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The crystal and molecular structure of tramazoline hydrochloride monohydrate, $C_{13}H_{18}N_3^+Cl^- \cdot H_2O$

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Tramazoline hydrochloride* / $C_{13}H_{18}N_3^+Cl^- \cdot H_2O$ / *Crystal structure* / *Sympathomimetic amine* / *α-Adrenergic agonist

Abstract. The crystal and molecular structure of tramazoline hydrochloride monohydrate, an α-adrenergic agonist with sympathomimetic action, has been studied by X-ray diffraction methods and refined to $R = 0.088$ ($R_w = 0.066$). It crystallizes in the orthorhombic space group *Pbca* with $a = 21.5224(11)$, $b = 8.9251(2)$, $c = 14.7149(4)$ Å, $V = 2826.58(18)$ Å^3, $Z = 8$, $M_r = 269.77$, $D_c = 1.268$ g/cm^3, $D_m = 1.263$ g/cm^3, $\lambda = 1.5418$ Å, $\mu = 23.568$ cm^{-1}, $F(000) = 1152$. The analysis indicates that the positive charge is dispersed over the nitrogen atoms of the molecule and the dihedral angle between the aromatic and dihydroimidazole groups is 126.7(2)°. The results have been compared with other structurally related α-adrenergic imidazoli-(di)ne agonists and antagonists.

Introduction

An important group of drugs capable of interacting with adrenergic receptors are the imidazoli(di)ne derivatives, and their action is selective for α-adrenergic receptors only (Ruffolo, Rosing and Waddell, 1979; Sander, Miller and Patil, 1975; Boudier et al., 1975; Boudier, Smeets, Brouwer and Van Rossum 1974). The 2-substituted imidazoli(di)nes are of major clinical significance and many of them have been widely used for their α-adrenergic agonist or antagonist activity (Gilman, Goodman, Rall and Murad, 1985).

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Tramazoline is an α-adrenergic agonist with sympathomimetic action and the hydrochloride form of the compound is used as a nasal decongestant (Stecher, 1968). Tramazoline contains a fused aromatic ring system linked to a dihydroimidazole ring through a NH bridge. The crystal structure analysis of tramazoline hydrochloride forms a part of our studies on the structural and conformational aspects of the α-adrenergics with a view to compare them with other structurally related α-adrenergic imidazoli(di)ne agonists and antagonists.

Experimental

Crystals were obtained from an aqueous solution of the commercially available compound by slow evaporation at room temperature (27° C). The crystal density measured by flotation in a mixture of bromoform and benzene, tallied with the calculated density for the tramazoline molecule with one molecule of water of crystallization. A crystal of approximate dimensions $0.20 \times 0.35 \times 0.30$ mm was used to determine the lattice parameters on a Philips PW1100 four-circle diffractometer. The refined cell parameters were obtained from the least-squares fit of angular 2θ positions of 90 reflections within $\theta < 45°$. Intensity data were collected with the same crystal in the same diffractometer with graphite monochromated Cu$K\alpha$ radiation upto $\theta_{max} = 65°$. The $\omega/2\theta$ scan technique and a scan width of 1.6° was used. 2345 unique reflections were measured in the range $h = 0$ to 25, $k = 0$ to 10, $l = 0$ to 11. Of these 1985 were considered as observed with $I \geqslant 2.5\sigma(I)$, where $\sigma(I)$ is the e.s.d. based on counting statistics. Two standard reflections remeasured every 90 min showed no significant intensity variation. The data were corrected for Lorentz and polarization effects but not for absorption.

Structure determination and refinement

The structure was solved by direct methods using the program MULTAN78 (Main et al., 1978). An E map generated from the phase set with the highest combined figure of merit located the chlorine atom and all the non-hydrogen atoms of the formula unit. All the H-atoms except the ones attached to the water molecule were located stereochemically. Structure refinement was done by least-squares methods by minimizing $\Sigma\omega(\Delta F)$ [where $\omega = 1/\sigma^2(F)$] for 18 anisotropically refined non-H atoms and 18 isotropically fixed H-atoms. Final $R = 0.088$, $R_w = 0.066$ and $S = 4.07$. Residual electron density was within ± 0.16 eÅ^{-3} in the final difference Fourier map. Scattering factors for the atoms were taken from the International Tables for X-ray Crystallography (1974) and the XRAY ARC

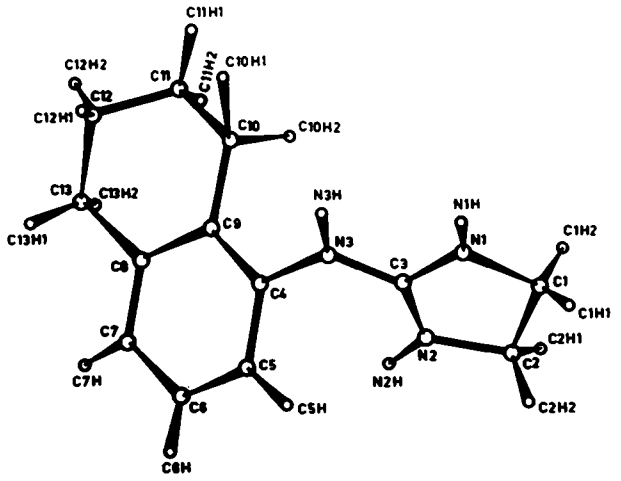

Fig. 1. Perspective view of tramazoline with the atom numbering scheme.

Table 1. Final coordinates ($\times 10^4$) and equivalent isotropic thermal parameters of the non-H atoms with e.s.d.'s in parentheses, $B_{eq} = 4/3\Sigma\Sigma b_{ij}\,(\bar{a}_i \cdot \bar{a}_j)$.

Atom	x	y	z	B_{eq} (Å^2)
Cl	1918(1)	3713(2)	6227(1)	5.15(6)
OW	2866(2)	3247(5)	123(3)	4.8(2)
N1	7889(2)	1832(5)	7288(3)	3.1(1)
N2	7589(2)	−13(6)	6358(3)	2.8(1)
N3	6829(2)	1212(5)	7284(3)	2.7(1)
C1	8483(3)	1256(8)	6919(5)	4.4(2)
C2	8265(3)	160(7)	6187(5)	3.9(2)
C3	7407(3)	1013(6)	6986(4)	2.5(2)
C4	6286(2)	438(6)	6959(4)	2.4(2)
C5	6175(3)	428(7)	6014(4)	2.9(2)
C6	5655(3)	−309(7)	5713(4)	3.7(2)
C7	5250(3)	−958(7)	6328(4)	3.6(2)
C8	5365(2)	−911(6)	7260(4)	2.7(2)
C9	5895(2)	−232(6)	7588(4)	2.1(1)
C10	6051(3)	−184(7)	8584(4)	3.0(2)
C11	5659(3)	−1297(9)	9138(4)	5.0(2)
C12	4990(3)	−1187(9)	8874(5)	5.4(3)
C13	4906(3)	−1660(7)	7900(5)	4.1(2)

program system (Vickery, Bright and Mallinson, 1971) was used for most of the calculations. The numbering scheme of the atoms in the structure are shown in Figure 1 and the final atomic parameters of the non-H atoms are given in Table 1. Lists of bond lengths, angles, anisotropic thermal

parameters, H-atom parameters, least-squares planes calculations and a table of observed and calculated structure factors have been deposited. [1]

Results and discussion

The intramolecular bond lengths and angles are normal. The average C–H and N–H distances in the structure are 0.992 and 0.938 Å respectively. The nitrogen atoms of the molecule are protonated, the positive charge being dispersed over all the three N atoms of the structure. The bond lengths and angles in the dihydroimidazole moiety are similar to those observed in clonidine hydrochloride (Cody and DeTitta, 1979) which also has a NH bridging group. The geometry of the linking N(3)H group is described by the bond angle 125.8(5)°. The short C(3)–N distances of 1.344(7), 1.343(7) and 1.332(7) Å in tramazoline are indicative of partial double bond character. A delocalization of the double bond has also been observed in the crystal structures of other adrenergic dihydroimidazo(li)dines like xylometazoline (Ghose and Dattagupta, 1986), tetrahydrazoline (Ghose and Dattagupta, 1989a), naphazoline (Podder, Mukhopadhyay, Dattagupta and Saha, 1983), tolazoline (Ghose and Dattagupta, 1989b), clonidine (Cody and DeTitta, 1979) are related analogs.

The dihyroimidazole ring is distorted from planarity, the atoms C(1) and C(2) being maximally deviated on opposite sides of this mean plane by −0.088(7) and 0.068(7) Å respectively. The aromatic ring C(4)–C(9) is planar within the limits of experimental error. The dihedral angle between the aromatic [C(4)–C(9)] and dihydroimidazole rings is 126.7(2)°.

The conformation of the molecule is defined by the torsion angles τ_1[C(5)–C(4)–N(3)–C(3)] and τ_2[C(4)–N(3)–C(3)–N(1)], where τ_1 defines the orientation of the C(3) atom with respect to the aromatic ring and τ_2 of the N(1) atom with respect to the aromatic ring. For tramazoline hydrochloride $\tau_1 = -51.5(7)°$ and $\tau_2 = 176.0(5)$.

The packing of the tramazoline hydrochloride monohydrate molecule as viewed down the *b* axis is shown in Figure 2 and the hydrogen bonding parameters are listed in Table 2. The crystal structure is stabilized by an extensive network of hydrogen bonds of the types N–H...Cl, O–H...Cl, and N–H...O. All the potential nitrogen, oxygen and chlorine atoms are involved in hydrogen bonding. N(1)–N1H...Cl forms a weak hydrogen bond. The structure contains polar columns parallel to the *c* axis surrounded by non-polar regions of hydrophobic aromatic moieties.

[1] Additional material to this paper can be ordered from the Fachinformationszentrum Energie-Physik-Mathematik, D-7514 Eggenstein-Leopoldshafen 2, Federal Republic of Germany. Please quote reference no. CSD 55502, the names of the authors and the title of the paper.

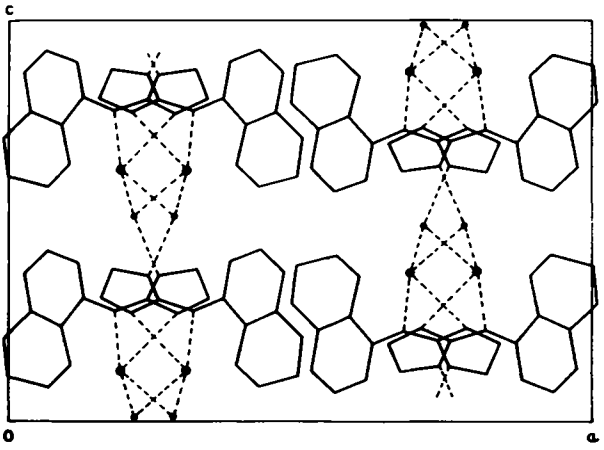

Fig. 2. Molecular packing of tramazoline hydrochloride monohydrate viewed down *b* axis. ● Cl atoms, ● O atoms.

Table 2. Hydrogen bond parameters.

Bond type D−H...A	Symmetry of A	D...A (Å)	D−H (Å)	H...A (Å)	<D−H...A (°)
N(3)−N3H...Cl	$1-x, y, 3/2-z$	3.133	0.936	2.222	164.2
N(2)−N2H...OW	$1-x, y-1/2, 1/2-z$	2.850	0.935	2.052	142.2
N(1)−N1H...Cl	$1/2+x, y, 3/2-z$	3.457	0.929	2.772	131.4
OW...Cl	$1/2-x, 1-y, z-1/2$	3.197			
OW...Cl	$x, 1/2-y, z-1/2$	3.140			

An important difference concerning the C−N bond lengths of the dihydroimidazole moiety has been observed between the crystal structures of some α-adrenergic agonists and antagonists. In the agonists like tramazoline, xylometazoline (Ghose and Dattagupta, 1986), naphazoline (Podder, Mukhopadhyay, Dattagupta and Saha, 1983), tetrahydrozoline (Ghose and Dattagupta, 1989a), clonidine (Cody and DeTitta, 1979), all the C(3)−N bonds in the dihydroimidazole moiety are seen to be similar in length. On the other hand in antagonists like tolazoline (Ghose and Dattagupta, 1989b), phentolamine (Leger, Dubost, Colleter and Carpy, 1983) and RS-21361 (Carpy, Montagut and Leger, 1984) the corresponding C(3)−N bond lengths have been found to be different.

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