Chapter II

Hydrogen bonding patterns in the crystal structures of 2-amino-4,6-dimethoxypyrimidinium hydrogen maleate (1), 2-amino-4,6-dimethoxypyrimidinium fumarate (2), 2-amino-4,6-dimethoxypyrimidinium hydrogen (2R, 3R)-tartrate 2-amino-4,6-dimethoxypyrimidinium hydrogen citrate (4), 2-amino-4,6-dimethoxypyrimidinium salicylate (5), 2-amino-4,6-dimethoxypyrimidinium 4-hydroxybenzoate monohydrate (6), 2-amino-4,6-dimethoxypyrimidinium hydrogen dipicolinate monohydrate (7) and 2-amino-4,6-dimethoxypyrimidinium gallate dihydrate (8)

2.1 Introduction

Many drugs are administered to the patients in the form of their maleate salts. Hence it is of interest to investigate the nature of the interactions between the drugs and the maleic acid. The crystal structures of maleates of some drug molecules (chlorpheneramine maleate,78 bis(2-aminopyridinium) maleate,79 glycinium maleate,80 L-alaninium maleate,81 L-phenylalaninium maleate82 and sarcosinium maleate83) have been reported in literature. From our laboratory, trimethoprim maleate84 and pyrimethamine hydrogen meleate85 have also been reported.

Fumaric acid (trans-butenedioic acid) is among the organic compounds widely found in nature, and is a key intermediate in the biosynthesis of organic acids. Fumaric acid is an organic dicarboxylic acid which crystallizes in two polymorphic forms: one in the monoclinic86 space group P2₁/c and the other in the triclinic87 space group P-1. The crystal structures of L-phenylalanine fumaric acid,88 quinolinium fumarate,89 2-aminopyridinium-fumarate-fumaric acid90 (2/1/1), guanidinium hydrogen fumarate,91 2,6-diaminopyridinium
hydrogen fumarate,\textsuperscript{92} DL-valine-fumaric acid\textsuperscript{93} and 2-aminopyrimidine-fumaric acid\textsuperscript{38} have been reported in literature.

Salicylic acid\textsuperscript{94} and its derivatives are widely used as analgesic. They are also used for various gastric tympany and also used externally as antiseptic and antifungal agents for various skin conditions. The crystal structure of salicylic acid and its complexes, for example, antipyrine-salicylic acid (salipyrine)\textsuperscript{95} and piperazinedione-salicylic acid\textsuperscript{96} (1:2) have been reported in literature.

4-hydroxybenzoic acid acts as antiseptics, antipyretic and bacteriostatic agents. The crystal structure of 4-hydroxybenzoic acid monohydrate,\textsuperscript{97,98} piperidinium p-hydroxybenzoate,\textsuperscript{99} p-hydroxybenzoic acid and p-hydroxybenzoic acid-acetone complex\textsuperscript{100} (2/1) and 2-amino-4,6-dimethylpyrimidine-4-hydroxybenzoic acid\textsuperscript{60} (1/1) have been reported.

Tartaric acid is used as an antioxidant. It is used as an additive in many foods, such as soft drinks, bakery products, and candies. Industrial uses include tanning, ceramics manufacture, and the production of tartarate esters for lacquers and textile printing. The crystal structure of (+)-tartaric acid,\textsuperscript{101} sarcosinium tartrate,\textsuperscript{102} L-prolinium tartrate\textsuperscript{103} and L-alaninium tartrate\textsuperscript{104} have been reported.

Pyridinecarboxylic acids are active in the human metabolism. Pyridinecarboxylic acids act as chelating agents of elements such as chromium, zinc, manganese, copper, iron and molybdenum in the body. They are involved in phenylalanine, tryptophan, alkaloids production and in quantitative detection of calcium. Pyridinecarboxylic acid forms a complex with zinc, which facilitates the passage of zinc through the gastrointestinal wall and into the circulatory system. The crystal structure of pyridine-2,6-dicarboxylic acid\textsuperscript{105} (dipicolinic acid), creatininium dipicolinate monohydrate,\textsuperscript{106} copper (II) and zinc(II) complexes of dipicolinic acid\textsuperscript{107} and trimethoprim dipicolinate pentahydrate\textsuperscript{108} have been reported in the literature.

In the present study, the crystal structures of 2-amino-4,6-dimethoxy pyrimidinium hydrogen maleate (1), 2-amino-4,6-dimethoxy pyrimidinium fumarate (2), 2-amino-4,6-dimethoxy pyrimidinium hydrogen (2R, 3R)-tartrate (3), 2-amino-4,6-dimethoxy pyrimidinium hydrogen citrate (4), 2-amino-4,6-
dimethoxy pyrimidinium salicylate (5), 2-amino-4,6-dimethoxy pyrimidinium 4-hydroxybenzoate monohydrate (6), 2-amino-4,6-dimethoxy pyrimidinium hydrogen dipicolinate monohydrate (7) and 2-amino-4,6-dimethoxy pyrimidinium gallate dihydrate (8) are being presented.

2.2. Experimental section

2.2.1. Preparation

Compounds 1, 2 and 5 were prepared by mixing a hot methanolic solution of 2-amino-4,6-dimethoxypyrimidine (Aldrich) with a hot methanolic solution of the corresponding acids [maleic acid/ fumaric acid/ salicylic acid (LOBA Chemie)] in a 1:1 molar ratio, and warming for half an hour over a water bath. The mixture was cooled slowly and kept at room temperature. After a few days colourless crystals were obtained.

Compounds 3 & 4 were prepared by mixing a hot methanolic solution (20 ml) of 2-amino-4,6-dimethoxy pyrimidine (Aldrich) and (2R,3R)-(+)-tartaric acid (37 mg, Loba Chemie) or citric acid (48 mg, Loba Chemie) in a 2:1 molar ratio, and warming for half an hour over a water bath. The mixture was cooled slowly and kept at room temperature. After a few days colourless crystals were obtained. Compounds 3 & 4 were obtained even if the starting materials were in a 1:1 molar ratio.

Compounds 6-8 were prepared by mixing a hot methanolic solution of 2-amino-4,6-dimethoxypyrimidine (Aldrich) with a hot aqueous solution of 4-hydroxybenzoic acid (34 mg)/ dipicolinic acid (41 mg)/ gallic acid (47 mg) (LOBA Chemie) in a 1:1 molar ratio, and warming for half an hour over a water bath. Each solution was cooled slowly and kept at room temperature. After a few days colourless crystals were obtained.

2.2.2. X-ray data collection

The X-ray data for compounds 1 & 2. were collected using Oxford Diffraction Gemini diffractometer provided with a graphite monochromated MoKα radiation. The data (θ range= 4.7° to 32.7° (compound 1) and 4.7° to
32.5° (compound 2)) were corrected for polarization and Lorentz effects. The absorption correction was performed by multi-scan using CrysAlis RED; Oxford diffraction.

The X-ray data for compounds 3-8, were collected using Bruker-Nonius Kappa CCD area detector diffractometer provided with a graphite monochromated MoKα radiation. The data (θ range = 4.7° to 32.7° (compound 1); 4.7° to 32.5° (compound 2); 3.2° to 27.5° (compound 3); 3.0° to 27.5° (compound 4); 3.8° to 27.5° (compound 5); 3.5° to 27.5° (compound 6); 3.2° to 27.6° (compound 7); 3.2° to 27.5° (compound 8)) were corrected for polarization and Lorentz effects.

2.2.3. Structure solution and refinement

In compounds 1, 2, 7 & 8, the data set contained no systematic absences. The E-statistics analysis reveals the centrosymmetric distribution. Among the reflections of the general type hkl, there is no systematic absence. This indicates that the lattice is primitive. Hence the space group P-1 was assigned. It was later confirmed by successful structure solution and refinement.

In the compounds 4-6, the E-statistics revealed the centrosymmetric distribution. Among the reflections of the general type hkl there are no systematic absences. This indicates that the lattice is primitive. In the 0k0 types of reflections, l odd are absent. This reveals 2₁ screw parallel to b-axis. The absence of h0l type of reflections with l odd, reveals c glide perpendicular to b-axis. Hence the space group P2₁/c was assigned.

In compound 3, among the reflections of the general type hkl, there is no systematic absence. This indicates that the lattice is primitive. Among the oko type of reflections, the l odd reflections are absent, revealing 2₁ screw parallel to b-axis. Hence the space group P2₁ was assigned. It was later confirmed by successful structure solution and refinement.

All the structures were solved by direct method using SHELXS97 and refined by full matrix least squares on F² using the program SHELXL97. For all the above crystal structures, (1-8) non-hydrogen atoms were refined with anisotropic factors. In compounds 1-5, all hydrogen atoms were positioned
geometrically and refined as riding model. In compounds 6-8, the hydrogen atoms of the water molecules were located in a difference Fourier map and refined as riding. The other hydrogen atoms were positioned geometrically and were refined using a riding model. The final R value was 0.073 for 1730 reflections I>2σ(I) in compound 1, 0.057 for 2159 reflections I>2σ(I) in compound 2, 0.049 for 2122 reflections I>2σ(I) in compound 3, 0.058 for 3425 reflections I>2σ(I) in compound 4, 0.054 for 2465 reflections I>2σ(I) in compound 5, 0.055 for 2415 reflections I>2σ(I) in compound 6, 0.064 for 2397 reflections I>2σ(I) in compound 7 and 0.049 for 5865 reflections I>2σ(I) in compound 8. The geometric calculations were carried out using PLATON97. The crystal data and the details of structure determination parameters are listed in Table 2.1 for compound 1, Table 2.2 for compound 2, Table 2.3 for compound 3, Table 2.4 for compound 4, Table 2.5 for compound 5, Table 2.6 for compound 6, Table 2.7 for compound 7 and Table 2.8 for compound 8. The atomic coordinates together with equivalent isotropic temperature factors for non-hydrogen atoms are listed in Table 2.9 for compound 1, Table 2.10 for compound 2, Table 2.11 for compound 3, Table 2.12 for compound 4, Table 2.13 for compound 5, Table 2.14 for compound 6, Table 2.15 for compound 7 and Table 2.16 for compound 8.

2.3. Results and Discussion

The ORTEP view of the title compounds 1-8 are shown in Figures 2.1a-2.1h. In compounds 1 & 5, the asymmetric unit contains an 2-amino-4,6-dimethoxypyrimidinium (HAMPY) cation and a hydrogen maleate/ salicylate anion. In compound 2, the asymmetric unit contains an 2-amino-4,6-dimethoxypyrimidinium cation and half of the fumarate anion. In compound 3, one 2-amino-4,6-dimethoxypyrimidinium cation (A), a hydrogen (2R, 3R)-tartrate anion and a neutral 2-amino-4,6-dimethoxypyrimidine molecule (B) constitute the asymmetric unit. In compound 4, the asymmetric unit contains two 2-amino-4,6-dimethoxypyrimidinium cation and a hydrogen citrate anion. In compound 6, the asymmetric unit contains an 2-amino-4,6-dimethoxypyrimidinium cation, a 4-hydroxybenzoate anion and a water molecule. In compound 7, the asymmetric unit contains an 2-amino-4,6-
dimethoxypyrimidinium cation, a hydrogen dipicolinate anion and a water molecule. In compound 8, the asymmetric unit contains two crystallographically independent 2-amino-4,6-dimethoxypyrimidinium cation, a gallate anion and two water molecule. In all the compounds, the pyrimidine rings are protonated at atom N1. Protonation of the pyrimidine base on the N1 site is reflected by an increase in bond angle at N1[C2-N1-C6= 120.4(2)° in compound 1, 117.92(11)° in compound 2, 119.9(2)° in cation A of compound 3, 120.60(16)° (cation A) and 119.70(16)° (cation B) in compound 4, 120.19(15)° in compound 5, 120.01(14)° in compound 6, 119.25(15)° in compound 7 and 120.15(12)° (cation A) and 117.94(12)° (cation B) in compound 8] when compared with that at the unprotonated atom N3[C2-N3-C4= 114.9(2)° in compound 1, 116.21(11)° in compound 2, 116.8(2)° in compound 3, 116.22(17)° (cation A) and 116.00(16)° (cation B) in compound 4, 116.08 (13)° in compound 5, 116.22(14)° in compound 6, 115.98(16)° in compound 7 and 116.40(12)° (cation A) and 115.18(12)° (cation B) in compound 8. The bond distances and bond angles are listed in Table 2.17 for compound 1, Table 2.18 for compound 2, Table 2.19 for compound 3, Table 2.20 for compound 4, Table 2.21 for compound 5, Table 2.22 for compound 6, Table 2.23 for compound 7 and Table 2.24 for compound 8.

2.3.1. Hydrogen bonding

In all the compounds, the carboxylate group of the respective anions [hydrogen maleate, fumarate, hydrogen (2R, 3R)-tartrate, hydrogen citrate salicylate 4-hydroxybenzoate, hydrogen dipicolinate and gallate] interacts with the aminopyrimidinium cation through a pair of N-H–O hydrogen bonds to form an eight-membered R\textsubscript{8}^2(8) ring motif.\textsuperscript{21,22} This motif is one of the 24 most frequently observed bimolecular cyclic hydrogen-bonded motifs in organic crystal structures.\textsuperscript{110}

In compound 1, two inversely related 2-amino-4,6-dimethoxypyrimidinium hydrogen maleate units form R\textsubscript{4}^4(16) motif through N-H–O hydrogen bonds. Further, C-H–O hydrogen bonds, interlink these adjacent forming a large ring motif of graph-set R\textsubscript{4}^4(28). The oxygen atom of the carboxyl group of the hydrogen maleate anion forms an intramolecular
hydrogen bond with the oxygen atom of the carboxylate group [with graph-set notation S(7)]. On the whole, the structure may be expressed as a supramolecular sheet shown in Figure 2.2.

In compound 2, the R$_2^2$(8)$^{21,22}$ motifs are centrosymmetrically paired via N-H…O hydrogen bonds to produce DDAA (D-hydrogen bonded donor and A-hydrogen bonded acceptor) array of quadruple hydrogen bonds. This can be represented by the graph-set notation R$_2^2$(8), R$_4^3$(8) and R$_2^2$(8) (Motif V). This type of motif has already been reported in trimethoprim formate$^{111}$, trimethoprim hydrogen glutarate$^{112}$, trimethoprim m-chlorobenzoate,$^{113}$ and pyrimethaminium 3,5-dinitrobenzoate.$^{114}$ These types of interactions are extended leading to the formation of a 2-D supramolecular sheet [Figure 2.3].

π-π stacking (Figure 2.4) interaction is noted between two aminopyrimidine groups, with a perpendicular separation and centroid-to-centroid distances of 3.2947(8) Å and 3.3326(8) Å, respectively, and a slip angle (angle between the centroid vector and the normal to the plane) of 8.65°. These are typical aromatic stacking values.$^{75}$

In compound 3, the carboxyl group of the tartrate anion interacts with atom N1B and the 2-amino-group of the neutral 2-amino-4,6-dimethoxypyrimidine molecule (B) through N-H…O and O-H…N hydrogen bonds to form an eight-membered ring [R$_2^2$(8)] (Figure 2.5). The 2-amino group of the 2-amino-4,6-dimethoxypyrimidinium cation (A) interacts with hydroxy group O5 through an N-H…O hydrogen bond, and the 2-amino group of molecule B interacts with one of the carboxylate atoms, O3, through an N-H…O hydrogen bond, forming a cyclic R$_4^3$(12) hydrogen-bonded motif. These type of interactions are extended along the c-axis to form a hydrogen-bonded supramolecular ribbon. In addition, both the carboxylate groups interact with adjacent hydroxy groups via intramolecular O-H…O hydrogen bonds, leading to a five-membered ring [S(5)]. Furthermore, these arrays are connected via C-H…O hydrogen bonds, resulting in a two-dimensional network. The pyrimidine rings of cation A exhibit stacking interactions with molecule B; the centroid-to-centroid distance and interplanar distances are 3.625 and 3.335 Å, respectively, the slip angle being 21.2° has also been observed.
In compound 4, the carboxylate group of the citrate anion interacts with cation B through a pair of N-H–O hydrogen bonds forming a similar R$_2^2$(8) ring motif. Typical intramolecular O-H–O hydrogen bond is observed in the anion. The 2-amino group of the cation B interacts with one of the carboxylate oxygen atom (O7) through an N-H–O hydrogen bond. The 2-amino group of the cation A interacts with hydroxy group [O5] through an N-H–O hydrogen bond. Such interactions extend along the c-axis to form a hydrogen-bonded supramolecular ribbon (Figure 2.6). In addition, the oxygen of the carboxyl group of the citrate anions forms O-H–O hydrogen bond with the carboxylate oxygen of symmetry related molecule, forming supramolecular chains, running along b-axis (Figure 2.7). This type of carboxyl-carboxylate interaction has been observed in the crystal structures of many acid salts and proteins.$^{115}$ This type of head-to-tail fashion has also been observed in the crystal structure of TMP hydrogen glutarate.$^{112}$

In compound 5, the R$_2^2$(8) motifs are centrosymmetrically paired via N-H–O hydrogen bonds to produce the DDAA (D=donor in hydrogen bonds, A=accepter in hydrogen bonds) array of quadruple hydrogen bonds. This can be represented by the graph-set notation R$_2^2$(8), R$_4^2$(8) and R$_2^2$(8) (Figure 2.8) (Motif V). This type of array has also been identified in trimethoprim hydrogen glutarate,$^{112}$ trimethoprim formate,$^{111}$ trimethoprim-$m$-chlorobenzoate$^{113}$ and pyrimethaminium 3,5-dinitrobenzoate.$^{114}$ The salicylate ions form a hydrogen-bonded supramolecular chain along the c-axis, via C-H–O hydrogen bonds, involving benzene hydrogen (C11) and one of the oxygen atoms of the carboxylate group, as shown in Figure 2.9. There is a typical intramolecular hydrogen bond between the phenolic –OH group and the carboxylate group of the salicylate anion [S(6)]. π-π stacking interactions between the aromatic rings are also observed. The pyrimidine ring of 2-amino-4,6-dimethoxypyrimidinium cation has stacking interactions with the benzene rings of salicylate anion, with a perpendicular separation of 3.280 Å, a centroid-to-centroid distance of 3.6363(8) and a slip angle of 21.03°.

In compound 6, the 2-amino-4,6-dimethoxypyrimidinium cations are centrosymmetrically paired through a pair of N2-H2A-N3 hydrogen bonds to form an R$_2^2$(8) ring motif$^{21,22}$ (Figure 2.10). Two inversion-related 4-
hydroxybenzoate anions are connected by water molecules via O-H...O and C-H...O1W hydrogen bonds, forming an R_4^4(16) ring motif. A similar type of C-H...O water hydrogen bond has been investigated on the basis of the structural data determined by neutron diffraction. The carboxylate groups are bridged by the intervening water molecules via O-H...O hydrogen bonds, resulting in a supramolecular chain along the b-axis. The water molecules act as hydrogen bond donors to the carboxylate group of the 4-hydroxybenzoate ion, and also act as hydrogen-bond acceptors to the hydroxy group of the 4-hydroxybenzoate ion, forming an O-H...O hydrogen-bonded sheet parallel to the (011) plane. π–π stacking interactions between aromatic rings are observed. The pyrimidine ring of the 2-amino-4,6-dimethoxypyrimidinium cation stacks with the benzene ring of the 4-hydroxybenzoate anion, with interplanar and centroid-to-centroid distance of 3.317 and 3.554 Å, respectively, and a slip angle of 18.9°.

In compound 7, inversion-related R_2^2(8) motifs (aminopyrimidine-carboxylate motifs) are further bridged by N-H...O hydrogen bonds on either side forming DDAA array of quadruple hydrogen bonds (Figure 2.11). This array is extended further on either side by O_{water}-H...O_{methoxy} hydrogen bonds, resulting in an array of six hydrogen bonds (ADDAAD). The water molecule plays a pivotal role, and five hydrogen-bonded fused rings are formed around the water molecule. Two inversion-related water molecules are bridged by two inversion-related carboxyl-OH groups, generating an R_4^4(8) ring motif. Each hydrogen atom of the water molecule acts as a bifurcated donor and the oxygen atom acts as a single acceptor. The water molecule-dipicolinate interaction via O-H...O and O-H...N hydrogen bonds leads to two hydrogen-bonded rings, viz. R_1^3(5) and R_2^2(7). Furthermore, these arrays are connected via a pair of C-H...O hydrogen bonds involving one of the oxygen atoms of the carboxylate group and methoxy group (C7 and C8) of the pyrimidinium cation, resulting in the formation of a 20-membered R_4^2(20) ring. π–π interaction is observed between two 2-amino-4,6-dimethoxypyrimidinium cations related by an inversion center. The centroid-to-centroid distance and interplanar distance are 3.310 and 3.253 Å, respectively, the slip angle being 10.7°.

In compound 8, in molecule A, the gallate anions, form a R_2^2(14) motif, with the inversely related moiety, through O-H...O hydrogen bond. Neighboring
such motifs are interlinked through (O1w) water molecule assisted by O-H-O hydrogen bonds, constituting a large ring of graph set notation R68(16) (Figure 2.12). In molecule B, the hydrogen-bonding pattern slightly differs, constituting a supramolecular ribbon of alternating N-H-O and N-H-N hydrogen bonds (Figure 2.13). A typical intramolecular O-H-O hydrogen bond [S(5)] is observed in the gallate anion. The hydrogen bonding geometries are listed in Table 2.25 for compound 1, Table 2.26 for compound 2, Table 2.27 for compound 3, Table 2.28 for compound 4, Table 2.29 for compound 5, Table 2.30 for compound 6, Table 2.31 for compound 7 and Table 2.32 for compound 8.

2.4. Supplementary Materials

The atomic coordinates and the isotopic displacement parameters for all hydrogen atoms, anisotropic displacement for all the non-hydrogen atoms, bond distance and bond angles involving the hydrogen atom and torsion angle [HAMPYMAL, HAMPYFUM, HAMPYL-TAR, HAMPYCIT, HAMPYSAL, HAMPY4-HBA, HAMPYDIPIC and HAMPYGAL] are given in Tables A.1.2.1, 1.2.2, 1.2.3, 1.2.4, 1.2.5, 1.2.6, 1.2.7 and 1.2.8 (Appendix 1), A.2.2.1, 2.2.2, 2.2.3, 2.2.4, 2.2.5, 2.2.6, 2.2.7 and 2.2.8 (Appendix 2), A.3.2.1, 3.2.2, 3.2.3, 3.2.4, 3.2.5, 3.2.6, 3.2.7 and 3.2.8 (Appendix 3) and A.4.2.1, 4.2.2, 4.2.3, 4.2.4, 4.2.5, 4.2.6, 4.2.7 and 4.2.8 (Appendix 4) respectively. The least squares plane calculations (Appendix. 5. txt & Tables A.5.2.1, 5.2.2, 5.2.3, 5.2.4, 5.2.5, 5.2.6, 5.2.7 and 5.2.8) and Fo-Fc Tables (HAMPYMAL, HAMPYFUM, HAMPYL-TAR, HAMPYCIT, HAMPYSAL, HAMPY4-HBA, HAMPYDIPIC and HAMPYGAL) are given in the CD attached at the end of the thesis.