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ORIGINAL RESEARCH PAPER

SYNTHESIS, THERMAL STUDIES AND CRYSTAL STRUCTURE OF 4-AMINOPYRIDINIUM SEMI-OXALATE HEMIHYDRATE

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Abstract: The title compound has been synthesized by grinding in an agate mortar. Its structure was characterized by TGA-DSC studies and single-crystal X-ray diffraction. This compound crystallize in the monoclinic system with space group C2/c, Z = 4, and unit cell parameters a = 16.109(2) Å, b = 5.748(7) Å, c = 20.580(3) Å, β = 107.36(1)°. The salt, $C_2HO_4^-{\cdot}C_5H_7N^+{\cdot}0.5\ H_2O$, is an ionic ensemble assisted by hydrogen bonds established between 4-aminopyridinium cations, oxalate anions and water molecules. The three components thus construct a supramolecular assembly with a three-dimensional hydrogen bonded framework.

Keywords: *hydrogen bonding patterns, multicomponent crystal, X-ray diffraction*

INTRODUCTION

Pharmaceutical co-crystallization plays a significant role in the development of new drugs mainly due to the fact that an active pharmaceutical ingredient (API) can be crystallized with different conformers improving their physical and chemical properties [1 – 3]. The main route to obtain good crystalline products, i.e. good quality and crystallinity, has been the formation of salts. Understanding the formation of salts as an acid-base reaction between the API and an acidic or basic substance is essential by the fact that most pharmaceutical compounds possess either acidic or basic functionality.
Two good candidates for the supramolecular formation of pharmaceutical co-crystals are the aminopyridine compounds and the carboxylic acids, due to their interesting non-covalent interactions such as hydrogen bonds. Aminopyridines are amine isomers which has been studied from the theoretical viewpoint because they contain a small number of atoms and provide model systems for larger molecules [4, 5], and are key intermediates for the synthesis of important pharmaceuticals and agrochemicals. Particularly, 4-aminopyridine (fampridine) is used in the treatment of neurological ailments, such as multiple sclerosis (MS), with tests showing that improves motor function in MS patients [6, 7].
Structurally, aminopyridines are excellent co-crystallizing compound with two hydrogen bonding groups suitable for the formation of intermolecular synthons. The amine group has two hydrogen bond donors and a second hydrogen bond acceptor is the lone pair on the N atom of the pyridine ring. This makes the molecule very versatile for a variety of hydrogen bonded interactions, especially in pharmaceutical co-crystals [8].
On the other hand, oxalic acid is a very strong dicarboxylic acid capable of generating infinite anionic aggregates through the complimentary hydrogen-bond functionalities of the carbonyl groups, which crystallized in the solid state as catamers (α-form) or dimers (β-form) [9]. Many pharmaceutical co-crystals have been obtained with carboxylic acids as cocrystal formers. Among them, oxalic acid provides a number of examples, including therapoline [10], caffeine [11] and γ-amino butyric acid [12].
From the interest in studying the formation of multicomponent crystals containing amino acids, amines, amides and carboxylic acids [13 – 16], we report here the structure of the ionic ensemble formed between oxalic acid (OXAL) and 4-aminopyridine (4AP), and its hydrogen-bonding patterns analysis.

MATERIALS AND METHODS

All the reagents used were obtained from Sigma-Aldrich (USA) and were used without any further purification.

Synthesis

The multicomponent compound was prepared by mixing 1.0 mmol (0.090 g) of oxalic acid and 1.0 mmol (0.094 g) of 4-aminopyridine (Figure 1).

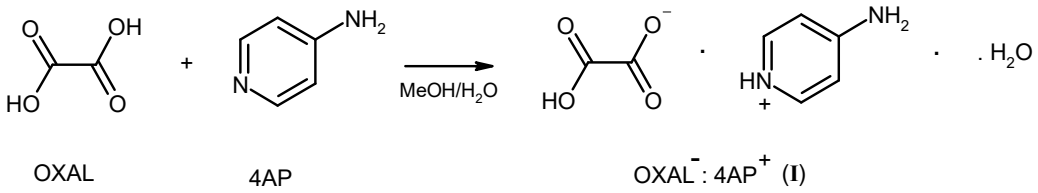

Figure 1. *Synthesis of 4-aminopyridinium semi-oxalate hemihydrate*

The reagents were ground in an agate pestle and mortar and dissolved in methanol/water mixture (1:1, 5 mL). Colorless crystals of (**I**) suitable for X-ray diffraction analysis were grown by slow evaporation.

Fourier Transform Infrared Spectroscopy (FT-IR) analysis

The FT-IR absorption spectrum was obtained as KBr pellet using a Perkin-Elmer 1600 spectrometer (Perkin-Elmer, USA).

Thermal analysis

Melting point was determined on an Electrothermal Model IA9100 apparatus (Electrothermal, USA). Thermogravimetric Analysis (TGA) and Differential Scanning Calorimetry (DSC) measurements of (**I**) was performed in a Perkin-Elmer TGA7 Thermogravimetric Analyzer (Perkin-Elmer, USA) coupled with a DSC 4000 console (Pekin-Elmer, USA). Sample was heated from 25 to 400 °C at a rate of 10 °C·min^{-1}, under a nitrogen flux of 100 mL·min^{-1}.

X-ray single-crystal crystallography

Colorless block crystal of the title compound with dimensions 0.6 × 0.5 × 0.4 mm was used for data collection. Diffraction data were collected at 296(2) K by ω-scan technique on a Bruker SMART APEX II CCD diffractometer (Bruker, Germany) equipped with MoKα radiation (λ = 0.71073 Å). The data were corrected for Lorentz-polarization and absorption effects. The crystal structure was solved by direct methods and refined by a full-matrix least-squares calculation on F^2 using the programs SHELXS (version 2016/1) and SHELXL (version 2016/6). The Cambridge Structural Database (CSD, version 5.37, May 2016) was used for structure analysis.

RESULTS AND DISCUSSION

FT-IR spectroscopic characterization of (I)

FT-IR: 3335 cm^{-1}, N-H (primary amine); 1681 cm^{-1}, C=O (acid group); 1634 cm^{-1}, N-H (primary amine); 1494 cm^{-1}, C-N (aromatic amine); 896 cm^{-1}, O-H (acid group); 757 cm^{-1}, C=O (acid group).

Thermal analysis of (I)

Figure 2 shows the thermal analysis results for (**I**).

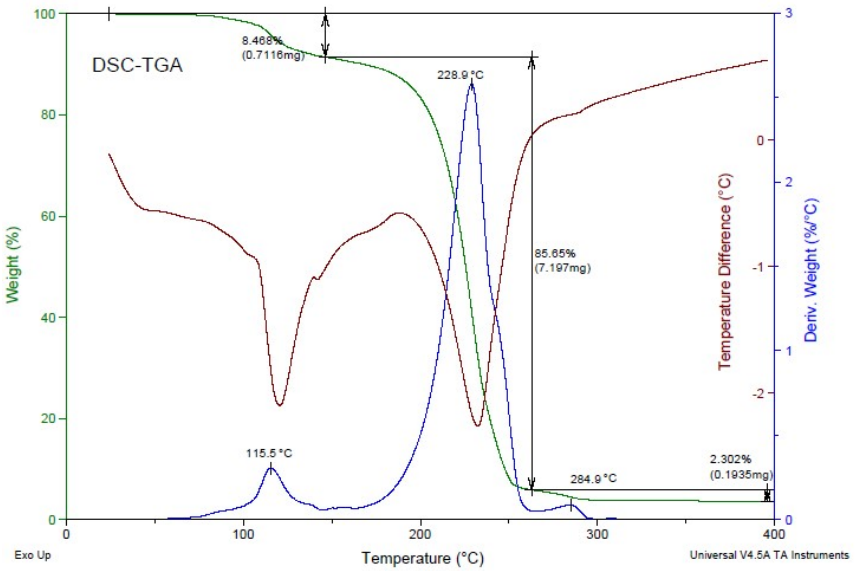

Figure 2. *TGA and DSC for the salt (**I**)*

A first endothermic peak at 115.5 °C corresponds to the crystallization water. A sharp endothermic peak observed at 228.9 °C corresponds to the compound melts, which was further confirmed by melting point analysis (227 - 229 °C). No traces of pure 4-aminopyridine (m.p. 158 °C) or oxalic acid (m.p. 210 °C) were found. The sample decomposed completely at 284.9 °C.

X-ray diffraction study of (I)

The H atom of the water molecule was located in the final difference Fourier map, their position was refined and their isotropic displacement parameters were set to 1.2 times the equivalent displacement parameter of the Ow atom. The other H atoms were placed at calculated positions and treated using a riding model, with C-H distances 0.96 - 0.98 Å and Uiso(H) = 1.2 Ueq(C)], N-H 0.86 Å and Uiso(H) = 1.2 Ueq(N)]. Figure 3 shows the molecular structure and the atom-labeling scheme of (**I**).

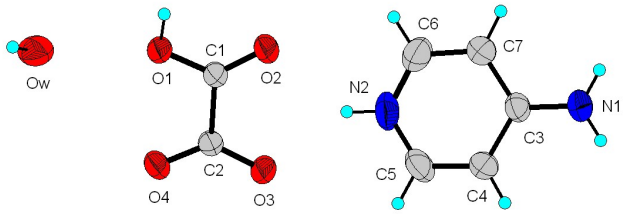

Figure 3. *The molecular structure of (**I**), showing the atomic numbering scheme (displacement ellipsoids are drawn at 50 % probability level; H atoms are shown as spheres of arbitrary radii)*

Table 1 shows the crystallographic data and structure refinement parameters and Table 2 shows selected geometrical parameters for (**I**). Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre (CCDC-1008430).

Table 1. *Crystal data, data collection and structure refinement of* ***(I)***

Chemical formula	$C_2HO_4^-\cdot C_5H_7N^+\cdot 0.5H_2O$	**CCDC**	1008430
Formula weight	386.32	**Radiation (MoKα)**	λ = 0.71073 Å
Crystal system	monoclinic	**θ range [°]**	2.1 - 29.1
Space group	C2/c	**hkl range**	-21 ≤ h ≤ 21 -7 ≤ k ≤ 6 -27 ≤ l ≤ 27
***a* [Å]**	16.109(2)	**Reflections**	
***b* [Å]**	5.748(7)	**Collected**	12301
***c* [Å]**	20.580(3)	**Unique (Rint)**	2273 (0.017)
β [°]	107.36(1)	**With I > 2σ(I)**	1920
V [Å^3]	1818.8(4)	**Refinement method**	Full-matrix least squares on F^2
Z	4	**Number of parameters**	127
dx [g·cm^{-3}]	1.411	**R(F^2) [I > 2σ(I)]**	0.0581
F [000]	808	**wR(F^2) [I > 2σ(I)]**	0.1461
μ [mm^{-1}]	0.119	**Goodness of fit on F^2**	1.15
Crystal size [mm]	0.6 x 0.5 x 0.4	**Max/min Δρ [e·Å^{-3}]**	0.83/-0.67

Table 2. *Selected geometrical parameters (Å, °) for* ***(I)***

C1-O1	1.322(2)	**C1-O2**	1.221(2)
C2-O3	1.263(2)	**C2-O4**	1.251(2)
C1-C2	1.570(3)	**N1-C3**	1.339(3)
N2-C5	1.351(3)	**N2-C6**	1.355(3)
O1-C1-O2	125.5(1)	**C5-N2-C6**	120.8(2)
O1-C1-C2-O4	5.8(2)	**O2-C1-C2-O3**	5.4(2)

A search in the Cambridge Structural Database (CSD, version 5.37, May 2016) shows 50 adducts containing 4-aminopyridine; all are salts. In this work, the multi component compound 4-aminopyridinium semi-oxalate hemihydrate (**I**) can be classified as a salt.

The asymmetric unit consists of one $OXAL^-$ anion acting as a semi-oxalate ion (for the carboxylate group, C2-O3 and C2-O4 are 1.263 (2) and 1.251 (2) Å, respectively), one $4AP^+$ ion with a positive charge residing on atom N2, and a half-molecule of water. This salt can be described as an ionic ensemble assisted by hydrogen bonds.

The semi-oxalate $OXAL^-$ has a planar conformation, with torsion angles O1-C1-C2-O4 and O2-C1-C2-O3 of 5.8(2)° and 5.4(2)°, respectively. A new search in the CSD (with R-factors less than 0.05) showed 94 structures with the semi-oxalate almost planar with torsion angles close to 0.0º, 55 structures in the range (2 - 10)º, 43 in the range (10 - 50)º, 13 in the range (50 - 90)º and only one structure in the bended conformation with torsion angle near 90º.

The molecular structure and crystal packing are stabilized mainly by two intermolecular O---H···O hydrogen bonds, reinforced by four N---H···O intramolecular interactions (Table 3).

Table 3. *Hydrogen bonds geometry (Å, º)*

D--H···A	D--H	H···A	D···A	D--H···A	Symmetry codes
O1---H1···O3	0.82	1.81	2.627 (4)	174	x, -1+y, z
Ow---H1w···O4	0.84(2)	1.99(2)	2.831 (4)	175(2)	x, -1+y, z
Intramolecular HB					
N1---H1A···Ow	0.86	2.060	2.912 (5)	169	-
N1---H1B···O4	0.86	2.050	2.904 (5)	173	-
N2---H2···O2	0.86	2.280	2.933 (5)	133	-
N2---H2···O3	0.86	2.160	2.918 (5)	147	-

The intramolecular O1---H1···O3 and Ow---H1w···O4 (x, -1+y, z), forming a semi-oxalate···semi-oxalate chains. The four intermolecular N--H···O hydrogen bonds produces hydrogen bonds that connect one 4-aminopyridine molecule with one semi-oxalate (N2---H2···O2 and N2---H2···O3) in a bifurcated mode, and one 4-aminopyridine molecule with one water and one semi-oxalate molecule (N1---H1···O2 and N1---H1···O3), respectively. These interactions are shown in Figure 4.

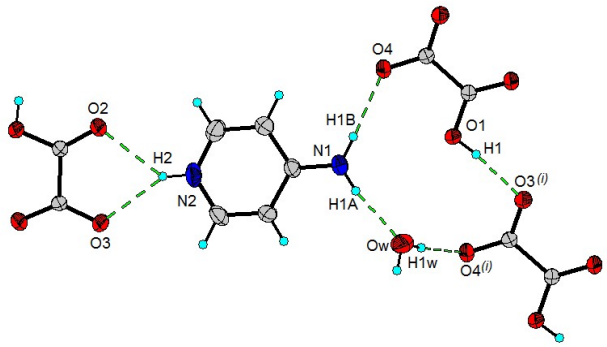

Figure 4. *A portion of the crystal packing shows all intermolecular (O--H···O) and intramolecular (N--H···O) hydrogen bonds formed in* ***(I)***

In the crystal structure of (**I**), with water molecules incorporated into the general three-dimensional hydrogen-bond network: each water molecule forms four hydrogen bonds with neighbors disposed tetrahedrally about it (Figure 5).

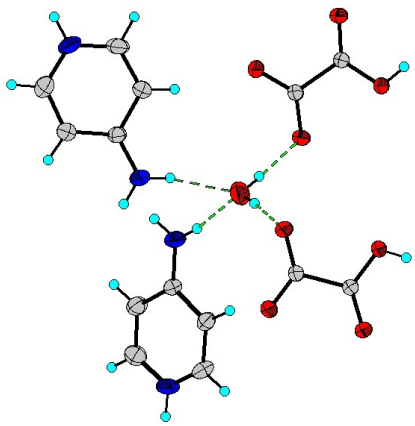

Figure 5. *The molecular tetrahedral coordination around the water molecule*

The $OXAL^-$ molecules interact with each other by means of hydrogen bonds of the type O1---H1···O3, forming linear ···semi-oxalate···semi-oxalate··· chains extending along the *b* axis which can be described by the graph-set motif C(5) [17]. These chains are connected through the Ow---H1w···O4$^{(i)}$ hydrogen bonds forming cycles with graph-set $R^6_6(22)$ in the *bc* plane as shown in Figure 6.

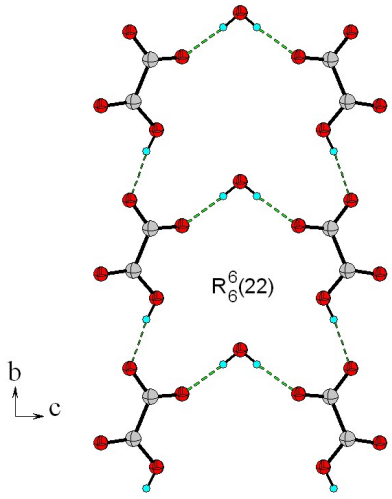

Figure 6. *Packing of the homomeric $OXAL^-$ molecules shows the cyclic structures with graph-set motif $R^6_6(22)$ in the bc plane*

On the other hand, Figure 7 shows how the homomeric 4-aminopyridinium cations are joined with water molecules forming dimer structures with graph-set motif $D^1_2(3)$ in the *ca* plane. The combinations of all interactions produce an intricate three-dimensional hydrogen bond network.

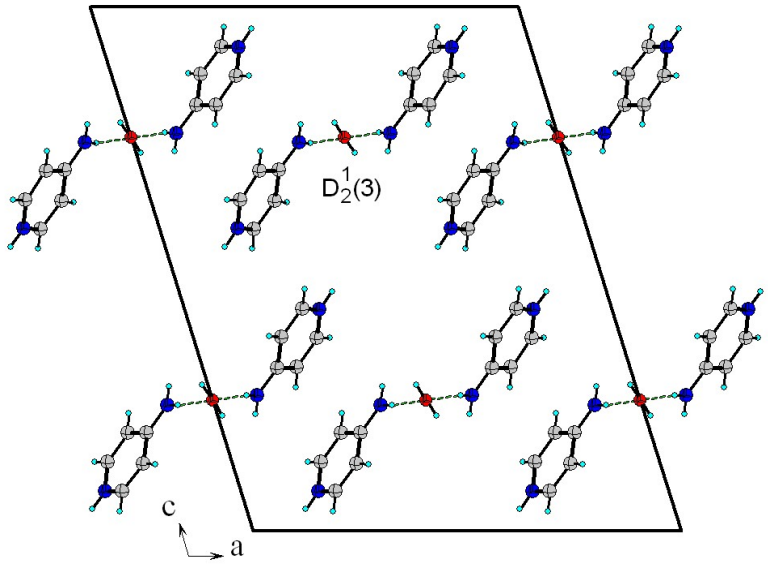

Figure 7. *Packing of the homomeric $4AP^+$ interactions shows the dimeric structures with graph-set motifs $D^1_2(3)$ in the ca plane*

CONCLUSIONS

A new multicomponent material, 4-aminopyridinium semi-oxalate hemihydrate, has been synthesized and structurally characterized. The crystal belongs to monoclinic system. The supramolecular structure and crystal packing are stabilized mainly by intermolecular O---H···O hydrogen bonds, reinforced by N---H···O intramolecular interactions, forming a three-dimensional network.

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