Crystal Structure of 1-(2,3,4-Trimethoxybenzyl)piperazine monohydrochloride

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Trimetazidine is an anti-ischemic agent. The structure of trimetazidine hydrochloride, $C_{14}H_{22}N_2O_3 \cdot HCl$, was determined by X-ray crystallography. The compound crystallizes in a monoclinic system, space group $P2_1/c$ and cell parameters: $a = 21.548(1)\text{\AA}$, $b = 7.6273(3)\text{\AA}$, $c = 9.5982(5)\text{\AA}$, $\beta = 100.651(2)^\circ$, $Z = 4$, $V = 1550.32(12)\text{\AA}^3$. The crystal structure was solved by direct methods and refined by full-matrix least-squares on F^2 to final values of $R1 = 0.055$ and $wR2 = 0.118$.

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Trimetazidine (1-(2,3,4-trimethoxybenzyl)piperazine) is an anti-ischemic agent free of hemodynamic effects. It reduces intracellular acidosis and electrolyte abnormalities by optimizing the oxygen demand of mitochondria, and by preventing a decrease in the intracellular ATP levels.¹

The crystal structure of trimetazidine dihydrochloride hemihydrate ($C_{14}H_{22}N_2O_3 \cdot 2HCl \cdot 1/2H_2O$) (I) was published by Tanaka *et al.* in 2005.² The title compound is trimetazidine monohydrochloride — $C_{14}H_{22}N_2O_3 \cdot HCl$ (II).

The title compound (Fig. 1) was prepared as follows: after trimetazidine dihydrochloride was dissolved in methanol, a stoichiometric KOH alkali solution (pH = 10) was added. In this way, colorless single crystals suitable for X-ray structure analysis were obtained. The crystal and experimental data are summarized in Table 1.

The molecular structure of the title compound, drawn by ORTEP-III,⁴ is shown in Fig. 2. The positions of all hydrogen atoms were calculated geometrically in the “riding” mode on the adjacent non-hydrogen atoms.

The piperazine ring takes a chair conformation in both structures I and II. The dihedral angle between the least-squares planes of the piperazine and phenyl rings is $60.3(6)^\circ$ for structure I and $73.6(5)^\circ$ for II. The torsion angle $N1C7C1C2$ is $98(1)^\circ$ in structure I and $-77.6(4)^\circ$ in structure II. One of three methoxy groups with the torsion angle $C5C4O3C14$ equal to $-7(1)^\circ$ (for I) and $-3.4(5)^\circ$ (for II) lies close to the phenyl plane. Two other methoxy groups with $C1C2O1C12$ and $C2C3O2C13$ torsion angles equal to $119(1)^\circ$ and $-115(1)^\circ$, respectively, for

structure I and $98.5(4)^\circ$ and $-76.8(4)^\circ$, respectively, for structure II, are on opposite sides of the phenyl ring. The bond lengths and angles are close to their standard values.⁶ There are two intermolecular N-H...Cl type hydrogen bonds in the structure: $N2 \cdots Cl1 = 3.073(3)\text{\AA}$, $H \cdots Cl1 = 2.177(1)\text{\AA}$, $\angle N2-H \cdots Cl1 = 172.9(2)^\circ$ and $N2 \cdots Cl1^* = 3.121(2)\text{\AA}$, $H \cdots Cl1^* = 2.234(2)\text{\AA}$, $\angle N2-H \cdots Cl1^* = 168.8(2)^\circ$. The chlorine atom marked by * has the symmetry operator $-1-x; -0, 5+y; -0, 5-z$.

In the crystal by means of the hydrogen bonds, the molecules form chains along crystallographic axis b (Fig. 3).

Acknowledgments

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Table 1 Crystal and experimental data

Chemical formula: $C_{14}H_{23}N_2O_3 \cdot Cl$	
Formula weight = 302.79	
$T = 190\text{ K}$	
Crystal system: monoclinic	Space group: $P2_1/c$
$a = 21.548(1)\text{\AA}$	
$b = 7.6273(3)\text{\AA}$	$\beta = 100.651(2)^\circ$
$c = 9.5982(5)\text{\AA}$	
$V = 1550.32(12)\text{\AA}^3$	$Z = 4$
$D_x = 1.297\text{ g/cm}^3$	
Radiation: Mo K_α , $\lambda = 0.71073\text{ \AA}$	
$\mu(\text{Mo } K_\alpha) = 0.26\text{ mm}^{-1}$	$F(0\ 0\ 0) = 648$
Crystal size: $0.35 \times 0.25 \times 0.15\text{ mm}^3$	
No. of reflections collected = 5850	
No. of independent = 2986	
θ range for data collection: 3.44 to 25.94°	
Data/Restraints/Parameters = 2986/0/181	
Goodness-of-fit on $F^2 = 0.9$	
Final R indices [$I > 2\sigma(I)$] $R1 = 0.0545$, $wR2 = 0.0912$	
R indices (all data): $R1 = 0.1711$, $wR2 = 0.1181$	
$(\Delta/\sigma)_{\max} < 0.001$	
$(\Delta/\rho)_{\max} = 0.24\text{ e\AA}^{-3}$	$(\Delta/\rho)_{\min} = -0.29\text{ e\AA}^{-3}$
Measurement: Bruker-Nonius KappaCCD ⁴	
Programs system: SHELXL-97 ⁵	
Structure determination: SHELXS-97 ⁵	
CCDC deposition number: 833734

Fig. 1 Chemical diagram of the title compound.

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Fig. 2 The ORTEP-III³ structure of 1-(2,3,4-trimethoxybenzyl)piperazine monohydrochloride, showing 50% probability ellipsoids; the hydrogen atoms are shown as small spheres of arbitrary radii.

Fig. 3 Formation of N-H...Cl hydrogen bond chains in the crystal structure.

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