Abstract

**Background:** Pyrimethamine [2,4-diamino-5-(p-chlorophenyl)-6-ethylpyrimidine] is an antifolate drug used in anti-malarial chemotherapy. Pyrimidine and aminopyrimidine derivatives are biologically important compounds owing to their natural occurrence as components of nucleic acids.

**Results:** In the crystal structures of two organic salts, namely pyrimethaminium benzenesulfonate monohydrate (1) and 2-amino-4,6-dimethylpyrimidinium 3-carboxy-4-hydroxy benzenesulfonate dihydrate (2), pyrimethamine (PMN) and 2-amino-4,6-dimethylpyrimidine (AMPY) are protonated at one of the nitrogens in the pyrimidine rings. In both the PMN and AMPY sulfonate complexes, the protonated pyrimidine rings are hydrogen bonded to the sulfonate groups, forming a hydrogen-bonded bimolecular ring motif with graph-set notation R$_{2}^{2}(8)$. The sulfonate group mimics the carboxylate anion’s mode of association, which is more commonly seen when binding with 2-aminopyrimidines. In compound 1, the PMN moieties are centrosymmetrically paired through a complementary DADA array of hydrogen bonds. In compound 2, two types of bimolecular cyclic hydrogen bonded R$_{2}^{2}(8)$ motifs (one involving the carboxylate group and the other involving sulfonate group) coexist. Furthermore, this compound is stabilized by intra and intermolecular O-H...O hydrogen bonds.

**Conclusion:** The crystal structures of pyrimethaminium benzenesulfonate monohydrate and 2-amino-4,6-dimethylpyrimidinium sulfosalicylate dihydrate have been investigated in detail. In compound 1, the R$_{2}^{2}(8)$ motif involving the sulfonate group is present. The role the sulfonic acid group plays in mimicking the carboxylate anions is thus evident. In compound 2, two types of bimolecular cyclic hydrogen bonded R$_{2}^{2}(8)$ motifs (one involving the carboxylate group and the other involving sulfonate group) coexist. In both the compounds base pairing also occurs. Thus homo and hetero synthons are present.
Background

Intermolecular interactions and hydrogen bond motifs that occur repeatedly in crystal structures are called supramolecular synthons. Synthons are the recognition motifs between building blocks that can be used to propagate networks or supramolecular assemblies [1]. Hydrogen bonding patterns involving sulfonate groups in biological systems and metal complexes are of current interest [2-6]. Such interactions can be used for designing supramolecular architectures. Numerous hydrogen-bonding patterns of aminopyrimidine-carboxylate interactions [7,8] have been reported in the literature. Recently, different types of hydrogen-bonding motifs in sulfonate salts have been examined using the Cambridge Structural Database (CSD) [9].

The 2,4-diaminopyrimidine antifolates have been reviewed in the literature [10]. The different types of hydrogen-bonding patterns present in diaminopyrimidine-carboxylates [11] and aminopyrimidine complexes, such as pyrimethamine (PMN) hydrogen maleate, PMN hydrogen succinate, PMN hydrogen phthalate [12], PMN formate [13], PMN sulfosalicylate monohydrate [14], PMN o-nitrobenzoate, PMN m-nitrobenzoate, PMN p-nitrobenzoate [15], trimethoprim (TMP) benzenesulfonate monohydrate, TMP sulfanilate monohydrate, TMP p-toluene sulfonate and TMP sulfosalicylate dehydrate [16] 2-amino-4,6-dimethylpyrimidine (AMPY) hydrogen sulfate [17], 2-amino-4,6-dimethylpyrimidine-cinnamic acid [18], and 2-amino-4,6-dimethylpyrimidine-4-hydroxy benzoic acid [19] co-crystal structures, have been reported from our laboratory.

Pyrimethamine [2,4-diamino-5-(p-chlorophenyl)-6-ethylpyrimidine] is an antifolate drug [20] used in antimalarial chemotherapy. The drug binds with great affinity to the bacterial enzyme dihydrofolate reductase (DHFR) [21]. PMN is also used along with other drugs for the treatment of opportunistic infections in patients with AIDS [22]. 2-aminopyrimidine and its derivatives are of particular interest as adduct formers because of their ability to form stable hydrogen-bonded chains via their stereochromically associated amine group and the ring N atoms [23]. Hydrogen bonding plays a key role in molecular recognition [24] and crystal engineering [25]. The present study deals with hydrogen bonding, the nature of hydrogen-bonded arrays and the supramolecular synthons present in the aminopyrimidine-sulfonate salts (Scheme 1).

Results and discussion

The three dimensional supramolecular architectures in such compounds can be analyzed in terms of various components such as motifs, chains, stacking interactions etc. The schematic representation of the hydrogen-bonded motifs observed in this study is shown in Figure 1. In the crystal structure of compound 1, the asymmetric unit contains a pair of pyrimethaminium (PMN) cations (A and B), benzenesulfonate anions (A and B) and a water molecule as shown in Figure 2. In compound 2, four molecules of 2-amino-4,6-dimethylpyrimidinium (AMPY) cations (A, B, C and D), two molecules of 3-carboxy-4-hydroxy benzenesulfonate (sulfosalicylate) anions (A and B), and two water molecules constitute the asymmetric unit (Figure 3). The PMN moieties are protonated at N1, leading to an enhancement of the internal bond angles at N1 [C2A-N1A-C6A 121.6(2)° and C2B-N1B-C6B 121.5(2)° in compound 1]. The angles are larger than the values observed in neutral pyrimethamine [116.25(18)° (molecule A) and 116.09(18)° (molecule B)] [26]. In compound 2, protonation of the pyrimidine base on the N1 site is reflected in the larger bond angle, as compared with the unprotonated site. The angles at the protonated N1 site are C2A-N1A-C6A 121.65(2)°; C2B-N1B-C6B 121.93(17)°; C2C-N1C-C6C 121.64(18)° and C2D-N1D-C6D 121.73(18)°. The similar angles at the unprotonated N3 nitrogen are 117.20(17)° (molecule A), 117.52(17)° (molecule B), 117.35(18)° (molecule C) and 117.68(18)° (molecule D). The geometry of the pyrimidine cation agrees with that of other pyrimidine cations reported in the literature [27]. In compound 1, the dihedral angles between the 2,4-diaminopyrimidine and the p-chlorophenyl are 78.50(12)° (molecule A) and 73.20(12)° (molecule B). These values are close to the values observed in the modelling studies carried out on the dihydrofolate reductase-pyrimethamine (DHFR-PMN) complexes [28]. The important torsion angles governing the orientation of the 6-ethyl group are C5A-C6A-
C7A-C8A (-105.3° in molecule A) and C5B-C6B-C7B-C8B (110.4°(3)° in molecule B). The lengths of the bonds connecting the pyrimidine and phenyl rings are 1.493(3)Å (molecule A) and 1.496(3)Å (molecule B). These values are in close agreement with those observed in the crystal structure of metoprine (1.495Å in molecule A and 1.478Å in molecule B) [29]. In compounds 1 and 2, the sulfonate group mimics the association of the carboxylate moiety and makes a hydrogen-bonded ring of graph-set notation R22(8) with the PMN and AMPY cations. The hydrogen-bonding geometry of the N-donors to the sulfonate group gave a mean value for the N-H...O hydrogen bond distances involving sulfonates that was slightly longer in range when compared with the carboxylate O atoms indicating that sulfonates form longer and weaker hydrogen bonds with N-donors than carboxylates. These trends are also observed in the present investigation, as indicated in Table 1. The hydrogen bonds formed between the sulfonates and the N-donors were generally linear [30]. In compound 1, the protonated pyrimeth-
bases involved in the pairing by hydrogen bonds, leads to the formation of a linear array of four hydrogen bonds. This is called a complementary DADA array (motif V) of quadruple hydrogen-bonding patterns (D stands for hydrogen-bond donor, and A stands for hydrogen-bond acceptor). The corresponding graph-set notations are R32(8), R22(8) and R32(8) (Figure 4). This type of DADA array of quadruple hydrogen bonds has been observed in some previously reported crystal structures [12].

In compound 2, two types of bimolecular cyclic hydrogen-bonded R22(8) motifs (motif I and motif II) are formed. Motif I involves protonated aminopyrimidinium cations (N1A and N1B), and the 2-amino group and sulfosalicylate anions (carboxylate group) (O5A and O6B). Motif II is formed by protonated aminopyrimidinium cations (N1C and N1D), and the 2-amino group and sulfosalicylate anions (sulfonate group) (O2B and O2A).

Table 1: Hydrogen bonding geometry for the compounds 1 and 2

| Compound | D-H...A | H...A | D...A | D-H...A |
|----------|---------|------|-------|---------|
| 1.       |         |      |       |         |
| N1A – H1A .. O3A | 1.90   | 2.733(3) | 164 |
| N1B – H1B .. O2B | 1.89   | 2.742(3) | 169 |
| N2A – H3A .. O1B | 2.15   | 2.980(3) | 161 |
| N2B – H3B .. O2A | 2.00   | 2.843(3) | 167 |
| N2A – H4A .. O1A | 1.99   | 2.847(3) | 175 |
| N2B – H4B .. O1B | 2.23   | 3.076(3) | 168 |
| N4A – H5A .. N3A | 2.16   | 3.013(3) | 170 |
| N4A – H6A .. O1B | 2.33   | 3.015(3) | 137 |
| N4B – H6B .. O1A | 2.43   | 3.079(3) | 133 |
| C10B – H10B .. O2A | 2.54   | 3.364(4) | 148 |

| 2.       |         |      |       |         |
| N1B–H1B1 .. O6B | 1.84   | 2.693 (2) | 168 |
| O1A–H1A .. O2A | 1.81   | 2.539 (2) | 147 |
| O1B–H1B .. O2B | 1.77   | 2.498 (2) | 147 |
| N1C–H1C .. O2B | 1.75   | 2.614 (2) | 179 |
| N1D–H1D .. O2A | 1.83   | 2.682 (2) | 174 |
| O1W–H1W .. O5B | 1.97   | 2.785 (2) | 139 |
| N1A–H1A1 .. O5A | 1.87   | 2.722 (2) | 168 |
| O1W–H2W .. O6A | 2.08   | 2.775 (2) | 127 |
| N2C–H2C1 .. O3B | 2.05   | 2.908 (2) | 173 |
| N2C–H2C2 .. O3D | 2.16   | 3.010 (3) | 169 |
| N2A–H2A1 .. O1W | 2.10   | 2.927 (2) | 162 |
| N2A–H2A2 .. O4A | 2.03   | 2.889 (2) | 172 |
| N2D–H2D1 .. O3C | 2.16   | 3.003 (3) | 165 |
| N2D–H2D2 .. O3A | 1.95   | 2.809 (2) | 173 |
| N2B–H2B1 .. O1W | 2.10   | 2.933 (2) | 164 |
| N2B–H2B2 .. O4B | 2.01   | 2.871 (2) | 177 |
| C5A–H5A .. O4A | 2.51   | 3.382 (2) | 156 |
| C5B–H5B .. O4B | 2.51   | 3.352 (2) | 151 |
| C5B–H5B .. O5B | 2.58   | 3.428 (3) | 152 |
| C11A–H11A .. O5A | 2.43   | 2.849 (2) | 107 |
| C11B–H11B .. O5B | 2.60   | 2.946 (2) | 103 |
| C8D–H8D2 .. O6B | 2.47   | 3.378 (3) | 159 |
| C14B–H14B .. O1B | 2.36   | 3.275 (3) | 169 |
| C7B–H7B3 .. O5A | 2.52   | 3.421 (3) | 156 |
| C7A–H7A1 .. O6B | 2.50   | 3.458 (3) | 174 |
| C7D–H7D3 .. O3B | 2.58   | 3.413 (3) | 145 |

(a) x-1, y-1, z-1; (b) x, y-1, z-1; (c) 2 - x, 1 - y, 1 - z; (d) 1 - x, 1 - y, 1 - z; (e) 1 - x, y, 1 - z; (f) 1 - x, 1 - y, 1 - z; (g) 2 - x, 1 - y, 1 - z; (h) 1 - x, -y, 1 - z; (i) x - 1, -y, 1 - z; (j) x - 1, y - 1, z.
and O6A) are bridged by the water molecule (O1 W) via O-H...O hydrogen bonds (Figure 7). In compound 1, PMNBSA, π-π stacking interactions between benzenesulfonate molecules are observed with a perpendicular separation of 3.356 Å, a centroid-to-centroid distance of 3.608(2) Å and a slip angle of 21.54° (Figure 8). In compound 2, AMPYSSA, the 2-amino-4,6-dimethylpyrimidinium cations (C), stack with sulfosalicylate anions A and B, with a perpendicular separation of 3.319 Å and 3.359 Å, a centroid-to-centroid distance of 3.529(11) Å and 3.554(11) Å and a slip angle of 17.49° and 19.30° respectively. A similar type of stacking is also observed between the 2-amino-4,6-dimethylpyrimidinium cation (D) and the sulfosalicylate anions (A and B), with a perpendicular separation of 3.238 Å and 3.360 Å, a centroid-to-centroid distance of 3.730(11) Å and 3.483(11) Å and a slip angle of 24.13° and 19.30° respectively (Figure 9). These are typical aromatic stacking values [34].

Conclusion
The crystal structures of pyrimethamine benzenesulfonate monohydrate and 2-amino-4,6-dimethylpyrimidinium sulfosalicylate dihydrate have been investigated in detail. In compound 1, the R$_2^2$(8) motif involving the sulfonate group is present. The role the sulfonic acid group plays in mimicking the carboxylate anions is thus evident. In compound 2, two types of bimolecular cyclic hydrogen bonded R$_2^2$(8) motifs (one involving the carboxylate group and the other involving sulfonate group) coexist. In both the compounds base pairing also occurs. Thus homo and hetero synthons are present. These synthons combine to form a supramolecular network. This observation is rel-

Figure 4
The hydrogen-bonded DADA array in the compound 1.
evant for many supramolecular architectures and crystal engineering.

Experimental
Compounds 1 and 2 were prepared by the mixing of hot methanolic solutions of PMN (62 mg, Shah Pharma-chem, India) or AMPY (Aldrich) and the corresponding acids -benzene sulfonic acid (40 mg, Merck) & 3-carboxy-4-hydroxy-benzene sulfonic acid (55 mg, Merck) in 1:1 molar ratio and warming over water bath for 20 min. After a few days blocks of colourless crystals of compound 1 and 2 were obtained.

X-ray Crystallography
X-ray diffraction data were collected on a Bruker Nonius Kappa CCD area detector diffractometer by using MoKa (λ 0.71073 Å) for compounds 1 and 2 at 120(2)K. The structures were solved by direct methods and refined by full-matrix least squares (on F²) SHELXS97 and SHELXL97 [34], with the graphics produced using PLATON97 [35]. All the non-hydrogen atoms were located from a Fourier map and refined anisotropically. All the hydrogen atoms for compounds 1 and 2 were positioned geometrically and refined as riding. In compound 1, the O1 W of water is disordered and the hydrogen atoms are not found. In compound 2, the water (O1 W) hydrogen atoms are located from difference Fourier map. The O2 W of water is disordered, the hydrogen atoms are not found. The crystal data and details of structural determination for the compounds 1 and 2 are given in Table 2. CCDC reference numbers: 611485 and 611479. All CIF information can be found in Additional file 1.

Figure 5
Hydrogen-bonding patterns involving carboxylate/sulfonate groups in compound 2 (I, II, IV and VI indicates hydrogen bonded motifs).
Figure 6
One dimensional chain made up of sulfosalicylate and AMPY molecule in compound 2.

Figure 7
A view of the supramolecular chain made up of sulfosalicylate and water molecule in compound 2.
Figure 8
A view of π-π stacking interaction between benzenesulfonate anions in compound 1.

Figure 9
π-π stacking interactions in compound 2.
Authors' contributions
This work was prepared in the research group of PTM. He proposed the work and drafted the manuscript. KB participated in the design and presiding the experiments and drafted the manuscript. DEL collected the X-ray data and drafted the manuscript.

Additional material

Additional file 1
Crystallographic Information. Contains all relevant CIF information. Click here for file
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