Preparation and Structural Assessment of Cocrystal Solvates and Cocrystal Salts of 1,3,5-Triazine-2,4,6-triamine with α-Hydroxycarboxylic Acids.†

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Abstract: In the present research, three cocrystals containing 1,3,5-triazine-2,4,6-triamine (melamine, me) were synthesized and characterized. The robustness of the amine-acid supramolecular synthon is discussed in the stoichiometry of the cocrystals of (me)·(H$_2$ga)·1/2H$_2$O (**I**), (me)·(Hme$^+$)·(Hma$^-$)·DMSO·3H$_2$O (**II**) and (Hme$^+$)·(Hma$^-$)·diox·2H$_2$O (**III**). The abbreviated designations used are glycolic acid (H$_2$ga), D,L-mandelic acid (H$_2$ma), dimethyl formamide (DMF), dimethyl sulfoxide (DMSO) and 1,4-Dioxane (diox). All the crystalline materials have been characterized by ^{1}H-NMR, ^{13}C-NMR, IR, and X-ray diffraction. The supramolecular assembly of each cocrystal is also analyzed and discussed.

1. Introduction

The understanding of non-covalent interactions in molecular crystals is very significant for the design of novel materials with tailored structures and properties [1]. The term non-covalent can be applied to a large range of intermolecular interactions including electrostatic interactions (ion-ion, ion-dipole and dipole-dipole interactions), coordinative bonding (metal-ligand), hydrogen bonding, halogen bonding, π-π stacking and Van der Waals forces [2]. The utilization of these interactions for directed self-assembly requires an understanding of their strength, distance and directionality. Specifically, hydrogen bonding has been called the master-key of molecular recognition. It is the most reliable interaction in the toolkit of the crystal engineering. It is both strong and directional. In a milieu where most of the interactions are weak and non-directional, strong and well directed interactions can have important effects on the establishment of a stable crystal structure [3]. With this in mind, a large number of crystal and cocrystal structures have been evaluated over recent decades and a series of frequently recurring hydrogen-bond motifs has been identified. Supramolecular synthons represent the fundamental building block of those systems, and the development in understanding of the scope and boundaries of the interactions responsible for formation of these synthons has also been reviewed in detail [4].

The triazine compound melamine (1,3,5-triazine-2,4,6-triamine, **me**) and some of its derivatives are interesting from a crystal engineering perspective due to its symmetry and the availability of

several hydrogen bond donor and acceptor functionalities; and have been widely used as precursors for self-assembling, as supramolecular aggregates, such as cyclic rosettes, linear and crinkled tapes and molecular strands and ribbons so as with the aim to investigate the molecular recognition and organisation via weak intermolecular interactions and to prepare chemical nanostructures and artificial receptors for biological compounds [5].

Melamine is an example of a compound containing complementary arrays of hydrogen bonding sites that forms in the solid state a 2D network in the solid state. Protonation of its triazine ring decreases the number of the active sites bringing about a decrease in the dimensionality of the arrangement [6].

Crystalline compounds containing partially protonated melaminium cations (**Hme+**, **H2me2+**) combined with different organic and inorganic counterions are widely reported in the literature; and most of these crystals contain only one melamine form, i.e. the neutral molecule, singly or doubly protonated melaminium cations, and there are very few works reporting the crystalline structure of neutral and protonated melamine (**me** and **Hme+**) [7].

It was noted that in the molecular complexes of me with polihydroxy carboxylic acids, carboxyl and hydroxyl groups participate on extensive hydrogen bonding. However, the collective influence of hydroxyl and carboxyl groups in the recognition with me has not been systematically evaluated [6]. In this context, in the present work we have prepared and analysed molecular complexes of me with both glycolic (**H2ga**) and mandelic (**H2ma**) α-hydroxy carboxylic acids and we describe three new examples of cocrystals containing a neutral melamine and a singly protonated melaminium cation in the same crystal, and we discuss these molecular complexes in terms of synthon formation, structural variations due to hydration or solvation and salt-to-co-crystal continuum.

2. Materials and Methods

All reagents and solvents were commercial products that were used as received, without further purification. Compounds were prepared by co-crystallization via solvent-drop grinding: Stoichiometric amounts of me with H2ga or H2ma were ground with a mortar and pestle for *ca.* 5-7 minutes with the addition of 10 μL of solvent per 50 mg of co-crystal formers. The resulting solutions were left to evaporate slowly at ambient conditions. The single crystals of (me)·(H2ga)·1/2H2O (**I**), (me)·(Hme+)·(Hma−)·DMSO·3H2O (**II**) and (Hme+)·(Hma−)·diox·2H2O (**III**), suitable for X-ray diffraction studies were obtained in 1–2 days from DMF, DMSO:H2O (1:1, v/v) and diox:H2O (1:1, v/v) solutions, respectively. Microanalyses (C, H and N) were carried out in 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 of **I** to **III** were deposited at the Cambridge Crystallographic Data Centre with CCDC Nos. 1011489, 1580155 and 1580156, respectively.
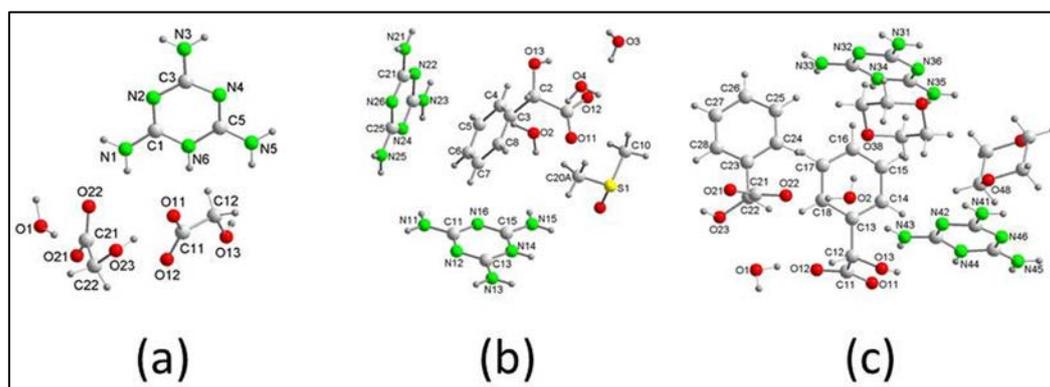
Figure 1. A perspective view showing the atom-numbering scheme, of: (**a**) (me+)·(Hga−)·1/2H2O, **I**; (**b**) (me)·(Hme+)·(Hma−)·DMSO·3H2O, **II**; (**c**) (Hme+)·(Hma−)·diox·2H2O, **III**.

3. Results and discussion

Compound **I** crystallizes in the $P2_1/n$ monoclinic space group. The asymmetric unit consists of a melaminium cation, in general position, half a water molecule and two independent glycolate monoanion halves (Fig. 1a), connected by extensive intermolecular hydrogen bonding of the types N-H···N, O-H···O and N-H···O. In the packing, planar chains of melaminium cations are arranged parallel to the [010] direction, with a double amine-pyridyl synthon of ring motif $R_2^2(8)$ between the neighbouring inverted **me⁺** units (Fig. 2). The motif for the hydrogen-bonded assembly of two melaminium cations is observed in many other melamine or melaminium structures as reported previously [9]. A **me⁺** cation can create three cyclic H-bonding motifs, graph set $R_2^2(8)$, two of them are utilized for H-bonding between the neighbouring cations, and the rest is provided for H-bonding between the adjacent carboxy group of **Hga⁻**, anions. The different molecular chains are connected via glycolate ions with typical hydrogen bond motifs between anion and cation hydrogen atoms such as $R_1^2(5)$ or $R_2^1(6)$. In the structure, however, there is also a significant amount of hydrogen networks that extend further, *e. g.* $R_4^4(12)$. Every oxygen atom is a H-bond acceptor for two or three NH functionalities. Besides, the crystallization water molecules participate in additional N–H···O and O–H···O interactions to form ring motifs $R_3^2(8)$ and $R_5^4(12)$, among others (Fig. 2).
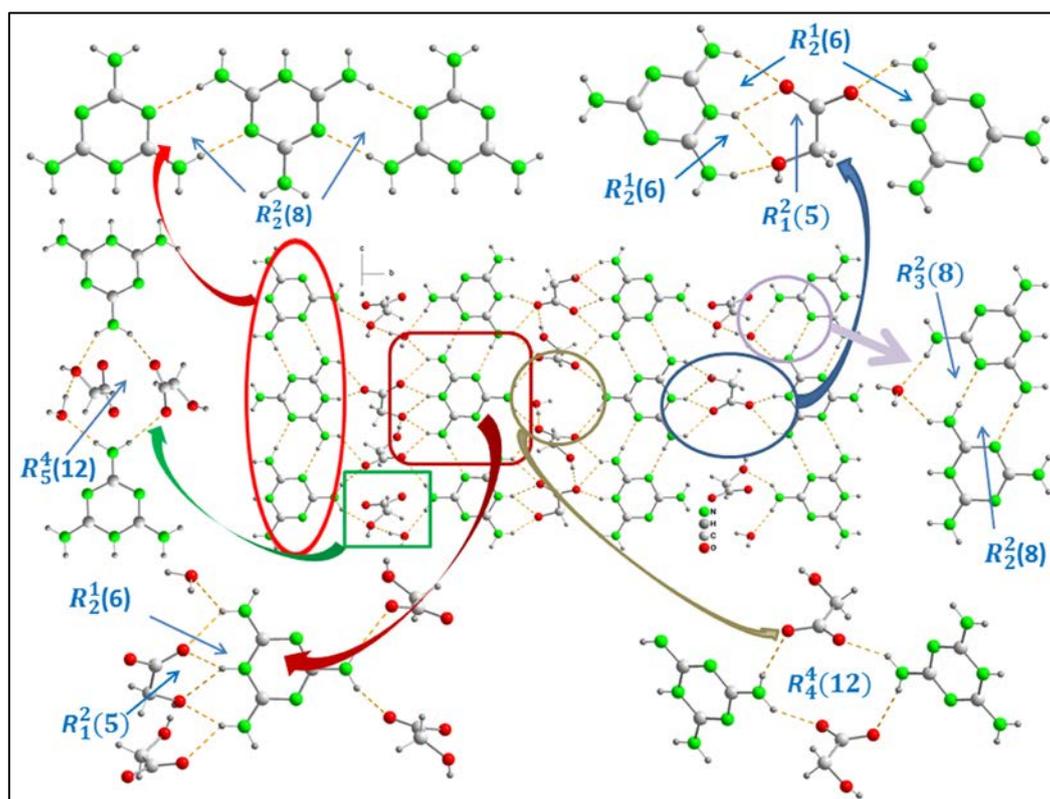

Figure 2. A partial packing diagram for (I), showing one layer of the two-dimensional network, the intermolecular interactions and the supramolecular synthons. Hydrogen bonds are shown as orange dashed lines.

Compound **II** crystallizes in the $C2/c$ monoclinic space group. The asymmetrical unit is formed by a neutral melamine molecule, a melaminium cation singly protonated at one of three ring N atoms, a monoanion D, L-mandelate, a DMSO molecule and three crystallization water molecules,

and this correspond to salt of a solvate (Fig. 1b). Thus (**II**) is a new example of a compound containing both a neutral melamine molecule and single protonated melaminium cation.

The melamine molecules are interconnected by pairs of almost lineal N-H···N hydrogen bonds forming 1D polymers, characterized by a $R_2^2(8)$ motif. Those chains contains both **me** and **Hme⁺** residues which alternate along the chain and run in the [100] direction (Fig. 3a). Such ribbons are frequently observed in cocrystals of melamine [8]. The **me** molecules and **Hme⁺** cations form N-H···O bonds with the carboxylate groups of **H₂ma** with $R_2^2(8)$ and $R_2^1(6)$ structural motifs. In addition, the $R_3^2(9)$ and $R_2^2(10)$ structural motifs are present due to the O-H···O bonds which form with a water molecule and between the molecules of **H₂ma**, respectively (Fig. 3b). Also, between the layers of melamine, water molecules are intercalated that give rise to structural motifs $R_5^4(14)$, $R_4^3(10)$ and $R_2^2(8)$. The DMSO molecules present in the crystal, also participate in forming hydrogen bonds N-H···O with the melamine, with the $R_3^2(8)$ motif (Fig. 3a). As a whole, these interactions generate an infinite 2D network along *a* axis (Fig. 3c), with a zigzag or herringbone appearance on the *bc* plane, which results in a 2D network with base vector [101] (Fig. 3d) and they are stacked along [010], where the centroid-centroid distance between the two types of melamine rings is 3.57 Å, indicating π–π interactions between the aromatic triazine rings of two contiguous chains (Fig. 3d).
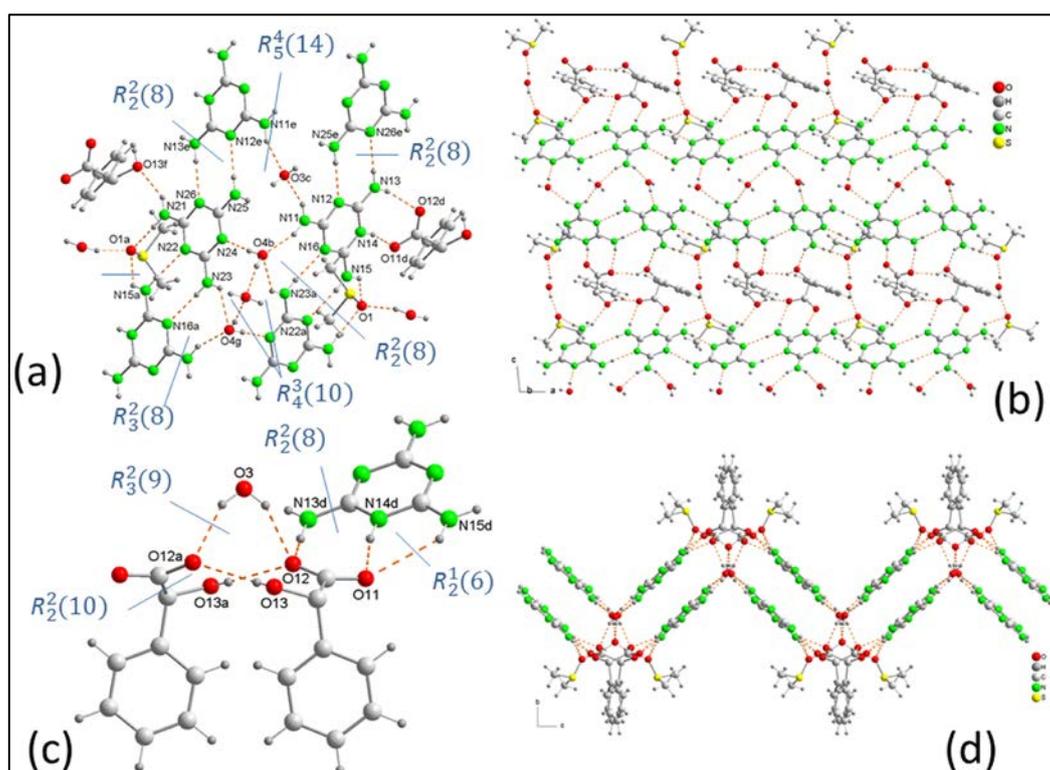

Figure 3. A partial molecular packing diagram of H-bonding interactions for **II**, indicating supramolecular synthons from different motifs. (b) Ribbons of melamine interconnected by hydrogen bonds parallel to the *ac*-plane. (c) Detail of the interactions between **Hme⁺**, **Hma⁻** and water molecules. (d) Network arrangement of **II** formed through intermolecular hydrogen bonding interactions Hydrogen bonds are shown as orange dashed lines.

The crystals of compound **III** belong to the triclinic space group $P\bar{1}$. The asymmetric unit consists of two melaminium cations, two D, L-mandelate monoanions, two water molecules, all in

general positions and two independent halves of 1,4-Dioxane molecules, since the solvent molecules are located at special positions (Fig. 1 c).

In the crystal packing of **III**, extensive hydrogen bond interactions are observed (Fig. 4a). A close analysis reveals that there are four types of secondary building units. A one-dimensional [(Hme⁺]∞ ribbon running along the *a*-axis, is formed by pairs of the almost linear N-H⋯N hydrogen bonds between two crystallographically independent **Hme⁺** cations. Such 1D chains features a N_4-involved $R_2^2(8)$ ring motif. On the other hand, an anionic [(Hma)⁻]₂ dimer from two crystallographic independent mandelate anions is formed by a pair of somewhat short but very strong O-H⋯H hydrogen bonds in an almost linear geometry (Fig. 4a). Thus, an O_4-involved $R_2^2(8)$ ring motif can be identified.
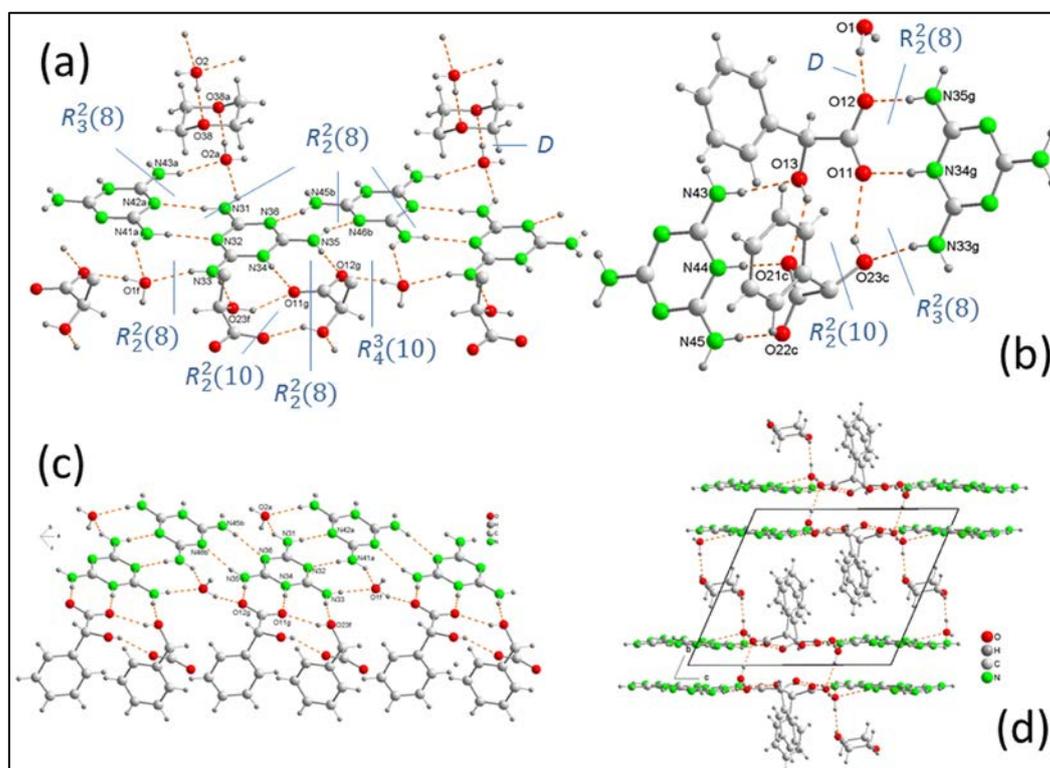
Figure 4. (a) Crystal packing diagram for **III** showing the intermolecular interactions and the supramolecular synthons. (b) Portion of the packing diagram showing the interaction linking the cations and anions. (c) Detail of the interactions between [(Hme⁺]∞ ribbons, [(Hma)⁻]₂ dimers and water molecules. (d) Molecular packing diagram of hydrogen bond and π–π stacking interactions in **III** along the *b*-axis. Hydrogen bonds are shown as orange dashed lines.

The combination of two adjacent [(Hme⁺]∞ ribbons through the hydrogen bonds and electrostatic interactions of the charge-balanced [(Hma)⁻]₂ dimers leads to a larger-scale one-dimensional chains which extends along the ac-plane to give 2D layers (Fig. 4b), generating, together with the water molecule O1, four new H-bonding patterns (i.e., N_2O_2-involved $R_2^2(8)$, N_2O_2-involved $R_3^2(8)$, N_3O-involved $R_2^2(8)$, and N_3O_2-involved $R_4^3(10)$ rings) (Fig. 4c). The diox molecules are connected to water molecules O_2 via single O-H⋯O hydrogen bonds which, in turn, are connected to **Hme⁺** cations via $R_3^2(8)$ hydrogen-bond motifs (Fig. 4a). Furthermore, the 2D layers stack along the ac-plane via inter-chain π–π packing interactions between pairs of the neighbouring aromatic triazine rings (Fig. 4d), with centroid-centroid distances of 3.58 Å.

Conclusions

Three novel cocrystals (**1**-**3**) based on melamine and glycolic and mandelic acid were prepared. This study demonstrates that hydrogen bond interactions between melamine and the other molecules can force melamine to crystallise in layers. In summary, three very intricate hydrogen bonded networks are observed in those compounds. The hydrogen bonds and electrostatic interactions of the partly deprotonated acids with the protonated and/or neutral melamine generate two-dimensional layers of (me)·(H_2ga)·1/2H_2O, a zigzag or herringbone double-layer of (me)·(Hme^+)·(Hma^-)·DMSO·3H_2O and a three-dimensional double-layer of (Hme^+)·(Hma^-)·diox·2H_2O, respectively. Furthermore it has been shown that solvent inclusion is possible in melamine crystal structures and that it plays a very important role in the formation of a layered arrangement of melamine molecules. Nevertheless, the influence of the counter-ion seems to be more important if strong N–H···O interactions can be formed. Synthons involving $R_2^2(8)$ interactions are favourable for the formation of doubly hydrogen-bonded complexes but other synthons can be taken into account for the formation of cocrystals of these compounds as well. Results also show that the π–π stacking interactions between the 1,3,5-triazine rings contribute to their overall three-dimensional packing.

Conflicts of Interest: The authors declare no conflict of interest.

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