

STRUCTURE OF IONIC COCRYSTALS PIPERIDINIUM 2-THIOBARBITURATE– 2-THIOBARBITURIC ACID

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The structure of ionic cocrystals of piperidinium 2-thioarbiturate with 2-thioarbituric acid $\text{PipeH}^+(\text{HTBA}^-)\text{H}_2\text{TBA}$ (**I**) (H_2TBA is 2-thioarbituric acid, Pipe is piperidine) is determined. The asymmetric unit of **I** contains a H_2TBA molecule in the form of thionemonocarbonyl tautomer, the HTBA^- ion, and the PipeH^+ piperidinium ion. The structure is stabilized by the intermolecular $\text{O}\cdots\text{O}$, $\text{N}\cdots\text{S}$, and $\text{N}\cdots\text{O}$ hydrogen bonds (HBs) forming a three-dimensional framework. The results of single crystal XRD and IR spectroscopy indicate the formation of strong $\text{O}\cdots\text{O}$ HB. The topological analysis of the HB network in **I** is performed.

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Barbituric acid (H_2BA), thiobarbituric acid (H_2TBA), and their derivatives are important active pharmaceutical ingredients [1]. Low solubilities, dissolution velocities, and thermal stability limit their application. To improve these characteristics, it is prospective to use so-called ionic cocrystals (ICCs) [2] or salt cocrystals [3] consisting of ionic and molecular components. The $\text{M}^{n+}(\text{HBA}^-)_x\text{H}_2\text{BA}\cdot n\text{H}_2\text{O}$ cocrystals ($\text{M} = \text{Na}, \text{K}$) with enhanced thermal stability as compared to H_2BA [3] and $\text{Rb}^+(\text{HBA}^-)\text{H}_2\text{BA}\cdot\text{H}_2\text{O}$ [4] have been already synthesized. It is of practical interest to obtain and examine the structure of ICCs based on barbituric acids formed by neutral molecules and their organic salts. It is scientifically valuable to have the information on the molecular association, identification, and packing of these ICCs. We have chosen for the study a compound consisting of neutral H_2TBA and its salt with the $(\text{PipeH})^+\text{HTBA}^-$ piperidinium cation. In some organic compounds containing PipeH^+ , short $\text{O}\cdots\text{O}$ distances (HBs) were found in the formation of hydrogen bonds [5]. It is noteworthy to investigate the prevalence of this phenomenon.

Experimental. Synthesis of $(\text{PipeH})^+(\text{HTBA}^-)\text{H}_2\text{TBA}$ (I**).** To a mixture of 0.2 g of H_2TBA (chemically pure) in 2 ml of water 2-3 ml of an aqueous solution of piperidine (Pipe, chemically pure) were added to pH 4-5. The colorless crystalline precipitate formed was filtered and washed with acetone. The yield with respect to H_2TBA was 60-70%. Colorless single crystals of compound **I** were obtained on slow evaporation of the filtrate during 2-3 weeks; they were filtered and dried between the sheets of filter paper.

Single crystal XRD study. The intensities of X-ray reflections from a $0.5\times 0.35\times 0.28$ mm crystal were measured at 296 K on a SMART APEX II single crystal diffractometer (Baikal Center of Collective Use, Siberian Branch, Russian

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Academy of Sciences) with a CCD detector (Bruker AXS), MoK α radiation, $\lambda = 0.7106 \text{ \AA}$. The unit cell corresponded to a triclinic system, the space group *P*-1 was determined from the analysis of the intensity statistics for all reflections. The model was found using the SHELXS software [6] by direct methods. In the result, the coordinates of all non-hydrogen atoms were determined. The obtained structure was refined by the least-squares method using the SHELXL97 software. The thermal parameters of all non-hydrogen atoms were refined in the anisotropic approximation. The coordinates of all hydrogen atoms, except those of the OH group, were idealized and refined together with heavy atoms within the riding model. The hydrogen atom of the OH group was found in the difference electron density maps and its coordinates were refined without any restrictions. The main crystallographic characteristics and the parameters of the experiment are as follows: $M_r = 373.45$, $a = 8.0849(7) \text{ \AA}$, $b = 9.5632(9) \text{ \AA}$, $c = 11.279(1) \text{ \AA}$, $\alpha = 91.951(3)^\circ$, $\beta = 105.343(3)^\circ$, $\gamma = 96.266(3)^\circ$, $V = 834.1(1) \text{ \AA}^3$, space group *P*-1, $Z = 2$, $D_x = 1.487 \text{ g/cm}^3$, $\mu = 0.348 \text{ mm}^{-1}$, $2\theta_{\text{max}} = 60.16^\circ$, 63965 measured reflections, 4904 independent reflections, $R_B = 3.27\%$, $wR(F^2) = 7.96\%$, $\Delta\rho_{\text{max}}/\Delta\rho_{\text{min}} = 0.428/-0.523 \text{ e/\AA}^3$.

The powder X-ray diffraction pattern of a polycrystalline sample of **I** at room temperature measured on a Bruker D8 ADVANCE diffractometer (the Krasnoyarsk Center of Collective Use, Siberian Branch, Russian Academy of Sciences), linear VANTEC detector, CuK α radiation coincided with that calculated from the single crystal data, which confirmed the identity of polycrystals and the studied single crystal.

The graphic representation of all crystal structures and molecules was prepared using the DIAMOND software [7]. The structure has been deposited with the Cambridge Structural Database under number CCDC 1450034. The data are available via the site www.ccdc.cam.ac.uk/data_request/cif.

Results and discussion. The asymmetric unit of compound **I** contains one neutral H₂TBA molecule in the form of a thionemonocarbonyl (enol) tautomer [8], one HTBA⁻ ion, and one PipeH⁺ piperidinium ion (Fig. 1). H₂TBA and the HTBA⁻ anion are linked by the O1B–H···O2A hydrogen bond forming a dimeric structural moiety (H₂TBA···HTBA)⁻. The lengths of the C–O, C–N, and C–C bonds and the respective bond angles in H₂TBA and HTBA⁻ coincided with those determined previously for other compounds [8, 9–17]. Using the PLATON software [18] we identified the absence of any other omitted symmetry elements and possible voids.

Compound **I** is ICCs with a composition described by the formula PipeH⁺(HTBA⁻)H₂TBA. The C–O bonds in H₂TBA have substantially different length (C4B–O1B = 1.302(1) \AA and C6B–O2B = 1.250(1) \AA), which is typical of the enol tautomer [8]. Due to electron density delocalization in the O₂=C₄–C₅H–C₆=O₂ atomic group, which is characteristic of the HTBA⁻ ion, the distances C4A–O1A = 1.268(1) \AA and C6A–O2A = 1.282(1) \AA slightly differ little from each other. The C2–S interatomic distances in the ion and the molecule, being 1.673(1) \AA and 1.680 (1) \AA respectively, almost coincide, as in other H₂TBA compounds [9–17].

The structure analysis showed the existence of seven intermolecular hydrogen bonds of the O–H···O, N–H···S, and N–H···O type (Table 1). Both ions and H₂TBA are involved in hydrogen bonds (HBs). Due to HBs, a three-dimensional

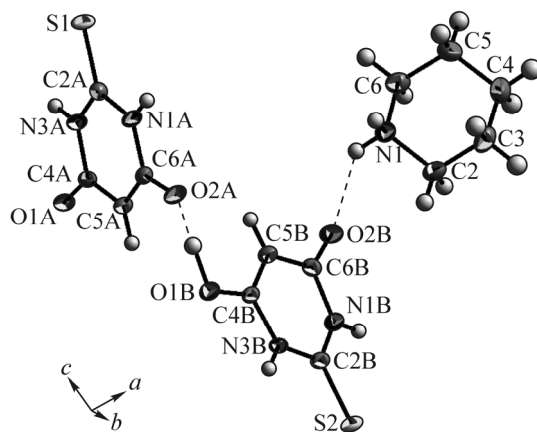


Fig. 1. Asymmetric unit of **I**.

TABLE 1. Hydrogen Bonds D–H···A (Å, deg) in the Structure of **I**

D–H···A	D–H	H···A	D···A	∠D–H···A
N1A–H1A···S2 ¹	0.86	2.60	3.427(1)	162
N1B–H1B···O2B ²	0.86	1.94	2.802(1)	174
O1B–H2B···O2A	1.13(2)	1.30(2)	2.435(1)	176(1)
N3A–H3A···O1A ³	0.86	2.02	2.843(1)	161
N3B–H3B···O1A ⁴	0.86	1.97	2.795(1)	161
N1–H11···O1A	0.89	2.10	2.897(1)	148
N1–H12···O2B ⁵	0.89	2.16	2.910(1)	141

Symmetry operation: ¹ 1–x, –y, 1–z; ² 1–x, 1–y, 1–z; ³ –x, –y, 2–z; ⁴ –x, –y, 1–z; ⁵ –1+x, y, z.

network forms, in which the $R_2^2(8)$, $R_4^4(20)$, $R_6^4(20)$ motifs can be identified. It should be noted that O–H···O HB is characterized by a short distance $d(\text{O} \cdots \text{O}) < 2.5 \text{ \AA}$ and a large bond length $d(\text{O}–\text{H}) = 1.13(2) \text{ \AA}$. It is known that in the formation of strong HBs, the $d(\text{O}–\text{H})$ distance increases by as much as 0.2 \AA [19]. As in the structure of **I**, in the formation of HBs in the $\text{BH}^+(\text{A}^-)\text{-HA}$ compounds (B = Pipe, 4-methylpyridine; HA = *para*-methylbenzoic acid) the short O···O distances of 2.50 \AA and 2.47 \AA respectively were also found [5], which could also be expected for other organic salts of the PipeH^+ cation. As judged by the geometric parameters of HBs (Table 1), O–H···O is strong [20] and it is this bond that mainly determines the structure of **I**. The distances between the centers of rings of the HTBA^- ions and H_2TBA molecules exceed 4.75 \AA , which excludes the π – π interaction.

The topological analysis of the HB network performed using the ToposPro software [21] revealed a binodal three-dimensional network $(2\text{-c})(4\text{-c})_2$, where the sites with coordination number 2 are the PipeH^+ ion and two other sites with coordination number 4 are the HTBA^- ion and a H_2TBA molecule. A further simplification of the network required the removal of the site with coordination number 2, i.e., the piperidinium ion. Consequently, a uninodal three-dimensional network $(4^6.6^4)$ known as sqc518 was obtained, in which the sites containing the HTBA^- ion and a H_2TBA molecule are topologically equivalent.

The IR spectrum (Nicolet 6700, the Shared Research Center at the Siberian Federal University) of **I** in KBr (v , cm^{-1}) is as follows: 3163–3047 s, 2962 s, 1640 vs, 1603 vs, 1534 s, 1403 m, 1378 m, 1286 m, 1175 m, 1149 m, 1018 w, 919 w, 864 w, 789 m, 566 vw, 530 m, 475 vw, 437 vw (vw is very weak, w is weak, m is medium, s is strong, and vs is very strong). For five H_2TBA polymorphs [8] the highest frequency $\nu(\text{CO})$ band is in a range of $1705\text{--}1750 \text{ cm}^{-1}$, and the $\nu(\text{CS})$ frequency varies from 1145 cm^{-1} to 1165 cm^{-1} [22]. For **I**, the $\nu(\text{CO})$ value is noticeably lower (1640 cm^{-1}) than that for H_2TBA , which agrees with the involvement of HTBA^- hydrogen atoms in strong HBs. The S atom is not involved in HBs, and the position of the $\nu(\text{CS})$ band peak at 1149 cm^{-1} within the error margin ($\pm 7 \text{ cm}^{-1}$) coincides with those observed for H_2TBA polymorphs III (1142 cm^{-1}) and V (1153 cm^{-1}) [22], in which the S atom also does not form HBs. Therefore, the IR spectroscopy results agree with the powder XRD data.

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