ÁCIDO MALÔNICO (1:1) COMPLEXO MOLECULAR DE 2-AMINOPIRIDINA: ESTRUTURA DE CRISTAL E ANÁLISE DE SUPERFÍCIE HIRSHFELD

MALONIC ACID (1:1) 2-AMINOPYRIDINE MOLECULAR COMPLEX: CRYSTAL STRUCTURE AND HIRSHFELD SURFACE ANALYSIS

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Received 26 November 2017; received in revised form 18 October 2018; accepted 22 October 2018

RESUMO

A co-cristalização é a combinação supramolecular de duas ou mais entidades químicas diferentes em uma rede cristalina através de interações não covalentes. Em particular, a preparação de co-cristais farmacêuticos oferece um meio para modificar as propriedades físico-químicas dos cristais sem alterar as propriedades químicas de uma molécula farmacêutica, melhorando várias propriedades físicas do fármaco puro tais como solubilidade, biodisponibilidade, estabilidade térmica, etc. Este trabalho mostra um bom exemplo de síntese e caracterização de um co-cristal que pode contribuir para a indústria farmacêutica. Neste estudo, difração de raios-X de monocristal foi utilizada para caracterizar estruturalmente o complexo molecular formado entre dois isômeros conformacionais farmacêuticos: 2-aminopiridina e ácido malônico. O composto do título foi sintetizado por trituração num almofariz de ágata. Sua estrutura foi caracterizada por difração de raios X. Este composto cristaliza no sistema monoclinico com grupo espacial $P2_1/n$, $Z = 4$, e parâmetros de célula unitária $a = 7.718(1) \text{ \AA}$, $b = 17.518(2) \text{ \AA}$, $c = 13.726(2) \text{ \AA}$, $\beta = 94.270(8)^\circ$, $V = 1850.6(4) \text{ \AA}^3$. O sal $C_3H_3O_4 \cdot C_5H_7N_2^+$ é um conjunto iônico auxiliado por ligações de hidrogênio estabelecidas entre ânions de malonato e cátions de 2-aminopiridina. Os dois componentes constroem, assim, uma montagem supramolecular com uma estrutura tridimensional de ligação de hidrogênio. A análise de superfície de Hirshfeld foi usada para analisar visualmente interações intermoleculares na estrutura cristalina.

Palavras-chave: *complexo molecular, estrutura do cristal, padrões de ligação de hidrogênio, análise de superfície de Hirshfeld*

ABSTRACT

Co-crystallization is the supramolecular combination of two or more different chemical entities in a crystalline lattice through non-covalent interactions. In particular, the preparation of pharmaceutical co-crystals offers a means to modify the physicochemical properties of crystals without altering the chemical properties of a pharmaceutical molecule, improving several physical properties of the pure drug such as solubility, bioavailability, thermal stability, etc. This work shows a good example of synthesis and characterization of a co-crystal which can contribute to the pharmaceutical industry. In this study, single-crystal X-ray diffraction was

used to characterize structurally the molecular complex formed between two pharmaceutical conformers; 2-aminopyridine and malonic acid. The title compound has been synthesized by grinding in an agate mortar. Its structure was characterized by X-ray diffraction. This compound crystallize in the monoclinic system with space group $P2_1/n$, $Z = 4$, and unit cell parameters $a = 7.718(1) \text{ \AA}$, $b = 17.518(2) \text{ \AA}$, $c = 13.726(2) \text{ \AA}$, $\beta = 94.270(8)^\circ$, $V = 1850.6(4) \text{ \AA}^3$. The salt, $C_3H_3O_4^- \cdot C_5H_7N_2^+$, is an ionic ensemble assisted by hydrogen bonds established between malonate anions and 2-aminopyridinium cations. The two components thus construct a supramolecular assembly with a three-dimensional hydrogen bonded framework. Hirshfeld surface analysis was used for visually analyzing intermolecular interactions in the crystal structure.

Keywords: *molecular complex, crystal structure, hydrogen bonding patterns, Hirshfeld surface analysis*

INTRODUCTION

The formation of multicomponent crystal of organic compounds is unexpected because the resulting crystal could be a cocrystal, in which the different components are neutral species, or a salt, in which the components are charged species (Morissette *et al.*, 2004). When one of the components is an active pharmaceutical ingredient (API) it is possible to prepare the so-called pharmaceutical cocrystals, which plays a significant role in the development of new drugs mainly due to the fact that an API can be crystallized with different conformers improving their physical and chemical properties (Desiraju, 2003; Aakeröy and Salmon, 2005; Vishweshwar *et al.*, 2006).

The preparation of these materials can be carried out by different methods such as recrystallization, growth from the melt or grinding (Blagden *et al.*, 2007), solvent choice and solubility (Jones *et al.*, 2005), and the chemistry of functional groups and pKa (Trask *et al.*, 2005). The main route to obtain good crystalline products, with API, has been the formation of salts, which is an acid-base reaction between the API and an acidic or basic substance.

Some homomeric or heteromeric synthons such as amide/amide (Aakeröy *et al.*, 2001), carboxylic acid/aminopyrimidine (Shan and Zaworotko, 2008) and amide/pyridine (Lemmeer *et al.*, 2008) favor the formation of these types of multicomponent crystals. Therefore, two good candidates for the pharmaceutical co-crystal formation are the aminopyridines and the carboxylic acids, due to the supramolecular heterosynthon formations. Carboxylic acids play a significant role in crystal engineering because they are self-complementary and they can form heterosynthons with a wide range of other functional groups (Bis and Zaworotko, 2005). Aminopyridines are key intermediates for the

synthesis of important pharmaceuticals and agrochemicals. Particularly, 2-aminopyridine is an important solid that is used in the production of the drugs piroxicam, sulfapyridine, tenoxicam, and tripeleminamine (Gouda *et al.*, 2017).

In this study, and as part of ongoing studies on multicomponent crystals (Belandria *et al.*, 2012; Mora *et al.*, 2013; Belandria *et al.*, 2013; Delgado *et al.*, 2015; Chacón *et al.*, 2017; Delgado *et al.*, 2017), we used malonic acid mixed with 2-aminopyridine, in order to prepare the 1:1 multicomponent 2-aminopyridinium semimalonate ($MAL^-:2AP^+$). The crystal structure and supramolecular hydrogen bond patterns study is performed and Hirshfeld surface analysis (Spackman and Byrom, 1997) was used for visually analyzing intermolecular interactions in the crystal structure.

MATERIALS AND METHODS

Synthesis

The molecular complex (Figure 1) was prepared as follows: equimolar quantities of malonic acid (0.1mmol, Aldrich, 98%) and 2-aminopyridine (0.1mmol, Aldrich, 98%) were pulverized in an agatha mortar with a pestle and dissolved in 5mL of methanol.

The mixture was placed in a reflux system for one hour at a constant temperature of 50 °C. Colorless crystals (I) of suitable size for X-ray diffraction experiments were obtained by the slow evaporation of the solution. Melting point 142-143°C.

X-ray powder diffraction

The X-ray powder diffraction patterns for malonic acid (MAL), 2-aminopyridine (2AP) and formed salt $MAL^-:2AP^+$ (I) were collected at room temperature in a Phillips PW-1250 (Phillips,

Netherland) goniometer using CuK α radiation. A small quantity of each compound was ground mechanically in an agate mortar and pestle and mounted on a flat holder covered with a thin layer of grease. The samples were scanned from 5-55° 2 θ , with a step size of 0.02° and counting time of 10s. Silicon was used as an external standard.

X-ray powder patterns comparison showed in Figure 2a evidence the formation of a new compound. For the MAL⁻:2AP⁺ (I) powder pattern, the 20 first measured reflections were completely indexed using the program Dicvol04 (Boultif and Löuer, 2004), which gave a unique solution in an monoclinic cell with parameters $a = 7.72 \text{ \AA}$, $b = 17.52 \text{ \AA}$, $c = 13.70 \text{ \AA}$, $\beta = 94.25^\circ$ in a P-type cell. In order to confirm the unit cell parameters, a Le Bail refinement (Le Bail, 2015) of the whole diffraction pattern without structural was carried out using the Fullprof program (Rodriguez-Carvajal, 2017). Figure 2b shows a very good fit between the observed and calculated patterns.

X-ray single-crystal crystallography

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

Chemical formula	C ₃ H ₃ O ₄ ⁻ ·C ₅ H ₇ N ₂ ⁺
Formula weight	198.18
Crystal system	monoclinic
Space group	P2 ₁ /n (No. 14)
$a(\text{\AA})$	7.7175(10)
$b(\text{\AA})$	17.518(2)
$c(\text{\AA})$	13.7263(19)
$\beta(^{\circ})$	94.270(8)
$V(\text{\AA}^3)$	1850.6(4)
Z	4
$d_x (\text{g cm}^{-3})$	1.423
$F(000)$	832
$\mu(\text{mm}^{-1})$	0.116
Crystal size (mm)	0.6 x 0.3 x 0.3
Radiation (MoK α)	$\lambda = 0.71073 \text{ \AA}$
Temperature (K)	296(2)
θ range ($^{\circ}$)	1.9 - 29.8
hkl range	-7 $\leq h \leq 10$; -23 $\leq k \leq 23$; -19 $\leq l \leq 17$

Reflections	
Collected	34574
Unique (R_{int})	4817 (0.067)
With $I > 2\sigma(I)$	1817
Refinement method	Full-matrix least squares on F^2
Number of parameters	253
$R(F^2) [I > 2\sigma(I)]$	0.1047
$wR(F^2) [I > 2\sigma(I)]$	0.2889
Goodness of fit on F^2	1.05
Max/min $\Delta\rho$ ($\text{e \AA}^{-3}$)	0.43/-0.31

Colorless block crystal of the title compound (0.6x0.3x0.3 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 [24] equipped with MoK α radiation ($\lambda = 0.71073 \text{ \AA}$). The data were corrected for Lorentz, polarization and absorption effects [25]. The structure was solved by direct methods using the SHELXS program [26] and refined by a full-matrix least-squares calculation on F^2 using SHELXL [27]. All H atoms were placed at calculated positions and treated using a riding model, with C-H distances 0.96-0.98 $\text{\AA}$ and $U_{\text{iso}}(\text{H}) = 1.2 U_{\text{eq}}(\text{C})$, N-H 0.86 $\text{\AA}$ and $U_{\text{iso}}(\text{H}) = 1.2 U_{\text{eq}}(\text{N})$. The Cambridge Structural Database (CSD, version 5.39, August 2018) was used for structure analysis (Groom and Allen, 2014).

Table 1 summarizes the crystal data, intensity data collection and refinement details for the title compound. Crystallographic data for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre (CCDC No. 1008422).

Hirshfeld surfaces analysis

Hirshfeld surface defines the contour of shape occupied by a molecule in the crystal structure and is constructed basing on the electron distribution calculated as the sum of spherical atom electron densities (Spackman and Byrom, 1997). Some properties can be plotted on Hirshfeld surface: (i) d_e is the distance from the Hirshfeld surface to the nearest nucleus outside the surface, (ii) d_i is the corresponding distance to the nearest nucleus inside the surface, and (iii) d_{norm} is a normalized contact distance and is the sum of these two (d_i and d_e) normalized by the

van der Waals radii quantities. Where atoms make intermolecular contacts closer than the sum of their van der Waals radii, these contacts will be highlighted in red on the d_{norm} surface. Longer contacts are blue, and contacts around the sum of van der Waals radii are white (McKinnon *et al.*, 2007). 2D fingerprint plots (Spackman and McKinnon, 2002) clearly identify each type of intermolecular interactions. They not only indicate which intermolecular interactions are present, but also the relative area of the surface corresponding to each kind of interaction. The most obvious characteristics of these plots are their pseudo-mirror symmetry about the diagonal where $d_i = d_e$. The pseudo-mirror symmetry of the 2D plots is a direct consequence of the molecule having both donor and acceptor roles in the same intermolecular interaction. Hirshfeld 3D surfaces and the associated 2D fingerprint information were generated using the program CrystalExplorer (version 3.1). All bond lengths to hydrogen were automatically modified to typical standard neutron values (C-H = 1.083 Å, N-H = 1.009 Å and O-H = 0.983 Å). The electrostatic potentials were mapped on the Hirshfeld surfaces using the STO-3G basis set at the level of Hartree-Fock theory over a range of ± 0.075 au.

RESULTS AND DISCUSSION:

Figure 3 shows the molecular structure and the atom-labeling scheme of $\text{MAL}^-:2\text{AP}^+$ (I). Table 1 shows the crystallographic data and structure refinement parameters and Table 2 shows selected geometrical parameters for (I).

This molecular complex (salt) can be described as an ionic ensemble assisted by hydrogen bonds. The asymmetric unit consists of two MAL^- anions acting as semi-carboxylate ions, i.e. semi-malonates and two 2AP^+ cations with positive charges residing on atoms N2 and N4 (Figure 3). The existence of semi-malonate ions is confirmed by checking the differences in the bond distances C1-O1 [1.301(8) Å] and C4-O5 [1.298(8) Å], compared with C1-O2 [1.212(9) Å] and C4-O6 [1.211(9) Å], with oxygen atom O1 and O5 being protonated. The remaining bond distances C3-O3 (C3-O4) and C6-O7 (C6-O8) are similar confirming delocalization of a negative charge on the other extreme of the molecules.

A proton transfer from the carboxyl group of malonic acids to atom N2 and N4 of 2-aminopyridine resulted in the salt formation. This protonation lead to the widening of C7-N2-C11

and C12-N4-C16 angles of the pyridine rings to $122.6(5)^\circ$, compared to $117.6(1)^\circ$ in the unprotonated 2-aminopyridine (Chao *et al.*, 1975). The C-N-C angle of pyridines is very sensitive to protonation. The complete protonation of the aminopyridine heterocycles in (I) is indicated by the enlarged C7-N2-C11 (C12-N4-C16) angles [average $122.6(5)^\circ$] and the reduced N2-C11-C10 (N4-C16-C15) angles [average $118.5(5)^\circ$].

A search in the Cambridge Structural Database (CSD, version 5.39, August 2018) (Groom and Allen, 2014) shows 86 adducts containing 2-aminopyridine with carboxylates. It has been found that there are 56 entries containing malonic acid forming adducts with anilines. Malonic acid exists in a diprotonated form (malonic) in 14 entries, in a monoprotonated form (semi-malonate) in 36 and in the form of a doubly charged anion (malonate) in 6 entries. In the crystal structure of (I) is confirmed the existence of semi-malonate ions.

Figure 3. Asymmetric unit of (I), showing the atomic numbering scheme (displacement ellipsoids are drawn at 25% probability level; H atoms are shown as spheres of arbitrary radii)

The crystalline structure of (I) is stabilized by three pairs of equivalent hydrogen bonds, which involve the carboxyl and amine groups, serving as both acceptors and donors in a set of head-to-tail interactions, as depicted in Figure 4. The geometrical parameters of these hydrogen bonds are summarized in Table 3.

In the crystal packing (Figure 4), the

protonated N1 (N3) and N2 (N4) atoms of 2-aminopyridines are hydrogen-bonded to the carboxylate oxygen atoms O3 (O8) and O4 (O7) via a pair of intermolecular N1---H1A...O3 (N3---H3A...O8) and N2---H2...O4 (N4---H4...O7) hydrogen bonds form rings with graph-set motif $R^2_2(8)$ (Etter, 1990; Etter *et al.*, 1990).

Besides, the protonated N1--H1B and N3--H3B atoms forms new hydrogen bonds N1---H1B...O6 (N3---H3B...O2) originating chains with graph-set $C^2_2(8)$. The $R^2_2(8)$ sets join into zigzag molecular chains along b axis, as depicted in Figure 5.

In addition, atoms O1 (O5) of the carboxyl groups of the hydrogen malonate anions forms intramolecular O1---H1...O3 (O5---H5...O8) hydrogen bond with the O atom of the carboxylate group, with graph-set notation S6, leading to a folded conformation. The crystal structure is further stabilized by four weak C---H...O hydrogen bonds.

Figure 4. A partial packing view (*bc* plane) of (*I*) showing the intermolecular (N--H...O) and intramolecular (O--H...O) hydrogen bonds. Broken lines indicate hydrogen bonds

Figure 5. A portion of the crystal packing of (*I*) in the *ba* plane showing the zigzag molecular chains along *b* axis

In order to visualize the intercontacts in the molecular structure, the Hirshfeld surface analysis was carried out for the title molecule. The Hirshfeld surface of (*I*) mapped over a *d*norm range of -0.5 to 1.5 Å is illustrated in Figure 6. The dominant interaction between the amino hydrogen and carboxylic oxygen atoms in (*I*) can be seen as bright red spots. The *d*norm surfaces plot of (*I*) is consistent with the analysis of the packing patterns as discussed in the X-ray crystal structure analysis.

The combination of *d*_e and *d*_i in the form of two-dimensional fingerprint plot gives the summary of intermolecular contacts in the crystal lattice. The fingerprint plots of the multicomponent 2-aminopyridinium semimalonate (*I*) are shown in Figure 7. It is evident from the fingerprint plots of this compound that O...H (41%) and H...H (33.1%) intercontacts play a central crucial role in the stabilization of molecules in the crystal structure.

Figure 6. Hirshfeld surface mapped with dn_{norm} for (I) visualizing the intercontacts of the molecules

Figure 7. 2D fingerprints for (I)

CONCLUSIONS:

The molecular complex formed between malonic acid and 2-aminopyridine was synthesized and characterized by single-crystal X-ray diffraction. This structure crystallizes in a monoclinic system with space group $P2_1/n$. This molecular complex (salt) can be described as an ionic ensemble assisted by hydrogen bonds. Crystal structure results and Hirshfeld surface analysis shows how the structure of (I) is built up from self-assembly of molecules via $N\cdots H\cdots O$ interactions, and further stabilized by weak $C\cdots H\cdots O$ hydrogen bonds.

This work shows a good example of synthesis and characterization of a co-crystal formed between the pharmaceutical conformer's 2-aminopyridine and malonic acid, which can contribute to the pharmaceutical industry.

ACKNOWLEDGMENTS:

This work was supported by CDCHT-ULA (grant C-1987-17-08-B), FONACIT (grant LAB-97000821) and LOCTI (grant 2007-0003).

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Figure 1. Synthesis of 2-aminopyridinium semi-malonate (I)

Figure 2. a) X-ray powder diffraction patterns for MAL, 2AP and MAL-:2AP+ (I). b) Le Bail fit of the powder diffraction data for (I)

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

C1-O1	1.301(8)	C1-O2	1.212(9)
C3-O3	1.262(7)	C3-O4	1.230(8)
C4-O5	1.298(8)	C4-O6	1.211(9)
C6-O7	1.239(7)	C6-O8	1.258(7)
C11-N1	1.329(7)	C11-N2	1.350(7)
N3-C16	1.333(7)	C16-N4	1.339(7)
C7-N2-C11	122.6(5)	N2-C11-C10	118.4(5)
C12-N4-C16	122.6(5)	N4-C16-C15	118.6(5)
N1-C11-N2	118.8(5)	N3-C16-N4	118.6(5)
O1-C1-C2-C3	3.4(9)	O5-C4-C5-C6	3.0(8)
O2-C1-C2-C3	-176.7(6)	O6-C4-C5-C6	-176.6(6)

Table 3 Hydrogen bonds geometry (Å, °) for (I)

D-H...A	D-H	H...A	D...A	D-H...A	Symmetry codes
N1---H1A...O3	0.86	2.00	2.951(6)	177	(i) $-\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$
N2---H2...O4	0.86	1.80	2.657(6)	171	(i) $-\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$
N1---H1B...O6	0.86	2.00	2.843(7)	166	(ii) $-x, -y, 1-z$
N3---H3A...O8	0.86	2.10	2.953(6)	177	(i) $-\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$
N4---H4...O7	0.86	1.80	2.659(6)	172	(i) $-\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$
N3---H3B...O2	0.86	2.00	2.847(7)	166	(iii) $\frac{1}{2}-x, \frac{1}{2}+y, \frac{1}{2}-z$
C2---H2A...O4	0.97	2.46	3.387(7)	159	(iv) $1-x, -y, -z$
C5---H5A...O7	0.97	2.44	3.370(7)	160	(v) $-x, -y, -z$
C7---H7...O6	0.97	2.58	3.484(8)	163	(iii) $\frac{1}{2}-x, \frac{1}{2}+y, \frac{1}{2}-z$
C12---H91O2	0.97	2.58	3.478(8)	163	(iv) $1-x, -y, -z$
Intramolecular HB	0.97				
O1---H1...O3	0.82	1.71	2.474(6)	155	-
O5---H5...O8	0.82	1.70	2.467(6)	154	-