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The methanol hemisolvate of amiloride hydrochloride

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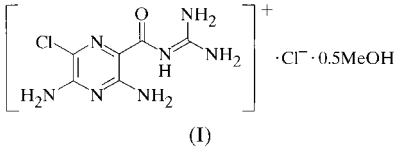
In the asymmetric unit of *N*-(3,5-diamino-6-chloropyrazin-2-ylcarbonyl)-*N*-(diaminomethylene)ammonium chloride methanol hemisolvate, $C_6H_9ClN_7O^+\cdot Cl^-\cdot 0.5CH_4O$, there are two crystallographically different amiloride molecules. Crystallographically identical amiloride molecules are stacked one above the other, alternately rotated by 180°. These stacks are arranged parallel to each other, forming layer *A*. The least-squares plane of the non-H atoms of the other molecules lying in layer *B* is tilted against the corresponding plane of the molecules in layer *A* by an angle of 79.89 (3)°. The methanol molecules and Cl^- anions are located between these layers, although the methanol molecules are closer to layer *A*.

Comment

Amiloride hydrochloride, a pyrazinecarboxamide derivative of guanidine, is a potassium-sparing diuretic. Selective binding to the mucosal membrane of distal tubular cells causes reduced potassium and hydrogen secretion and induces mild natriuresis. The area of application for amiloride is congestive heart failure and hypertension. It is often used in combination with thiazide and loop diuretics to prevent hypokalemia and metabolic alkalosis, the characteristic side effects of thiazide and loop diuretics (Laragh, 1982). In the 1960s, the first patents were registered on the dihydrate, the form in which



(I)

amiloride is used in drug preparations (Mazzo, 1986). It has been reported that amiloride dihydrate exists in two polymorphic forms (Jozwiakowski *et al.*, 1993). The crystal structures thereof are unknown, probably because the polymorphs are difficult to grow as single crystals. Amiloride crystallizes better in the presence of methanol, whereby two moles of amiloride accommodate one mole of methanol in the crystal, and it is the structure of this compound, (I), which is described in the present paper.

A perspective view of the molecules of (I) and the atom-labelling scheme is shown in Fig. 1, and Table 1 gives some selected geometric parameters.

The least-squares plane through the 11 non-H atoms of the pyrazine ring, the amino and chloro substituents, and a part of the side chain (C11, C12, N12, C13, C14, N11, C15, O11, N13, N14 and Cl11) indicates that this part of the molecule is planar. The r.m.s. deviation of the atoms is 0.0290 Å, with a maximum deviation of 0.0556 (8) Å for Cl11 lying on one side of the plane and of 0.0291 (14) Å for C14 lying on the other side. Furthermore, the least-squares plane through the four atoms of the guanidine group (N15, C16, N16 and N17) shows that they also lie in a plane. The angle between these two planes is 5.66 (9)°; therefore, the whole molecule is almost planar.

For the second amiloride molecule, the least-squares planes through the 11 non-H atoms of the pyrazine ring, the amino and chloro substituents, and the carbonyl group of the side chain (C21, C22, N22, C23, C24, N21, C25, O21, N23, N24 and Cl21), and through the four atoms from the guanidine side chain (N25, C26, N26 and N27), also indicate planarity. The r.m.s. deviation for the former is 0.0670 Å, with a maximum deviation of 0.1219 (17) Å for N24 lying on one side of the plane and of 0.1215 (15) Å for N23 lying on the other side. For the latter, the r.m.s. deviation is 0.0014 Å. The pyrazine ring and the guanidine group form an angle of 11.63 (7)°. Therefore, this molecule may also be regarded as planar.

The planarity of the two molecules is manifested through intramolecular hydrogen bonds between the carbonyl O atom and the H atoms of two amino groups, one belonging to the

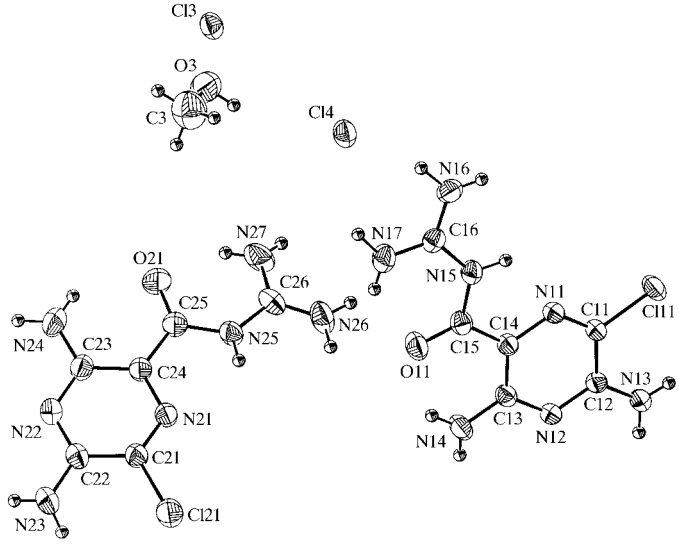


Figure 1
The molecular structure of (I) with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. The numbering scheme was chosen such that '1' prefixes all numbers in the first amiloride molecule and '2' for the second.

guanidine system and the other to the pyrazine ring, all taking part in stabilization effects. In addition, there is a hydrogen bond between N11 of the pyrazine ring and H15 of the protonated amide group, and another between N21 and H25 (Table 2).

The two amiloride molecules are connected by a hydrogen bond between the carbonyl O atom and atom H262 of the amino group. The amiloride molecules are protonated on N15 and N25. The bond distances shown in Table 1 involving C15, N15, C16, N16 and N17 for the first molecule and C25, N25, C26, N26 and N27 for the second molecule indicate that the positive charge is delocalized over all the atoms of the guanidine group.

The Cl3 ion is hydrogen bonded to two amiloride molecules and to the methanol molecule. The closest distance to the first amiloride molecule is 2.50 (2) Å, to the second 2.46 (2) Å and to the hydroxyl group of the methanol molecule 2.38 (4) Å. The Cl4 ion, however, forms hydrogen bonds only to the two amiloride molecules. The closest distance between the Cl4 ion and the first amiloride molecule is 2.23 (3) Å, and 2.44 (3) Å for the second (Table 2).

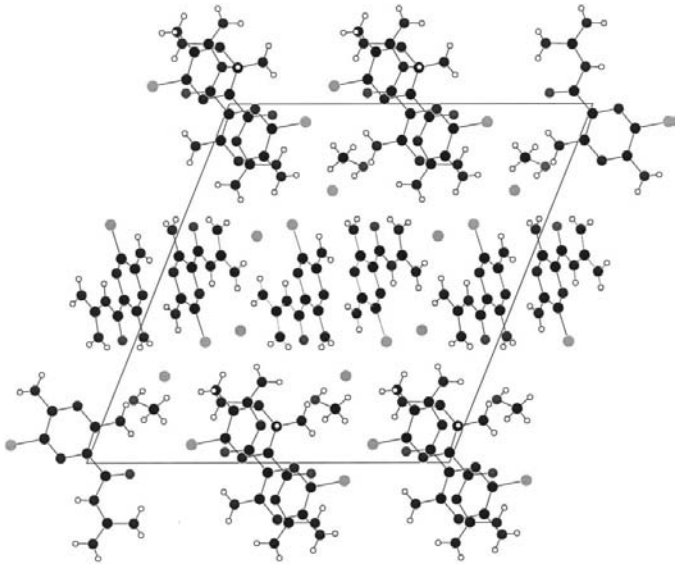


Figure 2
A packing diagram for (I) viewed along the *b* axis.

Fig. 2 shows the crystal packing in (I) along the *b* axis. The Cl^- ions and the methanol molecules lie between layers *A* and *B*, which are obtained by rotating amiloride molecules alternately by 180° and stacking one above the other. The methanol molecules are not equidistant from the two layers, but are closer to layer *A*. The non-H atoms of the amiloride molecules in the least-squares plane *B* are tilted against the corresponding plane *A* by an angle of about 79.89 (3)°. There is an N—H···O intermolecular bond from the protonated N25 atom to the methanol molecule, and a similar but weaker interaction from atom N26 through H262 to the same methanol O atom.

Experimental

Yellow needle-like crystals of (I) were obtained by dissolving amiloride hydrochloride (200 mg) in methanol (6 g). The warm solution was cooled to room temperature. As soon as the first crystals appeared, the beaker was sealed.

Crystal data

$C_6H_9ClN_7O^+\cdot Cl^-\cdot 0.5CH_4O$
M_r = 282.12
Monoclinic, $P2_1/a$
a = 18.044 (3) Å
b = 7.486 (3) Å
c = 19.052 (5) Å
β = 111.764 (15)°
V = 2390.1 (13) Å^3
Z = 8
D_x = 1.568 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 12–18°
μ = 0.54 mm^{-1}
T = 293 (2) K
Needle, yellow
0.6 × 0.3 × 0.3 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
5461 measured reflections
5201 independent reflections
4093 reflections with $I > 2\sigma(I)$
R_{int} = 0.015
θ_{max} = 27°
$h = -23 \rightarrow 21$
$k = 0 \rightarrow 9$
$l = 0 \rightarrow 24$
2 standard reflections
frequency: 120 min
intensity decay: none

Table 1
Selected geometric parameters (Å, °).

N15—C16	1.364 (2)	N25—C26	1.365 (2)
N16—C16	1.311 (2)	N26—C26	1.298 (3)
N17—C16	1.313 (2)	N27—C26	1.316 (3)
N16—C16—N15	117.39 (15)	N26—C26—N25	117.43 (17)
N17—C16—N15	121.07 (16)	N27—C26—N25	119.74 (18)
N16—C16—N17	121.54 (17)	N26—C26—N27	122.83 (18)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N13—H131···Cl11	0.82 (2)	2.62 (2)	3.0083 (18)	110.5 (17)
N13—H131···Cl3^{i}	0.82 (2)	2.50 (2)	3.2155 (18)	147.1 (18)
N13—H132···N12^{ii}	0.85 (2)	2.13 (2)	2.986 (2)	174.2 (19)
N14—H141···O11	0.88 (3)	2.05 (3)	2.731 (2)	133 (2)
N14—H142···Cl3^{iii}	0.82 (3)	2.60 (3)	3.384 (2)	162 (2)
N15—H15···N11	0.87 (2)	2.19 (2)	2.631 (2)	111.5 (15)
N15—H15···Cl4	0.87 (2)	2.823 (19)	3.5629 (18)	144.2 (16)
N16—H161···Cl4^{iv}	0.96 (3)	2.23 (3)	3.1684 (19)	165 (2)
N16—H162···Cl4	0.84 (2)	2.38 (2)	3.196 (2)	166 (2)
N17—H171···Cl4^{iv}	0.90 (3)	2.71 (3)	3.469 (2)	144 (2)
N17—H172···O11	0.81 (3)	2.08 (3)	2.664 (3)	130 (2)
N23—H231···Cl4	0.84 (3)	2.69 (3)	3.441 (2)	150 (2)
N23—H232···Cl3	0.84 (3)	2.57 (3)	3.350 (2)	153 (2)
N24—H241···O21	0.82 (2)	2.07 (2)	2.718 (3)	137 (2)
N24—H242···Cl3^{v}	0.88 (2)	2.46 (2)	3.2278 (19)	145.2 (19)
N25—H25···N21	0.77 (2)	2.24 (2)	2.664 (2)	114.9 (19)
N25—H25···O3^{vi}	0.77 (2)	2.33 (2)	2.992 (2)	144 (2)
N26—H261···Cl4^{vii}	0.83 (3)	2.44 (3)	3.238 (2)	161 (3)
N26—H262···O11^{vi}	0.85 (2)	2.49 (2)	2.994 (2)	118.7 (19)
N26—H262···O3^{vi}	0.85 (2)	2.05 (3)	2.831 (3)	152 (2)
N27—H271···Cl3^{vii}	0.73 (3)	2.74 (3)	3.3483 (19)	142 (2)
N27—H272···O21	0.87 (3)	1.95 (3)	2.633 (3)	134 (2)
O3—H3W···Cl3^{viii}	0.83 (4)	2.38 (4)	3.184 (2)	161 (3)

Symmetry codes: (i) $x, 1+y, z$; (ii) $2-x, 1-y, 1-z$; (iii) $2-x, -y, 1-z$; (iv) $\frac{3}{2}-x, y-\frac{1}{2}, 1-z$; (v) $x-\frac{1}{2}, -\frac{1}{2}-y, z$; (vi) $x-\frac{1}{2}, -\frac{1}{2}-y, z-1$; (vii) $1-x, -1-y, -z$; (viii) $2-x, -1-y, 1-z$.

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0515P)^2 + 0.5534P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.032$	$(\Delta/\sigma)_{max} = 0.037$
$wR(F^2) = 0.093$	$\Delta\rho_{max} = 0.38$ e Å^{-3}
$S = 1.11$	$\Delta\rho_{min} = -0.25$ e Å^{-3}
5201 reflections	Extinction correction: *SHELXL*97 (Sheldrick, 1997)
396 parameters	Extinction coefficient: 0.0051 (6)
All H-atom parameters refined	

The range of refined C—H distances is 0.87 (6)–0.93 (4) Å.

Data collection: *CAD*-4-*PC Software* (Enraf–Nonius, 1992); cell refinement: *CAD*-4-*PC Software*; data reduction: *SHELXS*97 (Sheldrick, 1997) and *OSCAIL* (McArdle, 2001, 1995); program(s) used to solve structure: *SHELXS*97 and *OSCAIL*; program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997) and *OSCAIL*; molecular graphics: *ORTEP*III (Burnett & Johnson, 1996), *ORTEP*-3 (Farrugia, 1997, 2000), *PLATON* (Spek, 2001) and *DIAMOND* (Brandenburg & Berndt, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: OS1141). Services for accessing these data are described at the back of the journal.

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