SÍNTESE E CARACTERIZAÇÃO ESTRUTURAL DO SAL DE TRANSFERENCIA DE PROTON DE ÁCIDO MALÔNICO 1:1 COM *P*-CLOROANILINA

SYNTHESIS AND STRUCTURAL CHARACTERIZATION OF THE 1:1 PROTON TRANSFER SALT OF MALONIC ACID WITH *P*-CHLOROANILINE

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RESUMO

O design de cristais multicomponentes oferece um meio para modificar as propriedades físico-químicas dos cristais sem alterar as propriedades químicas de uma molécula particular. Neste estudo, um cristal multicomponente, o sal de ácido malônico com *p*-cloroanilina, foi sintetizado e estruturalmente caracterizado. O referido composto foi preparado por moagem em gral de ágata e sua estrutura foi estudada pelo pó e por difração de raios-X de um cristal individual. Este composto cristaliza no sistema monoclinico com o grupo espacial $P2_1/c$, $Z = 4$ e parâmetros da célula unitária $a = 12.9776(7)\text{\AA}$, $b = 9.2308(5)\text{\AA}$, $c = 8.5170(5)\text{\AA}$, $\beta = 93.474(3)^\circ$. O composto multicomponente, semi-malonato de *p*-cloroanilínio, pode ser descrito como um conjunto iônico assistido por ligações de hidrogênio estabelecidas entre cátions de *p*-cloroanilínio e ânions de semi-malonato. A estrutura molecular e a embalagem de cristal são estabilizadas principalmente por interações intermoleculares $O-H \cdots O$ e $N-H \cdots O$ de ligações de hidrogênio. As moléculas formam uma montagem supramolecular com uma rede tridimensional ligada ao hidrogênio ao longo do plano *ca*.

Palavras-chave: Cristal multicomponente, cristalografia de raios-X, ligação de hidrogênio

ABSTRACT

The design of multicomponent crystals offers a means to modify the physicochemical properties of crystals without altering the chemical properties of a particular molecule. In this study, a multicomponent crystal, the salt of malonic acid with *p*-chloroaniline, was synthesized and structurally characterized. The title compound was prepared by grinding in an agate mortar, and its structure was studied by powder and single-crystal X-ray diffraction. This compound crystallize in the monoclinic system with space group $P2_1/c$, $Z=4$, and unit cell parameters $a = 12.9776(7)\text{\AA}$, $b = 9.2308(5)\text{\AA}$, $c = 8.5170(5)\text{\AA}$, $\beta = 93.474(3)^\circ$. The multicomponent compound, *p*-chloroanilinium semi-malonate, can be described as an ionic ensemble assisted by hydrogen bonds established between *p*-chloroanilinium cations and semi-malonate anions. The molecular structure and crystal packing are stabilized mainly by intermolecular $O-H \cdots O$ and $N-H \cdots O$ hydrogen bonds interactions. The molecules construct a supramolecular assembly with a two-dimensional hydrogen bonded network along the *ca* plane.

Keywords: Multicomponent crystal, X-ray crystal structure, hydrogen bonding

INTRODUCTION

The design of multicomponent crystals provides a means to modify physicochemical properties of crystals without changing the chemical properties of the molecule of interest. This is particularly useful in the case of pharmaceutical co-crystals, which 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 (Desiraju, 2003; Aakeröy and Salmon, 2005; Vishweshwar *et al.*, 2006; (Grothe *et al.*, 2016).

The main route to obtain good crystalline products has been the formation of salts, favored by the fact that most pharmaceutical compounds possess either acidic or basic functionality (Stahl and Wermuth, 2002).

One of the most important reactions in chemistry and biochemistry is proton transfer between donor and acceptor (Deechongkit *et al.*, 2004). These interactions are playing an important role in various chemical and biological processes such as stabilizing the biomolecular structures, controlling the speed of the enzymatic reactions and constructing supramolecular structures (Parker *et al.*, 2006).

Two good candidates for the pharmaceutical co-crystal formation are the aniline derivative compounds and the dicarboxylic acids, due to their interesting hydrogen-bonding interactions. Aniline derivatives have wide applications in dyes and pigments, agricultural chemicals and pharmaceuticals (Rappoport, 2007). Dicarboxylic acids, one of the important API compounds, possessing very good donors and acceptors are of special interest in forming strong intermolecular hydrogen bonds between cations, anions or molecular constituents when they form salts or cocrystals with amines and amides (Remenar *et al.*, 2003).

From the interest in studying the formation of multicomponent crystals containing amino acids, amines, amides and carboxylic acids (Belandria *et al.*, 2012; Mora *et al.*, 2013; Delgado *et al.*, 2015), we report here the structure of the ionic ensemble formed between malonic acid (MAL) and *p*-chloroaniline (PCA), and its hydrogen-bonding patterns analysis.

MATERIALS AND METHODS

Synthesis

The multicomponent compound was prepared by mixing malonic acid and *p*-chloroaniline in a 1:1 molar ratio (Scheme 1). 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.

X-ray powder diffraction

The X-ray powder diffraction patterns for malonic acid (MAL), *p*-chloroaniline (PCA) and *p*-chloroanilinium semi-malonate (MAL⁻:PCA⁺) were collected at room temperature in a Phillips PW-1250 goniometer using monochromatized 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 showed in Figure 1 evidences the formation of a new compound.

Figure 1. X-ray powder diffraction patterns for pure MAL, pure PCA and MAL⁻:PCA⁺ (**I**)

X-ray single-crystal crystallography

Colorless block crystal of the title compound with dimensions 0.6×0.2×0.2 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, 2009) equipped with MoK α radiation ($\lambda = 0.71073 \text{ \AA}$). The data were corrected for Lorentz-polarization and absorption effects (Bruker, 2010). The structure was solved by direct methods using the SHELXS program (Sheldrick, 2008) and refined by a full-matrix least-squares calculation on F^2 using SHELXL (Sheldrick, 2015). All H atoms were placed at 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 1.2Ueq (C, N, O). Crystallographic data for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre (CCDC No.1008424).

RESULTS AND DISCUSSION:

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

A search in the Cambridge Structural Database (version 5.37, May 2016) (Groom and Allen, 2014) shows 56 adducts containing malonic acid with anilines, and malonic acid exists in a diprotonated form (malonic) in 14 entries, in a monoprotinated form (semi-malonate) in 36 and in the form of a doubly charged anion (malonate) in 6 entries. Meanwhile, there are 13 structures containing *p*-chloroaniline adducts with carboxylates molecules, all of which are salts.

Figure 2. 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

In this work, the multicomponent compound MAL $^-$:PCA $^+$ can be classified as a salt. A proton transfer from malonic acid to the aniline N atom occurred, resulting in the formation of a salt. The asymmetric unit consists of one MAL $^-$ anion acting as a semi-malonate ion and one PCA $^+$ *p*-chloroanilinium cation with a positive charge residing on atom N1. The existence of a semi-malonate ion is confirmed by checking the differences in the bond distances C1-O1 (1.304 $\text{\AA}$) and C1-O2 (1.221 $\text{\AA}$), with oxygen atom O1 being protonated. The remaining bond distances C3-O3 (1.246 $\text{\AA}$) and C3-O (1.265 $\text{\AA}$) are similar confirming delocalization of a negative charge on the other extreme of the molecule. On the other hand, the amino group is positively charged as it has three hydrogen atoms linked to the nitrogen atom N1. This salt can be described as an ionic ensemble assisted by hydrogen bonds.

The mean planes of the carboxylate and carboxyl groups of the semi-malonate anion form a dihedral of $67.43(8)^\circ$, in contrast to the molecule alone which is almost perpendicular with $85.34(7)^\circ$ (Jagannathan *et al.*, 1994). In contrast to the single molecule where it forms The molecular structure and crystal packing are stabilized mainly by five intermolecular interactions; one O $\cdots$ H $\cdots$ O and four N $\cdots$ H $\cdots$ O hydrogen bonds. One intramolecular interaction N $\cdots$ H $\cdots$ O hold together both semi-malonate and *p*-chloroanilinium molecules (Table 3). All these interactions are shown in Figure 3.

Figure 3. A portion of the crystal packing shows all, O $\cdots$ H $\cdots$ O and N $\cdots$ H $\cdots$ O, intermolecular and intramolecular hydrogen bonds formed in MAL $^-$:PCA $^+$

The MAL $^-$ molecules interact with each other by means of hydrogen bonds of the type O1 $\cdots$ H1 $\cdots$ O4 ($-x, \frac{1}{2}+y, -\frac{1}{2}-z$), forming linear $\cdots$ semi-malonate $\cdots$ semi-malonate $\cdots$ chains extending along the *b* axis which can be described by the graph-set motif C(6) (Etter, 1990). Figure 4 shows the homomeric packing of the semi-

malonate anions.

On the other hand, Figure 5 shows how the homomeric *p*-chloroanilinium cations PCA^+ , form discrete molecules packing in the *bc* plane. The combinations of all interactions produce an bi-dimensional hydrogen bond network as shown in Figure 6.

Figure 4. Packing of the homomeric MAL^- molecules shows the chain structures with graph-set motif C(6) in the *bc* plane

Figure 5. Packing of the homomeric PCA^+ interactions shows the discrete molecules in the *bc* plane

Figure 6. Packing of the two-dimensional hydrogen bond network in $\text{MAL}^-:\text{PCA}^+$ (I)

CONCLUSIONS:

The proton transfer salt *p*-chloroanilinium semi-malonate ($\text{MAL}^-:\text{PCA}^+$) was synthesized and characterized by X-ray diffraction techniques. Single-crystal XRD was carried out to characterize the structure, showing that the crystal belongs to the monoclinic system. The structure of (I) is built up from self-assembly of molecules via $\text{O} \cdots \text{H} \cdots \text{O}$ and $\text{N} \cdots \text{H} \cdots \text{O}$ interactions, forming a two-dimensional network.

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

Chemical formula	C ₃ H ₃ O ₄ ⁻ ·C ₆ H ₇ ClN ⁺	CCDC	1008424
Formula weight	231.63	Radiation (MoK α)	λ = 0.71073 Å
Crystal system	Monoclinic	θ range (°)	1.6–31.6
Space group	P2 ₁ /c	hkl range	-18 $\leq$ h $\leq$ 19; -13 $\leq$ k $\leq$ 13; -12 $\leq$ l $\leq$ 12
a(Å)	12.9776(7)	Reflections	
b(Å)	9.2308(5)	Collected	31523
c(Å)	8.5170(5)	Unique (Rint)	3397 (0.025)
β (°)	93.474(3)	With I > 2 σ (I)	2811
V(Å ³)	1018.4(1)	Refinement method	Full-matrix least-squares on F ²
Z	4	Number of parameters	138
dx (g cm ⁻³)	1.511	R(F ²) [I > 2 σ (I)]	0.0467
F(000)	480	wR(F ²) [I > 2 σ (I)]	0.1561
μ (mm ⁻¹)	0.119	Goodness of fit on F ²	1.02
Crystal size (mm)	0.60 x 0.18 x 0.17	Max/min $\Delta\rho$ (e Å ⁻³)	0.44/-0.55

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

C1-O1	1.304(2)	C1-O2	1.221(2)
C3-O3	1.246(2)	C3-O4	1.265(2)
C1-C2	1.504(2)	C2-C3	1.527(2)
C7-N1	1.455(2)	C4-Cl1	1.739(2)
C1-C2-C3	115.2(1)	C6-C7-N1	119.2(1)
C5-C4-Cl1	119.7(1)	C8-C4-Cl1	119.0(1)

Table 3 Hydrogen bonds geometry (Å, °)

D-H...A	D-H	H...A	D...A	D-H...A	Symmetry codes
O1---H1...O4 ⁽ⁱ⁾	0.820	1.720	2.534(1)	179.0	⁽ⁱ⁾ -x, 1/2+y, -1/2-z
N1---H1A...O1 ⁽ⁱⁱ⁾	0.768(9)	2.316(5)	2.8768(16)	130.7(5)	⁽ⁱⁱ⁾ -x, 2-y, -z
N1---H1B...O4 ⁽ⁱⁱ⁾	0.768(7)	2.482(7)	2.9790(16)	123.9(6)	⁽ⁱⁱ⁾ -x, 2-y, -z
N1---H1A...O3 ⁽ⁱⁱⁱ⁾	0.768(9)	2.192(7)	2.7660(16)	132.0(2)	⁽ⁱⁱⁱ⁾ x, 3/2-y, 1/2+z
N1---H1C...O2 ^(iv)	0.768(11)	2.312(5)	2.7891(16)	121.3(7)	^(iv) x, 5/2-y, 1/2+z
Intramolecular HB					
N1--H1B...O3	0.768(7)	2.358(7)	2.9696(17)	137.4(6)	-

Scheme 1. Synthesis of *p*-chloroanilinium semi-malonate (MAL⁻:PCA⁺)