Thiobarbiturate and barbiturate salts of pefloxacin drug: Growth, structure, thermal stability and IR-spectra

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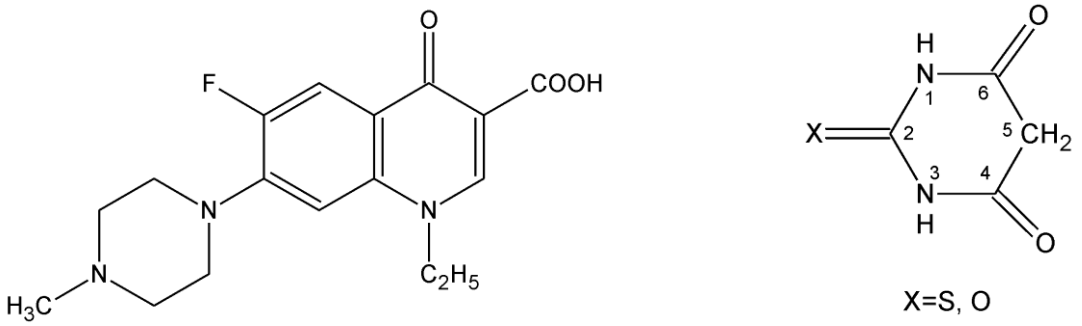
Abstract

Three new salts of pefloxacin (PefH) with thiobarbituric (H_2tba) and barbituric (H_2ba) acids, pefloxacinium 2-thiobarbiturate trihydrate, $PefH_2(Htba)\cdot 3H_2O$ (**1**), pefloxacinium 2-thiobarbiturate, $PefH_2(Htba)$ (**2**) and bis(pefloxacinium barbiturate) hydrate, $(PefH_2)_2(Hba)_2\cdot 2.56H_2O$ (**3**) are synthesized and structurally characterized by the X-ray single-crystal diffraction. In the structures of **1-3**, there are two intramolecular hydrogen bonds C–H...F, O–H...O and intermolecular hydrogen bonds N–H...O, O–H...O which form 2D plane network in **1** and the intermolecular hydrogen bonds N–H...O form the chains in **2** and **3**. In **1-3** the $Htba^-$ and Hba^- ions are connected with $PefH_2^+$ only one by intermolecular hydrogen bond N−H…O. In **2** and **3,** two $Htba^-$ and Hba^- ions are connected by two hydrogen bonds N−H…O. These pairs form infinite chains. All three structures are stabilized by π–π interactions between $PefH_2^+$ ions of the head-to-tail type. Compound **2** and **3** have been characterized by powder XRD, TG-DSC and FT-IR.

Keywords Thiobarbituric acid; barbituric acid; pefloxacin; salts; X-ray diffraction; infrared spectroscopy; thermal stability

1. Introduction

Fluoroquinolones (FxH) are the broad spectrum bactericidal antibiotics and work against both Gram-positive and Gram-negative bacteria. An important representative of this class is pefloxacin (PefH) (Fig. 1a) which widely used in clinical practice [1, 2]. It demonstrates moderate activity against anaerobes and Mycobactoria, to which the quinolone in general has low activity. The PefH is commonly used in the form of salt due to low solubility [3], for example, pefloxacinium methasulfonate, $PefH_2(CH_3SO_3)$. Further search for other pefloxacin salts with improved properties is of practical interest.



a) b)

Fig. 1 Schemes of pefloxacin (a) and barbituric acids (b): X=O in H_2ba and X=S in H_2tba

Barbiturates are a class of drug which used as anesthetics and sleeping agents and are utilized for the treatment different psychiatric disorders [4]. Barbituric and thiobarbituric acids (Fig. 1b) are the key compounds, which are used in synthesis of different their derivatives having important therapeutic value [5-8]. Barbituric acid (H_2ba) possesses specific, relatively weak acidic properties (pK_a ca. 4.03 [9]) resulting from the presence of two methylene hydrogen atoms. Thiobarbituric acid (H_2tba) is a stronger acid (pK_{a1} ca. 1.87 [10]) also resulting from the presence of two methylene hydrogen atoms. The existence of three polymorphs of anhydrous H_2ba and deihydrate [11-13], and six polymorphs of anhydrous thiobarbituric acid and hydrate [14] make these molecules interesting from the viewpoint of crystal engineering. They can be used as a building block to construct the supramolecular assemblies with distinctive properties. The possibility of non-covalent interactions ensures rich supramolecular chemistry of H_2tba and H_2ba compounds. On the other hand, the donor–acceptor features of these acids are important for the crystal design of pharmaceuticals, molecular recognition and catalytic activity [15]. It is of interest to obtain, study the structure and properties of salts which contain simultaneously two representatives of different pharmaceutically active classes, namely, fluoroquinolones and barbituric acids. The fundamental aim of the present work is to study the solid-state

pefloxacinium thiobarbiturate and pefloxacinium barbiturate structures. The molecular and supramolecular structures of fluoroquinolones with barbituric acids [16] which are currently absent in CSD are also useful. Here we report the synthesis data, IR spectra, and thermal stability of three salts, pefloxacinium 2-thiobarbiturate trihydrate, $PefH_2(Htba)\cdot 3H_2O$ (**1**), pefloxacinium 2-thiobarbiturate, $PefH_2(Htba)$ (**2**) and bis(pefloxacinium 2-thiobarbiturate) hydrate, $(PefH_2)_2(Htba)_2\cdot 2.56H_2O$ (**3**).

2. Experimental section

2.1. Reagents and synthesis

Pefloxacin (CAS 70458-92-3), thiobarbituric acid (CAS 504-17-6) and barbituric acid (CAS CAS 67-52-7) with the purity ≥98% were obtained from Sigma-Aldrich and used as received. Compounds **1**-**3** were prepared by the crystallization from the aqueous solution. For the synthesis of **2,** the PefH (0.6 mmol) was dissolved in water (5 cm^3) at 80 °C, then a solid H_2tba (0.6 mmol) was added to the resulting solution during stirring and the solution was kept at 80 °C up to total dissolution of H_2tba (pH=4.2). After it was slowly cooled firstly down to room temperature, and then down to 4 °C. After 20 minutes, the pale porange precipitate formed as fine rectangular crystals was filtered off, washed with acetone and air dried to a constant mass. Yield was 53%. Single crystal of **1** (gold prism) was grown by the continuous filtrate evaporation at 4 °C whithin 6 months. However, we could not get a sufficient amount of the single-phase compound **1**. Pale yellow compound **3** was prepared by a procedure analogous to that described for the preparation of **2**, but H_2ba (pH=4.6) was used instead of H_2tba. Выход 43%. Crystal of **2** and **3**, suitable for single crystal X-ray diffraction analysis, were grown by filtrate corresponding evaporation at 4 °C. Optical microscopy images of **2** and **3** crystals were obtained using a Nikon Eclipse LV100 Microscope and presented in Fig. 1S. Attempts to obtain other hydrates of these compounds by crystallization from an aqueous solution were unsuccessful.

Anal. Calc. for $C_{21}H_{30}FN_5O_8S$(**1**): C, 47.5; H, 5.69; N, 13.2; S, 6.03. Found: C, 48.0; H, 5.26; N, 13.6; S, 6.21%. Anal. Calc. for $C_{21}H_{24}FN_5O_5S$: C, 52.8; H, 5.07; N, 14.7; S, 6.72. Found: C, 52.5; H, 4.89; N, 14.3; S, 6.87% (**2**). Anal. Calc. for $C_{42}H_{50}F_2N_{10}O_{14.56}$ (**3**): C, 52.2; H, 5.22; N, 14.5. Found: C, 51.8; H, 5.13; N, 14.7%.

2.2. X-ray diffraction analysis

The intensity patterns were collected from single crystals **1**, **2** and **3** using the SMART APEX II and D8 Venture X-ray single crystal diffractometers (Bruker AXS) equipped with a CCD-detector, graphite monochromator and Mo Kα radiation source. The absorption corrections

were applied using the SADABS program. The structures were solved by the direct methods using package SHELXS and refined in the anisotropic approach for non-hydrogen atoms using the SHELXL program [17]. All hydrogen atoms were found via Fourier difference maps. Further the hydrogen atoms which are linked with C,N atoms in the $Htba^{-}$, Hba^{-} and $PefH^{+}$ ions were positioned geometrically as riding on their parent atoms with d(C–H) = 0.93-0.98 Å, d(N–H)=0.86-0.89 Å depending on geometry and $U_{iso}(H) = 1.2U_{eq}(C,N)$. All hydrogen atoms of the H_2O molecules and one H atom in OH group of $PefH^{+}$ ion were refined with bond length restraint d(O–H)=0.9 Å and $U_{iso}(H) = 1.2U_{eq}(O)$. The structure test for the presence of missing symmetry elements and possible voids was produced using the program PLATON [18]. The DIAMOND program is used for the crystal structure plotting [19].

Powder X-ray diffraction data of **2** and **3** were obtained using diffractometer D8 ADVANCE (Bruker) equipped by a VANTEC detector with a Ni filter. The measurements were made using Cu Kα radiation. The structural parameters defined by single crystal analysis were used as a basic in powder pattern Rietveld refinement. The refinement was produced using program TOPAS 4.2 [20]. Low *R*-factors and good refinement results shown in (Fig. 2S) indicate the crystal structures of the powder samples to be representative one of the **2** and **3** bulk structure.

2.3. Physical measurements

TGA was carried out on the simultaneous SDT-Q600 thermal analyzer (TA Instruments, USA) under dynamic air atmosphere (50 ml/min flow rate) within 22–350 °C at the scan rate of 10 °C/min. The qualitative composition of the evolved gases was determined by FT-IR spectrometer Nicolet380 (Thermo Scientific, USA) combined with a thermal analyzer and with the TGA/FT-IR interface (attachment for the gas phase analysis). This set up allows simultaneous accumulation of the DTA and TG data, and composition of the released gas phase. The compound weight was 5.603 mg for **2** and 6.302 mg for **3**. Platinum crucibles with perforated lids were used. The IR absorption spectra of the compounds in KBr were recorded over the range of 400–4000 cm^{-1} at room temperature on a FT-IR spectrometer Nicolet 6700 (Thermo Scientific, USA, SFU CEJU).

3. Results and discussion

3.1. Crystal structures of (1)

The unit cell of the pefloxacinium 2-thiobarbiturate trihydrate, $PefH_2^{+}(Htba^{-})\cdot 3H_2O$ (**1**), correspond to triclinic symmetry. Space group *P*-1 was determined from the statistical analysis of the reflection intensities. The main crystal data are shown in Table 1. The main bond lengths

and valence angles are shown in Table 1S. They coincide with those given in the literature for the $PefH_2^+$ ion [21-24] and $Htba^-$ ion [25-29].

The independent part of the unit cell contains one $PefH_2^+$ ion, one $Htba^-$ ion and three H_2O molecules (Fig. 1a). There are two intramolecular hydrogen bonds C–H...F, O–H...O (Figure 1a) and nine intermolecular hydrogen bonds N–H...O, O–H...O in the structure (Figure 2a, Table 2S) which form 2D plane network. This is 5-nodal net with stoichiometry (3-c)(3-c)(3-c)(4-c)(5-c) and with vertex symbol $(3.5.6.8^2.9)(3.5.6^2.7^2.8^3.9)(3.5.6)(5.6^2)(5.8^2)$ which is new [30].

Similar to **1**, the structures pefloxacinium methanesulfonate hydrates [22, 23] are also stabilized by hydrogen bonds involving the terminal piperazinyl N atom of the pefloxacinium and an O atom of the methanesulfonate ion, with strong N—H···O interactions and the carbonyl and carboxyl groups are also involved in a strong intramolecular O—H···O hydrogen bond. The H-bonds with the participation of two chains, each of which consists of two water molecules, bind two $Htba^-$ ions together and lead to a synthon $R_6^6(20)$. Each $Htba^-$ ion has two such ions in the nearest environment (Figure 2a). $PefH_2^+$ is connected with two H_2O molecules and two $Htba^-$ ions. In **1** the hydrogen bond donors are two N atom of thiobarbiturate ion, and the acceptors are two O atoms keto and carboxyl groups of $PefH_2^+$ cation. The most interesting motifs in this network are $R_3^3(10)$, $R_6^4(12)$, $R_6^5(14)$ and $R_6^6(20)$ (Figure 2a). The π-π interactions between $Htba^-$ and $PefH_2^+$ ions, and between two $PefH_2^+$ ions (in a head-to-tail manner) are stabilized structure. Similar the packing of $PefH_2^+$ ions observed in the structures of $(PefH_2^+)CH_3SO_3^-\cdot 2H_2O$ [23] $(PefH_2^+)CH_3SO_3^-\cdot 0.1H_2O$ [22] and $(PefH_2^+)_2PtCl_4^{2-}\cdot 2H_2O$ [24], The π-π interaction in **1** combines pefloxacinium cations to the pairs (Table 3S, Fig. 3Sa).

3.2. Crystal structures of (2)

The unit cell of $PefH_2^+(Htba^-)$ (**2**) correspond to monoclinic symmetry. Space group $P2_1/c$ was determined from the statistical analysis of the reflection intensities and extinction rules. The main crystal data are shown in Table 1. The main bond lengths and valence angles are shown in Table 1S. They coincide with those found earlier for **1** and given in the literature for ions $PefH_2^+$ [21-24] and $Htba^-$ [25-29].

The independent part of the unit cell contains one $PefH_2^+$ ion, one $Htba^-$ ion (Figure 1b). There are two intramolecular hydrogen bonds C–H...F, O–H...O (Figure 1b) and three intermolecular hydrogen bonds N–H...O in the structure (Figure 2b, Table 2S) which form chain along *a*-axis. $Htba^-$ ion in **2** has direct H-bond to $PefH_2^+$ like in $PefH_2(Htba)\cdot 3H_2O$. The number of intermolecular hydrogen bonds in compound **2** is much smaller in comparison with **1** due to absence of water molecules in compound, which can stabilize crystal structures when there is an imbalance in the number of acceptors and donors [31]. $PefH_2^+$ has two the hydrogen bond donors

(carboxylic acid, O–H; $(CH_3)NH^+$ group) and six potentially strong hydrogen bond acceptors (three N- and three O-atoms). $Htba^-$ ion has potentially two hydrogen bond donors (two NH groups) and five acceptors (two O-, two N- and one S-atoms). In the **2** an imbalance in the number of donors and acceptors в $PefH_2^+$ are partly compensated by active participation in the hydrogen bonding of $Htba^-$ ion (Figure 2b). The structure **2** is stabilized by intermolecular hydrogen bonds N–H...O between $Htba^-$ ions forming a centrosymmetric homosynton $R_2^2(8)$ and $C_2^2(10)$, and besides $Htba^-$ ions form infinite chains along *a*-axis. Also, there are π-π interactions between two rings of $PefH_2^+$ in structure (Table 3S, Figure 3Sb). Contrary to **1**, the $Htba^-$ ions in compound **2** are not involved in π–π interaction. However, π-π interactions between two rings of $PefH_2$ joint them to the pairs in **2**.

3.3. Crystal structures of (3)

The unit cells of $(PefH_2^+)_2(Hba^-)_2 \cdot 2.56H_2O$ (**3**) correspond to triclinic symmetry and space group *P*-1 was determined. The main crystal data are shown in Table 1. The main bond lengths and valence angles are shown in Table 1S.

The independent part of the unit cell contains two $PefH_2^+$ ions, two Hba^- ions, one ordered water molecule and two disordered H_2O molecules with partial occupations (Fig. 1c). Occupancies sum of all H_2O in the independent part of unit cell equal to 2.562(4). Hydrogen bonding could not be analyzed in detail because H atoms of disordered water molecules were not found. Anyway, there are two intramolecular hydrogen bonds C–H...F, O–H...O (Figure 1c), six intermolecular hydrogen bonds N–H...O (Figure 2c) and at least one O–H...O bond in the structure (Table 2S) which form chain along *a*-axis. Hydrogen bond pattern is similar with pattern of **2** (Figure 2b). The dominantly formed hydrogen bonding in **3** is N–H···O interaction, which leads to a centrosymmetric synthon $R_2^2(8)$ and to formation of infinite chain from Hba^- ions. Similar infinity chains from $Htba^-$ ions were observed in **2**. There are several π-π interactions between two rings of $PefH_2^+$ and Hba^- (Table 3S, Fig. 3Sc).

3.4. IR spectroscopy

The IR spectra of $PefH_2(Htba)$ (**2**) and $PefH_2)_2(Hba)_2 \cdot 2.56H_2O$ (**3**) are displayed in Figure 6S. They are very difficult to interpret due to numerous bands in a particular frequency range less than 1500 cm^{-1}. In the analysis of the IR spectra used the results of these studies [32-35]. The IR spectra of **2** (Figure 4S, curve 1) and **3** (Figure 4S, curve 2) markedly differ from spectra of initial reagents (PefH, H_2tba or H_2ba), which indicates the obtainment of new compounds. The very broad bands in the 3600-3400 cm^{-1} can be assigned to stretching modes of NH and OH for $PefH_2^+$, $Htba^-$ and Hba^- ions. In the region of stretching vibrations C=O in IR spectra of Hba^- ion the band with the highest frequency lies at 1688 cm^{-1} [34]. In alkaline and alkali earth metals

(M) thiobarbiturate bond M–O is weak and predominantly ion-dipole in nature, therefore one can assume that stretching vibrations C=O which were found in IR spectra of these compounds can be attributed to uncoordinated $Htba^-$ ions. The most high frequency band ν(C=O) in sodium thiobarbiturate is located at 1645 cm^{-1} [27], and in potassium thiobarbiturate it is located at 1630 cm^{-1} [36]. Therefore, the band associated with ν(C=O) of $Htba^-$ and Hba^- ions are located noticeably below 1700 cm^{-1}. So the bands at 1716 cm^{-1} for **2** and at 1706 cm^{-1} for **3** correspond to the stretching vibration ν(C=O) in COOH [35], and this proves the protonation of the carboxyl group PefH and in agreement with X-ray single crystal data. Low frequency of another very strong absorption band ν(C=O) at 1629 cm^{-1} in IR spectra of **2** and **3** can be explained by the participation of the O2 atom of $PefH_2^+$ in an intramolecular hydrogen bond O2–H...O1(Figure 1b,c) and/or it is assigned κ ν(C=O) in $Htba^-$ and Hba^- ions, respectively.

3.5. Thermal decomposition

According to TG curves, the mass of sample **2** remains unchanged up to ~270 ºC (Figure 5S), and there are no peaks in the DSC curve below this temperature. This confirms the anhydrous nature of the compound. The compound **2** melts with decomposition at T>270 ºC. The decomposition is accompanied by an endo effect at 275.3 ºC. The H_2tba melts with decomposition at 250.6 ºC [37], i.e. compound **2** is more thermal stable than H_2tba. According to the IR spectroscopic analysis of evolved gases during thermolysis, the H_2O, CO_2 and NH_3 are formed.

Both TG and DSC curves of **3** show two-step dehydration which is accompanied by two endo effects at 124.7 ºC and 244.1 ºC (Figure 6S). This is confirmed by the results of IR spectroscopic analysis of evolved gases, according to which, when heated to 260 ºC, only dehydration of the substance takes place, what is more the dehydration with two steps. The first stage of dehydration in the range of 60-150 ºC showed the weight loss (Δm) equal to 4.1%, but the second stage in the range of 235-260 ºC showed Δm=1.8%. Total weight loss (5.9%) is bigger than calculated weight loss taking in assumption total dehydration ($-2.5H_2O$, Δm_{theor}=4.66%). The observed difference can be explained by the partial overlap of the second stage of dehydration with the oxidative decomposition of the compound. The H_2ba melts with decomposition at 245.0 ºC [38], i.e. compound **3** is more thermal stable than H_2ba. Oxidative decomposition products are H_2O, CO_2, SO_2.

4. Conclusions

Crystallization of PefH with 2-thiobarbituric and barbituric acids resulted in the isolation of three new salts. Two intramolecular hydrogen bonds C–H...F, O–H...O (Figure 1) and intermolecular

hydrogen bonds N–H...O, O–H...O are stabilized the structures of **1-3** (Figure 2, Table 2S). The $Htba^-$ and Hba^- ions are connected with $PefH_2^+$ only by intermolecular hydrogen bond N−H…O. In **1** the hydrogen bond donors are two N atom of thiobarbiturate ion, and the acceptors are two O atoms keto and carboxyl groups of $PefH_2^+$ cation. However in **2-3** the H-bond donor is the positively charged piperazinium N atom in $PefH_2^+$, and the acceptor is one O atom keto group of $Htba^-$ or Hba^- ions. The dominantly formed hydrogen bonding in **2-3** is N−H···O interaction, which leads to a centrosymmetric synthon $R_2^2(8)$ and the forming of infinite chains of $Htba^-$ or Hba^- ions. Fluoroquinolones have potentially two strong hydrogen bond donors and 6-7 potentially strong hydrogen bond acceptors [39]. An imbalance in the number of donors and acceptors in fluoroquinolone salts can be compensated by incorporating water molecules into crystal lattices (as in **1**). Water molecules stabilize crystal structures by forming a diverse arrangement of supramolecular heterosynthons [40]. Another way of compensation of an imbalance in donors/acceptors ratio is the inclusion in the composition of fluoroquinolone salts of anions capable of self-association, for example, the $Htba^-$ and Hba^- ions, as in **2** and **3**. The structures **1-3** are stabilized by π–π interactions between $PefH_2^+$ ions of the head-to-tail type. These interactions connect $PefH_2^+$ ions in pairs in **1-2** or in infinite chains in **3** (Table 3S, Fig.2S). Also there are π-π interactions between $Htba^-$ and $PefH_2^+$ ions in **1**. IR spectra data are in agreement with X-ray single crystal diffraction analysis. Compounds **2** and **3** were found to be more thermal stable than H_2tba and H_2ba acids, respectively.

Supplementary data

The crystallographic data (excluding structure factors) for the structural analysis have been deposited with Cambridge Crystallographic Data Centre ((**1**) - CCDC 1537391; (**2**) - CCDC 1537392; (**3**) - CCDC 1537393). The information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(1223)336-033, E-mail: deposit@ccdc.cam.ac.uk, or www: www.ccdc.cam.ac.uk).

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Graphical Abstract

Table 1. Crystal structure parameters of **1-3**

Single crystal	$PefH_2(Htba)\cdot 3H_2O$ (**1**)	$PefH_2(Htba)$ (**2**)	$(PefH_2)_2(Hba)_2\cdot 2.56H_2O$ (**3**)
Moiety formula	$C_{21}H_{30}FN_5O_8S$	$C_{21}H_{24}FN_5O_5S$	$C_{42}H_{50}F_2N_{10}O_{14.56}$
Dimension (mm)	0.2×0.16×0.05	0.20×0.30×0.35	0.43×0.20×0.17
Color	Pale orange	Pale yellow	Pale yellow
Molecular weight	531.56	477.51	965.88
Temperature (K)	150	150	296
Space group, *Z*	*P*-1, 2	$P2_1/c$	*P*-1, 2
a (Å)	8.4651 (6)	12.0768 (9)	10.3252 (3)
b (Å)	9.3753 (6)	14.7120 (11)	13.8631 (4)
c (Å)	15.8077 (9)	12.2222 (9)	16.9586 (3)
α (º)	89.484 (2)	90	101.243 (1)
β (º)	88.735 (2)	95.109 (3)	92.514 (1)
γ (º)	78.147 (2)	90	109.471 (1)
V (Å^3)	1227.48 (14)	2162.9 (3)	2229.1 (1)
ρ_{calc} (g/cm^3)	1.438	1.466	1.439
μ (mm^{-1})	0.196	0.204	0.115
Reflections measured	11838	105889	24769
Reflections independent	5647	6337	10127
Reflections with $F > 4\sigma(F)$	3139	4737	7257
$2\theta_{max}$ (°)	55.27	60.16	55.02
h, *k*, *l* - limits	$-10 \le h \le 10$; $-12 \le k \le 12$; $-20 \le l \le 18$	$-17 \le h \le 17$; $-20 \le k \le 20$; $-17 \le l \le 17$	$-13 \le h \le 13$; $-17 \le k \le 17$; $-15 \le l \le 22$
R_{int}	0.0473	0.0869	0.0278
The weighed refinement of F^2	$w=1/[\sigma^2(F_o^2)+(0.0628P)^2]$	$w=1/[\sigma^2(F_o^2)+(0.0570P)^2+1.4849P]$	$w=1/[\sigma^2(F_o^2)+(0.1137P)^2+0.3971P]$
Number of refinement parameters	346	303	637
$R1$ [$F_o > 4\sigma(F_o)$]	0.0523	0.0468	0.0550
*wR*2	0.1060	0.1116	0.1704
Goof	0.905	1.060	1.039
$\Delta\rho_{max}$ (e/Å^3)	0.416	0.893	0.626
$\Delta\rho_{min}$ (e/Å^3)	-0.287	-0.328	-0.373
$(\Delta/\sigma)_{max}$	0.001	0.001	0.001

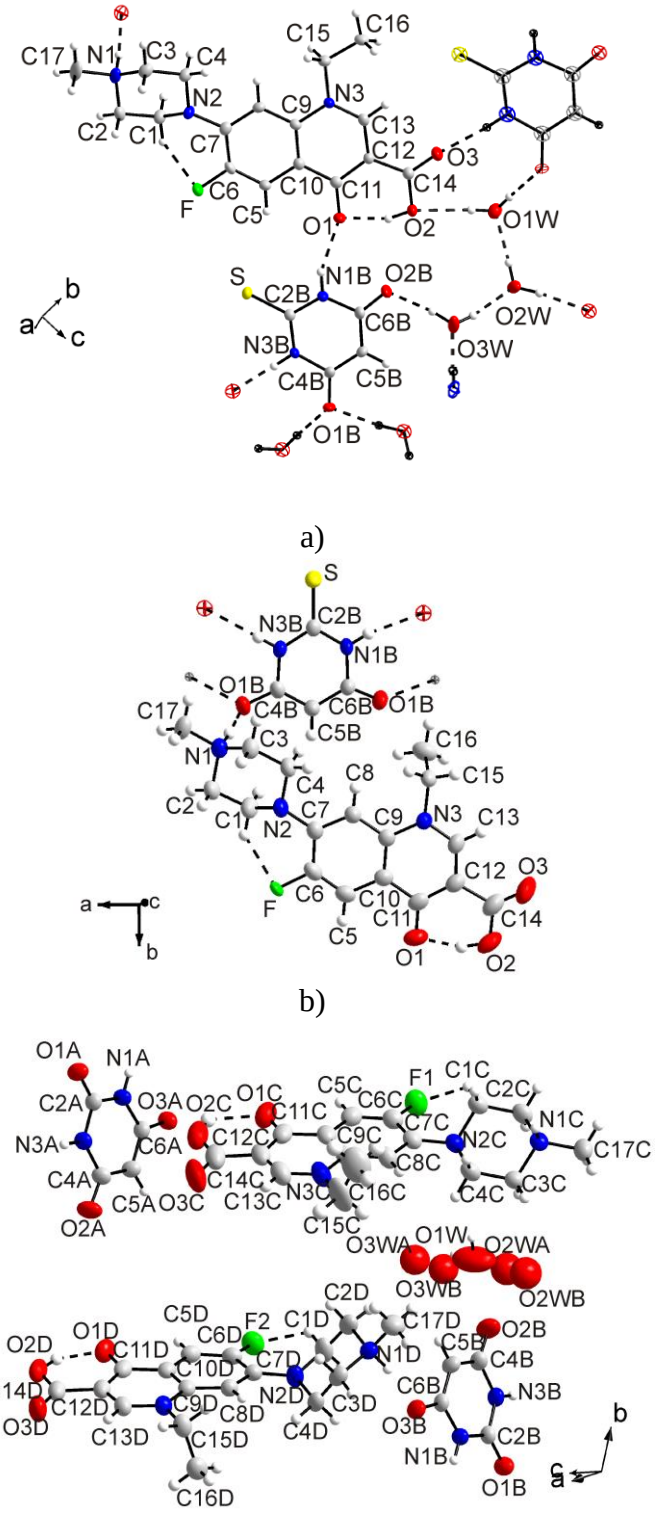
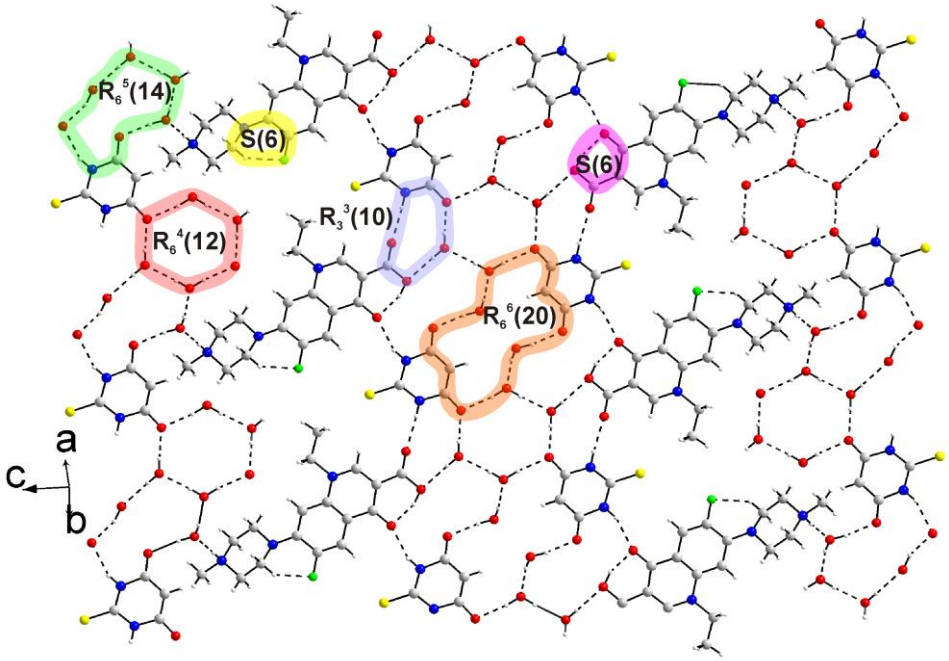
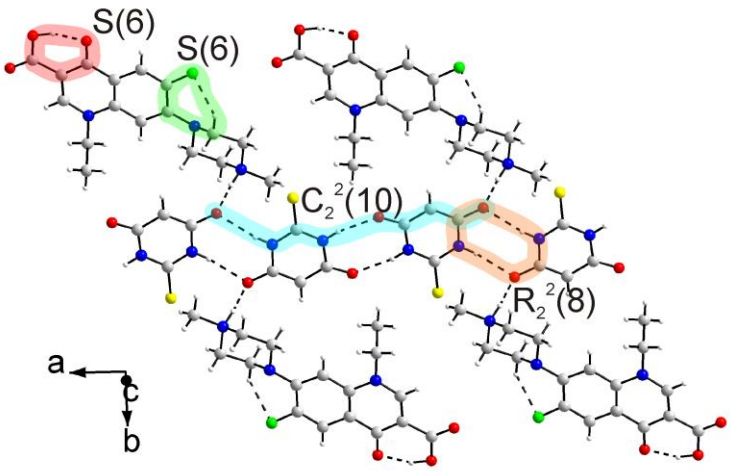


Figure 1. The asymmetric unit of the $PefH_2(Htba)\cdot 3H_2O$ (**1**) (a), $PefH_2(Htba)$ (b) and $(PefH_2)_2(Hba)_2\cdot 2.56H_2O$ (**3**) (c) unit cell. All atoms in the asymmetric unit are labeled. The neighboring symmetry-generated atoms are represented by principal ellipses with an individual color. The bonds linking asymmetric unit atoms with the symmetry-generated atoms and intermolecular hydrogen bonds are represented by dashed lines. The ellipsoids are drawn at the 50% probability level, except for the hydrogen atoms represented by spheres.



a)



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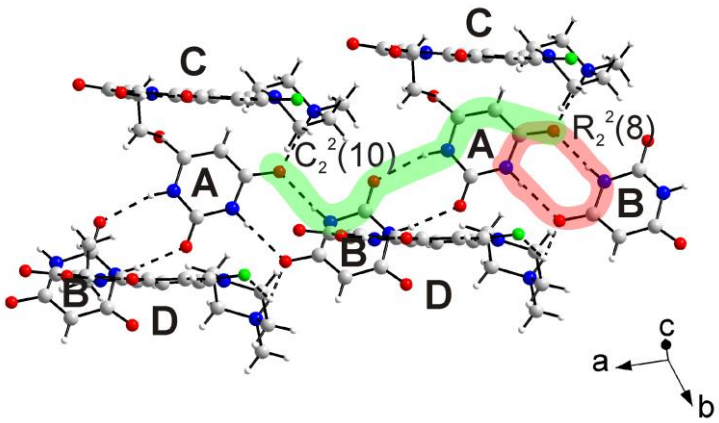


c)

Figure 2. Hydrogen bonding in **1** (a), **2** (b) and **3** (c). The H-bonds are marked by dashed lines, the H-bond motifs are marked by circles. Different Hba^- ions are marked by A, B labels and $PefH_2^+$ ions are marked by C, D labels in (**3**) (c).

Supported Information

Table 1S. Main geometric parameters (Å, º) of (**1-3**)

Geometry of pefloxacinium ion							
$PefH_2(Htba)\cdot 3H_2O$ (**1**)		$PefH_2(Htba)$ (**2**)		$(PefH_2)_2(Hba)_2\cdot 2.56H_2O$ (**3**)			
F—C6	1.354 (3)	F—C6	1.360 (2)	F1—C6C	1.355 (2)	F2—C6D	1.354 (2)
O1—C11	1.269 (3)	O1—C11	1.265 (2)	O1C—C11C	1.263 (3)	O1D—C11D	1.271 (2)
O2—C14	1.331 (3)	O2—C14	1.337 (2)	O2C—C14C	1.327 (4)	O2D—C14D	1.329 (3)
O3—C14	1.215 (3)	O3—C14	1.208 (2)	O3C—C14C	1.191 (4)	O3D—C14D	1.195 (3)
N1—C17	1.488 (3)	N1—C17	1.487 (2)	N1C—C17C	1.489 (2)	N1D—C17D	1.493 (3)
N1—C2	1.490 (3)	N1—C2	1.495 (2)	N1C—C2C	1.484 (3)	N1D—C2D	1.496 (3)
N1—C3	1.493 (3)	N1—C3	1.494 (2)	N1C—C3C	1.487 (2)	N1D—C3D	1.491 (2)
N2—C7	1.394 (3)	N2—C7	1.399 (2)	N2C—C7C	1.405 (2)	N2D—C7D	1.373 (2)
N2—C1	1.471 (3)	N2—C1	1.476 (2)	N2C—C1C	1.473 (2)	N2D—C4D	1.461 (3)
N2—C4	1.457 (3)	N2—C4	1.464 (2)	N2C—C4C	1.458 (2)	N2D—C1D	1.462 (2)
N3—C13	1.336 (3)	N3—C13	1.335 (2)	N3C—C13C	1.329 (3)	N3D—C13D	1.339 (2)
N3—C9	1.403 (3)	N3—C9	1.394 (2)	N3C—C9C	1.400 (3)	N3D—C9D	1.392 (2)
N3—C15	1.495 (3)	N3—C15	1.480 (2)	N3C—C15C	1.497 (4)	N3D—C15D	1.484 (2)
C1—C2	1.513 (3)	C1—C2	1.514 (2)	C1C—C2C	1.507 (3)	C1D—C2D	1.501 (3)
C3—C4	1.515 (4)	C3—C4	1.509 (2)	C3C—C4C	1.501 (3)	C3D—C4D	1.509 (3)
C5—C6	1.358 (3)	C5—C6	1.355 (2)	C5C—C6C	1.360 (3)	C5D—C6D	1.354 (3)
C5—C10	1.410 (3)	C5—C10	1.410 (2)	C5C—C10C	1.400 (3)	C5D—C10D	1.402 (3)
C6—C7	1.413 (4)	C6—C7	1.423 (2)	C6C—C7C	1.408 (3)	C6D—C7D	1.418 (3)
C7—C8	1.389 (4)	C7—C8	1.390 (2)	C7C—C8C	1.382 (3)	C7D—C8D	1.391 (2)
C8—C9	1.401 (3)	C8—C9	1.397 (2)	C8C—C9C	1.402 (3)	C8D—C9D	1.403 (2)
C9—C10	1.407 (3)	C9—C10	1.402 (2)	C9C—C10C	1.400 (3)	C9D—C10D	1.407 (3)
C10—C11	1.438 (3)	C10—C11	1.447 (2)	C10C—C11C	1.454 (3)	C10D—C11D	1.442 (3)
C11—C12	1.422 (3)	C11—C12	1.427 (2)	C11C—C12C	1.424 (4)	C11D—C12D	1.422 (3)
C12—C13	1.382 (3)	C12—C13	1.372 (2)	C12C—C13C	1.368 (4)	C12D—C13D	1.363 (3)
C12—C14	1.475 (3)	C12—C14	1.483 (2)	C12C—C14C	1.496 (3)	C12D—C14D	1.486 (3)
C15—C16	1.504 (4)	C15—C16	1.513 (2)	C15C—C16C	1.474 (5)	C15D—C16D	1.511 (3)

Geometry of thiobarbiturate and barbiturate ions							
$PefH_2(Htba)\cdot 3H_2O$ (**1**)		$PefH_2(Htba)$ (**2**)		$(PefH_2)_2(Hba)_2\cdot 2.56H_2O$ (**3**)			
S—C2B	1.659 (3)	S—C2B	1.686 (2)	O1A—C2A	1.231 (2)	O1B—C2B	1.233 (2)
O1B—C4B	1.268 (3)	O1B—C4B	1.274 (2)	O2A—C4A	1.247 (2)	O2B—C4B	1.249 (2)
O2B—C6B	1.249 (3)	O2B—C6B	1.241 (2)	O3A—C6A	1.276 (2)	O3B—C6B	1.275 (2)
N1B—C2B	1.353 (3)	N1B—C2B	1.349 (2)	N1A—C2A	1.364 (2)	N1B—C2B	1.366 (2)
N1B—C6B	1.405 (3)	N1B—C6B	1.409 (2)	N1A—C6A	1.387 (2)	N1B—C6B	1.385 (2)
N3B—C2B	1.364 (3)	N3B—C2B	1.346 (2)	N3A—C2A	1.358 (2)	N3B—C2B	1.355 (2)

N3B—C4B	1.393 (3)	N3B—C4B	1.401 (2)	N3A—C4A	1.394 (2)	N3B—C4B	1.387 (2)
C4B—C5B	1.386 (3)	C4B—C5B	1.383 (2)	C4A—C5A	1.403 (2)	C4B—C5B	1.398 (3)
C5B—C6B	1.401 (4)	C5B—C6B	1.409 (2)	C5A—C6A	1.378 (2)	C5B—C6B	1.386 (3)
C2B—N1B—C6B	126.2 (2)	C2B—N1B—C6B	124.7 (1)	C2A—N1A—C6A	124.0 (1)	C2B—N1B—C6B	124.2 (1)
N1B—C2B—N3B	114.4 (2)	N1B—C2B—N3B	116.2 (1)	N1A—C2A—N3A	115.9 (2)	N1B—C2B—N3B	115.7 (2)
N3B—C2B—S	123.0 (2)	N3B—C2B—S	121.2 (1)	N3A—C2A—O1A	122.6 (2)	N31B—C2B—O1B	122.7 (2)
C2B—N3B—C4B	125.5 (2)	C2B—N3B—C4B	125.0 (1)	C2A—N3A—C4A	125.1 (1)	C2B—N3B—C4B	125.3 (1)
N1B—C2B—S	122.7 (2)	N1B—C2B—S	122.6 (1)	N1A—C2A—O1A	121.6 (2)	N1B—C2B—O1B	121.6 (2)
C4B—C5B—C6B	121.6 (2)	C4B—C5B—C6B	121.4 (1)	C4A—C5A—C6A	121.6 (2)	C4B—C5B—C6B	121.5 (2)

Table 2S. Hydrogen-bond geometry in (**1-3**) structures (Å, °)

D—H	d(D—H)	d(H···A)	∠D—H···A	D···A	A	Transformation for A atom
$PefH_2(Htba)\cdot 3H_2O$ (**1**)						
N1—H0	0.98	1.66	166	2.621 (3)	O3W	x, y, -1+z
N1B—H1B	0.86	1.99	156	2.795 (3)	O1	x, y, z
N3B—H3B	0.86	1.98	175	2.836 (3)	O3	1+x, -1+y, z
O2—H2	0.88 (3)	1.69 (3)	158 (3)	2.534 (3)	O1	x, y, z
C1—H01A	0.97	2.21	124	2.867 (3)	F	x, y, z
O1W—H11W	0.86 (3)	1.90 (3)	176 (2)	2.759 (4)	O1B	1+x, 1+y, z
O1W—H12W	0.86 (3)	2.22 (3)	173 (3)	3.066 (3)	O2	x, y, z
O2W—H21W	0.90 (3)	2.84 (3)	171 (3)	2.734 (3)	O1B	2-x, 1-y, 1-z
O2W—H22W	0.87 (3)	1.88 (3)	176 (2)	2.747 (3)	O1W	x, y, z
O3W—H31W	0.84 (3)	1.86 (3)	169 (3)	2.693 (3)	O2W	x, y, z
O3W—H32W	0.87 (2)	1.76 (3)	172 (3)	2.622 (3)	O2B	x, y, z
$PefH_2(Htba)$ (**2**)						
N1—H0	0.98	1.73	175	2.705 (2)	O1B	x, y, z
N1B—H1B	0.86	1.99	169	2.835 (2)	O2B	1-x, 1-y, 1-z
N3B—H3B	0.86	2.09	155	2.892 (2)	O1B	2-x, -y, -z
O2—H2	0.96 (2)	1.57 (2)	159 (2)	2.492 (2)	O1	x, y, z
C1—H01A	0.97	2.21	127	2.893 (2)	F	x, y, z
$(PefH_2)_2(Hba)_2\cdot 2.56H_2O$ (**3**)						

N1C—H0C	0.98	1.69	174	2.672 (2)	O3A	x, y, z
N1D—H0D	0.98	1.71	166	2.672 (2)	O3B	x, y, z
N1A—H1A	0.86	2.12	178	2.979 (2)	O3B	x, 1+y, z
N1B—H1B	0.86	1.98	174	2.838 (2)	O3A	x, -1+y, z
N3A—H3A	0.86	2.15	163	2.984 (2)	O1B	1+x, 1+y, z
N3B—H3B	0.86	2.00	169	2.845 (2)	O1A	-1+x, -1+y, z
O2C—H2C	0.91 (4)	1.94 (3)	123 (3)	2.550 (3)	O1C	x, y, z
O2D—H2D	0.91 (2)	1.69 (2)	151 (3)	2.523 (3)	O1D	x, y, z
C1C—H1BC	0.97	2.27	124	2.927 (2)	F1	x, y, z
O1W—H12W	0.92	1.91 (3)	158 (3)	2.787 (3)	O2A	x, y, z

Table 3S. Parameters of the π–π interaction in (**1-3**)

Cg_i–Cg_j	d(Cg–Cg), Å	α, deg	β, deg	γ, deg	Cg_i_p, Å	Shift, Å
$PefH_2(Htba)\cdot 3H_2O$ (**1**)						
$Cg_1 – Cg'_1$	3.491 (2)	0.0 (1)	13.4	13.4	3.396 (1)	0.808
$Cg_1 – Cg'_2$	3.824 (2)	0.3 (1)	27.3	27.0	3.407 (1)	1.736
$Cg_2 – Cg'_3$	3.969 (2)	5.9 (1)	26.0	25.4	3.587 (1)	1.699
$PefH_2(Htba)$ (**2**)						
$Cg_{1A} – Cg'_{1B}$	3.654 (2)	4.9 (2)	14.4	17.5	3.484 (2)	1.102
$Cg_{1A} – Cg'_{2B}$	3.843 (3)	5.4 (2)	25.1	24.7	3.490 (2)	1.609
$Cg_{2A} – Cg'_{1B}$	3.914 (3)	1.8 (2)	25.6	25.4	3.536 (2)	1.678
$Cg_{2A} – Cg_3$	4.007 (2)	6.7 (2)	22.3	27.8	3.771 (2)	1.355
$Cg_{2B} – Cg_4$	3.894 (2)	3.6 (2)	24.9	25.7	3.509 (2)	1.688
$(PefH_2)_2(Hba)_2\cdot 2.56H_2O$ (**3**)						
$Cg_{1C} – Cg'_{1C}$	3.988 (1)	0.0 (1)	29.9	29.9	3.4576 (9)	1.988
$Cg_{1C} – Cg'_{2D}$	3.520 (1)	5.6 (1)	13.0	18.5	3.3383 (9)	1.116
$Cg_{1D} – Cg'_{2C}$	3.593 (1)	3.4 (1)	16.4	13.8	3.4891 (8)	0.858
$Cg_{1D} – Cg'_{1D}$	3.597 (1)	0.00 (9)	22.6	22.6	3.3208 (8)	1.382
$Cg_{1D} – Cg''_{2D}$	3.687 (1)	3.25 (9)	23.4	25.2	3.3349 (7)	1.572

(**1**): Cg_1 and Cg_2 are the centers of the rings in $PefH^+$. Cg_3 is the center of the ring $Htba^-$. Cg'_1 was obtained from Cg_1 by the transform (1-x,1-y,-z), Cg'_2 was obtained from Cg_2 by the transform (1-x,1-y,-z), Cg'_3 was obtained from Cg_3 by the transform (2-x,1-y,-z). Cg_i_p is the distance between the center of the ring Cg_i in the π-π interaction.

(**2**): Cg_{1C}, Cg_{2C} and Cg_{1D}, Cg_{2D} are the centers of the rings in $PefH^+$. Cg'_{1C} was obtained from Cg_{1C} by the transform (1-x,1-y,-z), Cg'_2 was obtained from Cg_2 by the transform (1-x,1-y,-z).

(**3**): Cg_1 and Cg_2 are the centers of the rings in $PefH^+$. Cg'_1 was obtained from Cg_1 by the transform (1-x,2-y,1-z), Cg'_{2D} was obtained from Cg_{2D} by the transform (1-x,1-y,1-z), Cg'_{2C} was obtained from Cg_{2C} by the transform (1-x,1-y,1-z), Cg'_{1D} was obtained from Cg_{1D} by the transform (2-x,1-y,1-z), Cg''_{1D} was obtained from Cg_{1D} by the transform (2-x,1-y,1-z).

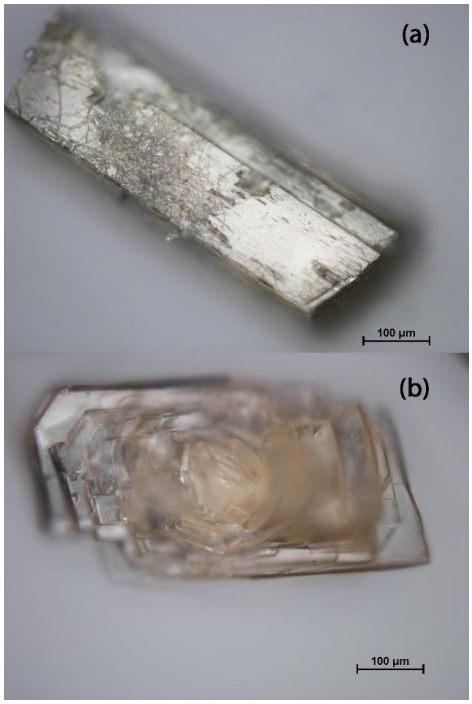
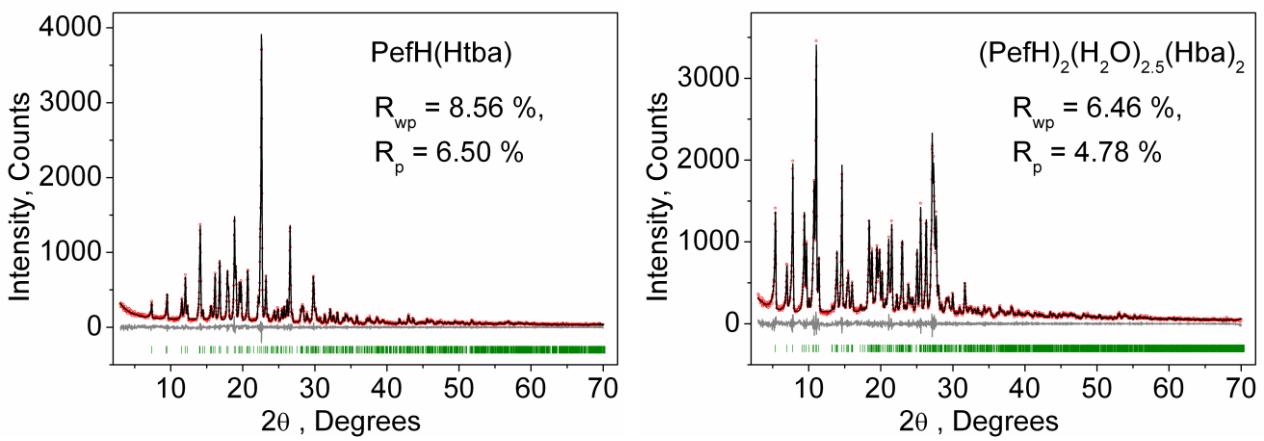
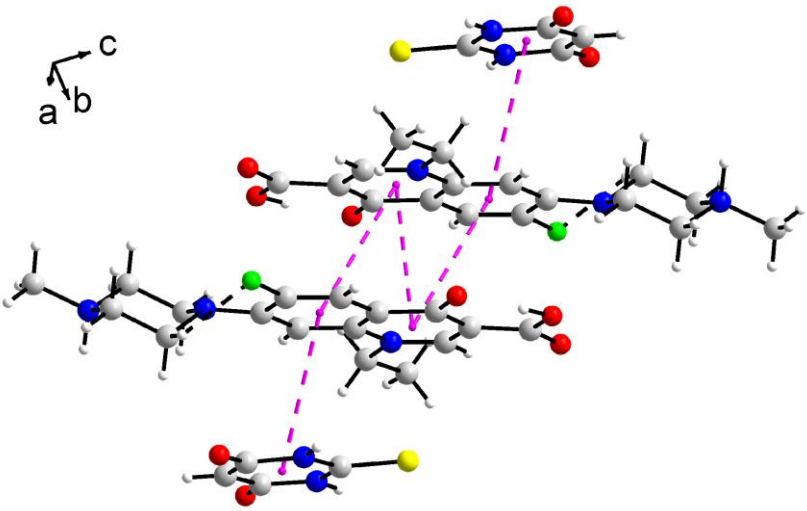


Figure 1S. Optical microscope images of (**a**) – $(PefH_2)_2(Hba)_2 \cdot H_2O$; (**b**) - $PefH_2(Htba)$ crystals

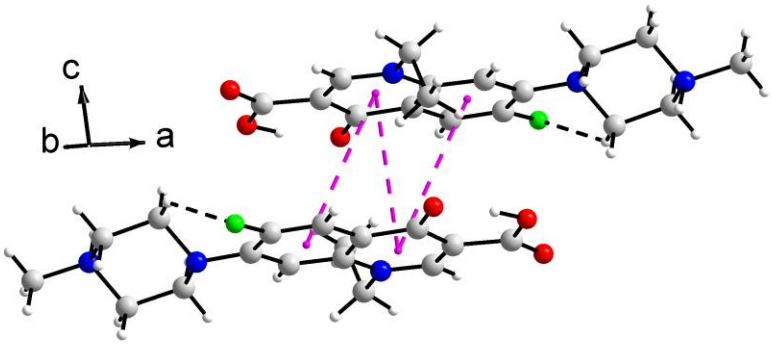


a) b)

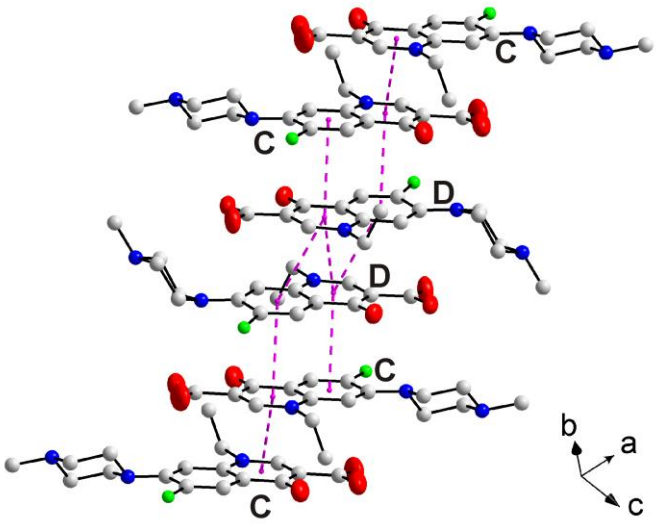
Figure 2S. Difference X-ray powder patterns of $PefH_2(Htba)$ (a) and $(PefH_2)_2(Hba)_2 \cdot 2.56H_2O$ (b).



a)



b)



c)

Figure 3S. π-π interactions the $Htba^{-}$…$PefH_2^{+}$, and $PefH_2^{+}$…$PefH_2^{+}$ ions in **1** (a), between the $PefH_2^{+}$ ions in (**2**) (b) and between the $PefH^{+}$ ions in (**3**) (c).

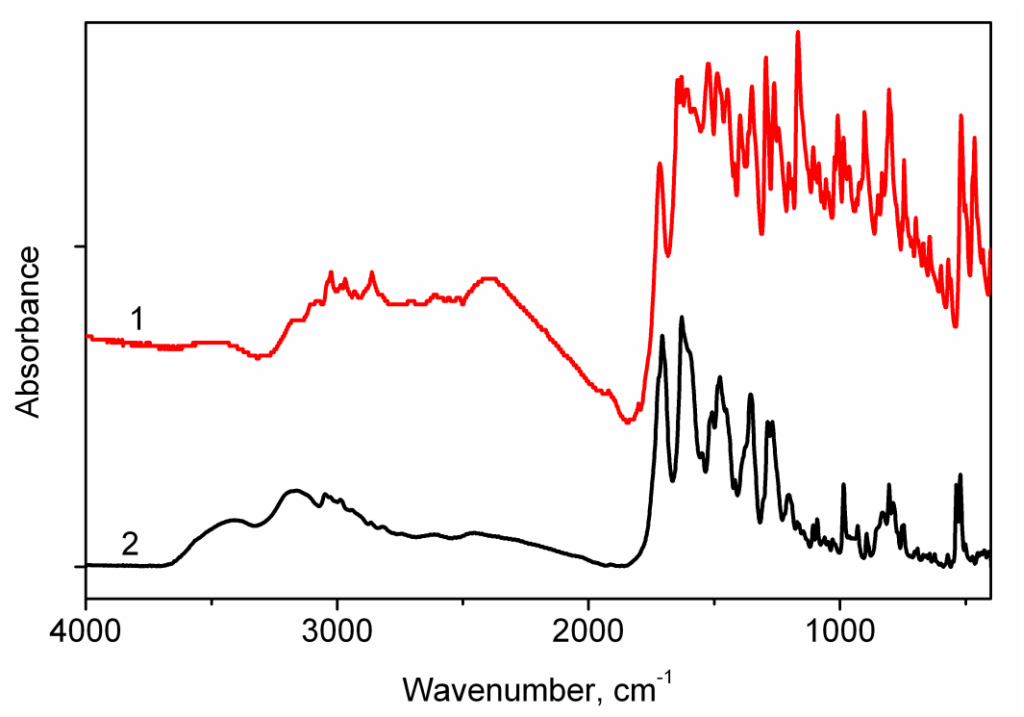


Figure 4S. IR-spectra of $PefH_2(Htba)$ (1), $(PefH_2)_2(Hba)_2 \cdot 2.56H_2O$ (2)

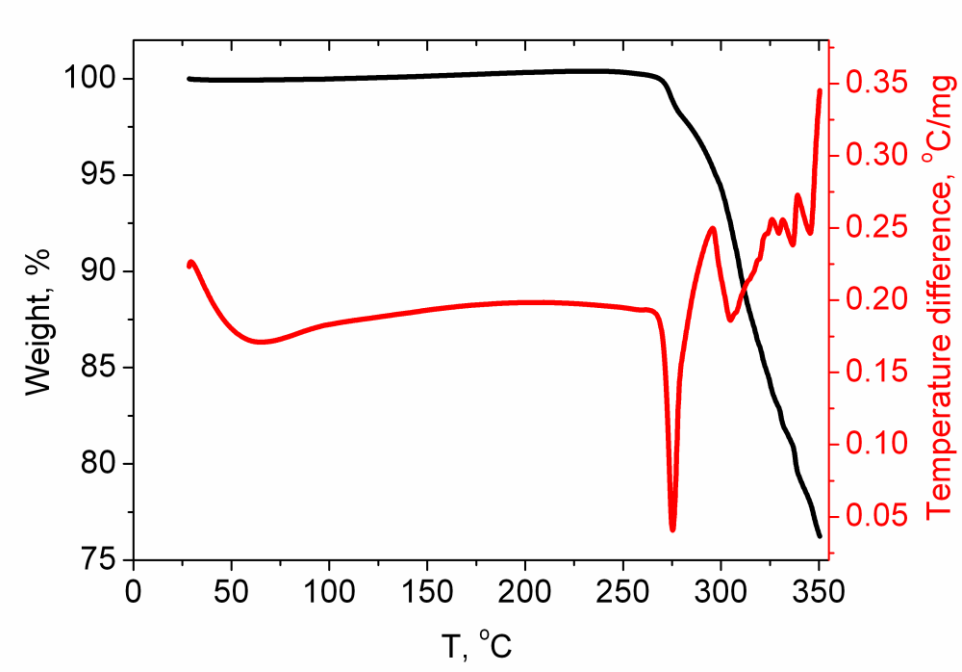


Figure 5S. TG and DSC curves of **2**. Dynamic air atmosphere

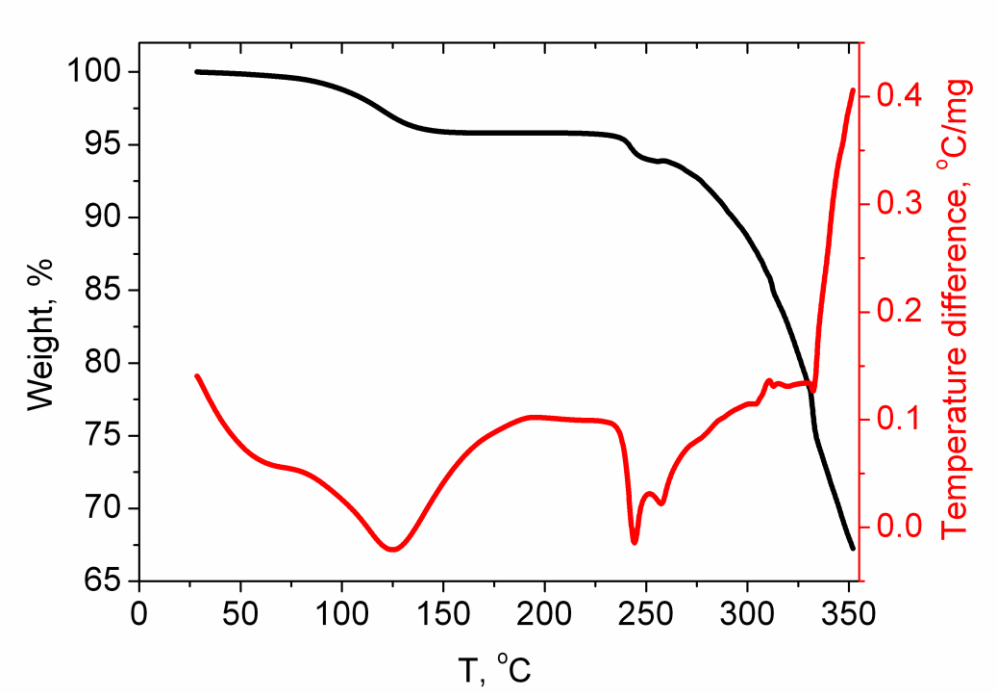


Figure 6S. TG and DSC curves for thermal decomposition of **3** under air atmosphere