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CRYSTAL AND MOLECULAR STRUCTURE OF β-(N-BENZOXAZOLINE-2-THIONE) PROPIONIC ACID AND ITS SALTS

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The crystal and molecular structures of β-(N-benzoxazoline-2-thione)propionic acid, its monoethanolammonium ($NH_2(CH_2)_2OH$) and ethylenediammonium ($NH_2(CH_2)_2NH_2$) salts are studied. In the salts the monoethyleneamine amine group participates in the deprotonation of one ethylenediamine – two β-(N-benzthiazolin-2-one)propionic acid molecules. The geometry of the molecules and intermolecular hydrogen and donor-acceptor bonds in crystals are analyzed. In the crystal structures weak interactions form a two-dimensional layer whose thickness corresponds to unit cell sizes.

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Benzoxazoline-2-thione derivatives have diverse biological activities. Bactericides [1-3], fungicides [4-8], herbicides [9, 10], phytohormones [11], and insecticides [12-14] have been known among them. It is worth noting that 2-alkylthio-6-nitrobenzoxazolines exhibit pronounced *in vitro* antitumor activity [15]. Compounds with tuberculostatic [16], parasympatholytic [17], and anesthetic [18] activities have also been known among them.

We have previously studied the crystal structures of the hydrate, solvate, and salts of α-(N-benzoxazolin-2-one)acetic acid [19] and showed that exocyclic active parts of benzoxazoline derivatives tended to form intra- and intermolecular hydrogen bonds in different crystal forms [19]. In particular, in α-(N-benzoxazolin-2-one)acetic acid, the mobile proton of the carboxyl group is easily deprotonated and is involved in the formation of diverse organic salts. The obtained crystal forms depend on the nature of the substrate, solvent, and reacting salt.

In continuation of studies on the synthesis and transformations of benzazales [20-23], it appeared interesting to synthesize a sulfuric analogue of α-(N-benzoxazolin-2-one)acetic acid – β-(N-benzoxazoline-2-thione)propionic acid. An increase in the number of methylene groups (from acetic to propionic acid) and the nature of active exo parts (from 2-one to 2-thione) in benzoxazoline causes changes in the molecular structure and intermolecular interactions in the crystal. In order to study the effect of these factors, in this work the crystal forms of benzoxazoline – β-(N-benzoxazoline-2-thione)propionic

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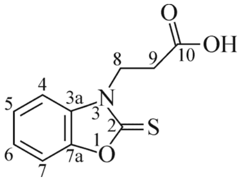
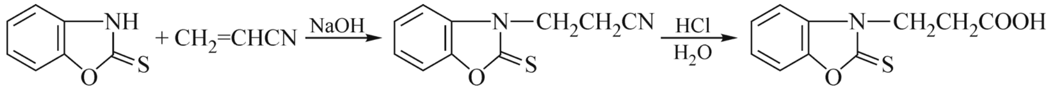
acid (**1**), its monoethanolammonium ($NH_2(CH_2)_2OH$) (**2**) and ethylenediammonium ($NH_2(CH_2)_2NH_2$) (**3**) salts are analyzed by single crystal X-ray diffraction and their molecular and crystal structures are studied.



EXPERIMENTAL

Synthesis of β-(N-benzoxazoline-2-thione)propionic acid. A mixture of 1.51 g (10 mmol) of benzoxazoline-2-thione and 1.59 g (30 mmol) of acrylonitrile in 50 ml of water was heated on a water bath at 60-70 °C for 6 h and left for a night. The precipitated crystals were filtered off, squeezed dry, transferred to a round-bottom flask, and 50 ml of concentrated HCl were added to them. The mixture was boiled at 100 °C for 4 h and left for a night. The precipitated crystals were filtered off, washed with water to a neutral reaction, and recrystallized from benzene. The yield of the compound with T_{melt} 140-142 °C was 1.89 g (85%).



Preparation of β-(N-benzoxazoline-2-thione)propionic acid crystals. Single crystals were obtained by slow evaporation of a β-(N-benzoxazoline-2-thione)propionic acid solution (100 mg) in an ethanol:water (3:1) mixture (4 ml) at a temperature of 25 °C. Prismatic colorless crystals were grown for three days.

Monoethanolammonium salt of β-(N-benzoxazoline-2-thione)propionic acid. To a solution of 0.1 g (0.52 mmol) of β-(N-benzoxazoline-2-thione)propionic acid in 4 ml of ethanol 32 μL of monoethanolamine was added. The mixture was kept in an ultrasonic bath (30 kHz) at 25 °C for 5 min. The solution was placed in a loosely closed bottle and kept at 25 °C for 10 days. The precipitated prismatic crystals were selected for the single crystal X-ray diffraction analysis.

Ethylenediammonium salt of β-(N-benzoxazoline-2-thione)propionic acid. To a solution of 0.1 g (0.52 mmol) of β-(N-benzoxazoline-2-thione)propionic acid in 4 ml of ethanol 16 μL of ethylenediamine were added. The mixture was kept in an ultrasonic bath (30 kHz) at 25 °C for 5 min. The solution was placed in a loosely closed bottle and kept at 25 °C for 9 days. The precipitated prismatic crystals were selected for the single crystal X-ray diffraction analysis.

Single crystal X-ray diffraction analysis. Experiments were performed on an Xcalibur® Oxford Diffraction diffractometer at room temperature (CuK_α radiation, graphite monochromator). Experimental intensities and other data were collected using the CrysAlisPro program [24]. Absorption correction was applied by Multiscan in the CrysAlisPro program package.

The structures were solved by direct methods using the SHELXS-97 program package [25] and refined by the full-matrix least squares technique using SHELXL-97 [26]. The data and molecular graphs were visualized using the XP program in the SHELXTL-Plus program package [27]. Table 1 lists the main parameters of X-ray crystallographic experiments and refinement calculations of the structures of crystals **1-3**.

Coordinates of hydrogen atoms (except NH groups) in the structure of **1** were found geometrically and refined with fixed isotropic displacement parameters ($U_{\text{iso}} = nU_{\text{eq}}$, where $n = 1.5$ for methylene groups and 1.2 for the others, and U_{eq} is the equivalent isotropic displacement parameter of the respective atoms). In amine groups the H atoms were found from difference electron density (ED) maps and refined isotropically. All positions of hydrogen atoms in the structures of **2** and **3** were found experimentally from difference ED maps and refined isotropically.

CIF files containing full X-ray crystallographic information on the structures studied have been deposited with CCDC under the number given at the end of Table 1 (http://www.ccdc.cam.ac.uk/deposit).

TABLE 1. Main Crystallographic Parameters and Characteristics of the X-ray Diffraction Experiment for the Structures of **1-3**

Parameter	**1**	**2**	**3**
Molecular formula	$C_{10}H_9NO_3S$	$C_{10}H_9NO_3S\cdot H_2N(CH_2)_2OH$	$2(C_{10}H_9NO_3S)\cdot H_2N(CH_2)_2NH_2$
M, g/mol	223.25	254.30	253.29
Space group; *Z*	$P2_1/c$; 4	$P2_1$; 2	$P\text{-}1$; 2
a, Å	17.030(5)	4.782(5)	4.738(5)
b, Å	4.725(5)	24.361(5)	5.834(5)
c, Å	12.591(5)	5.840(5)	21.481(5)
α, deg	90	90	94.297(5)
β, deg	96.862(5)	98.48(5)	91.975(5)
γ, deg	90	90	98.661(5)
V, Å^3	1005.9(12)	672.9(9)	584.7(8)
d, g/cm^3	1.474	1.403	1.439
Crystal dimensions, mm	0.6×0.2×0.08	0.5×0.4×0.1	0.4×0.18×0.1
θ scanning, deg	$5.23 \le \theta \le 79.02$	$5.23 \le \theta \le 79.02$	$4.13 \le \theta \le 76.16$
μ_{exp}, cm^{-1}	2.768	2.265	2.472
Number of reflections	1928	2390	2354
Number of reflections with $I > 2\sigma(I)$	1175	2219	1347
R_1 ($I > 2\sigma(I)$ and total)	0.0701 (0.1197)	0.0430 (0.0469)	0.0594 (0.1151)
wR_2	0.2317	0.1164	0.1440
GOOF	1.035	1.059	0.912
ED difference peaks, e/Å^3	0.41 and –0.37	0.35 and –0.21	0.28 and –0.28
CCDC	1470265	1470266	1470267

RESULTS AND DISCUSSION

The molecular structure of β-(N-benzoxazoline-2-thione)propionic acid, except the propionic acid moiety, is planar, i.e. the double ring with *exo* bonds in the above mentioned crystal forms is planar within ±0.011 Å (Fig. 1). Depending on the nature of the environment and a weak interaction, the propionic acid residue attached to the N3 atom can be arbitrarily located relative to the benzoxazoline-2-thione core in the crystal (free rotation about N3–C8, C8–C9, and C9–C10 bonds is possible). However, in the crystal of **1** this group is practically planar (with an accuracy of ±0.031 Å), but in the other structures (**2**, **3**) the exact planarity is not maintained (an average deviation from the plane is ±0.27 Å). The propionic parts are differently oriented relative to the plane of the benzoxazoline-2-thione core (angles between the planes are 93.4° (**1**), 19.6° (**2**), and 17.4° (**3**)).

Bond lengths and bond angles of the benzoxazoline-2-thione part in the structures of **1-3** are ordinary and agree well with those observed in related 6-phenyl substituted benzoxazoline-2-thiones [28, 29]. Due to deprotonation of the hydroxyl hydrogen atom in the planar carboxyl moiety of the structures of **2** and **3**, the carbon-oxygen bond is averaged and becomes almost as double being 1.252 Å (**2**) and 1.250 Å (**3**).

The crystal structure of β-(N-benzoxazoline-2-thione)propionic acid (**1**) contains H bonds of the O–H…O type and the O…S donor-acceptor interaction. The H atom of the hydroxyl group in propionic acid (O4) is directed to the carbonyl oxygen lone pair (O3) transformed by the center of symmetry, as a result of which the conjugated H bond forms. These conjugated (counter) H bonds are quite strong, which is indicted by the parameters of this bond. There is also an S…O3donor-acceptor interaction. The parameters of these weak interactions are summarized in Table 2. The analysis of weak intermolecular interactions found in the crystal of **1** shows that in the crystal a layer forms that has a thickness of the *a* cell parameter and is located in the plane of crystallographic *bc* axes.

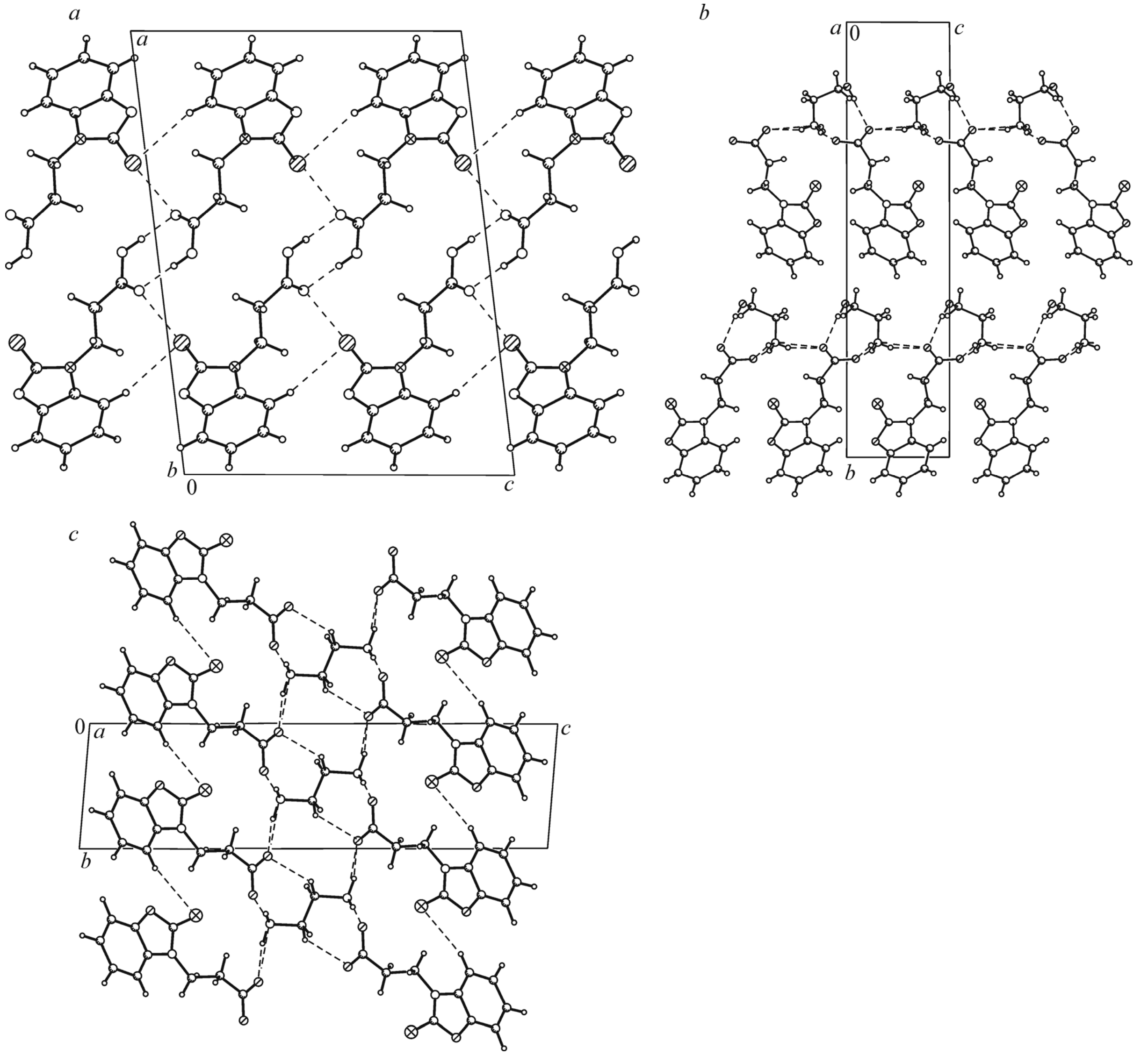


Fig. 1. Crystal structures of β-(N-benzoxazoline-2-thione)propionic acid in the projection on the (*ac*) plane (**1**) and its monoethanolammonium (**2**), ethylenediammonium (**3**) salts (in the projection on the (*bc*) plane). Dots show hydrogen bonds.

TABLE 2. Intermolecular Hydrogen Bonds in the Crystals of **1-3**

Structure	A…H–D	*d*(D–H), Å	*d*(H…A), Å	*d*(D…A), Å	∠(DHA), deg	Symmetry
1	O3…H–O4	0.91(8)	1.83(7)	2.733(7)	175(8)	1–*x*, –*y*, 2–*z*
	S…O3			3.180		*x*, 1/2–*y*, 1/2+*z*
2	O3…H–N1	0.83(4)	2.02(4)	2.815(5)	162(4)	1–*x*, 1/2+*y*, –*z*
	O3…H–N1	0.83(5)	2.05(5)	2.859(5)	167(4)	2–*x*, 1/2+*y*, –*z*
	O4…H–N1	0.74(6)	2.05(6)	2.760(5)	161(4)	2–*x*, 1/2+*y*, 1–*z*
	O4…H–O5	0.79(3)	1.97(4)	2.756(5)	173(3)	2–*x*, 1/2+*y*, –*z*
3	O3…H–N1	0.96(5)	1.79(5)	2.735(6)	166(4)	*x*, *y*, *z*
	O4…H–N1	0.95(5)	1.86(5)	2.801(6)	173(4)	*x*, 1+*y*, *z*
	O4…H–N1	0.81(4)	2.02(4)	2.815(6)	170(4)	1+*x*, 1+*y*, *z*
	S…C4–H4	0.93(5)	2.85(5)	3.758(6)	166(4)	–1+*x*, –1+*y*, *z*

Note. *d* is the distance, D is the donor, A is the acceptor.

Monoethanolammonium salt of β-(N-benzoxazoline-2-thione)propionic acid (**2**) forms, as expected, by the deprotonation of the carboxyl moiety in propionic acid (anion) and the protonation of the nitrogen atom in monoethanolamine (cation), which compose the asymmetric unit of the unit cell. Despite the absence of the asymmetric atom in molecular salt **2**, they crystallize in the $P2_1$ chiral space group.

The packing of the crystal structure of **2** contains intermolecular H bonds involving protonated NH_3, deprotonated carboxyl and hydroxyl groups of monoethanolamine. Table 2 lists these H bonds. Owing to these H bonds, layers form in the *ac* plane, and the thickness of this layer is a half of the *b* cell parameter. A part of the molecular packing in the crystal of 2 is shown in Fig. 1.

Ethylenediammonium salt of β-(N-benzoxazoline-2-thione)propionic acid (**3**) is formed by the deprotonation of carboxyl moieties of two β-(N-benzoxazoline-2-thione)propionic acid molecules (anions) and the protonation of two ethylenediamine nitrogen atoms (cation), i.e. the molecular ratio is 2:1. However, in the asymmetric unit of the crystal cell there are the deprotonated β-(N-benzoxazoline-2-thione)propionic acid molecule and a half of the protonated ethylenediamine molecule (it is in the special position: there is a center of symmetry in the middle of the molecule).

The crystal contains N–H…O type intermolecular H bonds between hydrogen atoms of the NH_3 group and oxygen atoms of the carboxyl group from the transformed molecules, which are given in Table 2. Analyzing the intermolecular contacts it is possible to draw the conclusion that due to translational symmetry elements (the crystal of **3** has the triclinic symmetry, *P*-1 space group) in the crystal a layer forms that is propagated along the *ab* axes and has a thickness corresponding to the large *c* parameter.

CONCLUSIONS

The crystal structures of β-(N-benzoxazoline-2-thione)propionic acid and its monoethanolammonium ($NH_2(CH_2)_2OH$), ethylenediammonium ($NH_2(CH_2)_2NH_2$) salts are studied. In the crystal structures weak interactions form two-dimensional layers whose thicknesses correspond to the unit cell parameters.

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