The Crystal and Molecular Structure of Tyramine Hemihydrate

A. M. ANDERSEN

Department of Chemistry, University of Oslo, Oslo 3, Norway

The crystal structure of tyramine hemihydrate has been determined by X-ray diffraction techniques. The title compound crystallizes in the orthorhombic space group $Pca2_1$ with two tyramine molecules and one molecule of water in the asymmetric unit. Unit cell dimensions are $a = 10.445$ Å, $b = 18.226$ Å, and $c = 8.221$ Å. Refinement by least-squares methods yielded a conventional R-factor of 0.051 for 904 observed reflections. Standard deviations in bond lengths are $0.007 - 0.012$ Å and in bond angles $0.7 - 0.9°$. The independent tyramine molecules are approximately related by pseudo-centers of symmetry, and are connected by rather short $O \cdots O$ and $N \cdots N$ hydrogen bonds, thereby forming infinite chains along the b-axis. Neighbouring chains are linked through hydrogen bonds to build double molecular layers in the crystals, and water molecules are situated between these double layers.

Tyramine is an indirectly acting sympathomimetic drug, causing the release of endogenous catecholamines from storage sites.

The present work was undertaken as part of a structural study of the free base form of sympathomimetic amines, in order to gain information of the molecular characteristics of this class of drugs. In this compound it is of particular interest to study the nature of the phenolic hydroxyl and amino group, since former structure investigations have demonstrated a zwitterionic character of the directly acting amines (—)adrenaline,[1] (—)noradrenaline,[2] and (—)phenylephrine.[3]
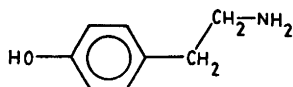
EXPERIMENTAL

Thin crystal plates of the title compound were grown from a hot aqueous solution of tyramine by slow evaporation at room temperature. The crystals appeared to contain two tyramine molecules and one molecule of water per asymmetric unit. A crystal of dimensions $0.30 \times 0.17 \times 0.05$ mm³ was used for the intensity measurements.

The systematic absences of reflections were consistent with space group $Pmca$ and $Pca2_1$ with two tyramine molecules in the asymmetric unit. The latter was chosen from considerations of the molecular packing in the crystals, and was confirmed by the structure analysis.

Unit cell parameters were obtained from a least-squares treatment of diffractometer measurements on 15 general reflections. The three-dimensional intensity data were recorded on a SYNTEX PI diffractometer with graphite crystal monochromated $MoK\alpha$ radiation, using $\omega - 2\theta$ scan technique. The scan speed varied between 1 and $1.3°$ min^{-1}, the scan range was $1.6°$, and the total background counting time was equal to the scan time. The measurements included 1251 unique reflections with $2\theta \leqslant 55°$. Of these, 347 reflections had $I < 2.5\sigma(I)$ and were classified as unobserved. The intensity data were corrected for Lorentz and polarization effects and scaled to an absolute level by Wilson's statistical method.

Atomic form factors used were those of Doyle and Turner[4] for oxygen, nitrogen, and carbon atoms, and of Stewart *et al.*[5] for hydrogen atoms.

Computers employed during the present study are described in Refs. 6 and 7.

CRYSTAL DATA

Tyramine hemihydrate, $C_8H_{11}NO.\frac{1}{2}H_2O$;
Space group $Pca2_1$, orthorhombic;
$a = 10.445(3)$ Å; $b = 18.226(6)$ Å, $c = 8.221(2)$ Å;
$V = 1565.12$ Å³; formula weight 146.19; $F(000) = 632$; $Z = 8$;
D_{obs} (flotation) $= 1.20$ g cm^{-3}; $D_{calc} = 1.241$ g cm^{-3}.

STRUCTURE DETERMINATION

The structure was determined by direct methods[6] and refined by full-matrix least-squares technique.

Table 1. Fractional atomic coordinates and thermal parameters with estimated standard deviations for non-hydrogen atoms. The anisotropic temperature factors are given by $\exp -2\pi^2(U_{11}a^{*2}h^2 + U_{22}b^{*2}k^2 + U_{33}c^{*2}l^2 + U_{12}a^*b^*hk + U_{13}a^*c^*hl + U_{23}b^*c^*kl)$.

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
OW	.2331(6)	.2654(2)	.3545(18)	.077(4)	.066(3)	.099(5)	.005(3)	.023(4)	−.011(4)
OA	.4157(4)	.2083(2)	.0966(11)	.067(4)	.033(2)	.066(5)	−.009(3)	−.024(4)	.009(3)
NA	.3975(6)	−.2147(3)	.2647(11)	.094(5)	.035(3)	.052(5)	.019(4)	.008(4)	−.001(3)
C1A	.3717(8)	−.0050(4)	.2759(13)	.049(5)	.036(5)	.023(4)	.004(4)	.008(4)	−.000(4)
C2A	.4724(8)	.0399(4)	.3274(15)	.048(5)	.038(4)	.044(7)	.005(4)	−.002(6)	.007(4)
C3A	.4875(8)	.1101(4)	.2720(14)	.040(5)	.048(5)	.045(6)	−.015(4)	−.019(5)	−.001(5)
C4A	.4013(8)	.1398(4)	.1555(12)	.054(5)	.039(4)	.033(6)	.005(4)	−.001(6)	−.004(4)
C5A	.3008(8)	.0958(4)	.1041(15)	.037(5)	.034(4)	.052(7)	.002(4)	−.016(5)	−.008(5)
C6A	.2866(8)	.0258(3)	.1615(13)	.045(5)	.036(4)	.042(7)	.004(4)	−.010(5)	−.011(5)
C7A	.3579(9)	−.0826(4)	.3358(15)	.042(5)	.038(4)	.046(7)	.002(4)	.004(5)	.002(4)
C8A	.4129(9)	−.1377(4)	.2165(15)	.073(6)	.038(4)	.047(6)	.008(4)	.016(6)	−.001(5)
OB	.5922(5)	.2806(2)	.2210(11)	.060(3)	.036(3)	.056(4)	.009(3)	−.004(4)	.002(3)
C1B	.6152(7)	.4965(4)	.0510(15)	.037(5)	.033(4)	.051(6)	.002(4)	.007(5)	.006(4)
C2B	.5203(8)	.4496(5)	.0012(14)	.045(5)	.056(6)	.041(7)	−.008(4)	−.009(5)	.006(5)
C3B	.5104(8)	.3784(4)	.0527(14)	.053(6)	.031(4)	.047(7)	−.005(4)	−.003(5)	.000(4)
C4B	.5980(7)	.3509(3)	.1618(13)	.034(4)	.026(4)	.049(6)	.005(3)	.006(5)	.001(4)
C5B	.6935(7)	.3969(4)	.2185(14)	.047(5)	.038(4)	.040(6)	.003(4)	−.004(5)	−.008(4)
C6B	.7033(8)	.4686(4)	.1597(14)	.036(5)	.039(4)	.056(8)	.010(4)	.001(5)	.014(5)
C7B	.6209(10)	.5742(5)	−.0056(15)	.054(6)	.044(5)	.039(7)	−.000(5)	.008(5)	−.004(5)
C8B	.5374(13)	.6239(5)	.0935(17)	.077(7)	.031(4)	.062(7)	−.004(5)	.018(8)	−.001(5)
NB	.5311(6)	.7020(3)	.0328(11)	.071(4)	.040(3)	.053(5)	−.006(3)	−.004(4)	−.002(3)

Table 2. Fractional atomic coordinates and isotropic thermal parameters with estimated standard deviations for hydrogen atoms.

Atom	x	y	z	B
H2A	.531(7)	.014(4)	.401(10)	6.7(25)
H3A	.550(5)	.135(2)	.294(7)	2.0(14)
H5A	.234(6)	.119(2)	.043(8)	3.0(17)
H6A	.200(6)	−.004(2)	.127(8)	4.2(18)
H71A	.276(3)	−.094(3)	.332(12)	4.8(24)
H72A	.419(7)	−.090(4)	.449(11)	6.8(25)
H81A	.535(5)	−.122(2)	.230(7)	1.5(11)
H82A	.354(6)	−.139(3)	.104(11)	6.9(21)
HNA1	.287(5)	−.236(2)	.288(8)	9.3(12)
HNA2	.397(7)	−.226(3)	.377(12)	9.3(21)
HNAB	.462(7)	.743(3)	.149(11)	9.3(17)
HOAB	.502(8)	.229(5)	.143(14)	9.3(32)
H2B	.466(6)	.467(3)	−.081(8)	3.3(19)
H3B	.440(8)	.332(4)	.013(12)	12.3(34)
H5B	.749(6)	.384(2)	.310(8)	2.3(14)
H6B	.771(6)	.501(2)	.207(7)	2.3(12)
H71B	.716(5)	.591(2)	−.020(9)	2.7(16)
H72B	.607(5)	.579(2)	−.108(8)	1.5(15)
H81B	.488(10)	.612(4)	.166(13)	8.0(37)
H82B	.584(7)	.632(3)	.189(10)	4.5(21)
HNB1	.491(5)	.702(3)	−.063(8)	9.3(15)
HNB2	.618(8)	.721(5)	.050(16)	9.3(42)
HOW1	.189(11)	.272(6)	.274(21)	9.3(49)
HOW2	.201(8)	.228(4)	.379(13)	9.3(23)

An E map computed with 379 reflections having $|E| > 1.0$ revealed fragments of the two independent tyramine molecules. After two successive Fourier refinement cycles the positions of the remaining non-hydrogen atoms could be established. The two molecules appeared to be aproximately related by a pseudo-center of symmetry located at $x = 0.50$, $y = 0.25$, $z = 0.16$. Three cycles of least-squares refinement with isotropic temperature factors yielded an R-factor of 0.22. A difference Fourier map calculated at this stage showed an isolated peak of height 2.5 e $Å^{-3}$, which was assumed to be an oxygen atom of a water molecule. Subsequent anisotropic refinement of all non-hydrogen atoms, including isotropic refinement of hydrogen atoms bonded to carbon in calculated positions, lowered the R-factor to 0.067. In a difference Fourier map there was observed electron density corresponding to one phenolic and five amino hydrogen atoms among the largest peaks. Of these, the phenolic and one amino hydrogen atom were situated near pseudo-centers of symmetry between the two independent oxygen and nitrogen atoms, respectively. Also peaks corresponding to water hydrogen atoms could be located. These hydrogen atoms were included in the last least-squares cycle with a common isotropic temperature factor. The final conventional R-factor is 0.051 and the weighted R-factor is 0.041. A total difference Fourier map showed no electron density exceeding 0.20 e $Å^{-3}$ in magnitude.

The final parameters for non-hydrogen atoms are listed in Table 1 and for hydrogen atoms in Table 2. Bond lengths and angles are given in Table 3. The numbering of the atoms is indicated in Fig. 1, which also presents the molecular arrangement in the crystals.

The structure factor list may be obtained from this institute upon request.

DESCRIPTION OF THE STRUCTURE

The independent tyramine molecules can both be described as consisting of two nearly planar parts: a phenol part and a fully extended ethylamine side chain. The deviations of the ring carbon atoms from a least-squares plane defined by these atoms are less than 0.007 Å in molecule A, and in molecule B less than 0.017

Table 3. Bond lengths (Å) and bond angles (°) with estimated standard deviations in parentheses.

	Molecule A	Molecule B
Bond length		
C1 − C2	1.398(12)	1.372(10)
C2 − C3	1.367(11)	1.369(11)
C3 − 34	1.421(11)	1.376(11)
C4 − C5	1.388(10)	1.383(10)
C5 − C6	1.369(10)	1.397(10)
C6 − C1	1.410(11)	1.380(11)
C1 − C7	1.505(10)	1.492(12)
C7 − C8	1.518(11)	1.498(12)
C8 − N	1.468(9)	1.511(11)
C4 − O	1.348(8)	1.372(7)
Bond angle		
C1 − C2 − C3	122.3(9)	123.6(9)
C2 − C3 − C4	120.5(9)	119.8(8)
C3 − C4 − C5	117.7(7)	118.6(7)
C4 − C5 − C6	121.1(9)	120.2(9)
C5 − C6 − C1	122.2(9)	121.3(8)
C6 − C1 − C2	116.3(7)	116.5(8)
C2 − C1 − C7	121.5(8)	121.8(9)
C6 − C1 − C7	122.1(8)	121.7(8)
C3 − C4 − O	121.6(8)	122.8(7)
O − C4 − C5	120.7(8)	118.6(8)
C1 − C7 − C8	112.0(8)	112.4(8)
C7 − C8 − N	114.7(8)	114.5(9)

Å. The deviations of the exocyclic atoms from the corresponding least-squares planes are 0.024 Å(OA), 0.037 Å(C7A), −0.007 Å(OB), and −0.042 Å(C7B). The dihedral angles C1 − C7 − C8 − N and C6 − C1 − C7 − C8 are −177.5 and 80.6°, respectively, for molecule A and −175.2 and −94.2° for molecule B. This is the conformation normally observed for phenylethylamine derivatives in the crystals.[1-3, 8]

None of the chemically equivalent bond lengths of the two independent tyramine molecules can within the error of the experiment be regarded as significantly different. The greatest discrepancy observed is between the two C − N bonds, which differ by more than 3σ. The C − N bond of molecule A (1.468 Å) corresponds to a normal C − NH$_2$ bond length, and that of molecule B (1.511 Å) agrees with the value usually found for a C − NH$_3^+$ bond. However, as there is a certain degree of correlation between the two molecules, it is question-
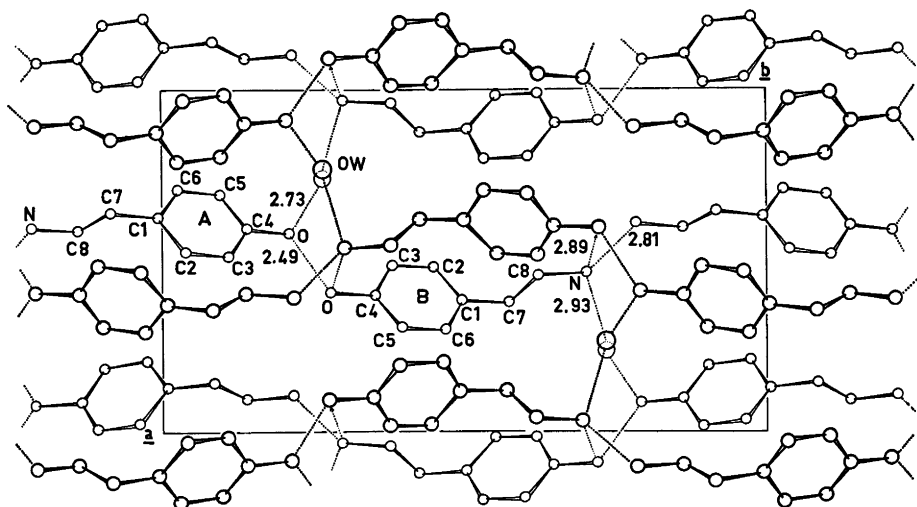
Fig. 1. The structure as viewed down the *c*-axis with hydrogen bonds (Å) indicated.

able if this difference can be regarded as real. Thus, the quality of the experiment does not allow any explicit conclusion regarding the characteristics of the tyramine molecules as compared with that of the free bases formerly investigated.[1-3] The latter molecules are observed to exist as zwitterions in the crystals having a protonated amino group and a negatively charged *meta* oxygen atom. There are, however, differences in the molecular packing arrangement of tyramine from that of the compounds just mentioned indicative of some disparities in molecular properties. The crystal structures of the free bases existing in a zwitterionic form [1-3] are all characterized by chains of ions, which are arranged head to tail with short contacts between positively charged nitrogen atoms and negatively charged oxygen atoms. In the tyramine crystals on the other hand, the crystallographic independent molecules are connected by rather short O···O (2.49 Å) and N···N (2.81 Å) hydrogen bonds across pseudocenters of symmetry. The crystals are thus consisting of chains of molecules connected head to head and tail to tail, as illustrated in Fig. 1. Although the hydrogen positions are uncertain, as may be seen from the temperature factors in Table 2, the electron density observed near the pseudocenters of symmetry indicates that one could describe the tyramine molecules as existing in the

crystals in a state intermediary that of neutral molecules and zwitterions. Thus, it seems that the tyramine molecules differ somewhat in character from that of adrenaline.[1] noradrenaline,[2] and phenylephrine,[3] for which an obvious zwitterionic state is observed.

A common feature for all of the free bases hitherto investigated is the presence of double molecular layers in the crystals. For tyramine the double layers run parallel to (100) and are produced by N···O hydrogen bonds between adjacent molecular chains. Specific for the tyramine crystals is the presence of water molecules, which are situated between molecular double layers and are linking these through hydrogen bonds. As the pseudosymmetry observed does not apply to the water molecules, the crystals also contain cavities across which there are only van der Waals contacts between the double layers of tyramine molecules. The hydrogen bond distances are given in Table 4a and are also indicated in Fig. 1. Short intermolecular contacts are presented in Table 4b. The water molecule is probably involved in two hydrogen bonds; one as a donor (to OA) and one as an acceptor (from NB). Furthermore, the tyramine molecule A is linked by hydrogen bonds to two neighbouring B molecules, whereas molecule B is hydrogen bonded to two A molecules and two B molecules within a double layer.

Table 4.

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a. Hydrogen bond lengths (Å)

OW···OA $(-x+\frac{1}{2},y,z+\frac{1}{2})$	2.73
NB···OW $(-x+1,-y+1,z-\frac{1}{2})$	2.93
OA···OB (x,y,z)	2.49
NA···NB $(x,y+1,z)$	2.81
NB···OB$(-x+\frac{1}{2},y,z-\frac{1}{2})$	2.89

b. Other intermolecular contacts (Å)

OW···OA (x,y,z)	3.04
OW···NB (x,y,z)	3.44
OW···C4A (x,y,z)	3.32
OA···NA $(-x+1,-y,z-\frac{1}{2})$	3.36
OA···C4B (x,y,z)	3.27
OA···C3B (x,y,z)	3.27
OB···C3A (x,y,z)	3.32
OB···C4A (x,y,z)	3.30
NA···OB $(x-\frac{1}{2},-y,z)$	3.43
C1A···C6A $(-x+\frac{1}{2},y,z+\frac{1}{2})$	3.62

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