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Structural Studies of Metabolic Products of Dopamine. II.* Crystal and Molecular Structure of the 1:1 Complex of 6-Hydroxydopamine Hydrochloride and its Oxidized, *p*-Quinonoid, Form

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The crystal structure of a red oxidation product of 6-hydroxydopamine (3,4,6-trihydroxyphenylethylamine) hydrochloride has been determined by X-ray methods. The red crystals were found to contain the hydrochlorides of both 6-hydroxydopamine and its oxidized, *p*-quinonoid, form. The two species form a 1:1 molecular complex in the crystals. The crystals are monoclinic, space group $P2_1/n$ with $a = 6.815(1)$, $b = 13.108(3)$, $c = 20.365(6)$ Å and $\beta = 95.43(2)°$. The structural parameters are refined to a conventional R-factor of 0.065. Standard deviations in the bond lengths are 0.007 – 0.01 Å and in bond angles 0.5 – 0.7°. The component molecules of the complex are stacked alternately along the *a*-axis. The crystal structure is stabilized through an extensive hydrogen bond system.

6-Hydroxydopamine, a natural oxidation product of dopamine, is known to be a chemical sympathectomic agent.[1] The mechanism of its activity has been extensively discussed and recent theories center on the ease of oxidation of this compound. The products formed during oxidation are considered to be possible neurotoxic agents as well as important intermediates in melanin formation.[1–7]

Investigations have shown that 6-hydroxydopamine readily autoxidizes to form a quinone and hydrogen peroxide.[7] The quinone, which theoretically can have either *o*- or *p*-quinonoid structure, may undergo ring closure to yield indoline and indole derivatives. The mechanism of this intramolecular cyclization is not established and different reaction products are reported.[1–4]

During recrystallization of 6-hydroxydopamine, red crystals appeared.[8] It was assumed that an oxidation had taken place and that the red compound formed was an intermediate in the formation of melanin. Regarding the discussion on the oxidation path of 6-hydroxydopamine, the structure determination of this oxidation product was considered to be of interest.

EXPERIMENTAL

The red crystals formed during recrystallization of 6-hydroxydopamine [8] were mostly found to be twinned, but single crystals could be obtained and were used in the present study.

Oscillation and Weissenberg photographs indicated monoclinic symmetry and the space group was found to be $P2_1/n$.

Unit cell parameters were determined and three-dimensional intensity data collected on a SYNTEX $P\bar{1}$ diffractometer using graphite monochromated Mo$K\alpha$ radiation. Unit cell parameters were obtained from a least-squares treatment of angular measurements of fifteen reflections. Diffraction data for 2364 reflections with $2\theta < 65°$ were recorded using the $\omega - 2\theta$ scanning mode; the scan range was 1.6° and the scan speed varied from 2 to 8° min^{-1} depending on the peak intensity. Background counts were measured at each end of the scan range, the ratio of the summarized background counting time to scan time being 0.7. The 1641 reflections having net intensities greater than

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Table 1. Fractional atomic coordinates and thermal parameters with estimated standard deviations for non-hydrogen atoms ($\times 10^4$). The temperature factor is given by $\exp-(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{12}hk + B_{13}hl + B_{23}kl)$.

Atom	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Cl1	7656(3)	2448(1)	890(1)	300(7)	32(1)	19(1)	−1(6)	29(3)	9(1)
Cl2	2469(4)	118(1)	685(1)	325(8)	46(1)	22(1)	−6(6)	24(3)	0(2)
O1A	3526(9)	−414(3)	3991(2)	405(21)	31(3)	22(2)	−52(14)	62(9)	−11(3)
O2A	3824(8)	1081(3)	4857(2)	368(19)	47(3)	13(1)	37(14)	29(8)	−3(3)
O3A	2218(9)	3532(4)	3127(2)	309(19)	63(4)	18(1)	29(15)	7(9)	6(4)
NA	2800(10)	2479(4)	1089(2)	348(22)	44(4)	16(2)	46(20)	48(10)	11(5)
C1A	2410(12)	1768(6)	2888(3)	161(24)	54(6)	12(2)	1(19)	35(11)	8(6)
C2A	2728(12)	772(6)	3103(3)	202(26)	60(6)	13(2)	−33(21)	29(11)	1(6)
C3A	3230(12)	566(5)	3769(3)	229(27)	31(5)	19(2)	−9(19)	36(12)	9(5)
C4A	3325(11)	1355(5)	4217(3)	125(22)	52(6)	10(2)	9(18)	21(10)	10(5)
C5A	3062(11)	2355(6)	4017(3)	179(22)	48(5)	12(2)	−31(20)	10(10)	1(5)
C6A	2554(10)	2535(6)	3351(3)	161(22)	42(5)	20(2)	24(21)	27(11)	12(6)
C7A	1785(12)	1984(6)	2166(3)	194(24)	71(6)	14(2)	−2(22)	24(11)	11(5)
C8A	3470(11)	2354(6)	1813(3)	224(24)	59(6)	15(2)	−45(22)	7(11)	9(5)
O1B	7412(8)	805(4)	2328(2)	350(20)	48(3)	10(1)	0(15)	5(8)	−10(3)
O2B	7738(9)	−838(4)	3092(2)	429(22)	31(3)	16(1)	6(15)	25(9)	−11(3)
O3B	8560(9)	1428(3)	4900(2)	445(21)	42(3)	11(1)	2(14)	5(9)	−3(3)
NB	7631(10)	5043(4)	4062(3)	377(25)	30(4)	23(2)	4(19)	65(11)	6(5)
C1B	7947(10)	2169(5)	3847(3)	122(21)	27(4)	14(2)	6(16)	29(10)	1(5)
C2B	7675(11)	1985(5)	3198(3)	195(24)	26(4)	17(2)	0(18)	27(11)	9(5)
C3B	7651(11)	954(5)	2923(3)	151(24)	44(5)	16(2)	12(18)	22(11)	−3(5)
C4B	7896(11)	72(5)	3390(3)	178(22)	38(5)	17(2)	33(20)	28(11)	9(5)
C5B	8302(11)	247(5)	4040(3)	202(24)	33(5)	14(2)	−44(19)	19(11)	4(5)
C6B	8302(12)	1270(5)	4298(3)	187(25)	36(5)	15(2)	−27(18)	18(11)	1(5)
C7B	7969(11)	3192(5)	4166(3)	185(25)	34(4)	14(2)	−5(17)	14(11)	−4(5)
C8B	7474(12)	4059(5)	3697(3)	214(25)	26(4)	20(2)	12(18)	25(12)	−3(5)

Table 2. Fractional atomic coordinates ($\times 10^3$) with estimated standard deviations for hydrogen atoms. The isotropic thermal parameter is $B = 4.2$ Å^2.

Atom	x	y	z
H2A	259(10)	13(5)	281(3)
H5A	328(11)	294(5)	439(3)
H71A	71(12)	248(6)	208(3)
H72A	118(12)	138(5)	198(3)
H81A	474(11)	180(5)	184(3)
H82A	400(12)	297(5)	191(3)
HO1A	378(13)	−44(6)	433(4)
HO2A	361(13)	153(5)	507(4)
HO3A	254(13)	394(6)	346(4)
HN1A	403(11)	265(6)	93(4)
HN2A	228(12)	316(6)	101(3)
HN3A	263(11)	170(5)	91(3)
H2B	743(12)	249(6)	291(3)
H5B	849(11)	−34(5)	441(3)
H71B	927(12)	324(5)	443(3)
H72B	692(12)	318(5)	446(3)
H81B	600(11)	404(6)	352(3)
H82B	862(11)	409(5)	335(3)
HO2B	794(13)	−118(6)	339(4)
HN1B	937(12)	507(6)	424(3)
HN2B	677(12)	499(6)	438(3)
HN3B	765(12)	554(6)	388(4)

$3\sigma(I)$ were considered to be observed, the remaining reflections were excluded from the further calculations.

The intensity data were corrected for Lorentz and polarization effects, the computer programs employed during this as well as the subsequent calculations are described in Ref. 9. Atomic form factors used were those of Doyle and Turner [10] for the chlorine ion, oxygen, nitrogen, and carbon and of Stewart *et al.*[11] for hydrogen.

CRYSTAL DATA

$C_8H_{12}O_3NCl.C_8H_{10}O_3NCl$
Space group $P2_1/n$, monoclinic
$a = 6.815(1)$ Å; $b = 13.108(3)$ Å; $c = 20.365(6)$ Å;
$\beta = 95.43(2)°$
$V = 1811.0$ Å^3; F.W. = 409.27; $F(000) = 856$;
$Z = 4$
D_{obs} (flotation) = 1.50 g cm^{-3};
$D_{calc} = 1.502$ g cm^{-3}

STRUCTURE DETERMINATION

The coordinates of the two chlorine ions were determined from a sharpened Patterson func-

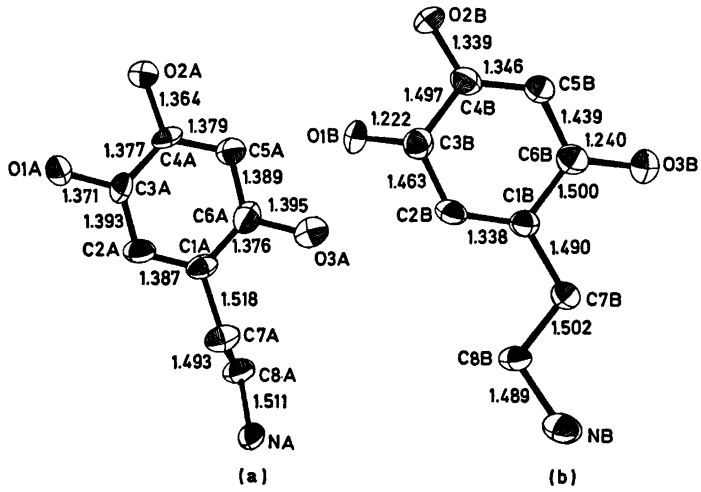

Fig. 1. Bond lengths and 50 % probability ellipsoids. (*a*) The 6-hydroxydopammonium ion. (*b*) The *p*-quinonoid ion. (The drawings were prepared using the computer program ORTEP.[18])

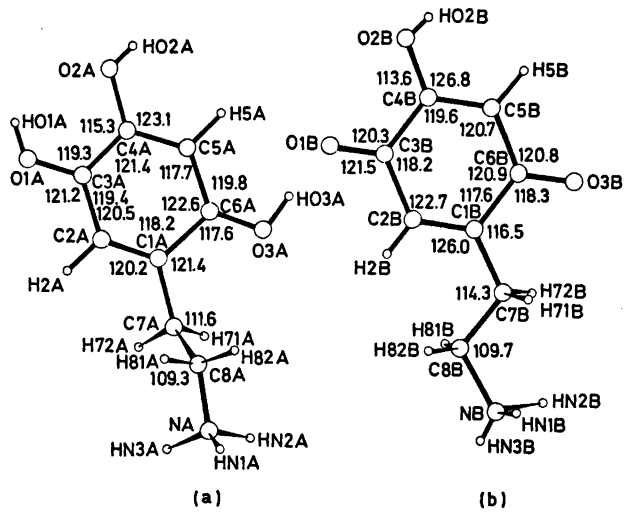

Fig. 2. Bond angles. (*a*) The 6-hydroxydopammonium ion. (*b*) The *p*-quinonoid ion.

tion and subsequent weighted Fourier maps [12] indicated the positions of the remaining non-hydrogen atoms. After a few cycles of least-squares refinement, anisotropic thermal parameters for the heavy atoms were introduced. Calculations of coordinates of the hydrogen atoms were based on stereochemical considerations. Further least-squares refinements with a common isotropic thermal parameter for the hydrogen atoms yielded a final conventional *R*-factor of 0.065 and a weighted *R*-factor of 0.056. The final parameters for non-hydrogen atoms are listed in Table 1 and for hydrogen atoms in Table 2.

An analysis of the molecular motions in terms of rigid body vibrations indicated that the cations could not be regarded as rigid units and the bond lengths were not corrected for thermal

Table 3. Deviations in Å of individual atoms from least squares planes.

(1) Through the benzene ring atoms.

C1A	0.002	O1A	−0.009
C2A	−0.005	O2A	−0.001
C3A	0.014	O3A	−0.010
C4A	−0.020	C7A	−0.073
C5A	0.017		
C6A	0.008		

(2) Through the quinone ring atoms.

C1B	0.020	O1B	0.054
C2B	0.009	O2B	−0.101
C3B	0.019	O3B	−0.020
C4B	−0.037	C7B	−0.048
C5B	0.025	C8B	−0.162
C6B	0.004	NB	−0.117

vibration effects. The ellipsoids of thermal motion of the two organic cations are illustrated in Fig. 1. Bond lengths and angles are presented in Fig. 1 and 2, respectively.

The structure factor list may be obtained from the authors upon request.

DESCRIPTION AND DISCUSSION OF THE STRUCTURE

The crystals were found to consist of a 1:1 molecular complex of 6-hydroxydopamine and its oxidized, *p*-quinonoid, form.

The 6-hydroxydopammonium ion. The structure of the 6-hydroxydopammonium ion corresponds closely to that of the pure compound [8] in bond lengths, angles and conformation. The hydroxyhydroquinone part of the molecule is nearly planar (*cf.* Table 3) and the ethylamine side chain is maximally extended. The dihedral angle C1A−C7A−C8A−NA is −175.7° and the angle between the benzene plane and the plane of the ethyl part of the side chain is 80.0°. This is the conformation found in most crystal structures of phenylethylamines.[13]

The p-*quinonoid ion.* The oxidized ion has a *p*-quinonoid structure with C=C and C=O bond lengths corresponding to those in *p*-benzoquinone.[14] The C−C single bond lengths in the ring are in the range from 1.439 Å to 1.500 Å but such variations are also found in other unsymmetrical substituted derivatives of *p*-benzoquinone.[14] The ethylamine side chain of the oxidized ion is fully extended but in contrast to the situation in the 6-hydroxydopammonium ion the side chain and the ring are almost coplanar. The deviation of the individual atoms from the least-squares plane through the quinone ring atoms are given in Table 3. The dihedral angle C1B−C7B−C8B−NB is 177.4° and C2B−C1B−C7B−C8B is −5.1°. Among the crystal structures of the phenylethylamines a similar coplanarity of the benzene ring and side chain is only found in (−)-adrenaline hydrogen (+)-tartrate.[13] In the latter study this exceptional arrangement of the ring and side chain may be explained by the dense packing of the structure and the unusually strong and elaborate hydrogen bond system in the crystals. A similar explanation for the unexpected planarity of the oxidized ion in the present investigation has not been found. The molecular packing and hydrogen bond system correspond closely to that found in the crystal structure of 5-hydroxydopamine hydrochloride,[15] which has the conformation usually encountered among related compounds. The bond lengths in the side chain of the *p*-

Table 4.
a. Hydrogen bonded interactions X−H···Y.

X	Y	X···Y	H···Y	X−H···Y
NA	Cl1	3.372	2.49	153
NA	Cl2	3.204	2.13	172
NA	O1A(*a*)	2.904	1.95	170
O1A	O2A	2.633	2.28	114
O2A	Cl1(*c*)	3.014	2.28	164
O3A	Cl2(*a*)	3.181	2.34	165
NB	Cl1(*a*)	3.161	2.55	140
NB	Cl2(*a*)	3.332	2.15	167
NB	Cl2(*c*)	3.324	2.65	130
O2B	Cl1(*a*)	3.086	2.37	156

b. Other short contacts.

	(Å)	
NA···O3B(*c*)	2.902	
NB···O1B(*a*)	3.000	$a=-x+\frac{1}{2},y+\frac{1}{2},-z+\frac{1}{2}$
O1A···O2A(*b*)	2.953	$b=-x,-y,-z$
C8B···O1B(*a*)	3.103	$c=x+\frac{1}{2},-y+\frac{1}{2},z+\frac{1}{2}$
C4B···O1A	3.386	
C5B···O1A	3.362	
C6B···O2A	3.366	
C7A···O1B	3.402	
C1A···C2B	3.358	

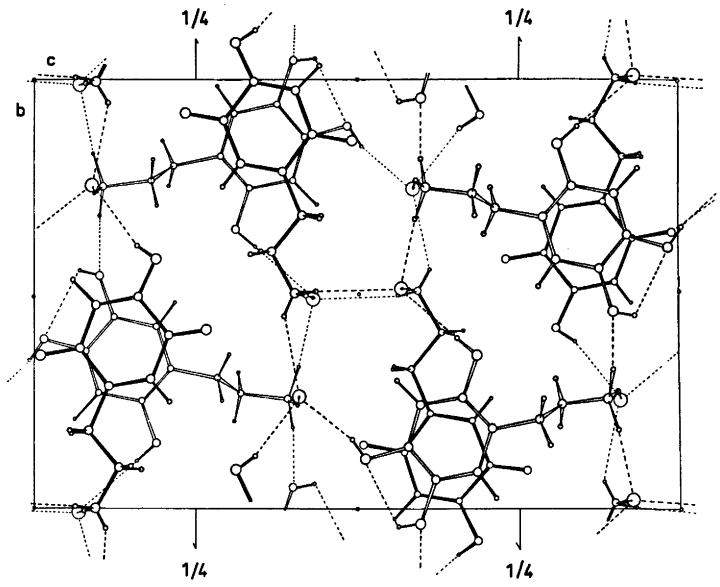

Fig. 3. The crystal structure as seen down the *a*-axis. The *p*-quinonoid ions are drawn with the marked bonds.

quinonoid ion are not significantly different from the normal values for these types of bonds.

Hydrogen bonding and molecular packing. The arrangement of the molecules in the crystals is illustrated in Fig. 3. The two components of the complex are stacked along the *a*-axis, the angle between the ring planes is 3.8°. The compound is thus possessing the characteristic geometry of crystalline π-molecular complexes with mixed stacks of almost parallel molecules of electron donating and accepting ability.[16] The distances from the center of the phenyl ring to the center of the two adjacent quinone rings within the stack are 3.49 and 3.42 Å, respectively. This separation of the component ring systems is larger than usually found for π-molecular complexes.[16] However, the component molecules are closer together than found in related aromatic one-component systems with a similar molecular arrangement. The distance between the centers of the benzene rings in 5-hydroxydopamine hydrochloride, also stacked along a crystallographic axis, is 3.94 Å.[15]

Crystalline 6-hydroxydopamine hydrochloride is colourless and the colour of the *p*-quinonoid form of 6-hydroxydopamine is reported to be yellow.[6,17] Thus, the interactions between almost parallel phenol and quinone rings in the present structure may possibly be the reason for the red colour of the crystals.

Short contacts assumed to represent hydrogen bonds in the crystals are presented in Table 4*a* and also in Fig. 3. In addition to these interactions there are N···O, O···O and C···O contacts in the range 2.9 – 3.1 Å (*cf.* Table 4*b*). These are not believed to represent hydrogen bonds because of unfavourable X – H···Y arrangements. Each 6-hydroxydopammonium ion is thus considered to be linked to four chlorine ions and two other 6-hydroxydopammonium ions through hydrogen bonds of the types N – H···Cl, N – H···O and O – H···Cl. Each oxidized ion appears to be connected to four chlorine ions by N – H···Cl and O – H···Cl hydrogen bonds. In the 6-hydroxydopammonium ion one phenolic hydrogen atom is situated less than 2.3 Å from the oxygen atom in *o*-position. This arrangement, which is not found in the pure compound, may indicate the presence of an intramolecular O – H···O hydrogen bond. The two component cations of the complex are not connected by hydrogen bonds and the strongest interactions between these cations are those between the rings stacked along the *a*-axis. The cations and

chlorine ions within a stack are linked by hydrogen bonds of the N–H···Cl type.

CHEMICAL IMPLICATIONS

The present investigation shows that the first oxidation product of 6-hydroxydopamine hydrochloride is the uncyclized *p*-quinone. This conclusion has been reached by other authors [1,3,5] on the basis of electrochemical and spectroscopic evidence. On standing in solution the *p*-quinone undergoes further reaction to yield melanin-like polymers by reaction paths that have been much discussed.[1–4] The formation of a complex of low solubility between the hydrochlorides of 6-hydroxydopamine and the *p*-quinone probably stabilizes the *p*-quinone and thus delays a further reaction.

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