

Crystal and Molecular Structure of a Sympathomimetic Amine, Tyramine Hydrochloride

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Abstract

The crystal and molecular structure of tyramine (4-hydroxyphenethylamine), a sympathomimetic amine, has been determined in the form of its hydrochloride by direct methods using X-ray diffractometer data. Tyramine hydrochloride ($C_8H_{11}NO \cdot HCl$) crystallizes in the orthorhombic space group $Pbcn$ with eight molecules per unit cell of dimensions $a = 19.973$ (2), $b = 10.768$ (2) and $c = 8.246$ (1) Å. The structure was refined by the full-matrix least-squares method leading to the final R value of 0.053. The ethylamine side chain attached to the planar phenol ring is also planar and maximally extended with the amino N atom at a distance of 5.14 Å from the centre of the phenol ring. The dihedral angle between these two planes is 69° . The structure is stabilized by a three-dimensional network of hydrogen bonds effected by two independent half-weighted Cl atoms occupying special positions on the twofold axes. The three-dimensional packing clearly indicates the presence of alternate hydrophobic and hydrophilic zones parallel to the bc plane.

Introduction

The present paper forms a part of our major programme of research on the structure and functions of bio-amines and their derivatives. Tyramine, a decarboxylated product of tyrosine, is somewhat similar in its action to adrenaline in raising blood pressure and stimulating smooth muscles. When injected intravenously in the system, tyramine causes relatively rapid and brief liberation of a neurotransmitter substance, nor-adrenaline, and thus produces the sympathomimetic effect. A preliminary account of this structure has been reported by Podder & Saha (1973) and the complete solution of the structure has been presented by Podder, Saha, Dattagupta & Saenger (1975). At the concluding stage of our work, it was brought to our notice that the

structure of the same compound has been solved almost simultaneously by Tomita and co-workers (Tamura, Wakahara, Fujiwara & Tomita, 1974). Though the gross structures obtained are comparable, appreciable differences in bond lengths and angles are observed. The R value and the standard deviations in bond lengths and angles as obtained by Tamura *et al.* (1974) are 0.114, 0.02 Å and 1° , whereas the corresponding values in this study are 0.053, 0.004 Å and 0.2° respectively.

Experimental

Single crystals were grown by slow evaporation of an aqueous solution of the title compound. The unit-cell dimensions were first determined from rotation and Weissenberg photographs using filtered Cu $K\alpha$ radiation and later more accurately on a Stoe four-circle single-crystal diffractometer. Systematic absences of reflections $h0l$ for l odd, $0kl$ for k odd and $hk0$ for $h + k$ odd indicate that the space group is $Pbcn$. Crystal data are given in Table 1.

Intensity data were collected using a crystal of dimensions $0.08 \times 0.12 \times 0.41$ mm on a Stoe four-circle automatic diffractometer with a graphite monochromator. Altogether 1307 reflections were measured in the $\theta/2\theta$ step scanning mode of 80 steps with a width $0.01^\circ \theta/0.02^\circ 2\theta$ per step and 0.8 s counting time. The background was measured by stationary-crystal and stationary-counter techniques for 13 s on each side of the peak. Three standard reflections were monitored

Table 1. *Crystal data*

Tyramine hydrochloride ($C_8H_{11}NO \cdot HCl$)

$a = 19.973$ (2) Å	$M_r = 173.64$
$b = 10.768$ (2)	$V = 1773.46$ Å ³
$c = 8.246$ (1)	$D_m = 1.30$ Mg m ⁻³
Space group $Pbcn$	$D_c = 1.31$
$Z = 8$	$\mu = 5.371$ mm ⁻¹

after each group of 100 measurements which did not show any noticeable change in intensity. The computer program used for solving the structure by the direct method was that of Long (1965). An *E* map was calculated using the phases of reflections corresponding to the set having the highest figure of merit. The two independent strong peaks in the *E* map were assigned to two half-weighted Cl atoms in the asymmetric unit. Other non-hydrogen atoms have also been located from the same *E* map. The atomic positions and the corresponding isotropic thermal parameters of the atoms were refined by the full-matrix least-squares method using *ORFLS* (Busing, Martin & Levy, 1962). After four cycles of refinement, the discrepancy factor *R* defined by $\sum ||F_o| - |F_c|| / \sum |F_o|$ came down to 0.17. One more cycle of refinement, applying anisotropic temperature factors to Cl atoms only, brought the *R* value to 0.12. H atoms were located at this stage from a difference Fourier map, utilizing stereochemical considerations as an additional aid. The temperature factors assigned to the H atoms were those of the heavier atoms to which they are attached. All the non-hydrogen atoms were then refined anisotropically while the H atoms were refined isotropically and after one cycle of refinement the *R* value came down to 0.08. As the shifts were less than their standard deviations, further refinement was stopped at this stage. It was then observed that a few reflections suffered from extinction effects and the necessary corrections were applied. Two more cycles of refinement yielded an *R* value of 0.053

Table 2. Positional parameters ($\times 10^4$) with standard deviations in parentheses

	<i>x</i>	<i>y</i>	<i>z</i>
Cl(1)	0	815 (0)	7500 (0)
Cl(2)	0	4974 (0)	7500 (0)
C(1)	3377 (1)	2666 (2)	9901 (3)
C(2)	2717 (1)	2762 (2)	10386 (3)
C(3)	2308 (1)	3723 (2)	9850 (3)
C(4)	2587 (1)	4597 (2)	8824 (3)
C(5)	3247 (1)	4517 (2)	8314 (3)
C(6)	3645 (1)	3549 (2)	8858 (3)
C(7)	1579 (1)	3799 (2)	10350 (3)
C(8)	1172 (1)	2783 (3)	9594 (3)
N	454 (1)	2896 (2)	9984 (2)
O	4292 (0)	3409 (1)	8365 (2)
H(C1)	3688 (18)	1972 (32)	10307 (44)
H(C2)	2511 (18)	2142 (32)	11122 (47)
H(C4)	2279 (16)	5290 (32)	8415 (42)
H(C5)	3427 (15)	5184 (33)	7546 (39)
H(C7)	1374 (17)	4563 (35)	9912 (43)
H'(C7)	1531 (17)	3686 (34)	11681 (47)
H(C8)	1192 (17)	2902 (30)	8326 (46)
H'(C8)	1299 (18)	2002 (33)	10052 (41)
H(N)	177 (18)	2284 (33)	9484 (48)
H'(N)	248 (17)	3528 (33)	9447 (46)
H''(N)	367 (19)	3045 (32)	10966 (52)
H(O)	4511 (17)	4185 (35)	8201 (45)

for all the observed reflections. The positional parameters of the atoms along with their estimated standard deviations are given in Table 2.*

Discussion

The intramolecular bond distances and angles are shown in Fig. 1. The mean standard deviations of all the distances and angles are 0.004 Å and 0.2° respectively. The values obtained by Tamura *et al.* (1974) are given in Table 3. The individual values of intramolecular bond lengths and angles compare well with corresponding parameters in other sympathomimetic amines. The aromatic C—C bond distances in the molecule vary from 1.381 to 1.391 Å, the average

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34018 (17 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. Bond lengths (Å) and angles (°) of tyramine hydrochloride as reported by Tamura *et al.* (1974) with the numbering scheme used in this work

Corresponding values obtained by us are given in parentheses for comparison. Average standard deviations in bond lengths and angles as obtained by Tamura *et al.* (1974) are 0.02 Å and 1° respectively and those of ours are 0.004 Å and 0.2° respectively.

C(1)—C(2)	1.430 (1.381)	C(1)—C(2)—C(3)	121.2 (121.7)
C(2)—C(3)	1.373 (1.391)	C(2)—C(3)—C(4)	119.0 (117.6)
C(3)—C(4)	1.381 (1.384)	C(3)—C(4)—C(5)	120.0 (121.8)
C(4)—C(5)	1.407 (1.387)	C(4)—C(5)—C(6)	120.1 (119.6)
C(5)—C(6)	1.381 (1.385)	C(5)—C(6)—C(1)	120.8 (119.7)
C(6)—C(1)	1.355 (1.389)	C(6)—C(1)—C(2)	118.8 (119.7)
C(3)—C(7)	1.529 (1.514)	C(1)—C(6)—O	118.1 (118.3)
C(7)—C(8)	1.496 (1.500)	C(5)—C(6)—O	121.2 (122.0)
C(8)—N	1.496 (1.474)	C(2)—C(3)—C(7)	121.3 (121.3)
O—C(6)	1.361 (1.363)	C(7)—C(3)—C(4)	119.7 (121.1)
		C(3)—C(7)—C(8)	110.8 (111.6)
		C(7)—C(8)—N	112.2 (112.1)
		τ_1	71 (69)
		τ_2	179 (178)

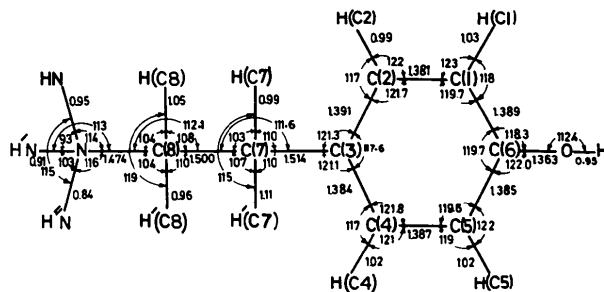


Fig. 1. Atomic numbering and structural formula of tyramine hydrochloride together with intramolecular bond angles and distances.

being 1.386 Å. The C(6)–O bond distance 1.363 Å, although shorter than the standard single C–O bond, agrees well with that of the corresponding bond in other similar amines. The angles in the benzene ring vary from 117.6 to 121.8°, the average being 120.0°. The equation of the least-squares plane passing through the atoms of the benzene ring as well as O and C(7) and the deviations of atoms from the plane are given in Table 4. It is interesting to note that the atoms O and C(7) are on one side of the least-squares plane whereas the atoms C(1) to C(6) of the benzene ring are on the other side, which resembles a boat-shaped structure, the benzene ring being the bottom of the boat.

The C–C distances in the ethylamine side chain, *i.e.* C(3)–C(7) and C(7)–C(8) are 1.514 and 1.500 Å respectively and are slightly shorter than the standard value 1.542 Å (Pauling, 1960). Such shortening has also been found in similar compounds studied by Carlström, Bergin & Falkenberg (1973). The C(8)–N bond length (1.474 Å) in the present compound agrees well with the standard C–N bond length 1.47 Å (Pauling, 1960) but is shorter than the standard C–N⁺ bond length 1.505 Å (Hahn, 1957). The equation of the least-squares plane passing through C(3), C(7),

Table 4. *Least-squares planes*

Equation of the least-squares plane through the atoms of the benzene ring, O and C(7): $-0.2807x - 0.5498y - 0.7866z = -9.8849$.

Deviations of atoms from the least-squares plane (Å)

C(1)	-0.005	C(5)	-0.008
C(2)	-0.013	C(6)	-0.013
C(3)	-0.010	C(7)	0.028
C(4)	-0.008	O	0.030

Equation of the least-squares plane through C(3), C(7), C(8) and N: $-0.1617x + 0.5733y - 0.8030z = -4.9984$.

Deviations of atoms from the least-squares plane (Å)

C(3)	0.027	C(8)	-0.027
C(7)	-0.027	N	0.027

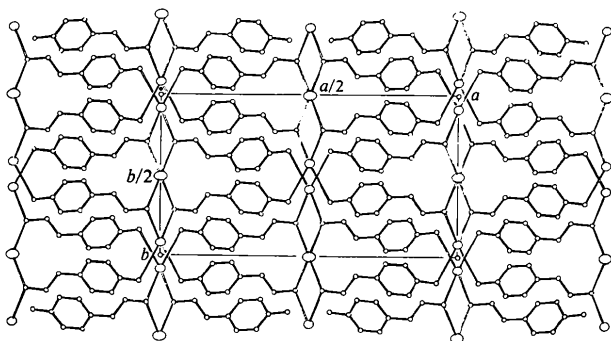


Fig. 2. Molecular packing diagram of tyramine hydrochloride down the *c* axis. Double lines indicate hydrogen bonds.

C(8) and N and the deviations of atoms from the plane are given in Table 4. The dihedral angle between this plane and that of the benzene ring is 69°. The lengths of the C–H and N–H bonds range from 0.95 to 1.11 Å and 0.84 to 0.95 Å respectively.

Hydrogen bonding and molecular packing

The three-dimensional arrangement of the molecules together with their hydrogen-bonding scheme viewed along the *c* axis is shown in Fig. 2. The hydrogen-bond distances and angles are given in Table 5. The structure may be visualized as Cl layers parallel to the *bc* plane with tyramine cations oriented lengthwise in between them. The structure is held together by a three-dimensional network of hydrogen bonds. There are four H atoms available for hydrogen-bond formation, three from the N⁺H₃ group and one from the OH group. All of them take part in the formation of hydrogen bonds of the types N⁺–H...Cl⁻ and O–H...Cl⁻. There are two Cl atoms Cl(1) and Cl(2), both of which act as acceptors. The two bonds of type N⁺–H...Cl⁻(2) are of lengths 3.17 and 3.22 Å and that of N⁺–H...Cl⁻(1) is 3.17 Å. The N–H...Cl angles involved in the above three cases are 150.5, 161.2 and 133.3° respectively. The O atom of the OH group is bonded to Cl(1) and the corresponding bond length and angle are 3.04 Å and 172.0° respectively. The tyramine molecule itself does not have a distinct hydrophobic and hydrophilic side, in contrast to nor-adrenaline but the three-dimensional packing diagram clearly indicates the presence of hydrophobic zones alternating with hydrophilic zones parallel to the *bc* plane.

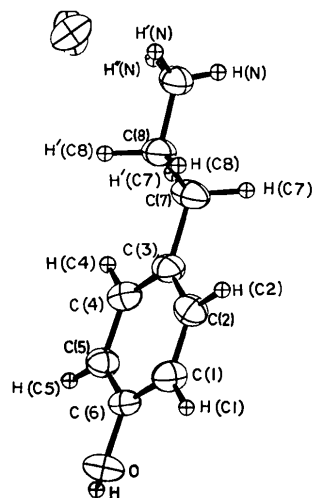


Fig. 3. ORTEP plot of tyramine hydrochloride. Thermal ellipsoids of non-hydrogen atoms are scaled to 50% probability.

Table 5. *Hydrogen-bond lengths (Å) and angles (°)*

<i>D</i> — <i>H</i> ... <i>A</i>	Position of acceptor atom	<i>D</i> ... <i>A</i>	<i>H</i> ... <i>A</i>	$\angle D$ — <i>H</i> ... <i>A</i>	$\angle H$ — <i>D</i> ... <i>A</i>
N—H(N)...Cl(1)	<i>x, y, z</i>	3.17	2.30	151.0	21.0
N—H'(N)...Cl(2)	<i>x, y, z</i>	3.17	2.29	161.2	13.5
N—H''(N)...Cl(2)	<i>x, 1 - y, ½ + z</i>	3.22	2.58	133.3	35.0
O—N(O)...Cl(1)	$\frac{1}{2} - x, \frac{1}{2} + y, z$	3.04	2.09	172.0	5.5

Conformation

Fig. 3 is an *ORTEP* plot of the molecule. The conformation of the ethylamine side chain and its relation to the benzene ring in tyramine hydrochloride are described by torsion angles τ_1 and τ_2 involving atoms C(4)—C(3)—C(7)—C(8) and C(3)—C(7)—C(8)—N respectively, the values of τ_1 and τ_2 being 69 and 178° respectively. These values agree well with those of most of the other sympathomimetic amines investigated. The phenethylamine side chain in the molecule is maximally extended (*trans* conformation) and the distance of the N atom from the centre of the ring has been found to be 5.14 Å, as in some other sympathomimetic amines, *e.g.* 5.14 Å in dopamine (Bergin & Carlström, 1968), 5.2 Å in hydroxyephedrine (Dattagupta & Saha, 1977) and 5.2 Å in phenylephrine (Bhaduri & Saha, 1975). In most of the sympathomimetic amines so far studied as well as in some structurally dissimilar sympathomimetic amines (Post & Kennard, 1974; Giesecke, 1973), this distance of the N atom from the centre of the benzene ring has been found to be around 5 Å. This distance appears to be a significant requirement for a compound to have sympathomimetic properties.

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The Conformation and Crystal Structure of *meso*-2,10-Dimethyl-3,11-dimethoxycarbonyl-1,6,9,13-tetraoxadispiro[4.2.4.2]tetradeca-2,10-diene

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Abstract

The crystal and molecular structure of the title compound, C₁₆H₂₀O₈, has been determined by single-crystal X-ray diffraction. The compound crystallizes in the monoclinic space group *P2₁/c* with two molecules

in a cell of dimensions $a = 9.199$ (1), $b = 12.423$ (1), $c = 8.047$ (1) Å, and $\beta = 114.87$ (1)°. The structure was solved by direct methods (*MULTAN*). Full-matrix least-squares refinement gave a final agreement index of $R = 0.054$ for 1166 observed reflections. The six-membered ring adopts the chair conformation around a