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Hydrogen-bonding patterns in trimethoprim picolinate and 2-amino-4,6-dimethylpyrimidinium picolinate hemihydrate

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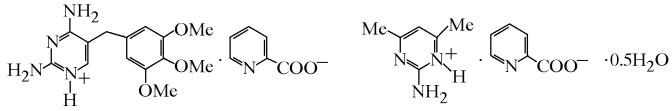
In the title compounds, namely 2,4-diamino-5-[(3,4,5-trimethoxyphenyl)methyl]pyrimidin-1-ium pyridine-2-carboxylate, $C_{14}H_{19}N_4O_3^+\cdot C_6H_4NO_2^-$, (I), and 2-amino-4,6-dimethylpyrimidin-1-ium pyridine-2-carboxylate hemihydrate, $C_6H_{10}N_3^+\cdot C_6H_4NO_2^-\cdot 0.5H_2O$, (II), the trimethoprim and 2-amino-4,6-dimethylpyrimidin-1-ium cations are protonated at one of the pyrimidine N atoms. In (I), bifurcated hydrogen bonds are observed between a picolinate O atom, the protonated N atom and the 2-amino group; the graph-set designator is $R_2^1(6)$. The pyrimidine moieties of the trimethoprim cations are centrosymmetrically paired through a pair of N—H···N hydrogen bonds. In addition to the base pairing, one of the picolinate O atoms bridges the 2- and 4-amino groups on either side of the paired bases, resulting in a complementary *DADA* array. In (II), the carboxylate group of the picolinate anion binds with the protonated pyrimidine N atom and the 2-amino group of the pyrimidine moiety through a pair of N—H···O hydrogen bonds, leading to the common ring motif $R_2^2(8)$. The water molecule, which resides on a twofold rotation axis, bridges the carboxylate group of the picolinate anion *via* O—H···O hydrogen bonds.

Comment

Hydrogen-bonding patterns involving aminopyrimidine and carboxylates have been observed in drug-receptor interactions, protein–nucleic acid interactions and supramolecular architectures (Desiraju, 1989). Studies of such interactions are also of current interest because of their applications in drug design and the crystal engineering of pharmaceuticals (Stanley *et al.*, 2005). Pyrimidine and aminopyrimidine derivatives are biologically important as they occur in nature as components of nucleic acid. Some aminopyrimidine derivatives are used as antifolate drugs (Hunt *et al.*, 1980; Baker & Santi, 1965). Trimethoprim [2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine, TMP] is a well known antifolate drug. It selectively inhibits the bacterial dihydrofolate reductase (DHFR) enzyme (Hitchings *et al.*, 1988). Picolinic acid (pyridine-2-carboxylic acid) is a well known terminal tryptophan metabolite (Mahler & Cordes, 1971). It induces apoptosis in leukaemia HL-60 cells (Ogata *et al.*, 2000). The crystal structures of a dinuclear oxomolybdenum(V) complex of picolinate (Okabe *et al.*, 2002), of *catena*-poly[[[bis(2-pyridinecarboxylato)copper(II)]-μ-benzene-1,2,4,5-tetracarboxylic acid] dihydrate] (Wang *et al.*, 2005) and of *trans*-dichloro(dimethyl sulfoxide)(2-picoline)platinum(II) (Melanson *et al.*, 1978) have been reported. In this paper, the crystal structures of trimethoprim (TMP) picolinate, (I), and 2-amino-4,6-dimethylpyrimidinium (AMPY) picolinate hemihydrate, (II), are described.



(I) (II)

Views of (I) and (II) are shown in Figs. 1(*a*) and 1(*b*), respectively. In (I), the asymmetric unit contains a trimethoprim cation and a picolinate anion. In (II), one 2-amino-4,6-dimethylpyrimidinium cation, one picolinate anion and one half-molecule of water (the O atom of the water molecule lies on a twofold axis) constitute the asymmetic unit. In both structures, the pyrimidine moieties are protonated at N1, leading to an increase in internal angles (see angles C2—N1—C6 in Tables 1 and 3) compared with neutral TMP (Koetzle &

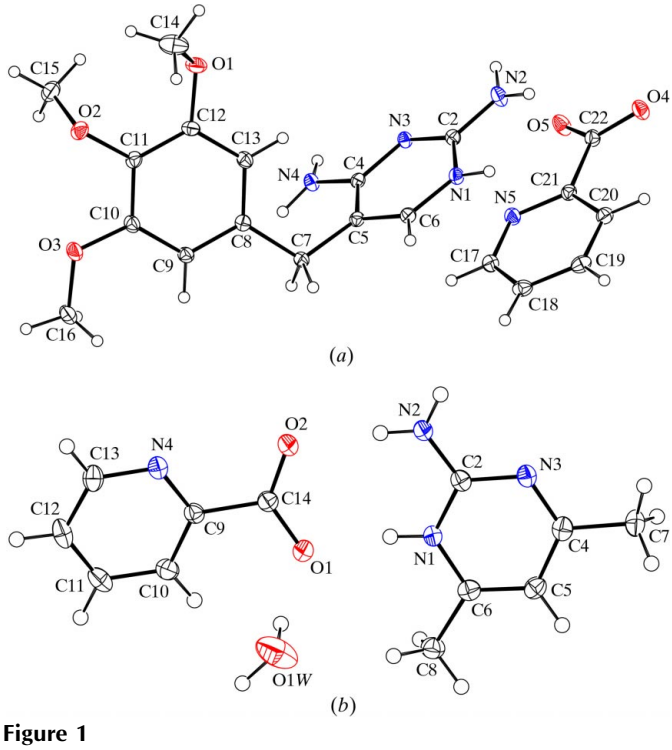


Figure 1
Views of (*a*) (I) and (*b*) (II), showing the atom-labelling schemes and 50% probability displacement ellipsoids. H atoms are shown as small spheres of arbitrary radii.

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Williams, 1976) and AMPY (Panneerselvam *et al.*, 2004). In (I), the dihedral angle between the pyrimidine and benzene rings is 76.06 (7)°. This value is close to that found in TMP–carboxylate salts (Raj, Stanley *et al.*, 2003). The C4—C5—C7—C8 and C5—C7—C8—C9 torsion angles are −68.79 (18) and 168.05 (14)°, respectively.

In (I), atom O5 of the carboxylate group accepts a H atom from protonated atom N1 and the 2-amino group of the pyrimidine ring, forming a cyclic hydrogen-bonded bimolecular pattern [graph-set $R_2^1(6)$; Etter, 1990; Bernstein *et al.*, 1995]. A similar pattern was also observed in the crystal structure of trimethoprim 3-carboxy-4-hydroxybenzenesulfonate dihydrate (Raj, Sethuraman *et al.*, 2003). This is different from the common $R_2^2(8)$ pattern observed in the crystal structures of aminopyrimidine–carboxylate salts (Stanley *et al.*, 2002). The pyrimidine moieties form base pairs through N4—H···N3 (Table 2) hydrogen bonds involving the 4-amino group and atom N3. In addition to the base pairing, a hydrogen-bonded acceptor (atom O4 from the picolinate anion) bridges the 4- and 2-amino groups on both sides of the pairing, leading to a complementary linear *DADA* array (*D* = donor in hydrogen bonds and *A* = acceptor in hydrogen bonds), with the rings having the graph-set notations $R_2^3(8)$, $R_2^2(8)$ and $R_2^3(8)$. The same type of *DADA* array has also been observed in the crystal structures of trimethoprim trifluoroacetate (Francis *et al.*, 2002) and a copper(II) phthalate trimethoprim complex (Raj, Muthiah *et al.*, 2003). The characteristic hydrogen-bonded rings observed in the structure aggregate into a supramolecular ladder consisting of a pair of chains, each of which is built up of alternating TMP and picolinate anions (Fig. 2).

In (II), the carboxylate group (atoms O1 and O2) of the picolinate anion interacts with protonated atom N1 and the 2-amino group of the pyrimidine moiety through a pair of N—H···O hydrogen bonds, leading to the common ring motif with graph-set notation $R_2^2(8)$ (Lynch *et al.*, 2004). This is reminiscent of the trimethoprim–carboxylate interactions observed in the DHFR–TMP complexes (Kuyper, 1989). The water molecule, which resides on a twofold rotation axis, bridges the carboxylate groups of the picolinate anions *via* O—H···O hydrogen bonds. One of the H atoms of the 2-amino group is also involved in bifurcated hydrogen bonding with carboxyl atom O2 and the pyridine N atom to form a five-membered hydrogen-bonded ring [$R_2^1(5)$; Fig. 3].

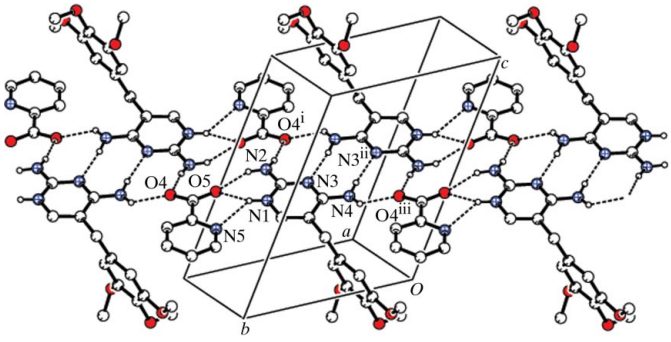

Figure 2
The hydrogen-bonding patterns (dashed lines) in (I). [Symmetry codes: (i) $2-x, 2-y, 1-z$; (ii) $1-x, 1-y, 1-z$; (iii) $x-1, y-1, z$.]

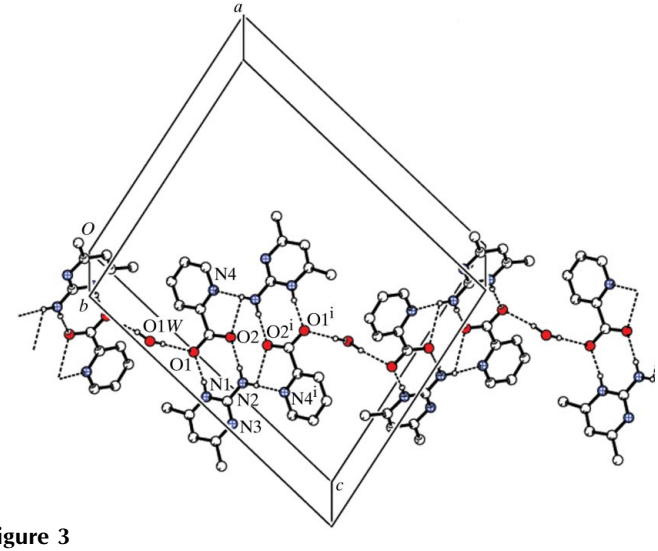

Figure 3
The hydrogen-bonding patterns (dashed lines) in (II). [Symmetry code: (i) $\frac{1}{2}-x, \frac{3}{2}-y, 1-z$.]

Experimental

A hot methanol solution of picolinic acid (61.5 mg, obtained from SD Fine Chemicals Ltd) was mixed with a hot aqueous solution of trimethoprim [for (I); 145 mg, obtained from Shilpa Antibiotics Ltd] or 2-amino-4,6-dimethylpyrimidine [for (II); 63.25 mg, obtained from Merck]. The mixtures were cooled slowly and kept at room temperature. After a few days, colourless block-shaped crystals of (I) and (II) were obtained from the corresponding solutions.

Compound (I)

Crystal data

$C_{14}H_{19}N_4O_3^+\cdot C_6H_4NO_2^-$
$M_r = 413.43$
Triclinic, $P\overline{1}$
$a = 9.0642\ (3)$ Å
$b = 10.2730\ (3)$ Å
$c = 12.1188\ (4)$ Å
$\alpha = 108.051\ (17)°$
$\beta = 98.741\ (2)°$
$\gamma = 107.517\ (2)°$
$V = 985.03\ (14)$ Å^3
$Z = 2$
$D_x = 1.394$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3758 reflections
$\theta = 3.1$–$27.6°$
$\mu = 0.10$ mm^{-1}
$T = 120\ (2)$ K
Block, colourless
0.22 × 0.20 × 0.16 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ and ω scans
17816 measured reflections
4537 independent reflections
3758 reflections with $I > 2\sigma(I)$
$R_{int} = 0.036$
$\theta_{max} = 27.6°$
$h = -11 \rightarrow 11$
$k = -13 \rightarrow 13$
$l = -15 \rightarrow 15$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.051$
$wR(F^2) = 0.141$
$S = 1.13$
4537 reflections
275 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0748P)^2 + 0.2682P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.47$ e Å^{-3}
$\Delta\rho_{min} = -0.47$ e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.138 (9)

Table 1
Selected geometric parameters (Å, °) for (I).

O1—C12	1.381 (2)	O3—C10	1.363 (2)
O1—C14	1.428 (2)	O3—C16	1.425 (2)
O2—C11	1.3826 (18)	O4—C22	1.255 (2)
O2—C15	1.429 (2)	O5—C22	1.253 (2)
C2—N1—C6	119.87 (14)	N1—C2—N3	121.87 (14)
C2—N3—C4	118.52 (14)	N1—C2—N2	118.21 (14)
N2—C2—N3	119.92 (14)	N3—C4—N4	116.74 (14)

Table 2
Hydrogen-bond geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O5	0.88	1.92	2.7308 (19)	151
N1—H1···N5	0.88	2.39	3.0441 (19)	131
N2—H2A···O4^{i}	0.88	2.00	2.8693 (19)	169
N2—H2B···O5	0.88	2.02	2.7982 (19)	147
N4—H4A···N3^{ii}	0.88	2.12	2.9966 (18)	173
N4—H4B···O4^{iii}	0.88	2.14	2.8412 (18)	137
C14—H14A···O2	0.96	2.56	2.899 (3)	101
C17—H17···O3^{iv}	0.93	2.49	3.141 (2)	128

Symmetry codes: (i) $-x+2, -y+2, -z+1$; (ii) $-x+1, -y+1, -z+1$; (iii) $x-1, y-1, z$; (iv) $-x, -y-1, -z$.

Compound (II)

Crystal data

$C_6H_{10}N_3^+\cdot C_6H_4NO_2^-\cdot 0.5H_2O$
M_r = 255.28
Monoclinic, $C2/c$
a = 15.7666 (4) Å
b = 8.7980 (1) Å
c = 18.5038 (4) Å
β = 102.7400 (10)°
V = 2503.55 (9) Å^3
Z = 8
D_x = 1.355 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2204 reflections
θ = 3.3–26.0°
μ = 0.10 mm^{-1}
T = 120 K
Block, colourless
0.4 × 0.2 × 0.1 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ and ω scans
16549 measured reflections
2451 independent reflections
2204 reflections with $I > 2\sigma(I)$
R_{int} = 0.026
θ_{max} = 26.0°
$h = -19 \rightarrow 19$
$k = -10 \rightarrow 10$
$l = -22 \rightarrow 22$

Table 3
Selected geometric parameters (Å, °) for (II).

O1—C14	1.2687 (18)	N3—C4	1.3270 (19)
O2—C14	1.2430 (18)	N3—C2	1.3558 (18)
N1—C2	1.3642 (17)	N4—C13	1.3409 (19)
N1—C6	1.3591 (18)	N4—C9	1.3410 (18)
N2—C2	1.3190 (18)		
C2—N1—C6	121.13 (12)	N1—C6—C8	116.34 (12)
C2—N3—C4	117.42 (12)	N1—C6—C5	118.40 (13)
C9—N4—C13	117.73 (12)	N4—C9—C14	116.70 (12)
N1—C2—N2	118.83 (12)	N4—C9—C10	122.74 (13)
N1—C2—N3	121.72 (13)	N4—C13—C12	123.12 (15)
N2—C2—N3	119.45 (12)	O1—C14—O2	126.11 (14)
N3—C4—C7	116.99 (12)	O2—C14—C9	117.86 (13)
N3—C4—C5	122.80 (13)	O1—C14—C9	116.03 (12)

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.060
$wR(F^2)$ = 0.143
S = 1.25
2451 reflections
171 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0834P)^2 + 1.0121P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.78 e Å^{-3}
$\Delta\rho_{min}$ = −0.82 e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.060 (4)

Table 4
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O1	0.88	1.80	2.6657 (15)	168
O1W—H1W···O1	0.99	2.00	2.9588 (14)	164
N2—H2A···O2^{i}	0.88	2.53	2.9166 (16)	108
N2—H2A···N4^{i}	0.88	2.09	2.9645 (16)	170
N2—H2B···O2	0.88	1.93	2.8125 (16)	175

Symmetry code: (i) $-x+\frac{1}{2}, -y+\frac{3}{2}, -z+1$.

For compound (I), all H atoms were placed in idealized positions and refined as riding, with C—H = 0.93–0.97 Å and N—H = 0.88 Å, and U_{iso}(H) = 1.2U_{eq}(C) or 1.5U_{eq}(methyl C,N). For compound (II), the H atoms of the water molecules were located in a difference Fourier map and refined as riding, with O—H = 0.98 Å and U_{iso}(H) = 1.5U_{eq}(O). The other H atoms were placed in idealized positions and refined as riding, with C—H = 0.95–0.98 Å and N—H = 0.88 Å, and U_{iso}(H) = 1.2U_{eq}(C,N). The highest peak in the final difference map was found at a distance of 1.29 Å from H13 and the deepest hole was 0.72 Å from C14.

For both compounds, data collection: *DENZO* (Otwinowski & Minor, 1997) and *COLLECT* (Nonius, 1998); cell refinement: *DENZO* and *COLLECT*; data reduction: *DENZO* and *COLLECT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *PLATON*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SQ1233). Services for accessing these data are described at the back of the journal.

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