

2,6-Dimethoxy-7,9-dimethylpurinium
iodide hemihydrateAlicja Kowalska,^{a*} Krystian Pluta^a and Kinga Suwińska^b^aDepartment of Organic Chemistry, The Medical University of Silesia, ul. Jagiellońska 4, 41-200 Sosnowiec, Poland, and ^bInstitute of Physical Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland
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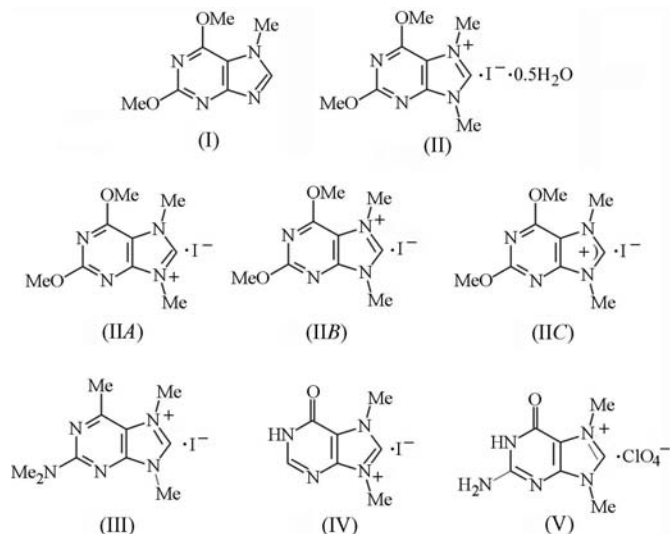
In the title compound, $C_9H_{13}N_4O_2^+ \cdot I^- \cdot 0.5H_2O$, the non-H atoms of the ionic components lie on a mirror plane in *Cmca*, with the O atom of the partial water molecule lying on a twofold rotation axis. Whereas one of the methoxy methyl groups is directed away from the adjacent *N*-methyl group, the other methoxy methyl group is directed towards its adjacent *N*-methyl group. The conformation of the methoxy methyl groups provides an explanation for the outcomes of intramolecular thermal rearrangements of 2,6-dialkoxy-7,9-dimethylpurinium salts.

Comment

Purinium salts exhibit interesting biological activity against adenocarcinoma and cytomegalovirus (Fujii & Itaya, 1999b), and affect pig brain ATPase (Fujii & Itaya, 1999a). Some substituted 6-methoxy-7,9-dimethylpurinium salts (isolated from *Heterostemma brownii* Hay – Asclepiadaceae) exhibit cytotoxic activity towards several tumor cell lines (Lin *et al.*, 1996, 1997), and some 2,6-dimethoxy-7,9-dimethylpurinium salts exhibit cytotoxic activity against alga *Chlorella vulgaris* (Kowalska & Sochacka, 2003). Purinium salts also play an important role in the synthesis of purine compounds *via* the Hilbert–Johnson reaction (Pliml & Prystas, 1967) or transglycosylation (Boryski, 1996). We found that quaternization of 2,6-dialkoxy- and 2(6)-chloroalkoxy-7-methylpurines with alkyl halides in aprotic solvents led mostly to 2,6-disubstituted 7,9-dialkylpurinium halides and 6-alkoxyhypoxanthines instead of 1,3,7-trialkylxanthines (Kowalska *et al.*, 1993; Kowalska & Maślankiewicz, 2001), although reaction of 2,6-dimethoxy-7-methylpurine, (I), with methyl iodide in a sealed tube at 373 K gave caffeine (Bergman & Heimbold, 1935). The absence of N1-alkylation was postulated to result from the conformations of the two alkoxy groups, causing steric hindrance at atom N1 (Kowalska *et al.*, 1993).

Recently, the structures of a few 7,9-dialkylpurinium salts (where the anion is iodide, bromide or perchlorate) have been analyzed (Sigel *et al.*, 2002; Nasiri *et al.*, 2005; Hocek *et al.*,

2005; Fu & Lam, 2005; Torii *et al.*, 2006). We have now determined the crystal structure of 2,6-dimethoxy-7,9-dimethylpurinium iodide as its hemihydrate, (II), to obtain information about the positions and conformations of the methoxy groups and the geometry of the imidazole ring in



comparison with (I) (Kowalska *et al.*, 1999) in an attempt to explain some results of the internal thermal O–N and N–N migrations of the alkyl groups (Kowalska & Maślankiewicz, 1997).

The non-H atoms of the cation of (II) (Fig. 1) all lie on a mirror plane in *Cmca*. For the methoxy groups, this permits complete overlap between the nonbonding *p*-type orbitals of the O atoms and the π -orbitals of the pyrimidine ring. Alkylation at atom N9 does not influence the conformation of the O2 methyl group as compared with that in (I). Whereas the bond lengths and angles (Table 1) in the pyrimidine ring of (II) are very close to those found in (I), the geometric details of the imidazole rings are different. The essential difference concerns the bonds and angles connected with atoms N7, C8 and N9. Whereas in (I) the N7–C8 bond is longer than the

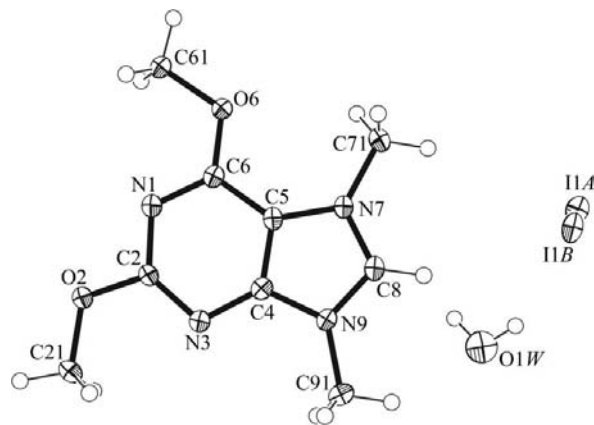


Figure 1

The molecular structure of (II), showing the atom labelling; the anion is disordered over two sites and the water molecule has an occupancy of 0.5. Displacement ellipsoids are drawn at the 30% probability level.

C8—N9 bond [1.349 (2) versus 1.312 (2) Å], in (II) the C8—N9 bond is longer [1.343 (4) versus 1.326 (4) Å]. There is also a change in the angles C5—N7—C8 [104.6 (1) versus 107.1 (3)° in compounds (I) and (II), respectively], N7—C8—N9 [115.1 (1) versus 110.6 (3)°] and C4—N9—C8 [103.6 (1) versus 107.3 (3)°]. Methyl atoms C71 and C91 are equally directed towards atom C8.

All these geometric details make this fragment of the imidazole ring more regular in (II) than in (I). The N7—C8 and N9—C8 bond lengths are also unequal in the recently reported 7,9-dimethylpurinium salts (Hocek *et al.*, 2005; Nasiri *et al.*, 2005; Sigel *et al.*, 2002) represented by structures (III)–(V), respectively (the differences in N—C bond lengths are in the range 0.016–0.025 Å). As the N7—C8 bond is shorter by 0.017 Å in salt (II), double-bond character can be assigned to this bond and the resonance structure is represented by formula (IIB). The presence of the second methyl group on the imidazole ring has some consequences in physicochemical properties. We found atom H8 to be much more acidic in purinium salt (II) than in purine (I). We observed the signal of

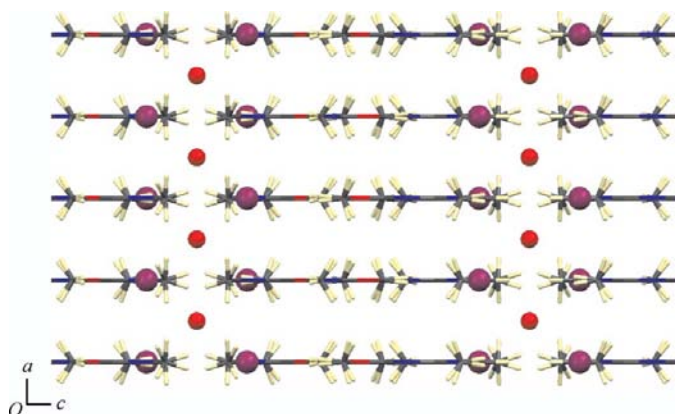


Figure 2
The packing of (II) along the *b* axis, showing the layer-type structure.

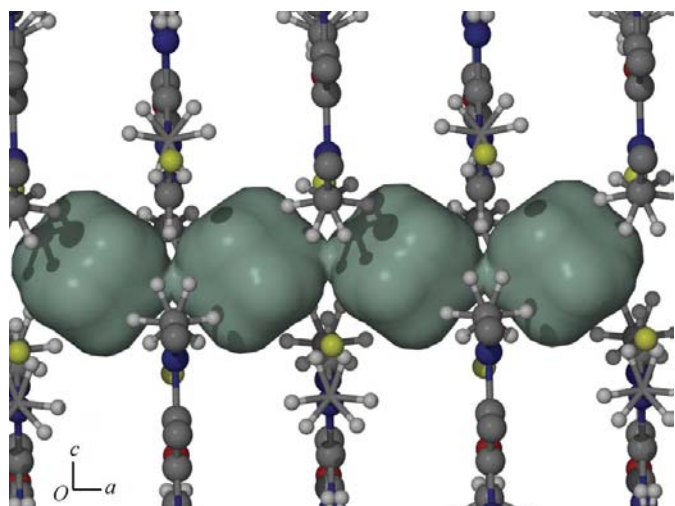


Figure 3
The interlayer cavities that accommodate the water molecules.

atom H8 to be strongly shifted downfield by 2.89 p.p.m. in ¹H NMR spectroscopy [7.75 and 10.64 p.p.m. in (I) and (II), respectively; Kowalska *et al.*, 1993; Kowalska, 2007]. The two *N*-methyl groups have very close chemical shifts (4.03 p.p.m. for N7CH₃ and 4.07 p.p.m. for N9CH₃) and the chemical shift of N7CH₃ is different from that in (I) (3.93 p.p.m.).

There is a close contact of 3.101 (4) Å between the *peri* substituents (O6···C71H₃) which is less than the sum of their van der Waals radii (3.40 Å; Pauling, 1960), meaning that the methoxy group is directed towards atom N1. We have reported that 2,6-dialkoxy-7,9-dimethylpurinium salts undergo O—N and N—N thermal rearrangement to give all four possible 1,3-dialkylxanthines *via* inter- and intramolecular alkyl group migration (Kowalska & Maślankiewicz, 1997). The very close intramolecular contacts, *i.e.* C61···N1 of 2.714 (4) Å, C21···N3 of 2.668 (4) Å and C91···N3 of 3.055 (4) Å, explain well the observed O6—N1, O2—N3 and N9—N1 methyl group migration as intramolecular rearrangement.

As the crystals of (II) were grown from aqueous solution, we found water molecules in the crystal structure, with the O atom located on a twofold rotation axis with an occupancy of 0.5. There is a weak C—H···O hydrogen bond between the cation and the partial water molecule (Table 2). There are also hydrogen bonds between the disordered iodide anions and water molecules (Table 2). The cations and anions are arranged in layers separated by 3.492 (2) Å (Fig. 2), while the water molecules are located in discrete cavities between the layers (Fig. 3).

Experimental

The title compound was obtained in 71% yield from the reaction of (I) with methyl iodide in acetonitrile at room temperature following the procedure described by Kowalska *et al.* (1993). Single crystals were grown from an aqueous solution at room temperature.

Crystal data

C ₉ H ₁₃ N ₄ O ₂ ⁺ ·I ⁻ ·0.5H ₂ O	<i>V</i> = 2595.12 (13) Å ³
<i>M_r</i> = 345.14	<i>Z</i> = 8
Orthorhombic, <i>Cmca</i>	Mo <i>K</i> α radiation
<i>a</i> = 6.9841 (2) Å	<i>μ</i> = 2.47 mm ⁻¹
<i>b</i> = 13.0977 (4) Å	<i>T</i> = 100 (2) K
<i>c</i> = 28.3695 (8) Å	0.21 × 0.15 × 0.08 mm

Data collection

Bruker KappaAPEXII diffractometer	15312 measured reflections
Absorption correction: analytical (Alcock, 1970)	2983 independent reflections
<i>T</i> _{min} = 0.640, <i>T</i> _{max} = 0.828	2699 reflections with <i>I</i> > 2σ(<i>I</i>)
	<i>R</i> _{int} = 0.064

Refinement

<i>R</i> [<i>F</i> ² > 2σ(<i>F</i> ²)] = 0.041	115 parameters
<i>wR</i> (<i>F</i> ²) = 0.082	H-atom parameters constrained
<i>S</i> = 1.19	Δ <i>ρ</i> _{max} = 0.74 e Å ⁻³
2983 reflections	Δ <i>ρ</i> _{min} = -0.99 e Å ⁻³

H atoms in the cation were treated as riding atoms in geometrically idealized positions, with C—H distances of 0.95 (ring) or 0.98 Å (CH₃), and with *U*_{iso}(H) = *kU*_{eq}(C), where *k* = 1.5 for the methyl

Table 1
Selected bond angles (°).

N3—C2—N1	129.7 (3)	C8—N9—C4	107.3 (3)
N3—C2—O2	119.2 (3)	C8—N9—C91	126.2 (3)
N1—C2—O2	111.1 (3)	C4—N9—C91	126.5 (3)
O6—C6—C5	118.9 (3)	C2—O2—C21	117.6 (2)
C6—N1—C2	117.7 (3)	C6—O6—C61	117.7 (2)
C2—N3—C4	110.4 (3)	I1A···O1W···I1A ⁱ	101.2 (2)
C8—N7—C5	107.1 (3)	I1B···O1W···I1B ⁱ	107.2 (2)
C8—N7—C71	125.5 (3)	I1A···O1W···I1B ⁱ	104.2 (2)
C5—N7—C71	127.4 (3)		

Symmetry code: (i) $-x + \frac{1}{2}, y, -z + \frac{1}{2}$.**Table 2**
Hydrogen-bond geometry (Å, °).

<i>D</i> —H··· <i>A</i>	<i>D</i> —H	H··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> —H··· <i>A</i>
C8—H8···O1W	0.95	2.51	3.131 (5)	123
C8—H8···I1B	0.95	2.98	3.852 (5)	154
O1W—H2W···I1A	0.85	2.85	3.580 (4)	146
O1W—H2W···I1B	0.85	2.55	3.290 (5)	145
O1W—H1W···I1A ⁱ	0.85	2.76	3.580 (4)	163
O1W—H1W···I1B ⁱ	0.85	2.49	3.290 (5)	157

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

groups and $k = 1.2$ otherwise. The H atoms of the water component could not be located in difference maps, but their positions were calculated as described by Nardelli (1999), and the water molecule was then refined as a rigid body [$O-H = 0.85 \text{ \AA}$ and $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{O})$]. Even applying an analytical absorption correction, there was a large ($> 6 \text{ e \AA}^{-3}$) peak in the Fourier electron-density maps approximately 0.5 \AA from the Γ^- anion. Applying a disorder of the Γ^- anion (4:1) gave better convergence of the refinement. The large displacement parameter of the water molecule, when compared with the other atoms, may be explained by possible disorder-induced formation of hydrogen bonds to the disordered Γ^- anion.

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* and *SCALEPACK*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEPIII* (Burnett & Johnson, 1996) and *X-SEED* (Barbour, 2001);

software used to prepare material for publication: *publCIF* (Westrip, 2008).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD3189). Services for accessing these data are described at the back of the journal.

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