Crystal Structure of 1-(*m*-Chlorophenyl)biguanide Hydrochloride

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C₈H₁₁Cl₂ N₅ is monoclinic, $P2_1/n$. The unit-cell dimensions at 293 K are $a = 9.3569(9)$, $b = 13.6832(14)$, $c = 18.4879(19)$ Å, $\beta = 98.411(2)^\circ$, $V = 2341.6(4)$ Å³, $D_x = 1.408$ g/cm³, and $Z = 8$. The R value is 0.043 for 4129 reflections. The monoclinic unit cell contains two crystallographic independent molecules, A and B. The Cl(1) and Cl(4) ions are coordinated to 5 and 6 N atoms, respectively. In the crystal, there are two hydrogen bonds between N5A and N3B:N5B and N3A of the neighboring molecules, and constitute the major intermolecular attraction and packing force. These two molecules make a centro-symmetric dimer.

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5-Hydroxytryptamine₃ (5-HT₃) receptors are unique among serotonin receptors in that, rather than being coupled to G proteins, they are ligand-gated ion channels.¹ Allosteric or cooperative interactions may occur at 5-HT₃ receptors. These interactions have also been suggested based on preliminary

studies using NG-108-15 cell membranes, which showed that the rate of dissociation of the 5-HT₃ receptor antagonist [³H]RS-42358 depends upon the ligand used to prevent rebinding.² To characterize further putative allosteric interactions at 5-HT₃ receptors, steady-state and kinetic radioligand binding studies have been conducted using the receptor agonist 1-(*m*-chlorophenyl)biguanide. This suggests that the binding of this agonists to unoccupied sites on the receptor can increase the receptor's affinity for prebound ligands, and thereby slow their dissociation.^{3,4}

In this paper, we describe an X-ray structure determination of 1-(*m*-chlorophenyl)biguanide hydrochloride. The crystals were prepared from a commercially available compound.

X-ray data for crystals of the title compound were collected by graphite-monochromatized Mo K_α radiation at 293 K. No absorption correction was applied. The structure was solved by direct methods and refined by full-matrix least-squares with anisotropic temperature factors for the non-hydrogen atoms. In both molecules, the C4, C5 atoms of the phenyl rings show relatively high temperature factors, which may be due to a localized molecular disorder. The hydrogen atoms bonded to C

Table 1 Crystal and experimental data

Formula: C ₈ H ₁₁ N ₅ Cl ₂
Formula weight = 248.12
Crystal system: monoclinic
Space group: $P2_1/n$ $Z = 8$
$a = 9.3569(9)$ Å
$b = 13.6832(14)$ Å
$c = 18.4879(19)$ Å
$\beta = 98.411(2)^\circ$
$V = 2341.6(4)$ Å ³
$D_x = 1.408$ g/cm ³
$\mu(\text{Mo } K_\alpha) = 0.531$ mm ⁻¹
$T = 293$ K
Colorless
$F(000) = 1024$
$0.42 \times 0.09 \times 0.04$ mm
Radiation: Mo K_α
θ scans with θ from 1.5 to 25°
$R = 0.0431$ (on F^2)
$wR = 0.0485$ (on F^2)
$(\Delta/\sigma)_{\text{max}} = 0.002$
$(\Delta\rho)_{\text{max}} = 0.331$ e Å ⁻³
$(\Delta\rho)_{\text{min}} = -0.265$ e Å ⁻³
No. of reflections measured = 18797
No. of reflections used = 4129
No. of parameters = 313
Goodness-of-fit = 0.802
Measurement: Bruker Smart Apex CCD diffractometer
Program system: SMART V 5.625 and SAINT V 6.23C
Structure determination: direct methods (SHELXS-97)
Refinement: full matrix least-squares (SHELXL-97)

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Fig. 1 Molecular structure of 1-(*m*-chlorophenyl)biguanide hydrochloride with atom labeling. Thermal ellipsoids are drawn at the 50% probability level.

Table 2 Final atomic coordinates and equivalent isotropic temperature factors ($\text{\AA}^2$)

Atom	x	y	z	U _{eq}
Cl1	0.04414(10)	0.09903(5)	0.08914(5)	0.0531(3)
Cl2	0.62450(15)	0.58380(8)	0.06880(8)	0.1397(6)
N1A	0.7991(3)	0.23582(18)	0.13644(15)	0.0554(9)
N2A	0.6957(3)	0.0903(2)	0.10399(18)	0.0570(10)
N3A	0.5694(3)	0.20863(16)	0.16262(14)	0.0433(8)
N4A	0.3871(3)	0.1312(3)	0.08038(18)	0.0635(10)
N5A	0.3493(3)	0.1725(2)	0.19438(18)	0.0509(9)
C1A	0.8034(4)	0.3369(3)	0.1522(2)	0.0518(10)
C2A	0.7137(4)	0.4021(3)	0.1098(2)	0.0677(12)
C3A	0.7325(5)	0.5010(3)	0.1232(3)	0.0810(15)
C4A	0.8360(6)	0.5350(3)	0.1782(3)	0.102(2)
C5A	0.9212(5)	0.4698(3)	0.2189(2)	0.1017(18)
C6A	0.9065(4)	0.3714(3)	0.2069(2)	0.0767(14)
C7A	0.6831(4)	0.1773(2)	0.13327(18)	0.0430(9)
C8A	0.4369(4)	0.1700(2)	0.1449(2)	0.0423(9)
Cl3	0.38389(16)	-0.10897(8)	0.43580(8)	0.1379(6)
Cl4	0.95829(10)	0.37591(5)	0.41495(5)	0.0544(3)
N1B	0.2028(3)	0.23733(19)	0.36821(17)	0.0543(9)
N2B	0.3058(3)	0.3827(2)	0.4035(2)	0.0601(11)
N3B	0.4318(3)	0.26683(16)	0.34204(14)	0.0437(8)
N4B	0.6157(3)	0.3394(3)	0.42646(19)	0.0647(11)
N5B	0.6529(3)	0.3031(2)	0.31167(17)	0.0526(10)
C1B	0.2008(4)	0.1357(3)	0.3527(2)	0.0516(10)
C2B	0.2913(4)	0.0718(3)	0.3951(2)	0.0645(12)
C3B	0.2761(5)	-0.0269(3)	0.3814(3)	0.0782(14)
C4B	0.1752(6)	-0.0616(3)	0.3269(3)	0.0984(19)
C5B	0.0868(5)	0.0020(3)	0.2850(2)	0.1000(17)
C6B	0.0987(4)	0.1010(3)	0.2973(2)	0.0678(12)
C7B	0.3193(4)	0.2961(2)	0.37176(19)	0.0436(9)
C8B	0.5630(4)	0.3048(2)	0.3610(2)	0.0423(9)

$$U_{eq} = (1/3) \sum_i \sum_j U_{ij} (a_i^* a_j^*) (a_i a_j).$$

Fig. 2 Crystal-structure drawing. The broken lines show Cl...H interactions.

atoms were assigned based on the expected bonding geometry, and the H atoms bonded to N atoms were found in a difference-Fourier map and refined. The software used to prepare the material for publication was PARST97.⁵ Table 1 summarizes the crystal and experimental data. The molecular structure is shown in Fig. 1. The bond lengths for non-H atoms are listed in Table 2.

The monoclinic unit cell contains two crystallographic-independent molecules, A and B. The Cl(1) and Cl(4) ions are

Table 3 Bond distances ($\text{\AA}$)

Cl2 - C3A	1.738(4)	N1A - C7A	1.343(4)
N1A - C1A	1.414(4)	N2A - C7A	1.320(4)
N3A - C7A	1.333(4)	N3A - C8A	1.344(4)
N4A - C8A	1.326(4)	N5A - C8A	1.316(4)
C1A - C6A	1.375(5)	C1A - C2A	1.385(4)
C2A - C3A	1.384(4)	C3A - C4A	1.377(5)
C4A - C5A	1.351(5)	C5A - C6A	1.367(4)
Cl3 - C3B	1.730(4)	N1B - C7B	1.349(4)
N1B - C1B	1.420(4)	N2B - C7B	1.337(4)
N3B - C7B	1.319(4)	N3B - C8B	1.332(4)
N4B - C8B	1.325(4)	N5B - C8B	1.329(4)
C1B - C2B	1.379(4)	C1B - C6B	1.379(4)
C2B - C3B	1.377(4)	C3B - C4B	1.363(5)
C4B - C5B	1.362(5)	C5B - C6B	1.374(4)

coordinated to the 5 and 6N atoms, respectively. The mean Cl...N distance is 3.264(4) $\text{\AA}$, which is slightly different compared with 3.272(2) $\text{\AA}$ in the 1-(*p*-chlorophenyl)biguanide hydrochloride.⁶ There is a close resemblance between the dimensions of the biguanide residues in this structure and in 1-(*p*-chlorophenyl)biguanide hydrochloride.⁶ Figure 2 shows the packing of the molecules in the unit cell. In the crystal, there are two hydrogen bonds between N5A and N3B and N5B and N3A of neighboring molecules, which constitute the major intermolecular attraction and packing force. These two molecules make a centro-symmetric dimer. The N5A...N3B, H5...N3B, N5B...N3A, H18...N3A distances are 3.016(4), 2.17(3), 3.041(4), 2.26(3) $\text{\AA}$ and the N5A-H5...N3B, N5B-H18...N3A angles are 172(3) and 174(3) $^\circ$, respectively. There are several N...Cl intermolecular interactions that stabilize the molecules in the crystal, such as: N2A...Cl1 ($x + 1, +y, +z$) 3.314(3) $\text{\AA}$; N2A...Cl4 ($-x + 3/2, +y - 1/2, -z + 1/2$) 3.264(3) $\text{\AA}$; N4A...Cl4 ($x - 1/2, -y + 1/2, +z - 1/2$) 3.225(4) $\text{\AA}$; N2B...Cl4 ($x - 1, +y, +z$) 3.291(3) $\text{\AA}$; N1B...Cl4 ($x - 1, +y, +z$) 3.187(3) $\text{\AA}$; N2B...Cl1 ($-x + 1/2, +y + 1/2, -z + 1/2$) 3.271(3) $\text{\AA}$, and N4B...Cl1 ($x + 1/2, -y + 1/2, +z + 1/2$) 3.285(4) $\text{\AA}$.

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