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The Crystal Structure of Serotonin Hydrogen Oxalate

A. AMIT,[a] L. MESTER,[a] B. KLEWE[b] and S. FURBERG[b]

[a] Institut de Chimie de Substances Naturelles, Gif-sur-Yvette, France and [b] Kjemisk institutt, Universitetet i Oslo, Oslo 3, Norway

An X-ray analysis of serotonin oxalate has been carried out. The space group is $P2_1/n$ with cell dimensions $a=18.385(5)$ Å, $b=5.620(2)$ Å, $c=12.034(4)$ Å, $\beta=96.57(2)°$. The structure was refined to $R=0.069$ for 1767 observed reflections. The serotonin cations have a nearly planar *trans* conformation and are linked by hydrogen bonds to the hydrogen oxalate anions, which form infinite chains.

The biological importance of serotonin (5-hydroxytryptamine) and related substances has prompted a number of investigations of their structure. Crystal structure analyses have been carried out on serotonin creatinine sulfate,[1] serotonin picrate,[2] and a number of structural relatives.[3-6] Different side-chain conformations have been found, which have been discussed with the view of establishing structure-activity relationships.[7,8] One of us has prepared sugar derivatives of serotonin, using the oxalate salt as starting material.[9] These compounds show unexpected biological behaviours.[10-12] It was thought to be of interest to determine the conformation of serotonin in its hydrogen oxalate salt.

EXPERIMENTAL

From a sample of serotonin oxalate supplied by Sigma Co., St. Louis, a single crystal of dimensions $0.37\times0.31\times0.06$ mm^3 was selected, coated by a thin layer of epoxy glue, and used for the X-ray diffraction work. Data were collected at room temperature on an automatic Syntex $P\bar{1}$ diffractometer using monochromatic Mo$K\alpha$ radiation and $\theta-2\theta$ scan technique; $2\theta_{max}=55°$, scan speed $1.5-3°$ min^{-1} (in 2θ), background to scanning time ratio 0.7. An experimental fluctuation of 2 % as calculated from the measurements of three monitoring reflections registered at regular intervals was included in the standard deviations based upon counting statistics. 1767 of the 3025 reflections had intensities greater than 2σ and were subsequently used in the refinement. The cell dimensions were determined from the measurements of all setting angles for 30 reflections.

On crystallization from methanol a different modification of serotonin oxalate was obtained. The crystals were unstable in air, turning opaque in the course of a few hours, but were stable in closed capillaries containing methanol. Weissenberg and precession diagrams showed these crystals to be orthorhombic, space group $P2_12_12_1$, with approximate cell dimensions $a=13.21$ Å, $b=19.5$ Å, $c=5.60$ Å. The density as measured by flotation corresponds to an additional cell content of four methanol molecules, and we believe these unstable crystals to be a methanol solvate of serotonin oxalate. They were not further investigated.

CRYSTAL DATA

Serotonin oxalate (5-hydroxy-3-indolethylammonium hydrogen oxalate). $C_{12}H_{14}N_2O_5$, *F.W.* $=266.25$. Space group $P2_1/n$, $a=18.385(5)$ Å, $b=5.620(2)$ Å, $c=12.034(4)$ Å, $\beta=96.57(2)°$, $V=1235.1$ Å^3, $Z=4$, $D_m=1.4$ g cm^{-3}, $D_x=1.43$ g cm^{-3}, λ(Mo$K\alpha$)$=0.71069$ Å, μ(Mo$K\alpha$)$=1.05$ cm^{-1}.

STRUCTURE DETERMINATION AND REFINEMENT

The structure was determined by the MULTAN program. The hydrogen atoms were localized from a difference electron density map. Full matrix least-squares refinement of $M=\Sigma[(F_o-F_c)/\sigma(F_o)]^2$ yielded a final R-value of 0.069 ($R_w=0.067$, "goodness of fit" $=2.67$), using anisotropic temperature factors

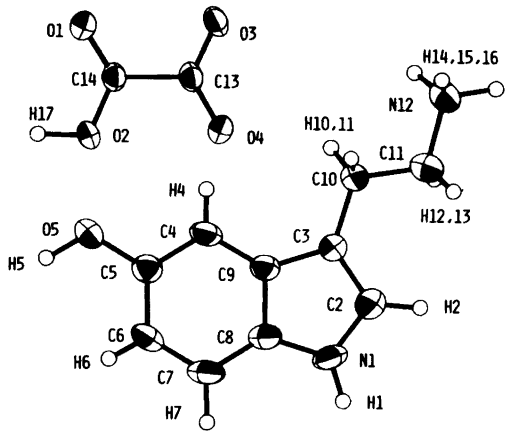

Fig. 1. Thermal ellipsoids viewed perpendicular to the cation and anion planes.

for heavy atoms and isotropic ones for the hydrogen atoms. The thermal ellipsoids are shown in Fig. 1. Atomic form factors were taken from Refs. 13 and 14. The final parameters are given in Table 1. A list of observed and calculated structure factors is available from one of the authors (S.F.) upon request. Bond distances and angles and hydrogen bond parameters are listed in Table 2. The numbering of atoms can be seen from Fig. 1. The figures have been prepared by the ORTEP 2 program. Other programs used are described in Ref. 15.

RESULTS AND DISCUSSION

As seen in Fig. 1, the ethylamine side-chain is in the extended *trans* planar conformation. The torsional angles C9–C3–C10–C11 and C3–C10–C11–N12 are 171.7 and 175.8°, respectively, and the entire serotonin cation is approximately planar except for the side chain hydrogen atoms. The conformation is similar to that found in, *e.g.*, serotonin-creatinine sulfate,[1] whereas non-planar conformations are observed in 5-methoxytryptamine.[4,6] Distances from a plane fitted to the indole ring are given in Table 3. The indole ring appears to be very slightly bent about C9–C8, the six-membered ring being planar to within 0.008 Å and the five-membered ring to within 0.002 Å, the angle between them being 1.0°. Bond lengths and angles agree within three times the estimated standard deviations with those given by Falkenberg and Carlström,[3] and found also in subsequent investigations,[4–6] except for C4–C9 and C10–C11, which both are about 0.03 Å shorter than expected. We do not, however, believe these deviations to be real.

The dimensions of the anion correspond closely to those reported in the literature.[16] The bond

Table 1. Positional and thermal parameters. The anisotropic temperature factor is $\exp[-2\pi^2(h^2a^{*2}U_{11}+\cdots+2klb^*c^*U_{23})]$.

ATOM	x	y	z	U11	U22	U33	U12	U13	U23
O1	.7866(2)	.7864(5)	.4487(2)	.0818(24)	.0319(17)	.0426(17)	-.0057(17)	.0278(17)	.0015(15)
O2	.8395(2)	.5524(5)	.2984(2)	.0589(21)	.0192(15)	.0428(17)	.0012(15)	.0167(15)	.0014(14)
O3	.8281(2)	1.1420(5)	.3788(2)	.0675(22)	.0210(15)	.0365(16)	-.0006(16)	.0075(15)	-.0008(14)
O4	.8888(2)	.9807(5)	.2257(2)	.0648(21)	.0312(16)	.0387(16)	-.0005(16)	.0215(15)	.0016(14)
O5	.5531(2)	-.1828(6)	.3688(2)	.0611(22)	.0475(21)	.0379(17)	.0108(18)	.0128(16)	-.0051(16)
N1	.3806(2)	.4243(7)	.1266(3)	.0473(24)	.0661(29)	.0249(19)	.0078(23)	-.0059(18)	.0022(22)
N12	.3203(3)	.8662(9)	.5545(3)	.0574(30)	.0497(27)	.0489(23)	.0116(26)	.0139(22)	-.0039(22)
C2	.3413(3)	.5620(9)	.2129(4)	.0481(27)	.0492(30)	.0411(25)	.0067(26)	.0062(21)	.0088(24)
C3	.3774(2)	.4823(7)	.3114(3)	.0369(24)	.0364(25)	.0318(21)	.0048(21)	.0025(19)	-.0005(20)
C4	.4698(3)	.1376(8)	.3479(4)	.0518(29)	.0426(27)	.0249(22)	-.0065(24)	.0099(21)	-.0045(21)
C5	.5044(2)	-.0411(8)	.2953(3)	.0447(26)	.0368(26)	.0334(22)	-.0004(24)	.0092(20)	.0018(21)
C6	.4994(3)	-.0736(9)	.1794(4)	.0545(32)	.0544(33)	.0346(25)	.0092(29)	.0118(23)	-.0144(28)
C7	.4424(3)	.0728(9)	.1149(3)	.0436(27)	.0663(35)	.0265(22)	-.0033(27)	.0034(21)	-.0101(25)
C8	.4068(2)	.2624(8)	.1679(3)	.0343(24)	.0529(29)	.0268(21)	-.0034(25)	.0023(19)	-.0027(22)
C9	.4210(2)	.2638(8)	.2846(3)	.0369(25)	.0420(27)	.0269(20)	.0010(22)	.0078(19)	-.0004(20)
C10	.3764(3)	.5618(10)	.4278(4)	.0656(36)	.0399(30)	.0317(24)	.0105(29)	.0043(24)	-.0002(24)
C11	.3213(3)	.7638(11)	.4385(4)	.0667(37)	.0536(35)	.0358(27)	.0097(33)	.0088(25)	-.0035(27)
C13	.8398(2)	.9748(7)	.3154(3)	.0437(27)	.0232(23)	.0385(22)	-.0018(21)	.0007(20)	.0031(19)
C14	.8124(2)	.7256(7)	.3582(3)	.0410(25)	.0246(23)	.0293(21)	-.0019(21)	.0028(19)	.0040(19)

ATOM	x	y	z	B	ATOM	x	y	z	B
H1	.341(3)	.436(9)	.052(4)	5.6(12)	H2	.384(2)	.691(7)	.202(3)	3.1(9)
H4	.478(3)	.168(8)	.423(4)	6.1(12)	H5	.585(3)	-.385(9)	.322(4)	7.1(14)
H6	.514(2)	-.189(7)	.148(3)	2.7(9)	H7	.429(2)	.044(8)	.031(3)	4.1(10)
H10	.428(3)	.678(10)	.458(4)	7.8(17)	H11	.377(2)	.467(7)	.485(3)	2.8(9)
H12	.321(3)	.887(10)	.398(4)	6.5(16)	H13	.278(4)	.676(12)	.427(5)	11.8(24)
H14	.371(3)	.957(11)	.574(5)	8.8(19)	H15	.324(3)	.788(11)	.684(5)	9.1(18)
H16	.284(3)	.988(11)	.564(4)	6.1(16)	H17	.818(4)	.388(15)	.328(6)	15.1(26)

Table 2. Bonding parameters.

BOND DISTANCES (A)

N1 -C2	1.367(6)	C4 -C5	1.384(6)	C8 -C9	1.407(5)	C11-N12	1.502(6)	O3 -C13	1.247(5)
C2 -C3	1.365(6)	C5 -C6	1.401(6)	C8 -N1	1.371(6)	C5 -O5	1.372(5)	O4 -C13	1.232(5)
C3 -C9	1.433(6)	C6 -C7	1.376(6)	C3 -C10	1.501(6)	O1 -C14	1.213(4)	C13-C14	1.553(5)
C9 -C4	1.377(6)	C7 -C8	1.386(6)	C10-C11	1.483(7)	O2 -C14	1.290(5)		

BOND ANGLES (°)

N1-C2-C3	109.7(4)	C4-C5-C6	120.5(4)	C9 -C3 -C10	123.4(4)	O1-C14-O2	125.8(4)
C2-C3-C9	106.7(4)	C5-C6-C7	121.2(5)	C3 -C10-C11	113.9(4)	O3-C13-C14	114.2(3)
C3-C9-C8	106.8(4)	C6-C7-C8	118.0(4)	C10-C11-N12	110.8(4)	O4-C13-C14	118.7(4)
C9-C8-N1	107.5(4)	C7-C8-C9	121.2(4)	C4 -C5 -O5	117.9(4)	O3-C13-O4	127.2(4)
C8-N1-C2	109.3(4)	C8-C9-C4	120.1(4)	C6 -C5 -O5	121.6(4)		
C3-C9-C4	133.1(4)	C7-C8-N1	131.3(4)	O1 -C14-C13	120.6(4)		
C9-C4-C5	119.0(4)	C2-C3-C10	129.8(4)	O2 -C14-C13	113.6(3)		

HYDROGEN BONDS

	BOND LENGTH (A)				ANGLE (°)		EQUIV. POS.		
O2 -H17	1.08	O2...O3	2.520	H17..O3	1.47	O2 -H17..O3	164	x,	-1+y, z
O5 -H5	1.01	O5...O4	2.735	H5...O4	1.73	O5 -H5...O4	172	3/2-x,	-3/2+y, 1/2-z
N1 -H1	.93	N1...O3	3.014	H1...O3	2.12	N1 -H1...O3	161	-1/2+x,	3/2-y, -1/2+z
N12-H14	.92	N12..O5	2.896	H14..O5	1.99	N12-H14..O5	167	1-x,	1-y, 1-z
N12-H15	1.08	N12..O4	2.874	H15..O4	1.89	N12-H15..O4	150	-1/2+x,	3/2-y, 1/2+z
N12-H16	1.06	N12..O1	3.144	H16..O1	2.13	N12-H16..O1	160	1-x,	2-y, 1-z
N12-H16	1.06	N12..O3	2.951	H16..O3	2.22	N12-H16..O3	124	1-x,	2-y, 1-z

Table 3. Distances (Å) from the least-squares plane of the nine indole ring atoms.

N1	0.010	O5	0.046
C2	0.009	C10	0.050
C3	−0.010	C11	−0.153
C4	0.004	N12	0.021
C5	0.013	H1	−0.026
C6	−0.002	H2	−0.043
C7	−0.010	H4	0.007
C8	−0.004	H5	0.138
C9	−0.012	H6	0.011
		H7	−0.078

lengths are significantly different in the two halves of the anion, and the twist angle between the COO planes is 6.7°. Values between 0 and 14° have been reported for this angle in hydrogen oxalates.[16]

The crystal packing is shown in Fig. 2. The hydrogen oxalate anions are linked together by strong unsymmetrical hydrogen bonds (length 2.520 Å) to roughly planar infinite chains, as is commonly found for these ions.[16] They run nearly parallel to *b*. The repeat distance in such chains is about 5.6 Å and it may be inferred that they occur also in the unstable solvate mentioned above, being parallel to *c* in this case. The serotonin cations occur as

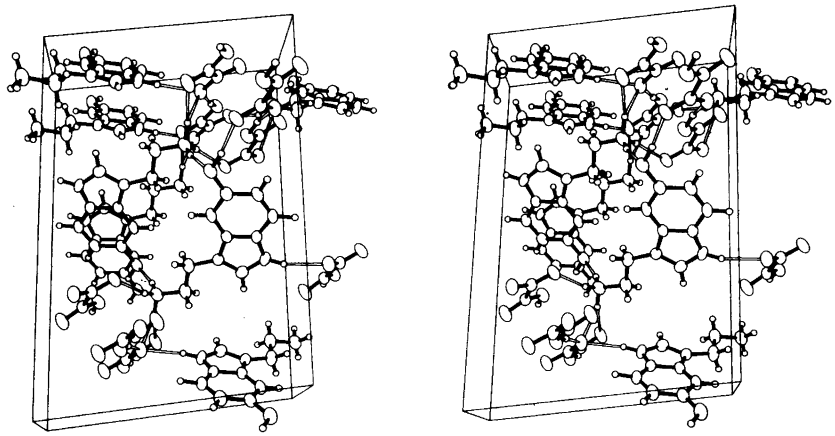

Fig. 2. Stereoscopic view of the structure in the *b* direction.

centrosymmetrical dimers formed by hydrogen bonds N12–H14···O5 between NH_3^+ and hydroxyl groups. The cations are linked to the anion chains by four hydrogen bonds (involving H1, H5, H15 and H16). One of these (H16) is possibly bifurcated, as indicated by the data on the hydrogen bonds given in Table 2.

The biological implications of the structure will be discussed in a forthcoming paper.[1,2]

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