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Multicomponent Crystalline Solid Forms of Pyridinecarboxamides and DL-2-Hydroxy-2-phenylacetic Acid †

Alfonso Castiñeiras, Isabel García-Santos * and Rocío Torres-Iglesias

Department of Inorganic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain; alfonso.castineiras@usc.es (A.C.); tir.gontade@gmail.com (R.T.-I.)

* Correspondence: isabel.garcia@usc.es; Tel.: +34-881-814-956

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Abstract: We have prepared co-crystals of racemic DL-2-Hydroxy-2-phenylacetic acid (DL-Mandelic acid, **DL-H_2ma**) with achiral 2-Pyridinecarboxamide (picolinamide, **pic**), 3-Pyridinecarboxamide (nicotinamide, **nam**), and 4-Pyridinecarboxamide (isonicotinamide, **inam**); they have been characterized by elemental analysis, single crystal and powder X-ray, IR spectroscopy and ^{1}H and ^{13}C NMR. The crystal packing is stabilized primarily by hydrogen bonding and, in some cases, through π–π stacking interactions. The analysis of crystal structures reveals the existence of the characteristic heterosynthons with the binding motif $R_2^2(8)$ (primary amide-carboxilic acid) between pyridinecarboxamide molecules and the acid. Other synthons involve hydrogen bonds such as (carboxyl)O-H···N(pyridine) and (hydroxyl)O-H···N(pyridine).

Keywords: pyridinecarboxamides; cocrystals; mandelic acid

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1. Introduction

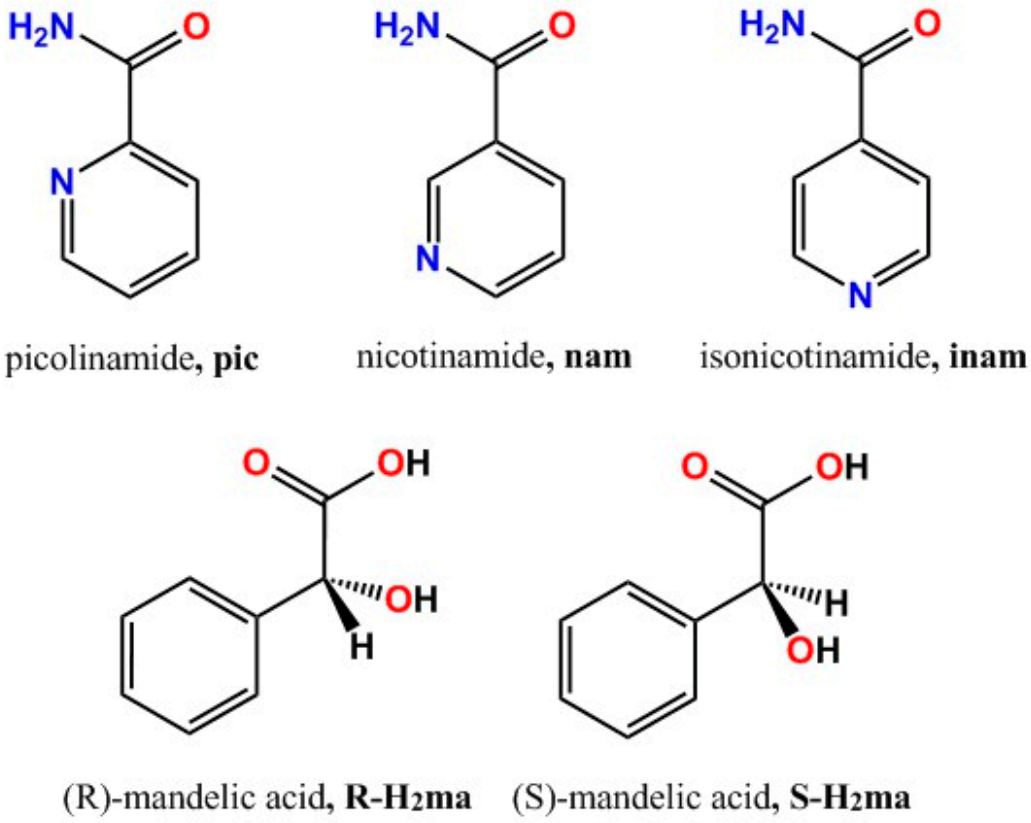
Crystal engineering is the rational design of functional molecular solids from neutral or ionic building blocks, using intermolecular interactions in the design strategy [1]. This field has its origins in organic chemistry and in physical chemistry. The recent development of crystal engineering as a research field has progressed alongside a significant interest in the origin and nature of intermolecular interactions and their use in the design and preparation of new crystalline structures [2].

Over the last decade, the concept of crystal and mostly co-crystal engineering has become increasingly interesting for both academic and industrial pharmaceutical researchers [3]. The main reason for this is its ability to enhance the physicochemical and biopharmaceutical properties of active pharmaceutical ingredients, without altering their chemical structure and, thus, maintaining their therapeutic activity. With new guidelines from the United States Food and Drug Administration and the European Medicines Agency regulating co-crystals, the development of pharmaceutical co-crystals has gained considerable momentum [4].

In order to prepare cocrystals, a supramolecular synthesis is used, in particular the design of homo and supramolecular heterosynthons is one of the most exploited. Although the preparation of cocrystals is not complex, the selection of the solvent can be critical to obtain a particular crystal phase of cocrystal. The role of the solvent in the nucleation of crystals and cocrystals is still far from completely understood.

The three isomers of pyridinecarboxamide—2-pyridine carboxamide or picolinamide (**pic**), 3-pyridinecarboxamide or nicotinamide (**nam**) and 4-pyridinecarboxamide or isonicotinamide (**inam**) (Scheme 1)—are a class of medicinal agents that can be classified as GRAS (generally regarded as safe) compounds. Nicotinamide and isonicotinamide are popular co-crystal formers, **nam** is vitamin B3 and, therefore, of pharmaceutical relevance [5], whilst Isonicotinamide is one of the most effectively used cocrystallizing compounds [6], as

the pyridine N atom of the isonicotinamide molecule readily acts as a hydrogen bond acceptor when faced with good hydrogen bond donors, such as carboxylic acids and alcohols [7]. In fact, the carboxylic acid···pyridine hydrogen bond has been identified as a robust yet versatile hydrogen bond and persists even in the presence of other good donors [8]. Cocrystals of picolinamide are rarely seen in the literature, despite being a structural isomer of **nam** and **inam**, and a strong inhibitor of poly(ADP-ribose)synthetase [9] and showing important biological activity with a coenzyme called NAD (nicotinamide adenine dinucleotide), which plays important roles in more than 200 amino acid and carbohydrate metabolic reactions [10]. Apart from pharmaceutical value, in general, pyridinecarboxamides are excellent cocrystallizing compounds. The amide group features two hydrogen bond donors and two lone pairs on the carbonyl O atom. A second hydrogen bond acceptor is the lone pair on the N atom of the pyridine ring. Consequently, these molecules are very versatile for a variety of hydrogen bonding interactions, especially in pharmaceutical cocrystals [11].



Scheme 1. Chemical diagram of H_2ma and the pyridinecarboxamide isomers.

DL-Mandelic acid (Scheme 1) is a useful precursor to various drugs, for example homatropine and cyclandelate, which are esters of mandelic acid, and it is also known to have antibacterial properties [12]. Generally, the profile of **DL-H$_2$ma** allows us to regard this compound as an excellent co-former for cocrystals with the aforementioned carboxamides. Indeed, given that **DL-H$_2$ma** is a substituted carboxylic acid containing a hydroxyl group on the adjacent carbon, it also possesses a set of sites capable of hydrogen bonding, both donor and acceptor in nature.

In light of these considerations, the main objective of this work is the design, preparation, and characterization of the physicochemical properties, and the identification of recurrent supramolecular patterns, within a new set of multicomponent pharmaceutical crystals that involve the three isomers of pyridinecarboxamide with DL-mandelic acid as co-former (Scheme 1).

2. Materials and Methods

DL-Mandelic acid and the pyridinecarboxamide isomers were purchased from Sigma-Aldrich. Commercially available solvents were used as received without further purification. Compounds were prepared by co-crystallization via solvent-drop grinding: Stoichiometric amounts of H_2ma with pic, nam, or inam were ground with a mortar and pestle for ca. 5–7 **min** with the addition of 10 μL of solvent per 50 mg of co-crystal formers. The resulting solutions were left to evaporate slowly under ambient conditions. The single crystals of pic-D-H_2ma, nam-L-H_2ma, and inam-L-H_2ma, suitable for X-ray diffraction studies, were obtained in 2–15 days from Ethyl acetate. Microanalyses (C, H, and N) were carried out using a Carlo-Erba 1108 elemental analyser. FT-IR spectra were recorded from KBr pellets over the range 4000–400 cm^{-1} on a Bruker IFS-66v spectrometer. For X-ray analysis, intensity data were collected at 100 K on a Bruker X8 KappaAPEXII diffractometer. Structures were solved by direct methods followed by difference Fourier calculations and were refined by a full-matrix least-squares procedure using SHELXLTL. The structures were deposited at the Cambridge Crystallographic Data Centre with CCDC Nos. 2072590–2072591.

3. Results and Discussion

The three crystals were obtained from the crystallization of solutions prepared by reacting the pyridinecarboxamide isomers with DL-mandelic acid in a molar ratio 1:1. Although the X-ray diffraction data were taken at 100 K, solid handling was always done at room temperature.

The co-crystallization processes have been carried out considering the pK_a of the mandelic acid and the pyridincarboxamide isomers as co-formers, with pK_a values of 3.85 (**DL-H_2ma**), based on the carboxylic group [13], 2.10 (**pic**), 3.35 (**nam**), and 3.61 (**inam**), based on pyridine nitrogen [14]. These compounds have been chosen to evaluate the degree of acid proton transfer to the co-formers, according to the ΔpK_a rule, which can contribute to the study of the sal/co-crystal continuum and provide information related to the ability to predict and control synthesis of co-crystals that contain mandelic acid [15]. According to this rule, it is generally accepted that a salt is formed when the value of ΔpK_a is greater than 3, while a value of ΔpK_a less than 0 should lead to the formation of co-crystals [16]. The values of ΔpK_a [pK_a (protonated base)-pK_a(acid)] calculated for **pic**, **nam**, and **inam** are −1.75, −0.50, and −0.24, respectively, so the formation of co-crystals is expected.

Crystal Structure Analysis

Co-crystallization of **DL-H_2ma** and **pic** in a 1:1 molar ratio from ethyl acetate produced plate-shaped lorless crystals that belonged to a 1:1 co-crystal, a new polymorph that differs from the one known with a 2:2 **pic-D-H_2ma** ratio. [17]. The crystal structure was solved in the monoclinic space group $P2_1/n$ with unit cell dimensions of a = 5.4240(3) Å, b = 26.1177(14) Å, c = 9.3622(5) Å, β = 104.715(2)°, and V = 1282.77(12) $Å^3$. The crystallographic asymmetric unit consists of one molecule each of **D-H_2ma** and **pic** (Figure 1a). The crystal structure features an acid–amide heterosynthon between **D-H_2ma** and **pic** involving O–H···O (2.547 Å, 168.3°) and N–H···O (2.929 Å, 166.6°) hydrogen bonds. The *anti*-N–H of the pic forms an N–H···O (2.947 Å, 126.3°) hydrogen bond with the same carboxylic oxygen atom and the hydroxyl O–H of the **D-H_2ma** forms an O–H···N (3.071 Å, 139.9°) hydrogen bond with the adjacent pyridine N of the **pic**, thus generating a four-component supramolecular unit that consists of each two molecules of **D-H_2ma** and **pic** (Figure 1b).

From the co-crystallization of **DL-H_2ma** and **nam**, a remarkable number of structures of different stoichiometries are known, in ratios 1:1, 2:1, 2:2, and 1:4 [18]. In this laboratory, the same **nam-D-H_2ma** (1:1) cocrystal was prepared by crystallization from ethyl acetate. Crystal structure analysis revealed that the co-crystal belongs to the monoclinic, $P2_1$ space group with one molecule each of **D-H_2ma** and **nam** in the crystallographic asymmetric unit (Figure 2a). The crystal structure features a hetero-synthon between the α-hydroxyl carbonyl group of **D-H_2ma** and the amide group of **nam** involving O–H···O (2.708 Å,

143.3°) and N–H···O (3.002 Å, 155.4°). These hetero-dimers are further joined by hydrogen bonds through O–H carboxylic acid and the pyridine N atom (2.684 Å, 175.0°), and the amide *anti*-N–H and hydroxyl O atom N–H···O (2.949 Å, 141.7°) to originate a new four-component supramolecular unit that is repeated along infinite ribbons (Figure 2b).

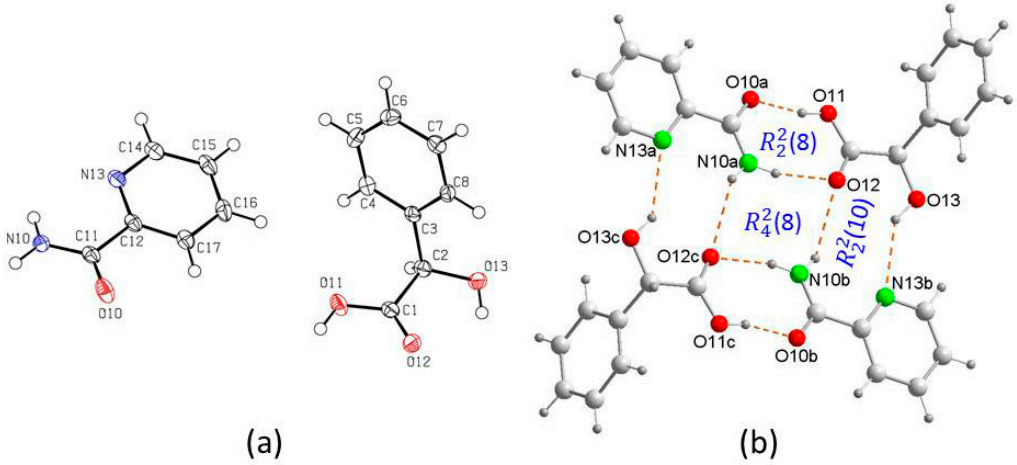


Figure 1. (**a**) Asymmetric unit of **pic-D-H$_2$ma** and (**b**) four-membered supramolecular unit in the crystal structure of **pic-D-H$_2$ma** (1:1) co-crystal.

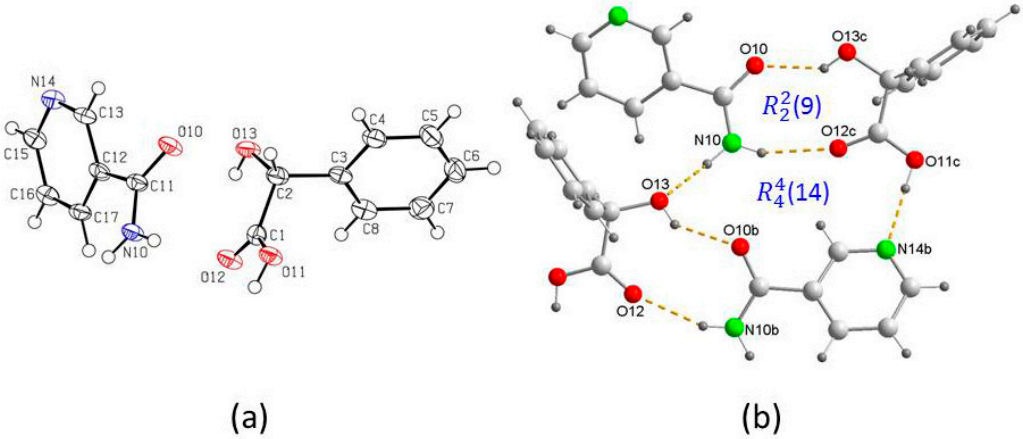


Figure 2. (**a**) Asymmetric unit of **nam-D-H$_2$ma** and (**b**) four-membered supramolecular unit in the crystal structure of the **nam-D-H$_2$ma** (1:1) co-crystal.

New 1:1 co-crystals of **DL-H$_2$ma** with **inam**, which is another positional isomer of pic, have also been prepared by crystallization in ethyl acetate, also previously prepared in warm ethanol [6]. Crystal structures revealed that the co-crystal belongs to the monoclinic, $P2_1/c$ space group with unit cell dimensions of a = 5.2201(8) Å, b = 27.662(4) Å, c = 9.1862(15) Å, β = 99.935(10)° and V = 1303.6(4) Å^3 with one molecule each of **L-H$_2$ma** and **inam** in the crystallographic asymmetric unit (Figure 3a). In the crystal structure, **L-H$_2$ma** and **inam** interact with each other via an acid–pyridine hetero-synthon involving an O–H···N (2.624 Å, 177.3°) hydrogen bond. The amide group forms amide–amide homosynthon dimers between **inam** molecules involving N–H···O (2.884 Å, 179.7°) that, at the same time, are attached to **L-H$_2$ma** molecules in two ways. One is through an O–H···N bond formed between the hydroxyl O–H and the amide O of the nearest neighboring dimer (2.775 Å, 162.9°), whereas the second one is via N–H···O (2.949 Å, 141.7°) between the amine *anti*-N–H and the hydroxyl oxygen of the **L-H$_2$ma** (Figure 3b).

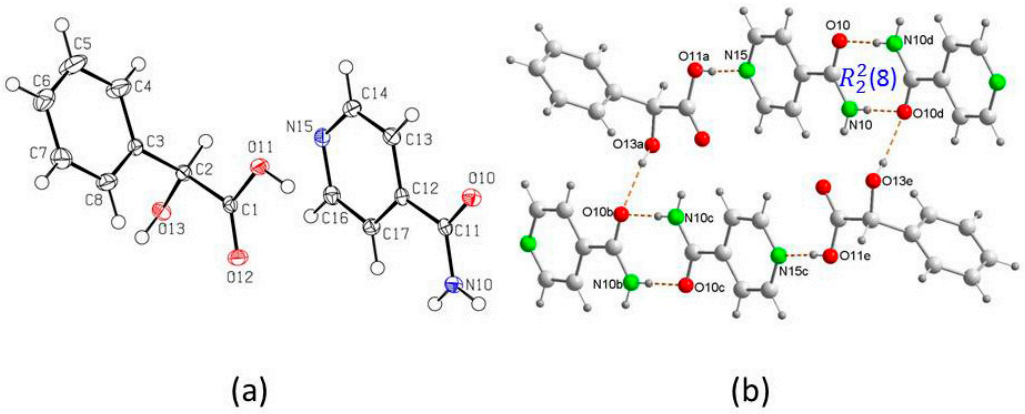


Figure 3. (**a**) Asymmetric unit of **inam-L-H_2ma**- and (**b**) four-membered supramolecular unit in the crystal structure of **inam-L-H_2ma** (1:1) co-crystal.

This research demonstrates the effectiveness and utility of dry grinding and milling with solvent drops in the preparation of pharmaceutical cocrystals. We have applied a synthon-based approach to construct cocrystals that would have similar architectures, but different symmetry properties. The difference in symmetry is introduced by utilizing several isomers of the same compound and a racemic cocrystal former. Three cocrystals of picolinamide, nicotinamide, and isonicotinamide with mandelic acid as a co-former were prepared in this way. Moreover, their crystalline and molecular structures were determined by single-crystal X-ray diffraction. Acid–amide and acid–pyridine supramolecular synthons were identified as recurring intermolecular interactions in the crystal structures that contain these functional groups. Co-formers for the co-crystal formation with mandelic were chosen given that they contain amide and pyridine groups. Crystal structure analysis of the cocrystals revealed that all the cocrystals feature heterosynthons. The position of the heterocyclic nitrogen of the pyridinecarboxamide isomers is essential to form typical intermolecular hydrogen bonds, such as amide–amide, amide-acid and pyridine-acid. Thus, while in **pic-D-H_2ma** the amide-acid and pyridine-α-hydroxyl heterosynthons are present (Figure 1b), in **nam-D-H_2ma** are amide-hydroxycarboxylic and pyridine-acid (Figure 2b), and in **inam-L-H_2ma**, amide-amide and pyridine-acid (Figure 3b). These results are relevant for understanding the nature of co-crystallization and pyridinecarboxamide isomers as prolific cocrystal formers.

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