X-ray Structure Analysis Online

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, $C_{14}H_{22}N_2O_3$·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)Å, b = 7.6273(3)Å, c = 9.5982(5)Å, β = 100.651(2)°, Z = 4, V = 1550.32(12)Å^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 ($C_{14}H_{22}N_2O_3$·2HCl·1/2H_2O) (I) was published by Tanaka *et al.* in 2005.[2] The title compound is trimetazidine monohydrochloride — $C_{14}H_{22}N_2O_3$·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)° for structure I and 73.6(5)° for II. The torsion angle N1C7C1C2 is 98(1)° in structure I and –77.6(4)° in structure II. One of three methoxy groups with the torsion angle C5C4O3C14 equal to –7(1)° (for I) and –3.4(5)° (for II) lies close to the phenyl plane. Two other methoxy groups with C1C2O1C12 and C2C3O2C13 torsion angles equal to 119(1)° and –115(1)°, respectively, for structure I and 98.5(4)° and –76.8(4)°, 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···Cl1 = 3.073(3)Å, H···Cl1 = 2.177(1)Å, ∠N2–H···Cl1 = 172.9(2)° and N2···Cl1* = 3.121(2)Å, H···Cl1* = 2.234(2)Å, ∠N2–H···Cl1* = 168.8(2)°. 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).

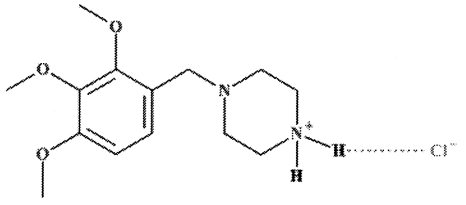

Fig. 1 Chemical diagram of the title compound.

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Table 1 Crystal and experimental data

Chemical formula: $C_{14}H_{23}N_2O_3$·Cl	
Formula weight = 302.79	
T = 190 K	
Crystal system: monoclinic	Space group: $P2_1/c$
a = 21.548(1)Å	
b = 7.6273(3)Å	β = 100.651(2)°
c = 9.5982(5)Å	
V = 1550.32(12)Å^3	Z = 4
D_x = 1.297 g/cm^3	
Radiation: Mo K_α, λ = 0.71073 Å	
μ(Mo K_α) = 0.26 mm^{-1}	F(0 0 0) = 648
Crystal size: 0.35 × 0.25 × 0.15 mm^3	
No. of reflections collected = 5850	
No. of independent = 2986	
θ range for data collection: 3.44 to 25.94°	
Data/Restrains/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 eÅ^{-3}	$(\Delta/\rho)_{min}$ = –0.29 eÅ^{-3}
Measurement: Bruker-Nonius KappaCCD[4]	
Programs system: SHELXL-97[5]	
Structure determination: SHELXS-97[5]	
CCDC deposition number: 833734	

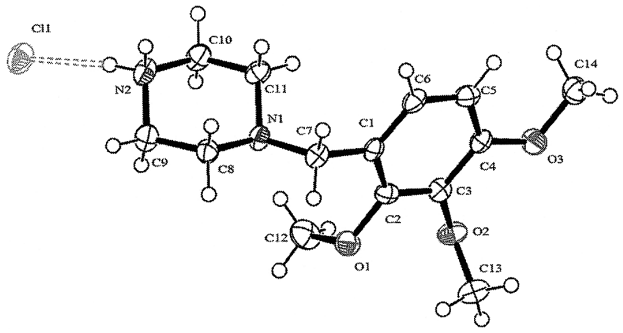

Fig. 2 The ORTEP-III[3] structure of 1-(2,3,4-trimethoxybenzyl) piperazine monohydrochloride, showing 50% probability ellipsoids; the hydrogen atoms are shown as small spheres of arbitrary radii.

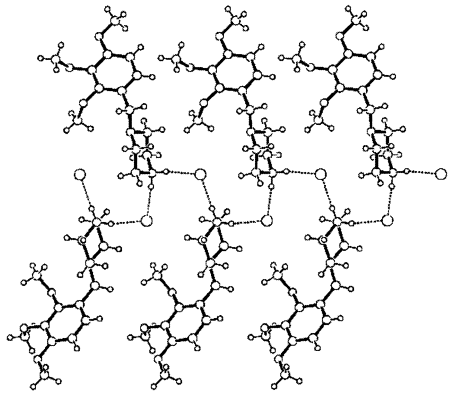

Fig. 3 Formation of N–H···Cl hydrogen bond chains in the crystal structure.

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