Research Article

Crystal Structure of Apraclonidine Hydrochloride

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Apraclonidine is used for the treatment of postsurgical elevated intraocular pressure. The crystal structure of its hydrochloride, $C_9H_{10}Cl_2N_4 \cdot HCl$, was determined by X-ray analysis. The crystal belongs to space group $P2_1/n$ with the cell dimensions $a = 9.665(10)$, $b = 11.8624(14)$, $c = 10.5675(11)$ Å, and $\beta = 92.199(9)^\circ$. The final R (all reflections) value is 0.053. Apraclonidine has a more twisted structure than its related drug of clonidine. The nitrogen atom bridging the two rings is protonated.

1. Introduction

Apraclonidine (2,6-dichloro- N^1 -(4,5-dihydro-1H-imidazol-2-yl)-1,4-benzenediamine) is a potent α -adrenergic agent similar to clonidine. The chemical structures of apraclonidine hydrochloride and clonidine are compared in Figure 1. Apraclonidine reduces aqueous humor formation. In clinical evaluation in the treatment of intraocular pressure, Robin et al. have showed that apraclonidine is effective in preventing the acute large postoperative intraocular pressure rise associated with argon laser iridotomy [1]. Apraclonidine is now used widely for the treatment of postsurgical elevated intraocular pressure. The additional amino group in apraclonidine makes it more polar than clonidine and reduces the penetration through the blood-brain barrier. Therefore, the pharmacological profile of apraclonidine is characterized by peripheral than central effects. Apraclonidine hydrochloride is clinically used now, but the crystal structure has not been determined yet. Therefore, the X-ray analysis of this drug was undertaken to disclose the inherent three-dimensional structure.

2. Method

Apraclonidine hydrochloride was purchased from Sigma-Aldrich Co. The single crystals of the compound were grown from a methanol solution. A colorless platelet crystal with the

size of $0.35 \times 0.30 \times 0.15$ mm was mounted on a glass fiber and used for data collection. The structure was solved by direct methods, and non-H atoms were refined by a full-matrix least squares method with anisotropic temperature factors. Positions of H-atoms attached to carbon and nitrogen atoms were geometrically calculated and located from difference Fourier synthesis, respectively. All H-atoms were refined by the riding model. The crystal and experimental data are given in Table 1.

3. Results and Discussion

An ORTEP drawing [2] of apraclonidine hydrochloride is shown in Figure 2. Selected bond lengths, bond angles, torsion angles, and possible hydrogen bonds in the crystal structure are given in Table 2. Bond lengths and angles are within the expected ranges. The dihedral angle between the least squares planes of the phenyl and imidazolidine rings is $86.65(5)^\circ$. In clonidine hydrochloride [3], the angle is 74.7° . The Cl–N1–C7–N3 torsion angle in apraclonidine is $168.2(1)^\circ$ and the corresponding angle in clonidine 178° . It means that in apraclonidine the imidazolidine ring is more twisted around the N1–C1 bond than that in clonidine. The exocyclic bond angles around the C7 atom are slightly asymmetrical with the N1–C7–N3 and N1–C7–N4 angles being $122.8(1)$ and

TABLE 1: Crystal and experimental data.

Formula: $C_9H_{10}Cl_2N_4 \cdot HCl$	Formula weight = 281.57
Crystal system: monoclinic	Space group: $P2_1/n$
$Z = 4$	
$a = 9.6615(10) \text{ \AA}$	$b = 11.8624(14) \text{ \AA}$
$c = 10.5675(11) \text{ \AA}$	$\beta = 92.199(9)^\circ$
$V = 1210.2(2) \text{ \AA}^3$	$D_x = 1.545 \text{ g/cm}^3$
No. of observations ($I > 2.00\sigma(I)$) = 1873	$\theta_{\max} = 68.20^\circ$ with Cu $K\alpha$
$R(I > 2.00\sigma(I)) = 0.048$	$(\Delta/\sigma)_{\max} = 0.000$
$(\Delta\rho)_{\max} = 0.48 \text{ e/\AA}^3$	$(\Delta\rho)_{\min} = -0.53 \text{ e/\AA}^3$
Measurement: Rigaku RAXIS-RAPID	Program system: CrystalStructure 4.0.1 [5]
Structure determination: SIR92 [6]	Refinement: full-matrix

FIGURE 1: Chemical diagrams of apraclonidine hydrochloride (a) and clonidine (b).

FIGURE 2: ORTEP structure of apraclonidine hydrochloride, showing 50% probability ellipsoids.

$125.6(1)^\circ$, respectively. There are five intermolecular hydrogen bonds in the crystal as illustrated in Figure 3 drawn by Mercury [4]. All nitrogen atoms are engaged in hydrogen bonds with the chloride ion. Although the intermolecular distance between the N2 and Cl1 [$x + 1/2, -y + 1/2, z + 1/2$] atoms is $3.132(1) \text{ \AA}$, no significant electron density corresponding to the hydrogen atom was observed between the two atoms on the difference Fourier map. On the other hand, two electron density peaks corresponding to the H2 and H3 atoms which are bonded to the N2 atom were located from the difference map. The relevant geometrical parameters shown in Table 2 indicate that these two $N2 \cdots Cl3$ contacts should be regarded

TABLE 2: Geometrical parameters.

(a) Selected bond lengths ($\text{\AA}$), bond angles ($^\circ$) and torsion angles ($^\circ$)	
Cl1–C2	1.730(1)
N1–C1	1.420(2)
N2–C4	1.355(2)
N3–C8	1.448(2)
N4–C9	1.463(2)
Cl2–C6	1.741(1)
N1–C7	1.329(2)
N3–C7	1.325(2)
N4–C7	1.320(2)
Cl1–C2–C1	118.43(9)
Cl2–C6–C1	118.76(9)
N1–C1–C2	121.4(1)
N1–C1–C6	122.0(1)
N1–C7–N3	122.8(1)
N2–C4–C5	120.1(1)
C7–N3–C8	111.5(1)
C7–N4–C9	111.0(1)
Cl1–C2–C3	119.09(10)
Cl2–C6–C5	118.08(8)
C1–N1–C7	122.8(1)
N1–C7–N4	125.6(1)
N2–C4–C3	121.6(1)
N3–C7–N4	111.6(1)
N3–C8–C9	103.0(1)
N4–C9–C8	102.9(1)
C7–N1–C1–C2	−86.6(1)
C1–N1–C7–N3	168.2(1)
C8–N3–C7–N1	177.1(1)
N1–C1–C2–Cl1	2.1(2)
C7–N1–C1–C6	96.2(1)
C1–N1–C7–N4	−12.2(2)
C9–N4–C7–N1	−177.9(1)
N1–C1–C6–Cl2	−4.9(2)

(b) Possible hydrogen bonds

Donor	H	Acceptor	D...A ($\text{\AA}$)	D–H ($\text{\AA}$)	H...A ($\text{\AA}$)	D–H...A ($^\circ$)
N1	H5	Cl3[I]	3.226(1)	0.90	2.38	157
N2	H2	Cl3[II]	3.418(1)	0.80	2.65	162
N2	H3	Cl3[III]	3.400(2)	0.94	2.52	156
N3	H7	Cl3[I]	3.338(1)	0.79	2.67	144
N4	H6	Cl3	3.213(1)	0.83	2.42	163

Symmetry operators:

[I] $x - 1/2, -y + 1/2, z - 1/2$.[II] $x - 1/2, -y + 1/2, z + 1/2$.[III] $-x + 3/2, y + 1/2, -z + 3/2$.

as weak hydrogen bonds. The $N3 \cdots Cl3$ hydrogen bond is also regarded as a rather weak hydrogen. In clonidine, however, N3 is not engaged in hydrogen bonding. Moreover, the N1 atom in clonidine forms a stronger hydrogen bond with

FIGURE 3: Packing diagram. Thin green lines denote intermolecular hydrogen bonds.

the chloride ion with the $N \cdots Cl$ distance being 3.09 Å. The corresponding hydrogen bond in apraclonidine, however, is not so strong with the $N \cdots Cl$ distance of 3.226(1) Å.

The Crystallographic Information Files (CIF) are given as Supplementary Material available online at <http://dx.doi.org/10.1155/2013/249672>.

4. Concluding Remarks

The molecular and crystal structures of apraclonidine hydrochloride were determined by X-ray analysis. Apraclonidine has a more twisted structure than its related drug of clonidine. The significant different patterns of the intermolecular hydrogen bonds observed in the crystals of apraclonidine hydrochloride and clonidine hydrochloride may contribute to their different drug deliveries. The crystallographic data presented in this work should be useful for designing new potent α -adrenergic agents.

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