Hydrogen bonding patterns in co-crystal structures of 2-amino-4, 6-dimethylpyrimidinedi
terephthalic acid (2/1) [1], 2-amino-4, 6-dimethylpyrimidine-succinic acid (1/1) [2], 2-
amino-4,6-dimethoxypyrimidine-succinic acid (2/1)[3]

7.1. Introduction

A co-crystal is a structurally homogeneous crystalline material that contains two or
more neutral building blocks that are present in definite stoichiometric amounts.

The emerging role of supramolecular chemistry and crystal engineering in
pharmaceutical science has been influenced significantly by the interest in pharmaceutical co-
crystals. Pharmaceutical co-crystals are co-crystals that are formed between an API (active
pharmaceutical ingredient) and a co-crystal former that is a solid under ambient conditions.
APIs contain functional groups that engage in more than one supramolecular event with itself,
a solvent molecule or co-crystal former thereby forming polymorphs, solvates or co-crystals
respectively. There are two types of molecular recognition facilitating the formation of
polymorphs, solvates and co-crystals. Functional groups that are self-complementary are
capable of forming either a supramolecular homosynthons (eg-acid-acid and amide-amide
homodimers or a supramolecular heterosynthon (carboxylicacid-amide heterodimers)\(^\text{144}\). The
knowledge of co-crystals is very important in the design of multicomponent pharmaceutical
solids\(^\text{145}\).

Applying these concepts, our area of interest lies in the study of hydrogen bonded
motifs and packing patterns in some of the aminopyrimidine-carboxylic acid co-crystal
systems. Pyrimidine and aminopyrimidine derivatives are naturally occurring components of
nucleic acid. Some pyrimidine derivatives act as antifolate drugs\(^\text{16,17}\). Aminopyrimidine-
carboxylate/carboxylic acid systems may adopt two different proton-limiting O’…H-N\(^+\) or O-
H…N structures\(^\text{146}\). The latter is a co-crystal where there is no proton transfer leading to the
formation of familiar $R_{2}^{2}(8)$ ring motif. The affinity between carboxylic acids and 2-aminopyrimidine has been employed in several drug design strategies. Interest in co-crystals has wide applications in materials for non-linear optics NLO, solvent-free organic synthesis, host-guest chemistry and formulation of APIs.

Etter and co-workers studied the hydrogen bonding motifs, packing patterns and intermolecular interactions of some of the co-crystal structures. The crystal structures of aminopyrimidine derivatives, aminopyrimidine carboxylates and aminopyrimidine co-crystals have already been reported. From our laboratory crystal structures of 2-amino-4,6-dimethylpyrimidinium bromide 2-amino-4,6-dimethylpyrimidine monohydrate, 2-amino-4,6-dimethylpyrimidinium barbiturate trihydrate, 2-amino-4,6-dimethylpyrimidinium picrate, 2-amino-4,6-dimethylpyrimidinium salicylate, 2-amino-4,6-dimethoxypyrimidinium 4-hydroxybenzoate monohydrate, 2-amino-4,6-dimethoxypyrimidinium salicylate, 2-amino-4,6-dimethylpyrimidine–cinnamic acid (1/2), 2-amino-4,6-dimethylpyrimidine–4-hydroxybenzoic acid (1/1), 2-amino-4,6-dimethoxypyrimidine–anthranilic acid (1/1), 2-amino-4,6-dimethoxypyrimidine–phthalic acid (1/1) and 2-amino-4,6-dimethoxypyrimidine-4-aminobenzoic acid (1/1) have been reported. In the present study, hydrogen bonding patterns in co-crystals of 2-amino-4,6-dimethylpyrimidinium-terephthalic acid [AMPYTERE] (2/1) [1], 2-amino-4,6-dimethylpyrimidine-succinic acid [AMPYSUCC] (1/1) [2] and 2-amino-4,6-dimethoxypyrimidine- succinic acid [MEOPYSUCC](2/1) are discussed.

7.2. Experimental section

7.2. 1. Preparation

Compound 1 [AMPYTERE], compound 2 [AMPYSUCC] were prepared by mixing a hot methanolic solutions of 2-amino-4,6-dimethylpyrimidine (30 mg, Aldrich) with methanolic solutions of terephthalic acid (41 mg, Merck) / succinic acid (29 mg, LOBA Chemie), in 1:1 molar ratio and warmed in a water bath for few minutes. The mixtures were cooled slowly at room temperature. After a few days colorless plate-like crystals were obtained for compound 1 and compound 2.
Compound 3 [MEOPYSUCC] was prepared by mixing hot methanolic solutions of 2-amino-4,6-dimethoxypyrimidine (38 mg, Aldrich) and succinic acid (29 mg, LOBA Chemie) in 1:1 molar ratio and warmed in a water bath for few minutes. The mixtures were cooled slowly at room temperature. After a few days colorless block like crystals were obtained.

7.2.2. X-ray data collection

For compounds 1-3, the X-ray data were collected using Bruker Kappa APEXII diffractometer\textsuperscript{57} provided with a graphite monochromated MoK\textsubscript{α} radiation. Preliminary cell parameters were determined by collecting 3678/7753/5024 intense and centered reflections for compounds 1-3. The data (θ range = 1.8° to 27.2° for compound 1, 2.5° - 25.0° for compound 2, 2.4° - 31.2° for compound 3) were corrected for polarization and Lorentz effects. The absorption correction was performed by multi-scan method using SADABS\textsuperscript{58}.

7.2.3. Structure solution and refinement

For compound 1: In the reflections of the type hkl, there is no systematic absence. This indicates that the cell is primitive. The data set contains the following systematic absences:
(i) 0k0 type reflections with k odd absent showing 2\textsubscript{1} screw parallel to b-axis.
(ii) h0l type reflections, with (h+l) odd absent, revealing the n-glide perpendicular to b-axis.
Hence the space group P2\textsubscript{1}/n was assigned unambiguously.
For compound 2:
(i) Among the hkl type of reflections, h+k+l odd absent
(ii) Among hk0 type of reflections, h,k odd absent

The first set of systematic absence revealed I-centered lattice. The second set of systematic absence revealed a glide perpendicular to c axis. Hence the space group Imma was assigned.

For compound 3: The data set contained no systematic absences. The E-statistics analysis reveals the centrosymmetric distribution and hence the space group P-1 was assigned. It was later confirmed by successful structure solution and refinement. The structures were solved by SHELXS97 and refined by SHELXL97\textsuperscript{59} program. In all the crystal structures (1 and
the non-hydrogen atoms were refined with anisotropic factors. All the hydrogen atoms were fixed geometrically and were refined as riding on their carrier atoms. In compound 2, all the hydrogen atoms were located from difference Fourier map and refined isotropically except the aromatic phenyl hydrogen atom (H5) which was treated as riding. The final R value is 0.0416 for 1685 reflections I>2σ(I) for compound 1, 0.0393 for 547 reflections I>2σ(I) for compound 2, 0.0459 for 2160 reflections I>2σ(I) for compound 3. The geometric calculations were carried out using PLATON9760. The crystal data and the details of structure determination parameters are listed in Table 7.1 for compound 1, Table 7.2 for compound 2 and Table 7.3 for compound 3. The atomic coordinates together with equivalent isotropic temperature factors for non-hydrogen atoms are listed in Table 7.4 for compound 1, Table 7.5 for compound 2 and Table 7.6 for compound 3.

7.3. Results and Discussion

ORTEP views of the compounds are shown in Figs 7.1a-7.1c. The asymmetric unit of compound 1 contains one 2-amino-4, 6-dimethylpyrimidine and half of a molecule of terephthalic acid. In compound 2, the asymmetric unit consists of half molecule of a molecule of 2-amino-4, 6- dimethylpyrimidine and half of a molecule of succinic acid. All the atoms (except the H10 methylene and H7A methyl hydrogen atom) lie in special positions. Mirror planes generate the remaining half of the 2-amino-4, 6-dimethylpyrimidine and succinic acid molecule. In compound 3, succinic acid lies on the crystallographic inversion centre. The asymmetric unit consists of one 2-amino-4,6-dimethoxy pyrimidine molecule and half of a molecule of succinic acid. In compounds 1-3, the N1 atom and the 2-amino group (N2-H2B) of the pyrimidine form an eight membered ring motif [graph set R2^2(8)7,10,65] with the acid molecule via N-H...O and O-H...N hydrogen bonds (Motif VII). This motif has also been observed in crystal structures of 2-aminopyrimidine-succinic acid (1/2)21, 2-aminopyrimidine-terephthalic acid164 and 2-aminopyrimidine-fumaric acid165. This motif has also been reported from our laboratory in the crystal structures of 2-amino-4, 6-dimethylpyrimidine-4-hydroxybenzoic acid (1/1)87 and 2-amino-4, 6-dimethoxypyrimidine-4-aminobenzoic acid (1/1)163. The observed bond lengths and bond angles (Table 7.7 for compound 1, 7.8 for
compound 2 and 7.9 for compound 3) are in agreement with the reported crystal structure of 2-aminopyrimidine\textsuperscript{143}.

### 7.3.1. Hydrogen bonding

In compound 1, the inversion related pyrimidine molecules form a base pair [R\textsubscript{2}^2(8) ring motif] via a pair of N-H...N hydrogen bonds involving the 2-amino group (N2-H2A) and pyrimidine N3 atom. This type of base pairing has been reported in the crystal structures of 2-amino-4,6-dimethylpyrimidinium picrate\textsuperscript{156} and 2-amino-4, 6-dimethylpyrimidinium salicylate\textsuperscript{157}. Two such independent R\textsubscript{2}^2(8) ring motifs generate a supramolecular ribbon along bc plane (Figure 7.2). Here aminopyrimidine is linked to both the heteromeric and homomeric eight membered R\textsubscript{2}^2(8) ring motifs. But in the crystal structure of 2-aminopyrimidine terephthalic acid\textsuperscript{164}, only heteromeric ring motifs are only observed. Further the crystal structure is stabilized by stacking interactions between the terephthalic acid molecules (Figure 7.3) with centroid-centroid distances of 3.9689(9) Å, slip angle of 29.31° and perpendicular separation of 3.461 Å. The observed values are in agreement with the aromatic stacking interactions\textsuperscript{76}.

In compound 2, the heteromeric N-H...O and O-H...N hydrogen bonded interactions lead to supramolecular ribbon as shown in Figure 7.4. Similar type of interactions are also seen in the crystal structure of 2-aminopyrimidine-succinic acid (1/1)\textsuperscript{166}. These interactions are also reported from our laboratory in the crystal structures of 2-amino-4, 6-dimethyl pyrimidine cinnamic acid(1/2)\textsuperscript{160} and 2-amino-4,6-dimethylpyrimidinium-terephthalic acid(2/1)\textsuperscript{167}.

In compound 3, the 2-amino group of the pyrimidine also acts as a hydrogen bonded donor to the O3 atoms to generate another eight membered ring with graph set notation [R\textsubscript{4}^2(8)]. The resulting hydrogen bonded motifs R\textsubscript{2}^2(8) R\textsubscript{4}^2(8) R\textsubscript{2}^2(8) result in DADA array of network of hydrogen bonds. The interactions are shown in Figure 7.5. These types of hydrogen bonds are also seen in 2-aminopyridinium-succinate-succinic acid (2/1/1)\textsuperscript{168}. The hydrogen bonding geometries are listed in Tables 7.10 (compound 1), 7.11 (compound 2) and 7.12 (compound 3).
7.4. Supplementary Materials

The atomic coordinates and the isotopic displacement parameters for all the hydrogen atoms, the anisotropic displacement parameters for all the non-hydrogen atoms, the bond distances bond angles involving the hydrogen atoms and the torsion angles in AMPYTERE, AMPYSUCC and MEOPYSUCC are given in Tables A 1.7.1, A 1.7.2 and A 1.7.3 (Appendix 1), A 2.7.1, A 2.7.2 and A 2.7.3 (Appendix 2), A 3.7.1, A 3.7.2 and A 3.7.3 (Appendix 3), A 4.7.1, A 4.7.2 and A 4.7.3 (Appendix 4) respectively. The least squares plane calculations (Appendix 5. txt & Tables A 5.7.1, A 5.7.2 and A 5.7.3) and Fo-Fc Tables [AMPYTERE.FCF, AMPYSUCC.FCF and MEOPYSUCC. FCF] are given in the CD attached at the end of the thesis.
PART II

Hydrogen bonding patterns in s-triazine carboxylate

Introduction

Triazines are class of N-heterocycles containing aromatic six membered ring with three carbon atoms and three nitrogen atoms. Triazines exist in three isomeric forms depending on the position of nitrogen atoms namely 1,2,3- triazine, 1,2,4-triazine and 1,3,5-triazine or s-triazine (Figure 1) respectively. Symmetrical 1,3,5-triazine is very common. The best known 1,3,5-triazine derivative is melamine with three amino substituents (2,4,6-triamino-1,3,5-triazine) which is used in the manufacture of resins. Triazine compounds are often used as the basis for various herbicides such as cyanuric chloride (2,4,6-trichloro-1,3,5-triazine), simazine (6-chloro-N,N’-diethyl-1,3,5-triazine-2,4-diamine) and atrazine (1-chloro-3-ethylamino-5-isopropylamino-2,4,6-triazine). Some triazine family compounds are used in pharmaceutical industry as coupling agents for the synthesis of peptides and as side chain of antibiotics, as well as in formulating bactericides and fungicides. They are also used as an industrial deodorant, preservatives in oil field applications and biocide in water treatment. Triazine derivatives exhibit antibacterial169, antitumour170, anticonvulsant171 and broad range of biological activities like antimicrobial and anti-angiogenesis effects172. Some examples of triazine derivatives and their uses are shown in Figure 2. WR99210(4,6-diamino-1,2-dihydro-2,2-dimethyl-1-[(2,4,5-trichlorophenoxy) propyloxy]-1,3,5-triazine), and its prodrug PS-15 represent a new class of highly active antifolate drugs that could be used in combination therapy against multidrugresistant parasites. WR99210 is a close structural analog of the antimalarial antifolate drug cycloguanil, which has pronounced activity in vitro against all plasmodium falciparum strains to date173.

The rational design of supramolecular structures can be realised through crystal engineering based on relatively weak intermolecular forces174. Among these forces, hydrogen bonding is by far the most common. This is especially true for biological structures1. The crystalline adducts of DNA/RNA pyrimidine bases when coupled with amino derivatives of
aromatic N-heterocycles via multiple hydrogen bonds mimic the base-pairing in nucleic acids\textsuperscript{175,176}. The protonated form of the aromatic N-heterocycles are capable of interacting with RNA through Watson-Crick pairing\textsuperscript{177} and the relevance of proton transfer in DNA/RNA systems was illustrated\textsuperscript{178}. The organic as well as inorganic complexes of N-heterocycles (s-triazines) or its salts form supramolecular structures by self-assembly of components containing complementary arrays of hydrogen-bonding sites\textsuperscript{179-181}. They form the familiar R\textsubscript{2}	extsuperscript{2}(8) ring motif with carboxylate/carboxylic acid (Figure 3) which is similar to diaminopyrimidines reported. The ring motif observed is robust and is one of the 24 most frequently observed bimolecular cyclic hydrogen bonded motifs in organic crystal structures\textsuperscript{20}. The possible base pairing exhibited by s-triazines are shown in Figure 4.

In recent years, many derivatives of triazine have been reported\textsuperscript{182}. The crystal structures of 2,4-diamino-1,3,5-triazine\textsuperscript{183}, 2, 4-diamino-6-methyl-1, 3, 5-triazine\textsuperscript{184}, 2, 4-diamino-6-methyl-1, 3,5-triazin-1-ium trifluoroacetate\textsuperscript{185}, 1:1 monohydrated molecular adduct of acetoguanaminium chloride with acetoguanamine\textsuperscript{186}, 2,4-diamino-6-methyl-1,3,5-triazine ethanol solvate\textsuperscript{187}, 2,4-diamino-6-methyl-1,3,5-triazine methanol solvate\textsuperscript{188}, 2,4,6-triamino-1,3,5-triazin-1-ium acetate acetic acid solvate monohydrate\textsuperscript{189}, 1,2,3-trihydroxybenzene–1,3,5-triazine (1/1)\textsuperscript{190}, 3-Amino-1,2,4-triazine\textsuperscript{191}, 2,4-diamino-6-phenyl-1,3,5-triazine\textsuperscript{192}, 2,6-diamino-4-phenyltriazinium chloride monohydrate\textsuperscript{193} and 4-(dimethylamino)benzaldehyde and 6-phenyl-1,3,5-triazine-2,4-diamine\textsuperscript{194} have been reported in literature. From our laboratory, salt of 2,4-diamino-6-phenyl-1,3,5-triazine-sorbic acid (1/1)\textsuperscript{195} has been reported.

Our present work is focused on s-triazine derivatives namely 2, 4-diamino-6-methyl-1,3,5-triazine/2,4-diamino-6-phenyl-1,3,5-triazine (Figures 5a and 5b). The hydrogen bonding interactions of triazines with carboxylates and the resulting supramolecular architectures are investigated in the forthcoming chapters.