

## The Structure of the Catecholamines. II. The Crystal Structure of Dopamine Hydrochloride

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The isomorphous crystals of the hydrochloride and the hydrobromide of dopamine,  $C_8H_{11}O_2N$ , are orthorhombic, space group  $Pbc2_1$  with four formula units in cells having the dimensions  $a=10.52$ ,  $b=11.13$ ,  $c=7.94$  Å and  $a=10.69$ ,  $b=11.47$ ,  $c=7.97$  Å respectively. The structure of the hydrochloride was determined three-dimensionally and refined by least-squares methods to a final  $R=0.084$ . The structure is stabilized by a network of hydrogen bonds with the chloride ions as acceptors.

### Introduction

Dopamine, 3,4-dihydroxyphenylethylamine or 3-hydroxytyramine, which in the body is synthesized from the amino acid L-tyrosine, is one of the natural catecholamines. It is a substance of great biological significance, being the immediate precursor of the neurotransmitting hormone noradrenaline, the structure of which has recently been determined by the authors (1967). In certain organs dopamine can reach relatively high local concentrations, especially in the central nervous system where it probably has a function of its own. Its physiological role, however, is not yet fully established.

### Experimental

The hydrochloride and hydrobromide of dopamine crystallize readily from aqueous solutions in colourless, orthorhombic plates which appear to be perfectly stable.

#### Crystal data

	Dopamine hydrochloride	Dopamine hydrobromide
Empirical formula	$C_8H_{11}O_2N \cdot HCl$	$C_8H_{11}O_2N \cdot HBr$
M.W.	189.64	234.10
$a$ (Å)	$10.515 \pm 0.002$	$10.69 \pm 0.02$
$b$ (Å)	$11.130 \pm 0.002$	$11.47 \pm 0.02$
$c$ (Å)	$7.938 \pm 0.002$	$7.97 \pm 0.02$
$V$ (Å) <sup>3</sup>	929.0	999
$D_m$ (g.cm <sup>-3</sup> ) (by flotation)	$1.356 \pm 0.002$	$1.592 \pm 0.002$
$D_x$ (g.cm <sup>-3</sup> ) ( $Z=4$ )	$1.355 \pm 0.001$	$1.59 \pm 0.01$
$\mu$ (cm <sup>-1</sup> ) for $\lambda=1.54$ Å	33.4	60.4

The systematic absences for both halides are  $h0l$  when  $l$  is odd and  $0kl$  when  $k$  is odd, which implies either the noncentric space group  $Pbc2_1$  or the centric  $Pbcm$ .

Since the latter requires the four molecules to be in the mirror plane and hence perfectly planar it can be disregarded. The hydrochloride crystal used for collecting three-dimensional data was trimmed to the dimensions  $0.014 \times 0.019 \times 0.011$  cm.

Integrated multiple film equi-inclination Weissenberg photographs of this crystal were taken with Ni-filtered Cu  $K\alpha$  radiation for the 0–6 layers about the  $c$  axis and, after remounting, for the 0–1 layers about the  $a$  axis thereby covering 88% of the effective copper sphere ( $\sin \theta < 0.985$ ). The photographic density of the integrated reflexions and of the corresponding background was determined in a microdensitometer. Of the 1063 reflexions accessible, 804 were actually above the threshold for observation. The 103 systematic absences were given zero intensity while the rest of the 259 non-observed reflexions were given half the threshold value. The intensities were corrected for film factors, for  $\alpha_1 - \alpha_2$  separation and for Lorentz and polarization factors but no corrections were made for extinction or absorption. The reflexions occurring in both the zones  $[100]$  and  $[001]$  were cross-correlated in order to get all reflexions on a common scale. The structure amplitudes were subsequently placed on an approximately correct level by the method due to Wilson (1942). Since the crystal data above suggested that dopamine hydrochloride and hydrobromide are isomorphous it was regarded as sufficient to record the  $hk0$  level of the latter only. Moreover in the centrosymmetric (001) projection it should be easy to locate the bromine atoms in order to facilitate the solution of the hydrochloride structure.

### Determination of the structure

The (001) Patterson projections of the hydrochloride and the hydrobromide were very similar, showing that these two halides of dopamine are isostructural. The prominent halogen-halogen peaks were located on the  $b$  axis. The reflexion satellites accordingly appeared with heights equal to the rotation peaks and two different sets of coordinates for the halogen atom could

be chosen:  $x=0.00$ ,  $y=0.07$  or  $x=0.00$ ,  $y=0.18$ . For several reasons the first alternative was regarded as the correct one. With bromine atoms only, an initial  $R$  value ( $R = \Sigma(|F_o| - |F_c|) / \Sigma|F_o|$ ) of 0.46 was gained. Using the signs obtained, the corresponding electron density map showed, beside the bromine maxima, five well-defined peaks which were used for further Fourier refinement. After two cycles of refinement the electron density map showed distinct peaks nicely fitting the anticipated configuration of the dopamine molecule. However, the relative heights of some of the peaks were not quite satisfactory and a least-squares refinement did not bring the  $R$  index below 0.17, which was regarded as too high to be acceptable. It became apparent that the wrong set of coordinates had been chosen and the other set was consequently tested. Even if the initial  $R$  value with the bromine atoms alone was slightly higher than that of the first alternative, two Fourier refinements rapidly brought the  $R$  index down to 0.12. The atomic  $x$  and  $y$  coordinates of the hydrobromide were then applied directly to the hydrochloride data and a two-dimensional least-squares refinement with a common isotropic temperature factor ( $B=2.4 \text{ \AA}^2$ ) resulted in an  $R$  index of 0.115. The electron density map of the (001) projection of the hydrochloride was also very satisfactory. From the projected bond lengths of the dopamine molecule and calculated close contacts with the chlorine atoms, preliminary  $z$  coordinates were found for further three-dimensional refinement.

### Refinement procedure

The structure was refined three-dimensionally on an IBM 7090 computer with the full matrix least-squares program by Busing, Martin & Levy (1962) and the form factors were those in Vol. III of *International Tables for X-ray Crystallography*. After four cycles of refinement with observed reflexions only and individual temperature factors, an  $R$  value of 0.129 was obtained. A decrease to 0.110 was gained after two additional cycles with anisotropic temperature factors. The introduction of 7 out of the 12 hydrogen atoms at probable positions did not improve the  $R$  index and three-

dimensional difference functions did not show peaks at expected hydrogen positions. An inspection of the structure factors showed that the strongest  $|F_o|$  were appreciably weaker than corresponding  $|F_c|$ , a situation characteristic for secondary extinction. Since no program for extinction correction was available the 25 strongest reflexions ( $|F_o| > 39$ ) were simply omitted from further calculations. In Table 3 these reflexions are given in parentheses. The subsequent refinement cycles resulted in an  $R$  index of 0.084 for observed reflexions only, and 0.098 with unobserved terms included. The final three-dimensional electron density map is shown in Fig. 1. Since a three-dimensional difference function calculated at this stage still failed to give adequate hydrogen positions the refinement was concluded at this point. The positional and thermal parameters for the final structure are given in Tables 1 and 2, in which the atoms are numbered to correspond with Fig. 1. The observed and calculated structure amplitudes are given in Table 3.

### Description of the structure

The molecules of dopamine are in an extended configuration parallel to the  $a$  axis. The shape of the molecule is shown in Fig. 2, which also gives the probability ellipsoids of thermal motion. The bond lengths and bond angles, uncorrected for thermal motion, are given in Tables 4 and 5 with their standard deviations.

Table 1. *Final fractional atomic coordinates and their standard deviations (in parenthesis)*

	$x/a$	$y/b$	$z/c$
C(1)	0.5493 (9)	0.0301 (8)	0.0531 (16)
C(2)	0.6755 (8)	0.0234 (7)	0.1178 (14)
C(3)	0.7226 (8)	0.1128 (8)	0.2233 (15)
C(4)	0.6470 (9)	0.2106 (8)	0.2658 (19)
C(5)	0.5215 (8)	0.2161 (8)	0.2042 (14)
C(6)	0.4734 (8)	0.1263 (10)	0.1003 (16)
C(7)	0.3350 (9)	0.1307 (10)	0.0420 (16)
C(8)	0.2531 (9)	0.0499 (10)	0.1494 (18)
N	0.1147 (7)	0.0641 (8)	0.1032 (14)
O(1)	0.7469 (7)	-0.0732 (6)	0.0719 (13)
O(2)	0.8459 (6)	0.0981 (6)	0.2845 (11)
Cl	0.0088 (2)	0.3251 (2)	0.2500

Table 2. *Anisotropic thermal parameters and their standard deviations (in parenthesis)*

$\beta_{ij}$  are the coefficients in the expression:  $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$

	$\beta_{11}$	$\beta_{22}$	$\beta_{33}$	$\beta_{12}$	$\beta_{13}$	$\beta_{23}$
C(1)	0.0040 (7)	0.0032 (7)	0.0089 (20)	-0.0002 (6)	0.0008 (10)	0.0002 (9)
C(2)	0.0038 (7)	0.0021 (6)	0.0079 (20)	-0.0003 (6)	-0.0001 (10)	-0.0007 (9)
C(3)	0.0046 (7)	0.0032 (6)	0.0053 (21)	-0.0011 (6)	0.0001 (11)	-0.0013 (9)
C(4)	0.0057 (8)	0.0036 (6)	0.0109 (22)	-0.0006 (6)	-0.0001 (14)	-0.0002 (12)
C(5)	0.0044 (8)	0.0040 (7)	0.0099 (23)	-0.0008 (6)	0.0011 (10)	-0.0008 (9)
C(6)	0.0028 (7)	0.0049 (7)	0.0089 (20)	-0.0002 (6)	0.0002 (10)	-0.0007 (10)
C(7)	0.0033 (7)	0.0064 (8)	0.0106 (25)	-0.0004 (7)	0.0011 (10)	0.0026 (11)
C(8)	0.0036 (8)	0.0057 (9)	0.0148 (26)	0.0001 (7)	-0.0002 (12)	0.0020 (13)
N	0.0036 (7)	0.0073 (8)	0.0111 (19)	0.0001 (6)	-0.0004 (9)	-0.0004 (11)
O(1)	0.0063 (7)	0.0037 (5)	0.0171 (18)	0.0026 (5)	-0.0025 (9)	-0.0034 (9)
O(2)	0.0047 (6)	0.0046 (5)	0.0125 (19)	-0.0009 (4)	-0.0017 (8)	0.0002 (8)
Cl	0.0058 (2)	0.0045 (2)	0.0156 (5)	-0.0017 (2)	-0.0007 (4)	0.0001 (4)

Table 3. Observed and calculated structure factors

Within each group are values of k, l, Fo, Fc, Acat and Bcat. Asterisks indicate unobserved reflexions. The 25 strongest reflexions (in parenthesis) were excluded from the final refinement procedure.

Table with multiple columns containing numerical data for various reflections, including indices (k, l), observed (Fo) and calculated (Fc) structure factors, and other parameters (Acat, Bcat). The table is organized into several sections labeled H=2, H=4, H=6, H=8, H=10, H=12, H=14, H=16, H=18, H=20, H=22, H=24, H=26, H=28, H=30, H=32, H=34, H=36, H=38, H=40, H=42, H=44, H=46, H=48, H=50, H=52, H=54, H=56, H=58, H=60, H=62, H=64, H=66, H=68, H=70, H=72, H=74, H=76, H=78, H=80, H=82, H=84, H=86, H=88, H=90, H=92, H=94, H=96, H=98, H=100.

Table 4. *Interatomic distances and standard deviations (in parenthesis)*

C(1)–C(2)	1.425 (12) Å	C(6)–C(7)	1.528 (12) Å
C(2)–C(3)	1.391 (13)	C(7)–C(8)	1.509 (15)
C(3)–C(4)	1.390 (12)	C(8)–N	1.510 (12)
C(4)–C(5)	1.409 (12)	C(2)–O(1)	1.360 (10)
C(5)–C(6)	1.391 (14)	C(3)–O(2)	1.394 (11)
C(6)–C(1)	1.388 (14)	O(1)···O(2)	2.750 (10)
N···Cl(x, y, z)	3.321 (10) Å		
N···Cl(x, ½–y, z–½)	3.259 (11)		
N···Cl(x̄, y–½, z)	3.182 (10)		
O(1)···Cl(1–x, y–½, z)	3.143 (8)		
O(2)···Cl(1+x, y, z)	3.065 (7)		

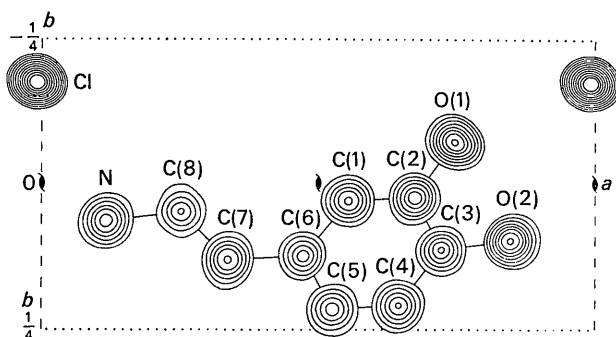
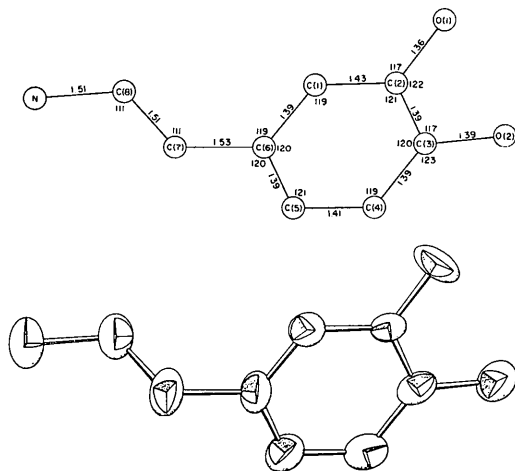
Fig. 1. Composite three-dimensional electron density map of dopamine hydrochloride between  $z=0$  and  $z=\frac{1}{2}$  projected on (001). Contours are at intervals of  $1 \text{ e.}\text{Å}^{-3}$  for the lighter atoms and  $2 \text{ e.}\text{Å}^{-3}$  for the chlorine atoms, beginning with the  $1 \text{ e.}\text{Å}^{-3}$  contour.

Fig. 2. Bond distances and angles (top) and a perspective drawing of the dopamine molecule showing the ellipsoids of thermal motion with a probability of 74 per cent (bottom).

Table 5. *Interatomic angles and standard deviations (in parenthesis)*

C(1)–C(2)–C(3)	120.7 (8)°	C(1)–C(6)–C(7)	119.4 (10)°
C(2)–C(3)–C(4)	120.2 (8)	C(6)–C(7)–C(8)	110.7 (9)
C(3)–C(4)–C(5)	119.1 (9)	C(7)–C(8)–N	110.5 (9)
C(4)–C(5)–C(6)	121.0 (9)	C(1)–C(2)–O(1)	117.3 (8)
C(5)–C(6)–C(1)	120.4 (8)	C(3)–C(2)–O(1)	122.0 (8)
C(6)–C(1)–C(2)	118.6 (9)	C(2)–C(3)–O(2)	117.2 (8)
C(5)–C(6)–C(7)	120.2 (9)	C(4)–C(3)–O(2)	122.6 (8)

The catechol part of the molecule is planar and the deviation of the atoms C(1)–C(6), O(1) and O(2) from the plane satisfying the equation:  $0.3370X + 0.5049Y + 0.7947Z = 4.9259$  are given in Table 6. The bond distances and bond angles within the molecule are almost identical with corresponding parameters in noradrenaline (Carlström & Bergin, 1967). The agreement with comparable bonds and angles in tyrosine (Srinivasan, 1959) and catechol (Brown, 1966) are also very good. The C(8)–N distance, (1.51 Å) is certainly longer than the normal single-bond length between the carbon and nitrogen atoms but fits the average value well (1.503 Å) for the C–NH<sub>3</sub><sup>+</sup> bond in  $\alpha$ -amino acids (Hahn, 1957).

The arrangement of the molecules in the crystal is depicted in Fig. 3, which also shows the probable hydrogen bonding system. The structure can be described as consisting of continuous chloride layers, perpendicular to the  $a$  axis, between which the organic cations are oriented lengthwise. The structure is held together by van der Waals forces and a complicated three-dimensional network of hydrogen bonds. All five protons of the nitrogen and the hydroxyl groups seem to participate in this network where each chloride ion acts as acceptor for five hydrogen bonds. The only types of hydrogen bonds are therefore O–H···Cl<sup>–</sup> and N<sup>+</sup>–H···Cl<sup>–</sup>. The oxygen–chlorine distances, 3.15 and 3.07 Å, with corresponding C–O···Cl angles of 128° and 113° are acceptable dimensions for genuine hydrogen bonds (Pimentel & McClellan, 1960). Similar O···Cl distances are also found in the hydrochlorides of the closely related compounds ephedrine (Phillips, 1954) and noradrenaline (Carlström & Bergin, 1967). Although the hydrogen atoms could not be localized in the present investigation it is evident that the nitrogen occurs in the tetrahedral configuration C–NH<sub>3</sub><sup>+</sup>. Not only is the C–N distance that of a C–NH<sub>3</sub><sup>+</sup> bond but there are also three short distances between the nitrogen atom and surrounding chloride ions, 3.18, 3.26 and 3.32 Å, with the roughly tetrahedral C–N···Cl angles of 102°, 125° and 109° respectively. Even if two of the distances are at the upper limit for commonly accepted N<sup>+</sup>–H···Cl values there seems

Table 6. *Deviations from the best plane through the catechol part of the molecule*

C(1)	+0.004 Å	C(5)	–0.004 Å
C(2)	+0.004	C(6)	–0.020
C(3)	+0.009	O(1)	+0.007
C(4)	+0.024	O(2)	–0.025

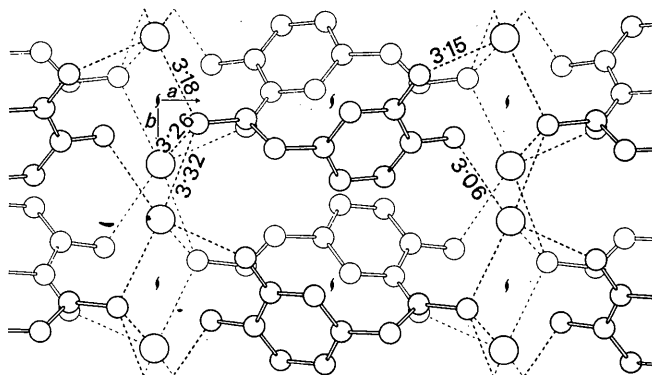


Fig. 3. Dopamine hydrochloride. Projection of the structure along the  $c$  axis showing intermolecular hydrogen bonds (Å).

little doubt that they really represent hydrogen bonds. There are no other short distances in the structure with the exception of the intramolecular O(1)···O(2) contact (2.75 Å) in the catechol part of the molecule. As was shown for catechol (Brown, 1966) and noradrenaline (Carlström & Bergin, 1967) there is no indication of a hydrogen bond between these two hydroxyl groups. The various temperature factors (Table 2) appear to be quite reasonable. However, the fact that the observed structure amplitudes were obviously impaired by secondary extinction makes it evident that the ellipsoids of thermal motion shown in Fig. 2 do not necessarily depict the true physical state.

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