SÍNTESE E ESTUDO ESTRUTURAL DO CONJUNTO IÔNICO (RS)-ÁCIDO NIPECÓTICO: ÁCIDO OXÁLICO: ÁGUA

SYNTHESIS AND STRUCTURAL STUDY OF THE IONIC ENSEMBLE (RS)-NIPECOTIC ACID: OXALIC ACID: WATER

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RESUMO

Cristais multicomponentes têm sido estudados nos últimos anos a partir dos pontos de vista das aplicações. São particularmente úteis no caso de co-cristais farmacêuticos pois desempenham um papel significativo no desenvolvimento de novos fármacos. Estes materiais são considerados bons alternativos às formulações farmacêuticas existentes, uma vez que podem ajudar a melhorar as propriedades farmacológicas tais como a solubilidade, estabilidade e biodisponibilidade. A difração de raios-X de cristal único foi usada para examinar a natureza das interações não covalentes no cristal multi-componente (RS)-nipecótico: ácido oxálico: água (1: 1: 1). Todas as três entidades são ligadas por interações intermoleculares. Os cristais são ortorrômbicos, grupo espacial *Pbca*, com $a = 11.184(4) \text{ \AA}$, $b = 11.895(4) \text{ \AA}$, $c = 16.781(6) \text{ \AA}$, $V = 2232.4(1) \text{ \AA}^3$, $Z = 8$. Nesta estrutura, um conjunto iônico assistido por ligações de hidrogênio, as moléculas são ligadas por ligações de hidrogênio $O-H \cdots O$ e $N-H \cdots O$, formando cadeias lineares semi - oxalato - semi - oxalato com *R* e *S*nipecóticas intercaladas Moléculas. A combinação destas interações intermoleculares conduz à formação de uma montagem molecular que pode ser descrita como uma bicamada bidimensional.

Palavras-chave: *Co-cristal farmacêutico, cristal multicomponente, estrutura de cristal de raios-X, ligação de hidrogênio*

ABSTRACT

Multi-component crystals have been studied during recent years from the applications points of view. Particularly are useful in the case of pharmaceutical co-crystals due they play a significant role in the development of new drugs. These materials are considered good alternatives to existing pharmaceutical formulations, as they may help to improve pharmacological properties such as solubility, stability and bioavailability. Single-crystal X-ray diffraction was used to examine the nature of non-covalent interactions in the multi-component crystal (RS)-nipecotic: oxalic acid: water (1:1:1). All three entities are linked by intermolecular interactions. The crystals are orthorhombic, space group *Pbca*, with $a = 11.184(4) \text{ \AA}$, $b = 11.895(4) \text{ \AA}$, $c = 16.781(6) \text{ \AA}$, $V = 2232.4(1) \text{ \AA}^3$, $Z = 8$. In this structure, an ionic ensemble assisted by hydrogen bonds, the molecules are linked by hydrogen bonds $O-H \cdots O$ and $N-H \cdots O$, forming linear chains semi - oxalato - semi - oxalato with *R* and *S*nipecotic molecules intercalated. The combination of these intermolecular interactions leads to the formation of a molecular assembly that can be described as a two-dimensional layer.

molecules are connected by O–H···O and N–H···O hydrogen bonds, forming linear semi-oxalate--semi-oxalate chains with intercalated *R* and *S* nipecotic molecules. The combination of these intermolecular interactions leads to the formation of a molecular assembly which can be described as a two-dimensional bilayer-like arrangement.

Keywords: pharmaceutical co-crystal, multicomponent crystal, X-ray crystal structure, hydrogen bonding

INTRODUCTION

Multi-component crystals containing pharmaceutical plays an important 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 (Vishweshwar *et al.*, 2006; Aakeröy *et al.*, 2010; Desiraju, 2013). The main route to obtain good crystalline products, with API, has been the formation of salts, an acid-base reaction between the API and an acidic or basic substance, which is favored by the fact that most pharmaceutical compounds possess either acidic or basic functionality. Functional groups that show a high tendency for multi-component formation include carboxylic acids, amines and amides (Almarsson and Zaworotko, 2004).

In particular, amino acids with oxalic acid form ionic ensembles assisted by hydrogen bonds, in which the oxalic acid exists as semi-oxalate or oxalate (Minkov *et al.*, 2012; Zakharov and Boldyreva, 2013; Braga *et al.*, 2013; Chimpri *et al.*, 2013).

An interesting group of amino acids, from the crystallographic point of view, are the isomers pipercolic, 2-piperidinecarboxylic acid (Bhattacharjee and Chacko, 1979; Stapleton and Tiekink, 2001; Cuervo *et al.*, 2002), nipecotic, 3-piperidinecarboxylic acid (Brehm *et al.*, 1976) and isonipecotic, 4-piperidinecarboxylic acid (Delgado *et al.*, 2001; Mora *et al.*, 2002) acids. They all crystallize as zwitterions. The *ortho* and *meta* isomers have a chiral center, and two stereoisomers *R* and *S* are present in the racemic mixtures. These amino acids compounds are an active pharmaceutical ingredient (API) classified as generally regarded as safe (GRAS) and approved by the food and drug administration (FDA) (Stahl and Wermuth, 2002).

The *meta*-substituted isomer, (*RS*)-nipecotic acid, is used as a drug intermediate and in the synthesis of γ -aminobutyric acid (GABA) uptake inhibitors (Muralidhar *et al.*, 1994). For its

part, oxalic acid is a strong dicarboxylic acid capable of generating infinite anionic aggregates through the complementary hydrogen-bond functionalities of the carbonyl groups (Derissen and Smith, 1974).

In recent years, we have been interested in a systematic study of multi-component crystals containing amino acids, amines, amides and carboxylic acids (Belandria *et al.*, 2012; Mora *et al.*, 2013; Delgado *et al.*, 2015), and the present paper reports the crystal structure of the ionic ensemble formed between (*RS*)-nipecotic acid, oxalic acid and water.

MATERIALS AND METHODS

Synthesis

The multi-component crystal (see Scheme 1) was prepared as follows: equimolar quantities of (*RS*)-nipecotic acid (0.1 mmol, Aldrich, 98%) and oxalic acid (0.1 mmol, Aldrich, 99%) were pulverized in an agatha mortar with a pestle and dissolved in 10 mL of water. The mixture was placed in a reflux system for three hours at a constant temperature of 70 °C. Colorless crystals of suitable size for X-ray diffraction experiments were obtained by the slow evaporation during two months of the reflux solution. Melting point 225–226 °C.

Scheme 1. Synthesis of the multi-component (I).

Fourier transform infrared spectroscopy

The FT-IR absorption spectrum was obtained as KBr pellet using a Perkin-Elmer 1600 spectrometer. FT-IR; [3420 cm⁻¹ t, OH (acid group)], 3240 cm⁻¹ [t, OH (crystallization water)], 1728 cm⁻¹ [t, C=O (acid group from (*RS*)-

nipecotic and oxalic acid)], 2602 cm^{-1} , [t, N-H (amino group of (RS)-nipecotic acid)].

Thermogravimetric Analysis

Thermogravimetric analysis (TGA) of (I) was performed in a Perkin-Elmer TGA-7 thermobalance. A sample of 5.1 mg of the multi-component was placed in an aluminum pan and heated from 25 to 300°C at a rate of $0.04^\circ\text{C min}^{-1}$, under nitrogen flux of 50 mL min^{-1} . The TGA of (I) showed two transitions. The first one is associated with the exit of the water molecule from the crystal lattice at 101°C . The second transition at 227°C results from melting and decomposition of (I).

Powder X-ray diffraction

The X-ray powder diffraction patterns for (RS)-nipecotic acid, oxalic acid and formed salt (I) were collected at room temperature in a Phillips PW-1250 goniometer using monochromatized $\text{CuK}\alpha$ 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 – $65^\circ 2\theta$, with a step size of 0.02° and counting time of 10 s. Silicon was used as an external standard. X-ray powder patterns showed in Figure 1 pieces of evidence the formation of a new compound.

Figure 1. X-ray powder diffraction patterns for (RS)-nipecotic acid, Oxalic acid and Salt (I)

Single-crystal X-ray diffraction

Colorless block crystal of the title compound with dimensions $0.4 \times 0.2 \times 0.1\text{ mm}$ was used for data collection. Diffraction data were

collected at 298 K by ω -scan technique on a Rigaku AFC7 Mercury diffractometer equipped with $\text{MoK}\alpha$ radiation ($\lambda = 0.71073\text{ \AA}$). The data were corrected for Lorentz-polarization and absorption effects. The structure was solved by direct methods using the SHELXS program (Sheldrick, 2008) and refined by a fullmatrixleast-squares calculation on F^2 using SHELXL (Sheldrick, 2015). All H-atoms were placed in calculated positions and treated using the riding model, with C-H distances of 0.97 – $0.98\text{ \AA}$, N-H distances of $0.86\text{ \AA}$ and O-H distances of $0.82\text{ \AA}$. The Uiso (H) parameters were fixed at 1.2 Ueq (C, N, O). The hydrogen atoms of the crystallization water molecule were localized in a difference Fourier map and refined isotropically in an independent manner. Table 1 displays the crystallographic data and the structure refinement parameters. Crystallographic data for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre, CCDC No. 892976 (CSD, 2016).

RESULTS AND DISCUSSION:

In the asymmetric unit of the title salt (I) (see Figure 2) there are three components: one (RS)-nipecotic cation ($\text{C}_6\text{H}_{10}\text{O}_2\text{NH}_2^+$), one semi-oxalate anion (HC_2O_4^-), and one molecule of water (H_2O). Table 2 shows bond lengths, bond angles and torsion angles for (I).

Figure 2. Asymmetric unit of Salt (I), showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 25% probability level

A search in the Cambridge Structural Database, version 5.37, May 2016 (CSD, 2016) shows only 5 structures with the nipecotic moiety. In the single molecule nipecotic is a zwitterionic amino acid with the carboxylate group in an equatorial position (Brehm *et al.*, 1976). A similar zwitterionic conformation has been found in its

hydrogen-bonded crystals with *p*-hydroxybenzoic acid (Dega-Szafran *et al.*, 2007) and *m*-hydroxy benzoic acid, salicylic acid (Bartoszak-Adamska, *et al.*, 2009). However, in the multi-component crystal of nipecotic acid with hydrochloric (Narasegowda *et al.*, 2005) and tartaric acids (Bartoszak-Adamska *et al.*, 2011) the nipecotic acid are protonated to form salts. All these structures are dehydrated.

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

CCDC	No. 892976
Chemical formula	C ₆ H ₁₂ NO ₂ ·C ₂ HO ₄ ·H ₂ O
Formula weight	237.21
Crystal system	Orthorhombic
Space group	Pbca
<i>a</i> (Å)	11.184(4)
<i>b</i> (Å)	11.895(4)
<i>c</i> (Å)	16.781(6)
<i>V</i> (Å ³)	2232.4(1)
<i>Z</i>	8
<i>d_x</i> (g cm ⁻³)	1.412
<i>F</i> (000)	1008
<i>μ</i> (mm ⁻¹)	0.125
<i>θ</i> range (°)	2.4-27.6
<i>hkl</i> range	-13 ≤ <i>h</i> ≤ 14 -13 ≤ <i>k</i> ≤ 13 -21 ≤ <i>l</i> ≤ 21
Reflections	
Collected	23407
Unique (<i>R</i> _{int})	2318 (0.053)
With <i>I</i> > 2σ(<i>I</i>)	1634
Refinement method	Full-matrix on <i>F</i> ²
Number of parameters	153
<i>R</i> (<i>F</i> ²) [<i>I</i> > 2σ(<i>I</i>)]	0.071
<i>wR</i> (<i>F</i> ²) [<i>I</i> > 2σ(<i>I</i>)]	0.180
Goodness of fit on <i>F</i> ²	1.16
Max/min Δρ (e Å ⁻³)	0.36/-0.22

The piperidinium ring in both nipecotinium cations (*R* and *S*) has a chair conformation with the carboxylic group in the equatorial position. The carboxylic O-H group has a *cis* orientation. The C1-O1 bond length of 1.292(4) Å suggests the protonation side at the O1 atom.

The semi-oxalate moiety is confirmed by the C-O distances: C7-O3 and C7-O4 are 1.298(3) and 1.212(3) Å, respectively, while for the oxalate ion C8-O5 and C8-O6 are 1.223(3) and 1.268(3) Å, respectively. The semi-oxalate anion has a planar conformation, with torsion angles O3-C7-C8-O5 -1.7(4)° and O4-C7-C8-O6

-1.1(4)°. A search in the CSD database (CSD, 2016) showed 94 structures with the semi-oxalate almost planar with torsion angles close to 0,0°. Table 3 shows the geometry of the hydrogen bonds in the multi-component salt (**I**). Figure 3 shows how the semi-oxalate moieties interact with each other through an O3--H3...O6 (-½+x, y, ½-z) hydrogen bond (see Table 3), forming semi-oxalate--semi-oxalate chains described by the graph-set C(5) (Etter, 1990).

Figure 3. Catameric coiled chains of oxalate molecules link by hydrogen bonds of the type O3--H3...O6.

Figures 4 and 5 shows the various hydrogen bonds involved in the construction of one layer between the semi-oxalate chains, with intercalated *R* and *S* nipecotic molecules. Semi-oxalate anions interact with the water molecule through O7--H7A...O4 and O7--H7B...O5, forming by combination with N1--H1A...O5 and N1--H1B...O4 interactions, a ring with graph-set *R*²₄(8). Semi-oxalate anions also interact with the NH₂⁺ group of nipecotic molecules forming two bifurcated hydrogen bonds. For its part, -COOH group of the amino acid forms a hydrogen bond with the water molecule through O1--H1...O7. All these interactions form a packing made up of a chain of edge-fused rings with graph-set notation *R*²₁(5)-*R*²₄(8)-*R*⁵₅ (Etter, 1990).

From a supramolecular point of view, the combination of these intermolecular interactions leads to the formation of a molecular assembly which can be described as a two-dimensional bilayer-like arrangement, parallel to *ca* plane (see Figure 5). The multi-component salt (**I**) packs in a bi-dimensional structure, with ribbed sheets running parallel to (010) plane, with the layers being separated by hydrophobic interactions at *c*/2 (see Figure 3).

Figure 4. View of one of the ribbed sheets layers running in the *ba* plane, showing the alternating chains of *R* and *S* nipecotic acid and semi-oxalate anions. H atoms not involved in hydrogen bonding have been omitted for clarity

Figure 5. View of the two-dimensional crystal packing of (I) in the *ca* plane, showing the ribbed sheets separated by hydrophobic interactions.

CONCLUSIONS:

The formation of multi-component crystals have been studied during recent years from the applications points of view, and are particularly useful in the case of pharmaceutical co-crystals. In particular, the multi-component salt formed by (*RS*)-nipecotic acid, oxalic acid and water was synthesized and structurally characterized. This compound (I) crystallizes in the *Pbca* orthorhombic space group and consists of an ionic ensemble assisted by hydrogen bonds. The combination of the intermolecular interactions in the crystal leads to the formation of a molecular assembly which can be described as a two-dimensional bilayer-like arrangement.

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

C1-O1	1.292(4)	C1-O2	1.204(4)
C7-O3	1.298(3)	C7-O4	1.212(3)
C8-O5	1.223(3)	C8-O6	1.268(3)
C5-N5	1491(4)	C6-N1	1.478(3)
O1-C1-O2	124.6(3)	C5-N1-C6	112.6(2)
O3-C7-C8-O5	-1.7(4)	O4-C7-C8-O6	-1.1(4)

Table 3 Hydrogen bonds geometry (Å, °)

D--H...A	D—H	H...A	D...A	D--H...A
O1--H1...O7	0.82	1.84	2.657(3)	175
N1--H1A...O3 ⁽ⁱ⁾	0.90	2.20	3.024(3)	151
N1--H1A...O5 ⁽ⁱ⁾	0.90	2.15	2.841(3)	133
N1--H1B...O4 ⁽ⁱⁱ⁾	0.90	2.16	2.976(3)	151
N1--H1B...O6 ⁽ⁱⁱ⁾	0.90	2.24	2.921(3)	132
O3--H3...O6 ⁽ⁱⁱⁱ⁾	0.82	1.69	2.461(3)	157
O7--H7A...O4 ^(iv)	0.82(6)	2.27(6)	2.927(4)	137(5)
O7--H7B...O5 ⁽ⁱⁱⁱ⁾	0.89(6)	1.91(6)	2.796(4)	176(6)

Symmetry codes: ⁽ⁱ⁾ 1/2+x,y,1/2-z, ⁽ⁱⁱ⁾ 1/2-x,1/2+y,z ⁽ⁱⁱⁱ⁾ -1/2+x,y,1/2-z ^(iv) -1/2-x,1/2+y,z.