COCRYSTAL 2,4-DIAMINO-6-PHENYL-1,3,5-TRIAZINE 4-HYDROXYBENZOIC ACID DIHYDRATE: CRYSTAL STRUCTURE AND HIRSHFELD SURFACE ANALYSIS

COCRYSTALUL 2,4-DIAMINO-6-FENIL-1,3,5-TRIAZINĂ – ACID 4-HIDROXIBENZOIC DIHIDRAT: STRUCTURĂ CRISTALINĂ ȘI ANALIZĂ A SUPRAFEȚEI HIRSHFELD

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Sumar. *Cocristalizarea concomitentă a 2,4-diamino-6-fenil-1,3,5-triazinei (Tr) cu acidul 4-hidroxibenzoic (HBA), în prezența tetrafluoroboratului de cobalt(II), a condus la formarea unui nou cocrystal organic cu compoziția Tr·HBA·2H₂O. Compusul studiat cristalizează în sistemul ortorombic, în grupul spațial necentrosimetric Pna2₁, cu Z = 4. Parametrii celulei unitare sunt: a = 12,291(3) Å, b = 6,9706(6) Å, c = 19,5957(15) Å, V = 1678,9(5) Å³. Analiza structurală prin difracție de raze X pe cristale unice a confirmat neutralitatea tuturor speciilor interconectate în cristal printr-un sistem extins de legături de hidrogen. Au fost identificate și descrise modele supramoleculare heteromerice de tip acid (HBA) – bază (Tr), acid – apă, precum și modele homomerice de tip bază (Tr) – bază (Tr), toate bazate pe legături de hidrogen. Distribuția interacțiunilor intermoleculare a fost evaluată cu ajutorul analizei suprafeței Hirshfeld, care a indicat impactul esențial al interacțiunilor ce implică atomi de hidrogen în structura cristalină.*

Cuvinte-cheie: *acid carboxilic, cocrystal, structură cristalină, 2,4-diamino-6-fenil-1,3,5-triazină, analiza suprafeței Hirshfeld.*

INTRODUCTION

1,3,5-Triazine and its derivatives are continuing to be in focus of materials science and crystal engineering as useful supramolecular agents. In particular, 2,4-diamino-6-

phenyl-1,3,5-triazine (Tr) possesses a wide range of useful pharmacological properties [1, p.40; 2, p.3301]. The availability of two amino-groups attached to the Tr molecular scaffold provides the possibility for diverse hydrogen bonding, while their combination with triazine moiety represents good opportunity for crystal engineering of coordination networks [3, p.3568] and organic cocrystals [4, p. 4813]. The reported examples disclosed the Tr cocrystals with pharmaceuticals [5, p. 4 in SI] and biologically relevant compounds [6], and the improvement of pharmacological profile of the final cocrystals in comparison with the individual components was demonstrated in some cases [7, p. 9]. The choice of the suitable co-ligand /coformer is crucial in crystal design. In this study an attempt was undertaken to combine two pharmacologically relevant molecules, 2,4-diamino-6-phenyl-1,3,5-triazine (Tr), and 4-hydroxybenzoic acid (HBA) in one coordination network. 4-Hydroxybenzoic acid is reported to have antibacterial, antifungal, antialgal, antimutagenic, and estrogenic activity [8]. It is also used as trapping agent to study hydroxyl radical generation during cerebral ischemia, and as preservative in drugs, cosmetics, pharmaceuticals, and food [9, p. 109]. On the other hand, HBA molecule bears the functional groups favorably arranged for the supramolecular crystal design [10, p. 1094]. Serendipitously, the novel organic cocrystal, $TrHBA{\cdot}2H_2O$ (Tr=2,4-diamino-6-phenyl-1,3,5-triazine; HBA=4-hydroxybenzoic acid) that combines two pharmacophores was obtained whose crystal structure is reported for the first time.

MATERIALS AND METHODS

All reagents were purchased from commercial sources and used without further purification. X-ray single crystal data were collected at a room temperature on an Xcalibur E diffractometer equipped with a charge-coupled device (CCD) area detector and a graphite monochromator utilizing MoKα radiation (λ =0.71073 Å).

Synthesis of $Tr{\cdot}HBA{\cdot}2H_2O$

We weighed 0.0018 g (0.1 mmol) of 2,4-diamino-6-phenyl-1,3,5-triazine (Tr), 0.0013 g (0.1 mmol) of 4-hydroxybenzoic acid (HBA), and 0.0034 g (0.1 mmol) of cobalt (II) tetrafluoroborate hexahydrate. These were dissolved in 8 ml of CH_3CN and vigorously stirred at room temperature (20 °C) until completely dissolved. The solution was then placed in a sealed, PTFE-lined, stainless-steel autoclave and heated for three days at 90 °C, after which it was allowed to slowly cool to room temperature. After this, the solution was filtered, and light orange crystals gradually grew on the walls of the vessel over 5 days.

X-ray structure solution and refinement

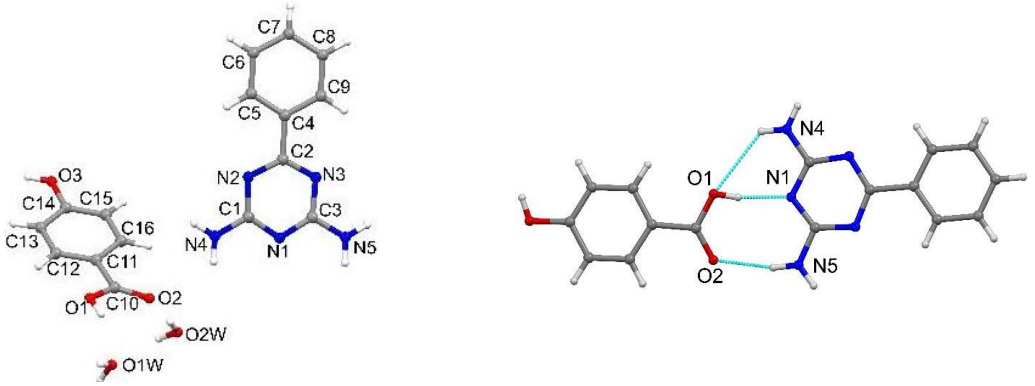
All calculations to solve the structure and to refine the model proposed were carried out with the programs SHELXS-2014 and SHELXL-2014 [13, p.6, 14, p.24]. The C-bound H-atoms were positioned geometrically and treated as riding atoms

using SHELXL default parameters with $U_{iso}(H) = 1.2U_{eq}(C)$; the N(O)-bound H-atoms were found from differential Fourier maps at the intermediate stages of the refinement and their positions were restrained during the refinement. Crystal data for compound Tr·HBA·2H_2O: $C_{16}H_{19}N_5O_5$, Mr = 361.36, orthorhombic, space group *Pna*2_1, *a* = 12.291(3), *b* = 6.9706(6), *c* =19.5957(15) Å; *V* =1678.9(5) A^3; *Z* = 4; D_{calc} = 1.430 g cm^{-3}; *F(000)* =760; μ = 0.109 mm^{-1}; R_1 = 0.0462, wR_2 = 0.0827 for 1172 independent reflections with $I > 2\sigma(I)$; R_1 = 0.0664, wR_2 = 0.0922 for all 1507 independent reflections, GOOF = 1.093. CIF file was deposited in Cambridge Crystallographic Data Centre (CCDC) (https://www.ccdc.cam.ac.uk/structures/) with the CCDC deposition number 2457515.

RESULTS AND DISCUSSION

Crystal structure

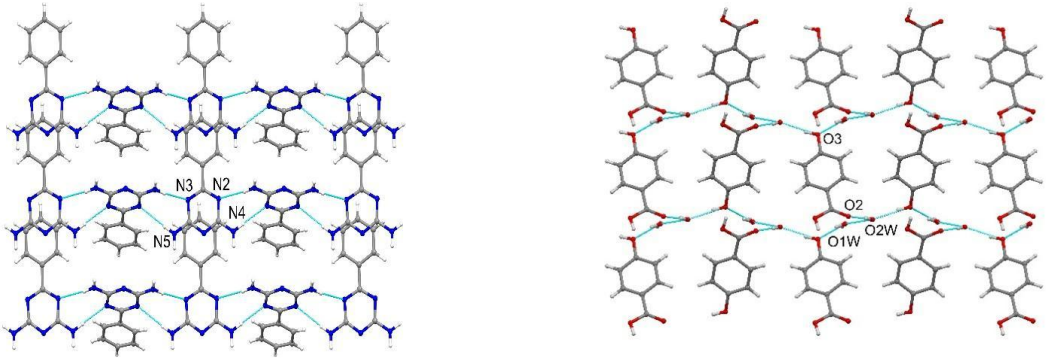
Cocrystal Tr·HBA·2H_2O belongs to the orthorhombic crystal system and crystallizes in the noncentrosymmetric *Pna*2_1 (No 33) space group, with *Z*=4. The asymmetric unit comprises four neutral species, one Tr, one HBA, and two water molecules (Fig. 2a). Both Tr-base and HBA-acid molecules have the geometries typical for these species in the neutral form. The lack of the acid-base proton transfer is confirmed by location of H-atoms in the close proximities of O(1) and O(3) atoms in the HBA molecule; those H-atoms were refined finally using the SHELXL constraints. The differentiation of the C-O bond distances in the carboxylic group which are O(1)-C(10) 1.312(8) Å and O(2)-C(10) 1.229(9) Å, also justifies in favour of neutrality of this molecule. The variation of the intramolecular C-N-C bond angles in the triazine cycle of Tr molecule occurs in a narrow range, C(3)-N(1)-C(1) 114.8(5) º, C(2)-N(2)-C(1) 113.4(6) º, C(2)-N(3)-C(3) 113.0(6) º, that is also typical for the neutral molecule. In the HBA molecule the carboxylic group is twisted out of the plane of the phenyl ring as indicated by the Ph/COOH interplanar angle of 12.0(8) º. In the Tr molecule the twisted angle between the phenyl and triazine cycles is equal to 7.1(2) º, thus indicating the small deviation from planarity. The availability of strong H-donors (-NH_2 and -OH groups) and strong H-acceptors (-C=O, O(H_2O) and >N) in the system explains the richness of intermolecular interactions in the forms of heteromeric and homomeric supramolecular synthons stabilizing the crystal structure [11, p. 4603]. The pairing of main components, Tr and HBA occurs *via* H-bonding triad in the form of two fused heterosynthons, very common amino-pyridine-carboxylic heterosynthon $R_2^2(8)$ [12 p. 130], and an auxiliary one, $R_2^2(7)$ (Fig. 2b, Table 1). This H-bonded triad provides planarity of the acid-base binary unit. The interplanar angle between two molecular scaffolds is of 3.01(8) º.



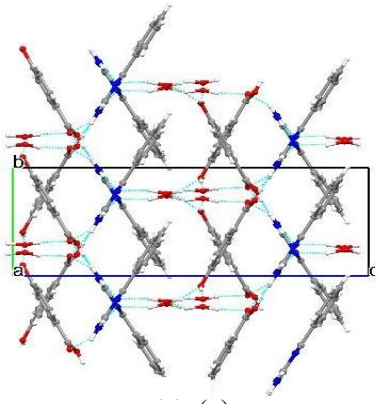
(a) (b)

Figure 1. a) Content of the asymmetric unit in the title compound
b) Tr-HBA association pattern

Besides, the Tr molecules are associated in the homomeric H-bonded chain running along the crystallographic *a*-axis via alternation of two similar twisted H-bonded $R_2^2(8)$ ring patterns (fig. 2a). Each Tr molecule acts as a double H-donor and a double H-acceptor (DDAA) within the homomeric chain. The Tr/Tr interplanar angle between the molecules in chain is equal to 59.05 º. These H-bonded …Tr…Tr… supramolecular chains pack in a zipper-like interdigitated mode forming the stacking walls parallel to the [0 0 1] crystallographic plane with an infinite 1D - stacking along the crystallographic *b*-axis between the overlapping triazine and phenyl cycles of the translated Tr molecules, the Cg(centroid Ph)…Cg(centroid Tr) separation being of 3.937 Å. Parallel to the homomeric Tr walls, the HBA and two-membered aqua cluster O1w-O2w form their own H-bonded supramolecular layer (fig. 2b) where water molecules mediate the neighbouring HBA molecules along the crystallographic *a*-axis, and HBA mediate water molecules along the crystallographic *b*-axis (fig. 2b).



(a) (b)



(c)

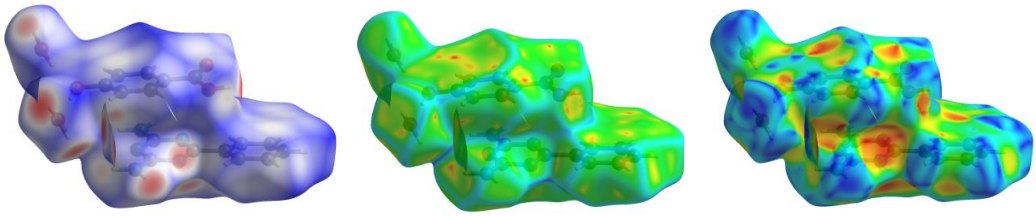
Figure 2. Fragments of crystal packing in the title cocrystal. a) combination of H-bonded and *π*-*π* self-association patterns for Tr; b) H-bonded layer of HBA and water molecules; c) view of crystal packing along the *a*-axis.

Table 1. Hydrogen bond distances (Å) and angles (°) in the title compound

D-H...A	d(H...A), Å	d(D...A), Å	∠(DHA), °	Symmetry transformation for acceptor
N(4)-H(4A)···O(1)	2.64	3.280(6)	132	*x, y*-1, *z*
N(4)-H(4A)···O(2)	2.51	3.061(7)	123	*x*-1/2, -*y*+1/2, *z*
N(4)-H(4B)···N(3)	2.20	3.058(7)	175	*x*-1/2, -*y*+1/2, *z*
N(5)-H(5A)···O(2)	2.07	2.910(6)	165	*x, y*-1, *z*
N(5)-H(5B)···N(2)	2.34	3.194(7)	174	*x*+1/2, -*y*+1/2, *z*
O(1)-H(1A)···N(1)	1.81	2.619(5)	172	*x*, *y*+1, z
O(3)-H(3A)···O(2W)	1.84	2.655(7)	170	*x*, *y*, *z*
O(1W)-H(1W)···N(2)	2.35	3.148(6)	155	-*x*-1/2, *y*-1/2, *z*-1/2
O(1W)-H(2W)···O(3)	1.96	2.803(7)	169	*x*, *y*, *z*
O(2W)-H(3W)···O(1W)	1.91	2.722(6)	155	*x*-1/2, -*y*-1/2, *z*
O(2W)-H(4W)···O(2)	2.08	2.946(7)	176	*x*-1/2, -*y*+1/2, *z*

Hirshfeld surface and 2D fingerprint plot analysis

The Hirshfeld surfaces and their associated 2D fingerprint plots for the cocrystal were calculated by taking the single-crystal X-ray data as input [15, p.1008] (fig. 3). The bright red spots on the d_{norm} surface indicate the existence of short intermolecular hydrogen bonds, O-H…O and N-H…O due to amino, hydroxyl groups and water molecules. The white area corresponds to the van der Waal interactions of the atoms identified as H…H interactions. The blue area indicates the neighbouring atoms which are too far to interact with each other. The orange spots indicate the C–H …π interactions (Fig. 3b, c). The 3D views show that HBA and Tr entities are in parallel planes corresponding to one another.



(a) (b) (c)

Figure 3. 3D Hirshfeld surfaces of the title cocrystal mapped with
a) d norm (min: -0.7668, mean: 0.3843, max:1.1187); b) Curvedness (min: -3.4198, mean: -0.9583, max: 0.8936); c) Shape index (min: -0.9938, mean: 0.2234, max: 0.9972)

The distribution of intermolecular interactions in the cocrystal is given in the 2D fingerprint plots summarizing all the available contacts and the specific ones (fig. 4). The H…H contacts show the largest contribution of 49.8%, the next most meaningful are the O…H / H …. O and N..H/H…N contacts with contributions of 19.3 and 11.7%, respectively rationalized as sharp neighbouring spikes in the bottom right and left regions of the fingerprint plots. The C...H/H…C close contacts of 11.7% are represented as a pair of wings in the upper part of the fingerprint plot, and comprise 11.7% of the total Hirshfeld surface. All the other, non-H interactions, were recorded with decreasing low percentage for C…C (3.5%), C…O/O…C (1.9%), C...N/N…C (1.5%) etc, indicated that hydrogen bonding was the main driving force in stabilizing this structure.

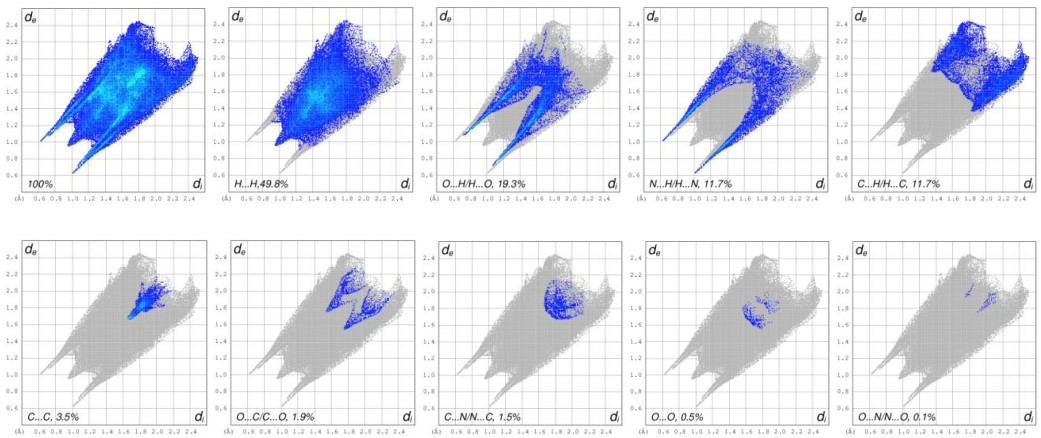


Figure 4. Two-dimensional fingerprint plots for the title compound with indication of percentage contribution of each specific group interactions

CONCLUSIONS

The cocrystal Tr·HBA·$2H_2O$ was obtained using solvent mediated crystallization method. The variety of hydrogen bonds, NH...O, OH...O, NH…N are the main driving forces that impact the crystal structure and are complemented by - stacking interactions between Tr and HBA planar scaffolds. Hirshfeld surface analysis gave the deeper inside in the quantitative distribution of intermolecular interactions in the crystal. The present study extends our knowledge about specific interactions and association patterns in the adducts of 2,4-diamino-6-phenyl-1,3,5-triazine with carboxylic acids. The study of the useful properties of this cocrystal system is in progress.

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