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Crystal structure of methyl 3,5-diamino-6-chloropyrazine-2-carboxylate

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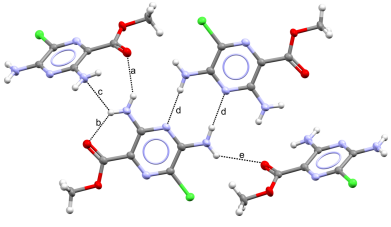
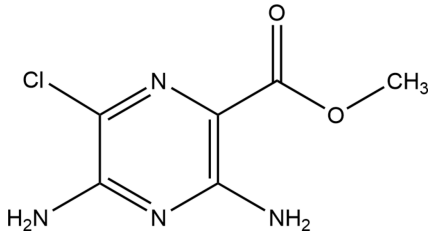
The crystal structure of methyl 3,5-diamino-6-chloropyrazine-2-carboxylate, $C_6H_7ClN_4O_2$, obtained from amiloride hydrochloride by heating in methanol is reported. Although the synthesis and chemical characterization of this compound have previously been described, its crystal structure has not been reported. The molecular structure is essentially planar, with a maximum deviation of −0.105 Å from the mean plane defined by the thirteen non-hydrogen atoms. The crystal packing is consolidated by five distinct N—H···*X* hydrogen-bond interactions, where *X* = N, O, or Cl. This structural analysis provides new crystallographic information on an amiloride-derived compound and contributes to the understanding of its molecular conformation and supramoecular organization in the solid state.

1. Chemical context

The natriuretic and antikaliuretic properties of certain nonsteroidal acylguanidine derivatives were reported by Bickling and colleagues in 1965 (Benos, 1982). This observation subsequently led to the synthesis of amiloride. Amiloride hydrochloride (3,5-diamino-*N*-carbamimidoyl-6-chloropyrazine-2-carboxamide) is a synthetic pyrazine derivative widely used in combination with other diuretics for the treatment of hypertension and heart failure. It acts on the kidneys by promoting the excretion of excess water and sodium in the urine while limiting potassium loss (Sun & Sever, 2000). Görlitzer and colleagues (2001) investigated the reactivity of the different functional groups in amiloride under various reaction conditions, including carboxylate and carboxylic acid formation, as well as cyclization reactions. Among the products obtained, they identified the title compound, which was prepared by heating amiloride in methanol (Görlitzerl *et al.*, 2004). Although the title compound (Fig. 1) has been extensively reported in the literature (Görlitzerl *et al.*, 2004; Bi *et al.*, 1992; Grabowski *et al.*, 1971; Shepard & Halczenko, 1979) in terms of its synthesis and characterization, to the best of our knowledge, its crystal structure has not yet been reported.





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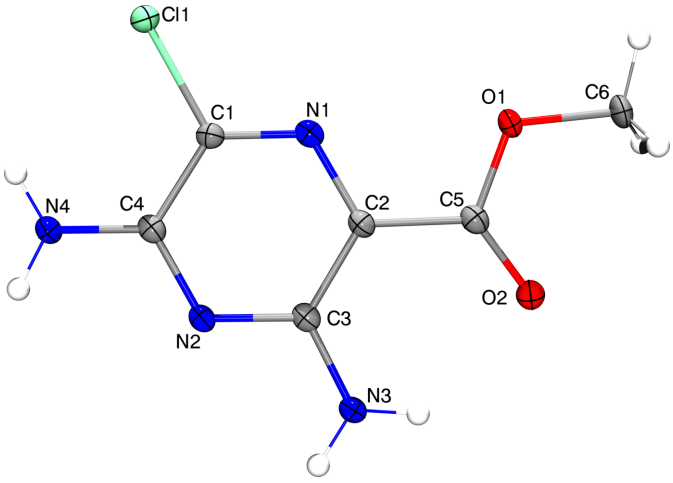

Figure 1
The molecular structure of methyl 3,5-diamino-6-chloropyrazine-2-carboxylate, with displacement ellipsoids drawn at the 50% probability level.

2. Structural commentary

The compound crystallizes in the monoclinic system, in the centrosymmetric space group $P2_1/n$. The molecular structure of the title compound is essentially planar (Fig. 2), with a maximum deviation of −0.105 Å (for atom O2) from the mean plane defined by the thirteen non-hydrogen atoms, including the aromatic ring and its substituents, as well as the two carbon atoms and the two oxygen atoms of the ester group. This structural feature is similar to that observed in previously reported compounds containing the 3,5-diamino-6-chloro-*N*-(diaminomethylene)pyrazine core. As shown in Fig. 3, an intramolecular N3—H3*B*···O2 hydrogen bond (Table 1) with graph-set motif $S(6)$ is formed.

3. Supramolecular features

In the crystal structure of the title compound, five distinct N—H···*X* hydrogen bonds are observed, where *X* corresponds to either an N, O or Cl atom. These hydrogen bonds are labeled (a)–(e) in Fig. 3, and their corresponding geometric parameters are listed in Table 1. The hydrogen bonds present in the crystal structure give rise to inter- and intramolecular rings, as well as chains of different sizes. Fig. 4

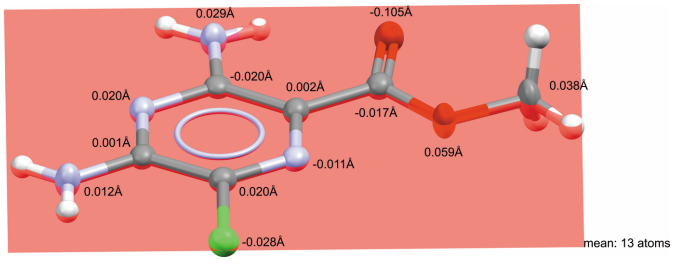

Figure 2
Deviations from the plane defined by the non-hydrogen atoms in the structure.

Table 1
Hydrogen-bond geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N3—H3*A*···O2^{i}	0.85 (1)	2.36 (1)	3.1014 (15)	147 (2)
N3—H3*B*···O2	0.85 (1)	2.14 (1)	2.7591 (15)	129 (1)
N3—H3*B*···N3^{i}	0.85 (1)	2.51 (2)	3.0559 (18)	123 (1)
N4—H4*A*···N2^{ii}	0.86 (1)	2.18 (1)	3.0419 (16)	177 (2)
N4—H4*B*···O2^{iii}	0.85 (1)	2.65 (1)	3.3277 (16)	138 (1)

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

illustrates selected examples: (I) a chain described by the graph-set notation $C_2^2(9)$, involving hydrogen bonds c and d and extending along the [111] direction; (II) a chain described by $C_2^2(12)$, involving hydrogen bonds a and d and extending along the [101] direction; and (III) a chain described by $C_2^2(8)$, involving hydrogen bonds a and c and extending along the c-axis direction.

4. Database survey

A search of the Cambridge Structural Database (CSD, Version 6.02, Updated Sep 2026; Groom *et al.*, 2016) revealed

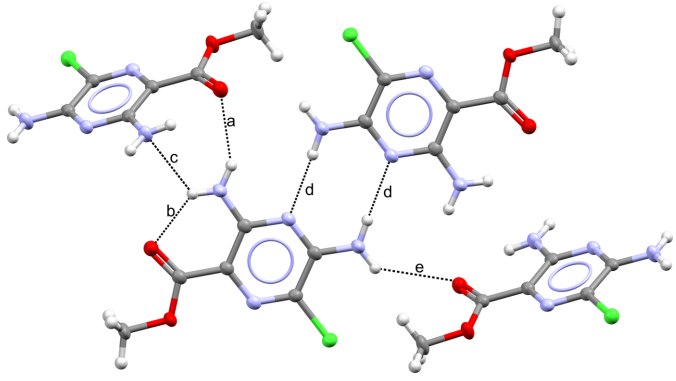

Figure 3
Hydrogen bonds (labeled a–e) identified in the crystal structure.

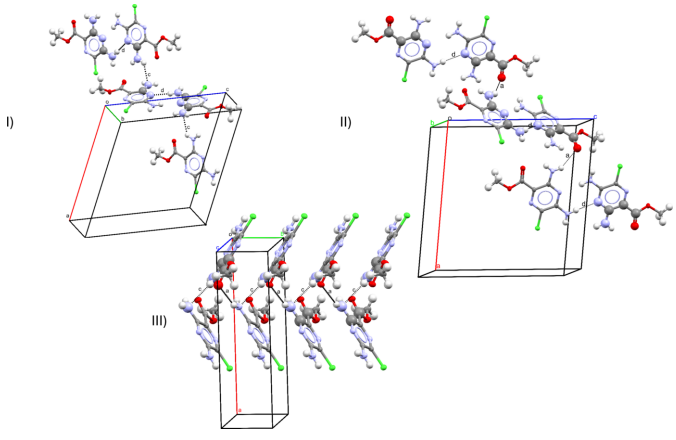

Figure 4
Supramolecular chains formed through hydrogen bonding.

no previous structural reports for the title compound. However, several amiloride derivatives containing the 3,5-diamino-6-chloro–(diaminomethylene)pyrazine core have been reported (Refcodes FEBDIA: Żesławska *et al.*, 2004; JENNOI: Schönberger *et al.*, 2014; TIJMII: Pretscher *et al.*, 2001; TUPJEU: Ton & Bolte, 2010; XEFTUA: Bejagam *et al.*, 2017; XUCHAE: Görlitzerl *et al.*, 2001).

5. Synthesis and crystallization

Following the method described by Görlitzerl *et al.* (2004), amiloride (0.10 g, Merck/Sigma-Aldrich) was heated in methanol for 30 min without prior purification. Slow evaporation of the solution at room temperature produced colorless crystals (0.06 g, 68% yield).

6. Refinement

Crystal data, data collection parameters, and structure refinement details are summarized in Table 2. The hydrogen atoms attached to the C6 methyl group were refined using a riding model with the *SHELXL* command HFIX 137. The hydrogen atoms on the amino nitrogens (N3 and N4) were located in a difference-Fourier map and refined with restrained distances.

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_6H_7ClN_4O_2$
M_r	202.61
Crystal system, space group	Monoclinic, $P2_1/n$
Temperature (K)	100
a, b, c (Å)	14.093 (3), 3.9904 (7), 14.607 (3)
β (°)	99.662 (3)
V (Å^3)	809.8 (2)
Z	4
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.44
Crystal size (mm)	0.39 × 0.09 × 0.05
Data collection	
Diffractometer	Bruker APEXII CCD
Absorption correction	Multi-scan (*SADABS*; Krause *et al.*, 2015)
T_{min}, T_{max}	0.668, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	8077, 2030, 1809
R_{int}	0.026
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.667
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.028, 0.069, 1.08
No. of reflections	2030
No. of parameters	131
No. of restraints	4
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.41, −0.22

Computer programs: *APEX2* (Bruker, 2014), *SAINT* (Bruker, 2014), *SHELXS97* (Sheldrick 2008), *SHELXL2019/2* (Sheldrick, 2015) and *SHELXTL* (Sheldrick, 2008).

Acknowledgements

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Crystal structure of methyl 3,5-diamino-6-chloropyrazine-2-carboxylate

Diego Martínez-Otero and Daniel Alejandro Montes de Oca-Maravilla

Computing details

Methyl 3,5-diamino-6-chloropyrazine-2-carboxylate

Crystal data

$C_6H_7ClN_4O_2$
$M_r = 202.61$
Monoclinic, $P2_1/n$
$a = 14.093$ (3) Å
$b = 3.9904$ (7) Å
$c = 14.607$ (3) Å
$\beta = 99.662$ (3)°
$V = 809.8$ (2) Å^3
$Z = 4$
$F(000) = 416$
$D_x = 1.662$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 3059 reflections
$\theta = 2.8$–$28.3°$
$\mu = 0.44$ mm^{-1}
$T = 100$ K
Needle, colourless
0.39 × 0.09 × 0.05 mm

Data collection

Bruker APEXII CCD diffractometer
Radiation source: Incoatec ImuS
Mirrors monochromator
ω scans
Absorption correction: multi-scan (SADABS; Krause *et al.*, 2015)
$T_{min} = 0.668$, $T_{max} = 0.746$
8077 measured reflections
2030 independent reflections
1809 reflections with $I > 2\sigma(I)$
$R_{int} = 0.026$
$\theta_{max} = 28.3°$, $\theta_{min} = 2.2°$
$h = -18\rightarrow18$
$k = -5\rightarrow5$
$l = -19\rightarrow19$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.028$
$wR(F^2) = 0.069$
$S = 1.08$
2030 reflections
131 parameters
4 restraints
Primary atom site location: structure-invariant direct methods
Secondary atom site location: difference Fourier map
Hydrogen site location: mixed
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0268P)^2 + 0.4793P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.41$ e Å^{-3}
$\Delta\rho_{min} = -0.22$ e Å^{-3}

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
Cl1	0.67556 (2)	1.13555 (8)	0.80771 (2)	0.01553 (9)
O1	0.42632 (7)	0.7620 (3)	0.54896 (6)	0.0174 (2)
O2	0.30381 (7)	0.4870 (3)	0.59752 (6)	0.0179 (2)
N1	0.52068 (8)	0.8535 (3)	0.71669 (7)	0.0130 (2)
N2	0.46358 (8)	0.5756 (3)	0.87330 (7)	0.0133 (2)
N3	0.33007 (8)	0.3431 (3)	0.78483 (8)	0.0158 (2)
H3A	0.3154 (12)	0.255 (4)	0.8334 (8)	0.019*
H3B	0.2988 (10)	0.283 (4)	0.7322 (8)	0.019*
N4	0.59655 (8)	0.8037 (3)	0.96509 (8)	0.0175 (2)
H4A	0.5779 (12)	0.702 (4)	1.0110 (9)	0.021*
H4B	0.6487 (9)	0.916 (4)	0.9705 (12)	0.021*
C1	0.57019 (9)	0.8986 (3)	0.79845 (8)	0.0127 (2)
C2	0.43886 (9)	0.6688 (3)	0.70790 (8)	0.0128 (2)
C3	0.41053 (9)	0.5280 (3)	0.78814 (8)	0.0125 (2)
C4	0.54372 (9)	0.7594 (3)	0.88084 (8)	0.0129 (2)
C5	0.38255 (9)	0.6270 (3)	0.61420 (9)	0.0141 (2)
C6	0.37563 (10)	0.7347 (4)	0.45420 (8)	0.0206 (3)
H6A	0.413183	0.844962	0.412123	0.031*
H6B	0.312570	0.843146	0.449176	0.031*
H6C	0.366907	0.497717	0.437299	0.031*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Cl1	0.01372 (15)	0.01689 (16)	0.01601 (15)	−0.00174 (12)	0.00254 (11)	0.00110 (12)
O1	0.0166 (5)	0.0256 (5)	0.0097 (4)	−0.0037 (4)	0.0008 (3)	0.0021 (4)
O2	0.0159 (5)	0.0231 (5)	0.0145 (4)	−0.0025 (4)	0.0023 (4)	−0.0004 (4)
N1	0.0140 (5)	0.0124 (5)	0.0131 (5)	0.0024 (4)	0.0037 (4)	0.0006 (4)
N2	0.0142 (5)	0.0147 (5)	0.0113 (5)	0.0017 (4)	0.0028 (4)	0.0014 (4)
N3	0.0158 (6)	0.0192 (6)	0.0124 (5)	−0.0029 (4)	0.0025 (4)	0.0028 (4)
N4	0.0164 (5)	0.0247 (6)	0.0113 (5)	−0.0039 (5)	0.0021 (4)	0.0013 (5)
C1	0.0123 (6)	0.0123 (6)	0.0140 (5)	0.0010 (5)	0.0033 (5)	0.0013 (5)
C2	0.0138 (6)	0.0131 (6)	0.0120 (5)	0.0018 (5)	0.0031 (4)	0.0009 (5)
C3	0.0132 (6)	0.0113 (6)	0.0134 (5)	0.0040 (5)	0.0031 (4)	0.0012 (5)
C4	0.0140 (6)	0.0131 (6)	0.0121 (5)	0.0034 (5)	0.0034 (4)	0.0007 (5)
C5	0.0151 (6)	0.0144 (6)	0.0132 (5)	0.0025 (5)	0.0034 (5)	0.0005 (5)
C6	0.0215 (7)	0.0294 (8)	0.0096 (5)	−0.0050 (6)	−0.0013 (5)	0.0020 (5)

Geometric parameters (Å, º)

Cl1—C1	1.7464 (13)	N3—H3B	0.854 (9)
O1—C5	1.3326 (15)	N4—C4	1.3389 (16)
O1—C6	1.4513 (15)	N4—H4A	0.862 (9)
O2—C5	1.2297 (16)	N4—H4B	0.854 (9)
N1—C1	1.2906 (16)	C1—C4	1.4306 (16)

N1—C2	1.3563 (17)	C2—C3	1.4162 (17)
N2—C4	1.3358 (17)	C2—C5	1.4719 (17)
N2—C3	1.3529 (16)	C6—H6A	0.9800
N3—C3	1.3469 (17)	C6—H6B	0.9800
N3—H3A	0.848 (9)	C6—H6C	0.9800
C5—O1—C6	116.04 (10)	N3—C3—N2	116.22 (11)
C1—N1—C2	118.84 (11)	N3—C3—C2	122.70 (11)
C4—N2—C3	118.82 (11)	N2—C3—C2	121.08 (12)
C3—N3—H3A	121.3 (11)	N2—C4—N4	118.70 (11)
C3—N3—H3B	119.4 (11)	N2—C4—C1	118.69 (11)
H3A—N3—H3B	118.4 (16)	N4—C4—C1	122.60 (12)
C4—N4—H4A	117.3 (12)	O2—C5—O1	123.54 (12)
C4—N4—H4B	119.4 (11)	O2—C5—C2	124.29 (11)
H4A—N4—H4B	123.1 (16)	O1—C5—C2	112.16 (11)
N1—C1—C4	123.20 (12)	O1—C6—H6A	109.5
N1—C1—Cl1	117.89 (9)	O1—C6—H6B	109.5
C4—C1—Cl1	118.90 (10)	H6A—C6—H6B	109.5
N1—C2—C3	119.38 (11)	O1—C6—H6C	109.5
N1—C2—C5	117.82 (11)	H6A—C6—H6C	109.5
C3—C2—C5	122.80 (12)	H6B—C6—H6C	109.5
C2—N1—C1—C4	0.80 (19)	C3—N2—C4—C1	0.01 (18)
C2—N1—C1—Cl1	179.66 (9)	N1—C1—C4—N2	−0.49 (19)
C1—N1—C2—C3	−0.64 (18)	Cl1—C1—C4—N2	−179.34 (9)
C1—N1—C2—C5	178.71 (11)	N1—C1—C4—N4	178.92 (12)
C4—N2—C3—N3	−179.44 (11)	Cl1—C1—C4—N4	0.06 (18)
C4—N2—C3—C2	0.12 (18)	C6—O1—C5—O2	−0.25 (19)
N1—C2—C3—N3	179.72 (12)	C6—O1—C5—C2	−179.60 (11)
C5—C2—C3—N3	0.4 (2)	N1—C2—C5—O2	−174.46 (12)
N1—C2—C3—N2	0.19 (18)	C3—C2—C5—O2	4.9 (2)
C5—C2—C3—N2	−179.12 (12)	N1—C2—C5—O1	4.89 (17)
C3—N2—C4—N4	−179.42 (12)	C3—C2—C5—O1	−175.79 (11)

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N3—H3*A*···O2^{i}	0.85 (1)	2.36 (1)	3.1014 (15)	147 (2)
N3—H3*B*···O2	0.85 (1)	2.14 (1)	2.7591 (15)	129 (1)
N3—H3*B*···N3^{i}	0.85 (1)	2.51 (2)	3.0559 (18)	123 (1)
N4—H4*A*···N2^{ii}	0.86 (1)	2.18 (1)	3.0419 (16)	177 (2)
N4—H4*B*···Cl1	0.85 (1)	2.62 (2)	3.0227 (12)	110 (1)
N4—H4*B*···O2^{iii}	0.85 (1)	2.65 (1)	3.3277 (16)	138 (1)

Symmetry codes: (i) −*x*+1/2, *y*−1/2, −*z*+3/2; (ii) −*x*+1, −*y*+1, −*z*+2; (iii) *x*+1/2, −*y*+3/2, *z*+1/2.