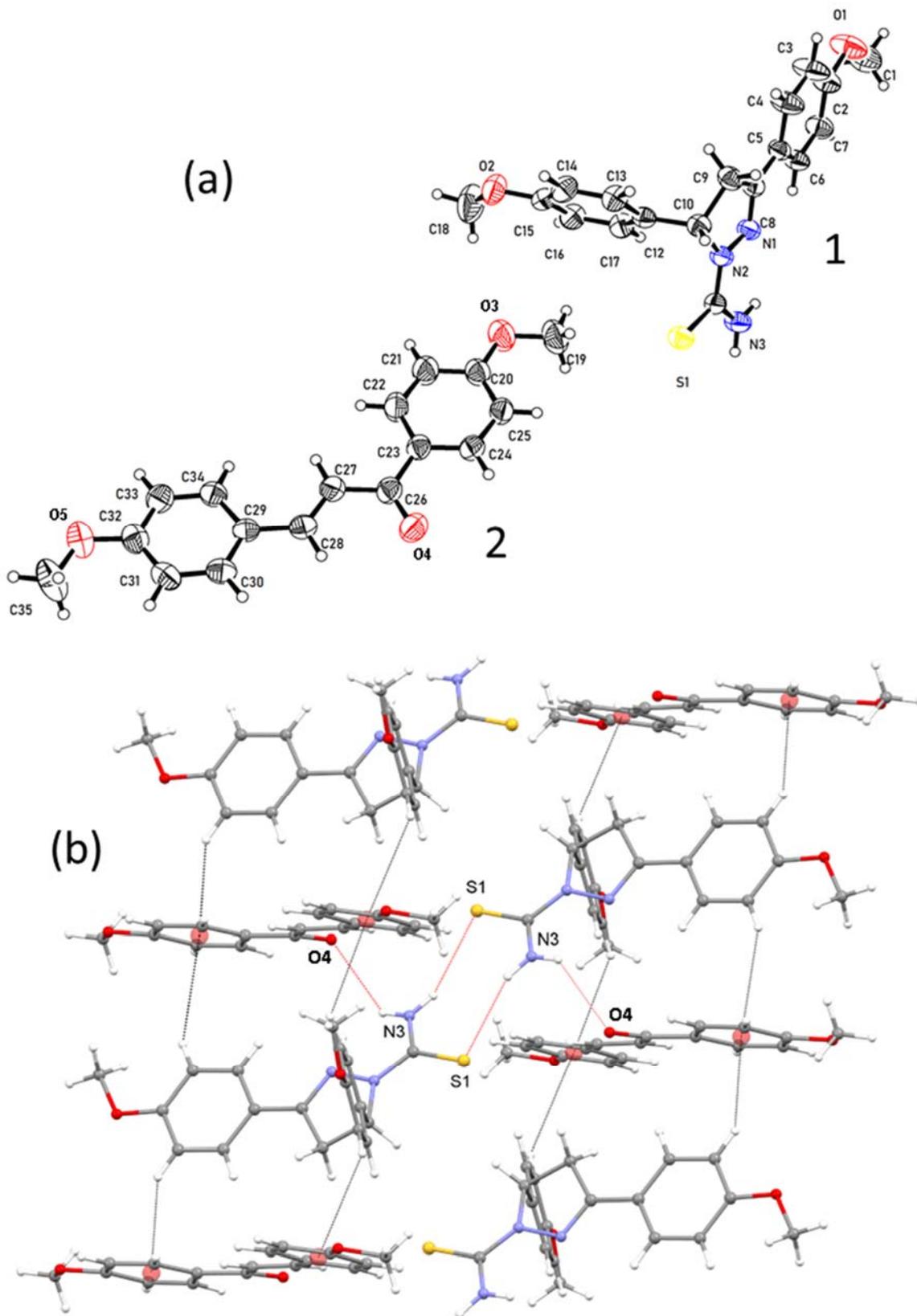


Figure 2. (a): The molecules of 1 and 2 in cocrystal 1–2 showing anisotropic displacement ellipsoids drawn at 50% probability level and (b): a segment of the structure of 1–2 showing intermolecular contacts.

Table 2. Selected geometrical parameters.

Molecule 1	1–2	1–DMF	lit. 1 [19]
Ring twist angle (°)			
A/B	3.38 (21)	4.73(14)	6.48
B/C	77.59 (11)	83.30(6)	84.41
Max deviation from ring B plane/Å	0.278(4)	0.373(3)	0.357
Torsion angle (°)			
C1–O1–C2–C7	0.88 (50)	179.85(19)	179.48
C16–C15–O2–C18	7.69 (46)	4.06(33)	0.70
C17–C12–C10–N2	17.47 (35)	15.13(24)	26.80
Molecule 2	1–2	lit. 2 [33]	lit. 3 [35]
Ring twist angle (°)			
D/E	5.14(3)	4.29	57.58
Torsion angle (°)			
C19–O3–C20–C25	2.66 (46)	170.65	178.66
C35–O5–C32–C31	2.50 (47)	170.57	174.76

In the crystal, molecule **2** was essentially planar with a maximum deviation from the least-squares plane of 0.191(4) Å. The same planarity in the molecule was also observed in the structure of one polymorph of pure **2** (lit. 2 in Table 2) [35]. The difference between the molecule in cocrystal **1–2** and in this pure form, however, is in the orientation of both methoxy groups which were rotated by *ca* 180° relative to the O–C(phenyl) bonds (Table 2, torsion angles C19–O3–C20–C25 and C35–O5–C32–C31). Molecule **2** in the other polymorph (lit. 2) was not planar, with a twist angle of 57.58° between the rings.

In cocrystal **1–2**, intermolecular hydrogen bonding contacts with geometry (N3–H3A ... O4 = 132.2°, N3 ... O5 = 3.159(3) Å and N3–H3B ... S1 = 154.8°, N3 ... S1 = 3.412(2) Å) occurred as shown in Figure 2b. C–H ... π interactions with H-to-ring-centroid contact distances of *ca* 3 Å also occurred in the structure.

3.2. Crystal Structure of Solvate 1–DMF

The crystal structure of the 1–DMF solvate contained molecules of **1** and DMF in a 1:1 ratio (Figure 3a). The DMF site was disordered with two components with occupancies of 0.854(3) and 0.146(3). The twist angles between rings **A**, **B**, and **C** were similar to those observed for molecule **1** in the structure of cocrystal **1–2** (Table 2) with the largest difference being *ca* 8° in the **B**/**C** twist angle. The main difference in the conformation of the molecule of **1** was the orientation of one of the methoxy groups (C1, O1) which was still in the plane of the phenyl group but rotated by *ca.* 180° about the O–C (phenyl) bond. Like in the molecule **1** in cocrystal **1–2**, ring **B** was in envelop conformation but the deviation from the least squares plane of the rest of the atoms of 0.373(3) Å was observed for atom C8 (i.e., not C10).

N–H ... O hydrogen bonding was observed between two molecules of **1** with geometry (N3–H3A ... O2 = 155.2°, N3 ... O2 = 3.101(2) Å) and between **1** and DMF with geometry (N3–H3B ... O3 = 171.5°, N3 ... O3 = 2.888(5) Å) as shown in Figure 3b. C–H ... π interaction also occurred between centro-symmetrically related molecules and involved methylene and phenyl groups with a H-to-centroid distance of 2.851 Å.

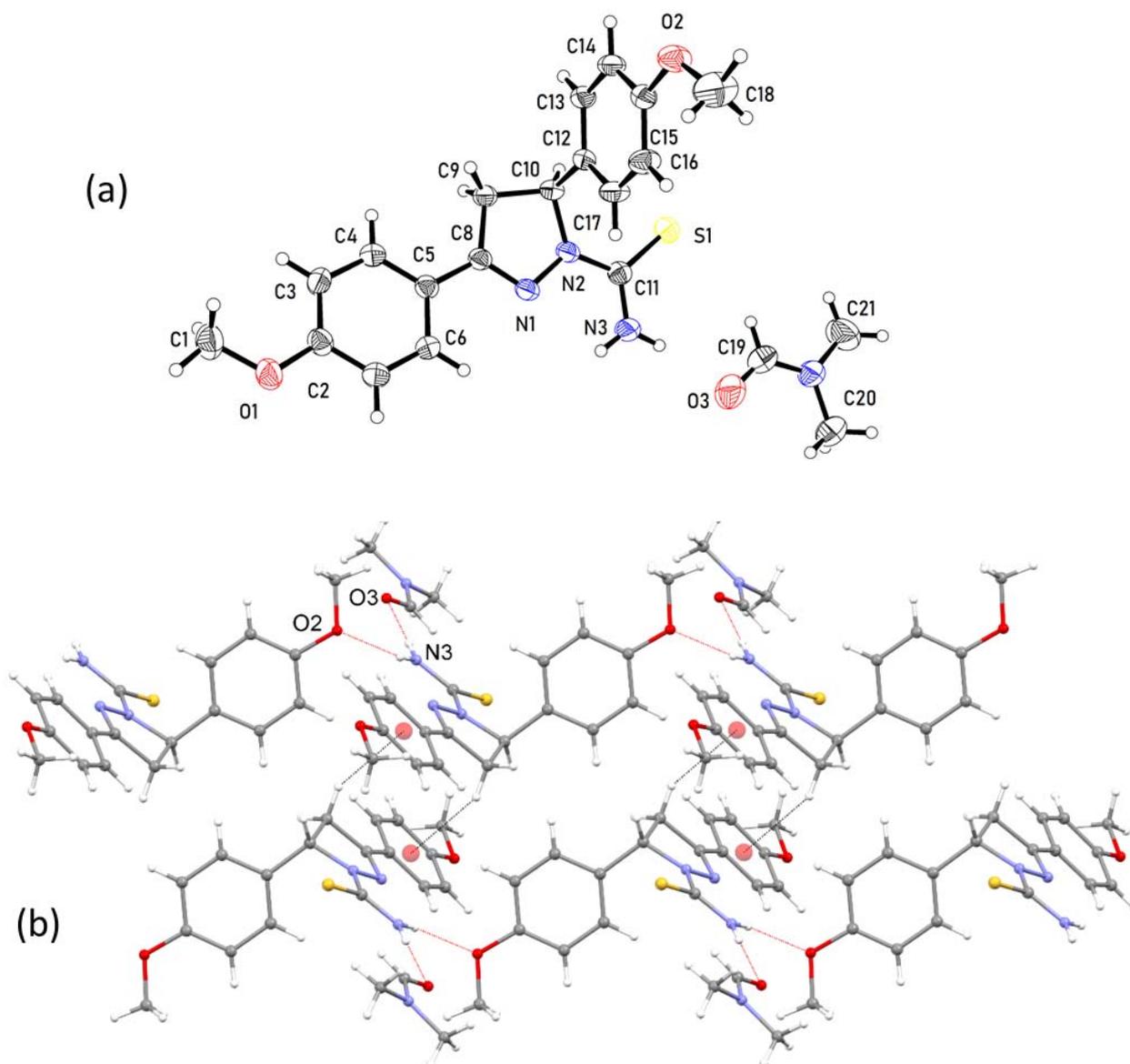


Figure 3. (a): The asymmetric unit of the 1-DMF solvate showing the main component of the disordered DMF solvent with anisotropic displacement ellipsoids drawn at 50% probability level and (b): a segment of the structure of 1-DMF showing intermolecular contacts.

3.3. Comparison of Intermolecular Contacts for Molecule 1

As already stated, the crystal structures of pure **1**, as well as cocrystal **1-2** and the 1-DMF solvate, enabled a comparison of intermolecular interactions of **1** in different crystalline environments. The electron density map surface for a molecule of **1** is shown in Figure 4. The blue color indicates the most negative regions on the surface of the molecule. These regions were located mainly on the oxygen and sulfur atoms of the molecule, with the most prominent region being in the vicinity of the sulfur atom. It was no surprise, therefore, that these atoms acted as hydrogen bond acceptors. What was notable was that the degree of participation by different acceptors in hydrogen bonding varied from structure to structure.

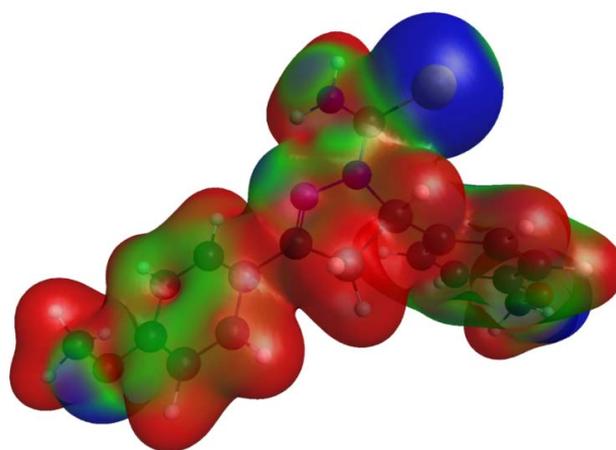


Figure 4. Electron density map for 1 with negative and positive regions represented in blue and red colors, respectively.

The Hirshfeld surface [36] is particularly useful in analysis as it provides a visual representation of close intermolecular contacts. Figure 5a,b show two views of the surface for the molecule of 1 in the structure of cocrystal 1–2. The closest intermolecular contacts, shown in red, involved the sulfur atom (which accepts an N–H . . . S contact) and the two hydrogen atoms of the amine group (which form N–H . . . S and N–H . . . O contacts). Notably, the methoxy oxygen atoms were not involved in close contact, with the N–H group preferring to interact with the carbonyl oxygen atom of molecule 2.

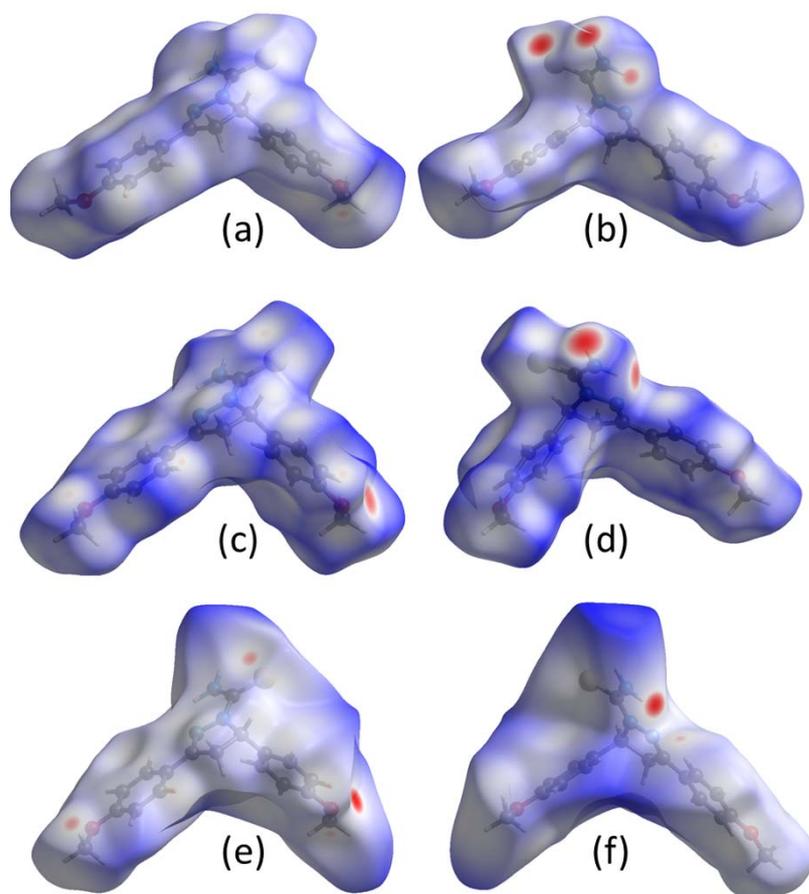


Figure 5. Hirshfeld surfaces for molecule 1 in the crystal structures of (a,b): cocrystal 1–2, (c,d): 1–DMF solvate, and (e,f): pure 1.

Figure 5c,d show the surfaces for the molecule of **1** in the **1**-DMF solvate structure. The amine group formed a close contact (N–H . . . O) with the carbonyl group of the DMF molecule. A short contact was also observed for one methoxy oxygen (N–H . . . O) but the S atom was not involved as closely as in cocrystal **1**-**2**.

In the structure of pure **1**, one hydrogen atom of the NH₂ group interacted with a methoxy oxygen atom (Figure 5e,f). The other N–H hydrogen did not form close contact with the other methoxy oxygen and sulfur atoms, accepting C–H contacts instead.

4. Conclusions

Two new types of multicomponent crystals containing molecule **1** were obtained and characterized. The materials were a 1:1 cocrystal of molecules **1** and **2** and a solvate containing a 1:1 ratio of molecule **1** and DMF. Comparing the two structures with the known structure of the pure material showed that the molecular conformations of the backbone of **1** were generally similar, but the orientation of the methoxy groups may vary.

Thus, one of the two methoxy groups of molecule **1** assumed a different conformation in cocrystal **1**-**2** relative to the structures of **1**-DMF solvate and pure **1**.

Examination of intermolecular contacts indicated clearly that different combinations of the available hydrogen bonding options for molecule **1** were preferred in the three crystal structures. The possible hydrogen bonding in the crystals included N–H . . . O=C, N–H . . . OMe, and N–H . . . S contacts. Both N–H hydrogen atoms were involved in hydrogen bond formation in cocrystal **1**-**2** and **1**-DMF solvate but only one N–H hydrogen atom took part in pure **1**. The S atoms in both the structures of pure **1** and cocrystal **1**-**2** participated, but the S atom in the **1**-DMF solvate did not. Oxygen atoms of both methoxy groups took part in bonding in pure **1**, but only one was involved in the **1**-DMF solvate and none in cocrystal **1**-**2**.

Additionally, the N–H group formed an N–H . . . O hydrogen bond preferentially with the C=O carbonyl group rather than interacting with a methoxy oxygen or sulfur atoms, as illustrated by cocrystal **1**-**2** and **1**-DMF solvate.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/cryst12050663/s1>, ¹H and ¹³C NMR spectra, CIFs and checkcif reports for compounds **1** and **2**.

Author Contributions: Conceptualization: B.M.K. and G.A.E.-H.; methodology: B.M.K., B.F.A.-W., M.S.B. and G.A.E.-H.; X-ray crystal structures: B.M.K.; investigation: B.M.K., B.F.A.-W., M.S.B. and G.A.E.-H.; writing—original draft preparation: B.M.K., B.F.A.-W. and G.A.E.-H.; writing—review and editing: B.M.K. and G.A.E.-H. All authors have read and agreed to the published version of the manuscript.

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