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The Crystal and Molecular Structures of 1:1 Molecular Complexes between Tryptophan Metabolites – 5-Methoxyindole-3-acetic Acid:5-Methoxytryptamine and Indole-3-acetic Acid:5-Methoxytryptamine

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Two 1:1 molecular complexes, 5-methoxyindole-3-acetic acid (5-MIAA):5-methoxytryptamine (5-MT) and indole-3-acetic acid (IAA):5-methoxytryptamine (5-MT) crystallize in the monoclinic space group $P2_1/c$. Unit-cell dimensions are $a=12{\cdot}418$ (3), $b=6{\cdot}346$ (2), $c=26{\cdot}496$ (4) Å and $\beta=104{\cdot}64$ (1)° for 5-MIAA:5-MT, and $a=11{\cdot}847$ (8), $b=6{\cdot}714$ (8), $c=23{\cdot}648$ (4) Å and $\beta=95{\cdot}35$ (5)° for IAA:5-MT. The crystal structure of 5-MIAA:5-MT was solved by a direct method and phases from this complex were used for the structure determination of IAA:5-MT. By block-diagonal least-squares refinements, the R values dropped to 0·080 for 5-MIAA:5-MT and 0·077 for IAA:5-MT. The interaction between the acid and amine components in both 5-MIAA:5-MT and IAA:5-MT takes the form of an ion pair (salt bridge) between the positive charge at the terminal amino N of 5-MT and the negative charge at the carboxyl O of 5-MIAA (or IAA). The molecular packing and hydrogen-bonding systems are similar in both complexes: the amino group and indole N of 5-MT are hydrogen-bonded to the carboxyl O of 5-MIAA (or IAA); the indole N of 5-MIAA or IAA is not involved in hydrogen bonding. The molecules in both structures are held together by three-dimensional frameworks of hydrogen bonds around the twofold screw axis to form an infinite helical array in the **b** direction.

Introduction

Various biological and biochemical investigations of biogenic monoamines have been reported. 5-MT, one of the biogenic monoanimes, occurs in the pineal gland, where it is synthesized from serotonin by a methylating enzyme, hydroxyindole-*O*-methyltransferase (HIOMT) (Axelrod & Weissbach, 1961).

Through its metabolic pathway, 5-MT is usually converted to 5-MIAA (Erspamer, Ferrini & Glässer, 1960; Kveder & McIsaac, 1961), but it is also well known that 5-MT is excreted into urine to a certain extent (Franzen & Gross, 1965; Dreux & Halter, 1970).

It is supposed that 5-MT is excreted into urine in spite of its high reactivity because it can form a molecular complex with an acid in a living body as protection against enzymatic action. Therefore, we investigated the complex formation between 5-MT and a series of acid compounds found in the living body (Table 1).

Of these complexes, 5-MIAA:5-MT and IAA:5-MT are of most interest because 5-MIAA and IAA are both final products of the tryptophan metabolic pathway, so that interaction between 5-MT and these acids

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might be possible in a living body; moreover, 5-MIAA occurs in the same organ as 5-MT (Lerner, Case, Biemann, Heinzelman, Szmuszkovicz, Anthony & Krivis, 1959; McIsaac, Farrell, Taborsky & Taylor, 1965; Miller & Maickel, 1970; Koslow & Green, 1973). In this paper, the crystal and molecular structures of these two complexes are described and the conformational change in the individual molecules which accompanies the complex formation is also discussed.

Experimental

Equimolar mixtures of 5-MT with 5-MIAA or IAA were dissolved in 50% ethanol–water solutions and, after evaporation under reduced pressure, the complexes were obtained. Preliminary oscillation and Weissenberg photographs showed the crystals of both complexes to be monoclinic with space group $P2_1/c$ from systematic absences: $h0l$ with $l=2n+1$ and $0k0$ with $k=2n+1$. The crystallographic data are shown in Table 2.

The density was measured by the flotation method in a benzene–carbon tetrachloride mixture. Three-dimensional intensity data were collected with a computer-controlled four-circle diffractometer and Ni-filtered Cu $K\alpha$ radiation. By means of the $\omega/2\theta$ scan technique, totals of 1402 (for 5-MIAA:5-MT) and 1864 (for IAA:5-MT) independent reflexions with $I>3\sigma(I)$ were obtained within $\sin\theta/\lambda<0{\cdot}55$ Å^{-1}. The intensities of three standard reflexions measured after every 50 reflexions of the data set showed no decrease during the run. The scan speed was 2° min^{-1} and 10 s background measurements were performed at each end of the scan. All numerical calculations were carried out on an NEAC-2200-700 computer of the computation centre of this University, with *The Universal Crystallographic Computing System* (1973). In the structure factor calculation, the atomic scattering factors cited in *International Tables for X-ray Crystallography* (1974) were used.

Structure determination

5-MIAA:5-MT

The reflexions were adjusted to an absolute scale by Wilson statistics. A $\sum_2$ list was then computed for 129 reflexions with normalized structure factors, E, greater than 2·0.

Phases for these reflexions were determined by means of the symbolic addition procedure. To specify the origin, three reflexions were chosen to have positive signs and a further four reflexions were specified by symbols *a* to *d*, as shown in Table 3.

Table 2. *Crystal data*

	IAA:5-MT	5-MIAA:5-MT
Formula	$C_{21}N_3O_3H_{23}$	$C_{22}N_3O_4H_{25}$
Molecular weight	365·44	395·46
Space group	$P2_1/c$	$P2_1/c$
a	11·847 (8) Å	12·418 (3) Å
b	6·714 (8)	6·346 (2)
c	23·648 (4)	26·496 (4)
β	95·35 (5)°	104·64 (1)°
V	1872·80 Å^3	2020·28 Å^3
Z	4	4
D_m	1·285 g cm^{-3}	1·305 g cm^{-3}
D_x	1·295	1·305

Table 3. *Starting set for 5-MIAA:5-MT*

Sign	h	k	l	$\|E\|$	$\sum_2$ pairs	Probability
+	3	2	9	4·599	21	0·982–1·000
+	5	5	−13	3·262	9	0·963–0·998
+	9	2	−10	3·941	12	0·959–0·999
a	2	1	4	3·336	21	0·933–1·000
b	0	5	9	3·190	12	0·933–1·000
c	8	4	−7	2·610	8	0·932–0·999
d	3	5	−9	3·448	14	0·941–0·997

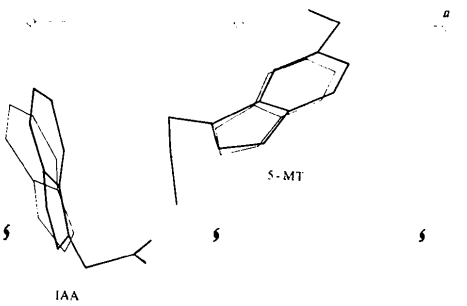


Fig. 1. The final configuration of the IAA:5-MT complex (thick line) derived from the indole coordinates of 5-MIAA:5-MT (thin line).

Table 1. *Some physical data for the complexes of 5-MT with some final metabolites*

				Calculated (%)			Found (%)		
Complex	M.p.	Formula	M.W.	C	H	N	C	H	N
5-MT+(I)*	181–183 °C	$C_{22}H_{25}N_3O_4$	395·46	66·82	6·37	10·63	66·66	6·64	10·72
5-MT+(II)*	189–192	$C_{21}H_{23}N_3O_3$	365·44	69·02	6·34	11·50	68·98	6·10	11·26
5-MT+(III)	157–158	$C_{19}H_{22}N_2O_3$	326·40	69·92	6·79	8·58	69·86	6·75	8·77
5-MT+(IV)	133–134	$C_{19}H_{22}N_2O_4$	342·40	66·65	6·48	8·81	65·78	6·66	–

(I) 5-MIAA. (II) IAA. (III) Phenylacetic acid. (IV) *p*-Hydroxyphenylacetic acid.

* Complex found by Taborsky (1964).

By manual calculation, the phases of the remaining 122 reflexions were determined. The three-dimensional E map ($a=+$, $b=c=d=-$) revealed reasonable positive peaks corresponding to the heavy atoms.

The structure was refined by a full-marix least-squares method with isotropic thermal parameters for all the non-H atoms, and then by a block-diagonal least-squares method with anisotropic temperature factors. At this stage R was 0·11, and a difference Fourier synthesis was computed in order to find the positions of the H atoms. As a result, all the H atoms, except the methyl H atoms of the 5-MIAA molecule, were properly located. The methyl group appears to undergo free rotation since the methyl C atom has a large temperature factor.

The final cycle of refinement was carried out by a block-diagonal least-squares method with anisotropic temperature factors for all non-H atoms and with isotropic temperature factors for 22 H atoms. R was reduced to 0·080.

IAA:5-*MT*

The similar cell dimensions and Patterson diagrams of the two complexes suggest that their molecular packing might be quite similar. Therefore, a Fourier synthesis was carried out with the phases calculated from the two indole rings determined in the 5-MIAA:5-MT complex. The positions of all the non-H atoms of the IAA:5-MT complex were easily found on the electron density map. In Fig. 1 the thin lines indicate

Table 4. *Final positional and thermal parameters with their estimated standard deviations in parentheses for* 5-*MIAA*:5-*MT*

The anisotropic temperature factors are expressed in the form: $\exp[-(B_{11}h^2+B_{22}k^2+B_{33}l^2+B_{12}hk+B_{13}hl+B_{23}kl)]$. Final thermal parameter for hydrogen atoms: overall isotropic 4·6 Å^2. Positional parameters $\times 10^4$ for C, N, O, $\times 10^3$ for H; $B_{IJ}\times 10^4$.

	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C(1*A*)	3254 (7)	12020 (15)	2658 (3)	54 (7)	243 (31)	15 (2)	12 (24)	5 (6)	−15 (12)
C(2*A*)	2253 (7)	11215 (15)	2825 (4)	63 (8)	209 (29)	20 (2)	−24 (26)	29 (6)	−10 (13)
C(3*A*)	1614 (7)	9470 (14)	2507 (4)	45 (7)	183 (28)	19 (2)	−4 (23)	28 (6)	−26 (12)
C(4*A*)	1016 (7)	9540 (15)	1958 (4)	64 (8)	235 (31)	18 (2)	−24 (25)	23 (6)	−14 (13)
C(5*A*)	961 (8)	11064 (17)	1576 (4)	66 (8)	285 (33)	21 (2)	−10 (28)	18 (7)	−17 (14)
C(6*A*)	286 (9)	10608 (20)	1091 (4)	86 (10)	464 (49)	22 (2)	77 (36)	−1 (8)	0 (18)
C(7*A*)	−337 (8)	8728 (22)	990 (4)	69 (9)	633 (55)	20 (2)	−80 (38)	9 (7)	−102 (20)
C(8*A*)	−254 (9)	7126 (20)	1371 (4)	98 (11)	443 (47)	26 (3)	−90 (37)	33 (9)	−60 (18)
C(9*A*)	444 (8)	7660 (16)	1864 (4)	64 (8)	269 (34)	22 (2)	−76 (27)	20 (7)	−23 (14)
C(10*A*)	1359 (8)	7549 (16)	2700 (4)	59 (8)	276 (33)	23 (2)	−35 (26)	23 (7)	9 (14)
C(11*A*)	983 (13)	13395 (31)	627 (6)	167 (17)	928 (91)	40 (4)	11 (67)	73 (14)	100 (33)
N(1*A*)	666 (7)	6428 (7)	2299 (3)	91 (8)	299 (30)	28 (2)	−66 (26)	30 (7)	−2 (14)
O(1*A*)	3648 (6)	13746 (11)	2840 (3)	131 (7)	275 (23)	21 (1)	−154 (23)	25 (5)	−51 (10)
O(2*A*)	3685 (5)	10939 (10)	2370 (3)	84 (6)	195 (20)	27 (2)	−21 (18)	44 (5)	−38 (9)
O(3*A*)	153 (7)	12001 (16)	665 (3)	137 (9)	677 (43)	29 (2)	43 (33)	−8 (7)	84 (16)
C(1*B*)	3226 (8)	6316 (18)	1598 (4)	70 (9)	378 (40)	23 (2)	32 (32)	31 (7)	−44 (16)
C(2*B*)	3870 (8)	6531 (18)	1190 (4)	78 (9)	339 (37)	19 (2)	46 (30)	21 (7)	−15 (15)
C(3*B*)	4749 (8)	4887 (14)	1221 (3)	84 (9)	163 (26)	16 (2)	38 (25)	21 (6)	−10 (12)
C(4*B*)	5609 (7)	4924 (14)	942 (3)	66 (8)	208 (29)	12 (2)	31 (25)	1 (6)	10 (12)
C(5*B*)	5875 (7)	6332 (15)	589 (4)	66 (8)	243 (31)	16 (2)	25 (27)	10 (6)	−17 (13)
C(6*B*)	6769 (8)	5856 (16)	396 (4)	78 (8)	299 (34)	13 (2)	−9 (28)	9 (6)	26 (13)
C(7*B*)	7429 (8)	4053 (18)	533 (4)	71 (8)	386 (40)	17 (2)	17 (31)	17 (7)	−7 (15)
C(8*B*)	7163 (8)	2632 (17)	874 (4)	73 (9)	290 (35)	19 (2)	−21 (28)	−2 (7)	−19 (14)
C(9*B*)	6242 (8)	3086 (17)	1077 (3)	79 (9)	343 (37)	10 (2)	−25 (29)	11 (6)	30 (13)
C(10*B*)	4099 (8)	3067 (15)	1508 (4)	84 (9)	231 (32)	18 (2)	27 (28)	27 (7)	18 (14)
C(11*B*)	6468 (9)	8839 (19)	−193 (4)	126 (12)	392 (43)	18 (2)	−21 (38)	31 (8)	23 (17)
N(1*B*)	3929 (6)	6853 (13)	2132 (3)	74 (7)	316 (29)	16 (2)	−22 (23)	14 (5)	−21 (11)
N(2*B*)	5802 (7)	1943 (12)	1418 (3)	104 (8)	229 (26)	15 (2)	54 (24)	14 (5)	12 (11)
O(1*B*)	7131 (6)	7094 (12)	35 (3)	99 (7)	409 (29)	26 (2)	1 (23)	40 (5)	53 (11)

	x	y	z		x	y	z
H(1*A*)	172 (8)	1256 (16)	283 (4)	H(5*B*)	292 (8)	472 (16)	160 (4)
H(2*A*)	252 (8)	1069 (16)	322 (4)	H(6*B*)	426 (8)	812 (16)	124 (3)
H(3*A*)	138 (8)	1254 (15)	166 (4)	H(7*B*)	331 (8)	636 (16)	82 (3)
H(4*A*)	−86 (7)	850 (16)	61 (3)	H(8*B*)	543 (8)	780 (16)	47 (3)
H(5*A*)	−73 (7)	570 (16)	129 (3)	H(9*B*)	814 (7)	383 (16)	37 (3)
H(6*A*)	167 (8)	700 (16)	313 (4)	H(10*B*)	764 (7)	115 (17)	98 (4)
H(10*A*)	37 (8)	489 (16)	232 (4)	H(11*B*)	440 (8)	251 (16)	175 (4)
H(1*B*)	477 (8)	656 (16)	228 (3)	H(12*B*)	676 (8)	949 (16)	−52 (4)
H(2*B*)	381 (8)	573 (16)	239 (4)	H(13*B*)	634 (8)	986 (16)	11 (4)
H(3*B*)	382 (8)	842 (16)	222 (3)	H(14*B*)	562 (8)	832 (16)	−41 (4)
H(4*B*)	249 (8)	734 (16)	151 (4)	H(15*B*)	611 (7)	67 (16)	167 (3)

the indole rings used for the calculation and the thick lines show the final position of the IAA and 5-MT molecules obtained on the electron density map. The structure was refined by a procedure similar to that described for 5-MIAA:5-MT. All H atoms were found by a difference Fourier synthesis, and the final R was 0·077.

Results and discussion

The atomic coordinates and thermal parameters with their estimated standard deviations are given in Table 4 for 5-MIAA:5-MT and in Table 5 for IAA:5-MT.*

* A list of structure factors for each complex has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31921 (6 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

The final bond lengths and angles involving non-H atoms are shown in Fig. 2 (5-MIAA:5-MT) and Fig. 3 (IAA:5-MT), where the average standard deviations are about 0·010–0·015 Å for the bond lengths and 0·5–0·8° for the bond angles of 5-MIAA:5-MT and 0·009–0·010 Å, 0·5–0·8° for the bond lengths and angles of IAA:5-MT.

In both complexes the angle C(5*B*)–C(6*B*)–O(1*B*) is larger than C(7*B*)–C(6*B*)–O(1*B*); by 12·8° in 5-MIAA:5-MT and by 11·6° in IAA:5-MT. This was also observed in the related compounds containing a methoxy group: melatonin (9°) (Wakahara, Fujiwara & Tomita, 1972), 5-methoxy-*N*,*N*-dimethyltryptamine.HCl (10°) (Falkenberg & Carlström, 1971) and 5-MIAA (11°) (Sakaki, Wakahara, Fujiwara & Tomita, 1975). This may result from the *cis* orientation of the C(6*B*)–C(5*B*) and C(11*B*)–O(1*B*) bonds with respect to the C(6*B*)–O(1*B*) bond causing the bond angle C(5*B*)–

Table 5. *Final positional and thermal parameters with their estimated standard deviations in parentheses for IAA:5-MT*

The anisotropic temperature factors are expressed in the form: exp $[-(B_{11}h^2+B_{22}k^2+B_{33}l^2+B_{12}hk+B_{13}hl+B_{23}kl)]$. Final thermal parameter for hydrogen atoms: overall isotropic 3·6 Å^2. Positional parameters $\times 10^4$ for C, N, O, $\times 10^3$ for H; $B_{ij}\times 10^4$.

	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C(1*A*)	3132 (5)	12040 (8)	2757 (3)	55 (5)	121 (13)	9 (2)	18 (13)	2 (4)	3 (7)
C(2*A*)	1977 (5)	11326 (9)	2892 (3)	64 (5)	135 (14)	15 (2)	−7 (14)	20 (5)	−12 (8)
C(3*A*)	1502 (5)	9654 (9)	2521 (3)	40 (4)	130 (14)	18 (2)	−6 (13)	23 (4)	1 (8)
C(4*A*)	1159 (5)	9761 (9)	1928 (3)	43 (4)	184 (16)	13 (2)	5 (14)	17 (4)	1 (8)
C(5*A*)	1144 (6)	11280 (11)	1522 (3)	93 (6)	214 (19)	19 (2)	11 (18)	32 (6)	28 (10)
C(6*A*)	725 (8)	10899 (15)	972 (4)	155 (9)	426 (30)	12 (3)	−12 (29)	17 (7)	45 (13)
C(7*A*)	299 (8)	8975 (16)	823 (4)	160 (10)	518 (36)	12 (3)	−80 (32)	−8 (7)	−23 (14)
C(8*A*)	325 (7)	7428 (13)	1210 (4)	106 (7)	355 (26)	17 (3)	−91 (23)	3 (6)	−19 (12)
C(9*A*)	758 (5)	7839 (10)	1758 (3)	57 (5)	224 (18)	13 (2)	−30 (15)	−1 (5)	−15 (9)
C(10*A*)	1312 (5)	7736 (9)	2692 (3)	66 (5)	164 (16)	14 (2)	−9 (15)	3 (5)	11 (8)
N(1*A*)	885 (4)	6633 (8)	2223 (3)	74 (5)	156 (13)	19 (2)	−61 (13)	0 (4)	0 (7)
O(1*A*)	3354 (4)	13837 (6)	2842 (2)	95 (4)	104 (9)	20 (1)	−56 (10)	20 (4)	−19 (6)
O(2*A*)	3808 (3)	10801 (6)	2583 (2)	54 (3)	113 (9)	16 (1)	−14 (9)	12 (3)	−18 (5)
C(1*B*)	3756 (5)	7454 (9)	1517 (3)	75 (5)	128 (14)	12 (2)	22 (14)	11 (5)	−5 (8)
C(2*B*)	3637 (5)	5539 (10)	1160 (3)	64 (5)	204 (17)	12 (2)	−26 (15)	3 (5)	−16 (9)
C(3*B*)	4693 (5)	4342 (8)	1173 (3)	69 (5)	112 (14)	11 (2)	−20 (13)	7 (4)	−12 (7)
C(4*B*)	5691 (5)	4742 (8)	890 (3)	76 (5)	113 (13)	7 (2)	7 (14)	2 (4)	16 (7)
C(5*B*)	5990 (5)	6302 (9)	530 (4)	74 (5)	147 (15)	13 (2)	−22 (15)	10 (5)	16 (8)
C(6*B*)	7021 (6)	6230 (10)	334 (3)	96 (6)	224 (18)	11 (2)	−68 (18)	5 (5)	7 (9)
C(7*B*)	7783 (6)	4623 (11)	454 (3)	93 (7)	281 (21)	13 (2)	−27 (19)	5 (5)	−28 (10)
C(8*B*)	7485 (6)	3082 (9)	805 (3)	93 (6)	220 (18)	13 (2)	68 (18)	−6 (5)	−32 (9)
C(9*B*)	6460 (5)	3166 (9)	1022 (3)	69 (5)	161 (15)	11 (2)	31 (15)	8 (5)	−18 (8)
C(10*B*)	4884 (6)	2602 (9)	1467 (3)	89 (6)	130 (15)	11 (2)	−27 (15)	4 (5)	−8 (8)
C(11*B*)	6681 (8)	9271 (11)	−180 (4)	158 (10)	219 (20)	17 (2)	−101 (23)	20 (7)	31 (11)
N(1*B*)	3993 (4)	7032 (7)	2130 (3)	66 (4)	94 (11)	9 (11)	−3 (11)	10 (3)	−5 (6)
N(2*B*)	5962 (6)	1863 (3)	1370 (2)	124 (6)	121 (12)	10 (2)	6 (14)	5 (4)	9 (7)
O(1*B*)	7430 (5)	7650 (8)	−20 (2)	122 (5)	326 (16)	20 (2)	−104 (15)	31 (4)	38 (8)

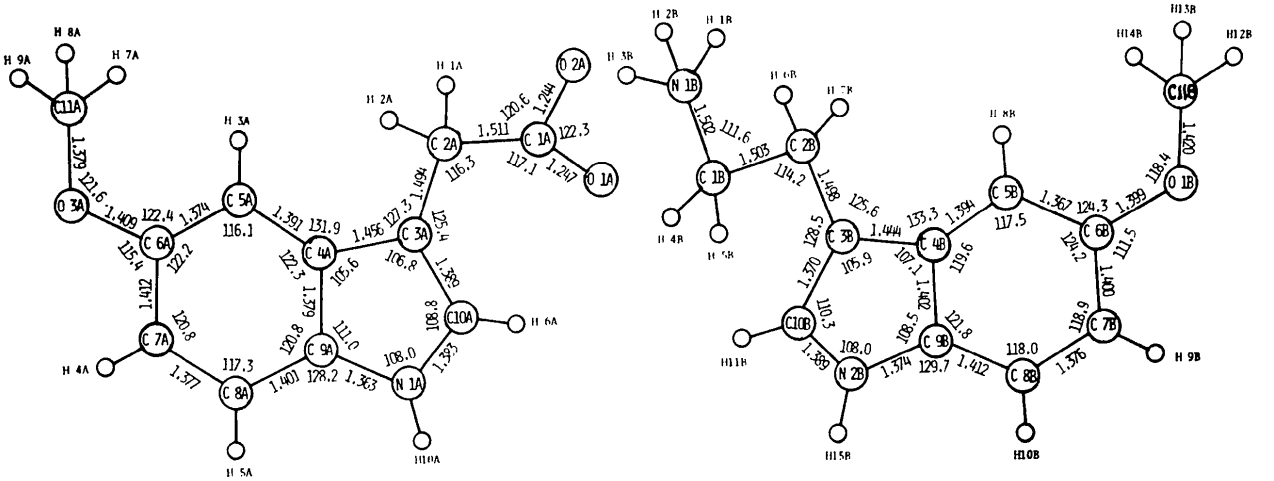
	x	y	z		x	y	z
H(1*A*)	135 (6)	1255 (11)	285 (3)	H(5*B*)	443 (6)	835 (11)	138 (3)
H(2*A*)	208 (6)	1086 (11)	332 (3)	H(6*B*)	324 (6)	591 (11)	74 (3)
H(3*A*)	155 (6)	1273 (11)	165 (3)	H(7*B*)	292 (6)	468 (11)	130 (3)
H(4*A*)	76 (6)	1207 (11)	63 (3)	H(8*B*)	642 (6)	747 (11)	42 (3)
H(5*A*)	−9 (6)	876 (11)	37 (3)	H(9*B*)	867 (6)	462 (11)	27 (3)
H(6*A*)	−7 (6)	594 (11)	108 (3)	H(10*B*)	808 (6)	189 (11)	90 (3)
H(7*A*)	143 (6)	713 (11)	312 (3)	H(11*B*)	434 (6)	189 (11)	174 (3)
H(8*A*)	60 (6)	519 (11)	225 (3)	H(12*B*)	701 (6)	1014 (11)	−45 (3)
H(1*B*)	484 (6)	655 (11)	224 (3)	H(13*B*)	646 (6)	1015 (11)	19 (3)
H(2*B*)	394 (6)	829 (11)	231 (3)	H(14*B*)	584 (6)	874 (11)	−38 (3)
H(3*B*)	369 (6)	593 (11)	235 (3)	H(15*B*)	632 (6)	1074 (11)	164 (3)
H(4*B*)	296 (6)	829 (11)	145 (3)				

Table 6. *Hydrogen-bond dimensions*

Symmetry code

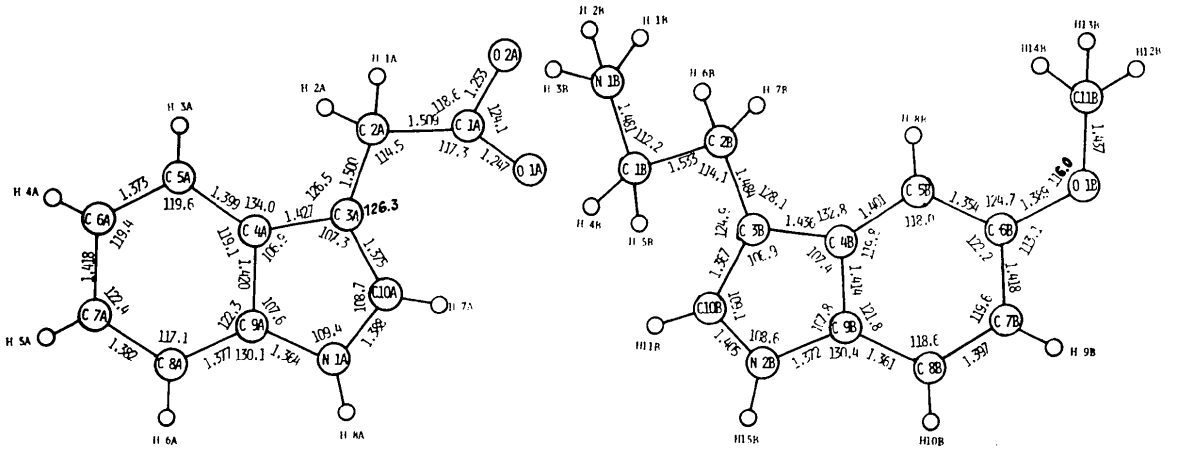
Original molecule	x, y, z
(I)	$x, 1+y, z$
(II)	$1-x, \frac{1}{2}+y, \frac{1}{2}-z$
(III)	$1-x, \frac{3}{2}+y, \frac{1}{2}-z$

Donor	Acceptor (original molecule)	Distance $D\cdots A$	Distance H$\cdots A$	Angle D–H$\cdots A$
5-MT:5-MIAA				
Original	N(1*B*)–H(3*B*)$\cdots$O(2*A*)	2·70 Å	1·7 Å	170°
(I)	N(1*B*)–H(2*B*)$\cdots$O(1*A*)	2·80	1·8	172
(II)	N(1*B*)–H(1*B*)$\cdots$O(2*A*)	2·95	2·0	162
(III)	N(2*B*)–H(15*B*)$\cdots$O(1*A*)	2·76	1·7	159
5-MT:IAA				
Original	N(1*B*)–H(3*B*)$\cdots$O(2*A*)	2·76	1·8	180
(I)	N(1*B*)–H(2*B*)$\cdots$O(1*A*)	2·86	2·0	145
(II)	N(1*B*)–H(1*B*)$\cdots$O(2*A*)	2·76	1·7	173
(III)	N(2*B*)–H(15*B*)$\cdots$O(1*A*)	2·81	1·8	170



5-MIAA 5-MT

Fig. 2. Bond lengths and angles for non-hydrogen atoms in 5-MIAA:5-MT.



IAA 5-MT

Fig. 3. Bond lengths and angles for non-hydrogen atoms in IAA:5-MT.

C(6*B*)–O(1*B*) to be larger because of repulsion between C(5*B*) and C(11*B*). The molecular arrangements, viewed along **b**, of 5-MIAA:5-MT and IAA:5-MT are depicted in Figs. 4 and 5 respectively.

As already predicted, the molecular packing in the two complexes is similar. The molecular complex is formed by the salt bridge between the positive charge, NH_3^+, on the amino side chain of 5-MT and the negative charge, COO^-, on the carboxyl group of 5-MIAA or IAA. Besides the electrostatic interaction, the amino group and indole N atom of 5-MT are hydrogen-bonded to the carboxyl O of 5-MIAA or IAA; the possible hydrogen bonds are summarized in Table 6. However, as in the case of 5-hydroxy-DL-tryptophan (Wakahara, Kido, Fujiwara & Tomita, 1973) the indole N atom of 5-MIAA or IAA does not take part in any

Table 7. *Deviations of atoms from the least-squares planes* (Å)

Distances marked with an asterisk refer to atoms defining the plane.

Equations of the least-squares planes with the formula $m_1X+m_2Y+m_3Z=d$ in orthogonal space

Plane	m_1	m_2	m_3	d
5-MT:IAA				
Indole ring of IAA	0·94091	−0·26069	−0·21628	−1·80261
Carboxyl group	−0·27842	0·19567	−0·94032	−5·39341
Indole ring of 5-MT	0·33052	0·50278	0·79873	5·43799
Aminoethyl group	−0·99504	−0·00623	0·09930	−3·76978
5-MT:5-MIAA				
Indole ring of 5-MIAA	0·86729	−0·42349	−0·26164	−3·92883
Carboxyl group	−0·40836	0·45214	−0·79298	−2·89580
Indole ring of 5-MT	0·42611	0·48719	0·76228	6·05933
Aminoethyl group	0·27226	−0·95269	0·13509	−2·45834

Deviations from the planes

5-MT:IAA

	IAA Indole ring	IAA Carboxyl group
C(1*A*)	1·209	0·011*
C(2*A*)	−0·061	−0·003*
C(3*A*)	−0·024*	0·737
C(4*A*)	−0·001*	2·149
C(5*A*)	0·021*	3·215
C(6*A*)	0·007*	4·517
C(7*A*)	−0·020*	4·738
C(8*A*)	−0·012*	3·671
C(9*A*)	0·011*	2·386
C(10*A*)	−0·018*	0·159
N(1*A*)	0·038*	1·187
O(1*A*)	1·088	−0·004*
O(2*A*)	2·307	−0·004*

	5-MT Indole ring	5-MT Aminoethyl group
C(1*B*)	−1·292	0·0*
C(2*B*)	0·065	0·0*
C(3*B*)	0·011*	−1·233
C(4*B*)	0·006*	−2·555
C(5*B*)	0·000*	−3·071
C(6*B*)	−0·014*	−4·364
C(7*B*)	0·000*	−5·237
C(8*B*)	0·014*	−4·714
C(9*B*)	0·001*	−3·403
C(10*B*)	−0·006*	−1·316
C(11*B*)	0·029	−4·194
N(1*B*)	−2·358	0·0*
N(2*B*)	−0·012*	−2·643
O(1*B*)	−0·011	−5·027

5-MT:5-MIAA

	5-MIAA Indole ring	5-MIAA Carboxyl group
C(1*A*)	0·880	0·024*
C(2*A*)	−0·228	−0·006*
C(3*A*)	−0·030*	0·373
C(4*A*)	0·014*	1·659
C(5*A*)	0·016*	2·808
C(6*A*)	0·012*	3·875
C(7*A*)	−0·027*	3·844
C(8*A*)	−0·013*	2·704
C(9*A*)	0·012*	1·589
C(10*A*)	−0·020*	−0·408
C(11*A*)	0·598	5·133
N(1*A*)	0·038*	0·347
O(1*A*)	0·612	−0·010*
O(2*A*)	2·006	−0·008*
O(3*A*)	0·033	5·091

	5-MT Indole ring	5-MT Aminoethyl group
C(1*B*)	−0·250	0·0*
C(2*B*)	0·008	0·0*
C(3*B*)	−0·012*	1·312
C(4*B*)	−0·003*	1·533
C(5*B*)	0·007*	0·680
C(6*B*)	0·011*	1·273
C(7*B*)	−0·013*	2·629
C(8*B*)	−0·007*	3·459
C(9*B*)	0·003*	2·890
C(10*B*)	0·005*	2·512
C(11*B*)	0·258	−0·755
N(1*B*)	−1·715	0·0*
N(2*B*)	0·018*	3·499
O(1*B*)	0·043	0·572

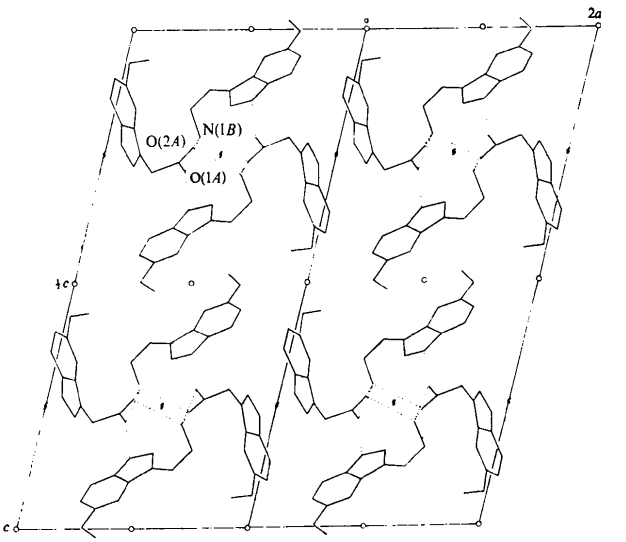


Fig. 4. Molecular packing of 5-MIAA:5-MT viewed along **b**. The dotted lines represent the possible hydrogen bonds.

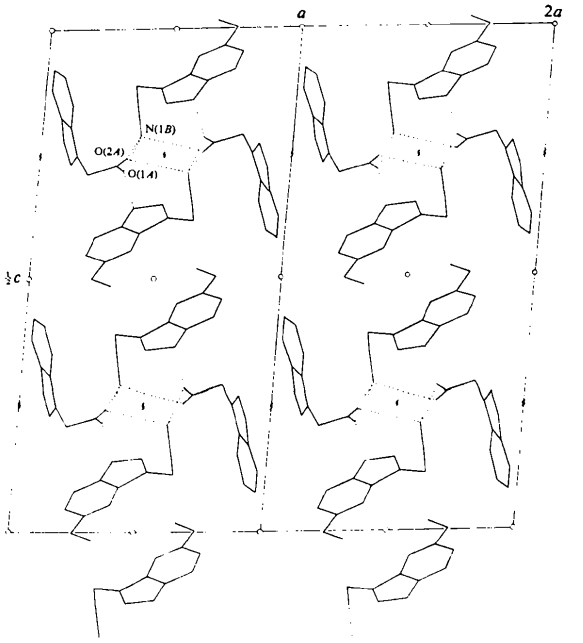


Fig. 5. Molecular packing of IAA:5-MT viewed along **b**. The dotted lines represent the possible hydrogen bonds.

hydrogen bonding. It is worthwhile to note that non-polar indole planes are stacked by van der Waals forces between adjacent molecules related by a centre of symmetry. In both crystals, the complex molecules are arranged around the twofold screw axis to form an infinite helical array with two complex pairs per turn parallel to **b**.

The planarities of the four parts of the molecular complex, the two indole rings, a carboxyl group and an aminoethyl group, were examined by the equations of the least-squares planes. The results are listed in Table 7. The C(2*A*) atom of 5-MIAA:5-MT deviates considerably from the indole-ring plane as compared with IAA:5-MT. As the C(2*A*) atom usually lies on the indole ring plane, crystalline IAA:5-MT is expected to be more stable than 5-MIAA:5-MT, which may be the reason for its melting point being 6–10°C higher than that of 5-MIAA:5-MT (Table 1).

The dihedral angles between the relevant planes in the individual molecules of the complexes are given in Table 8 in comparison with those reported for the free component molecules 5-MT, determined by Quarles, Templeton & Zalkin (1974), IAA, by Karle, Britts & Gum (1964) and 5-MIAA, by Sakaki, Wakahara, Fujiwara & Tomita (1975). It is of interest that the dihedral angle between the indole ring and carboxyl group in 5-MIAA (59·53°) differs considerably from that in 5-MIAA:5-MT (109·76°).

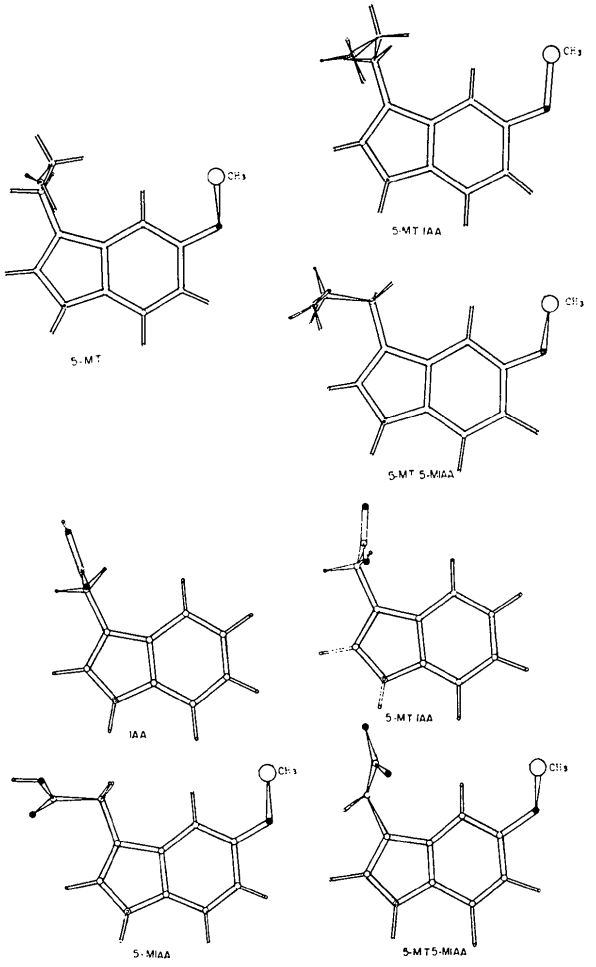


Fig. 6. Comparison of the molecular conformations of 5-MT, IAA and 5-MIAA found in crystals of free molecules and complexes.

Table 8. *Intra- and intermolecular dihedral angles* (°)

(*a*) Comparison of intermolecular dihedral angles

	Free	5-MIAA: 5-MT	IAA:5-MT
5-MT			
Between indole ring and aminoethyl group	91·85*	75·81	75·37
IAA			
Between indole ring and carboxyl group	89·99†	–	96·29
5-MIAA			
Between indole ring and carboxyl group	59·53‡	109·76	–

(*b*) Comparison of intermolecular dihedral angles

	5-MIAA: 5-MT	IAA:5-MT
Between indole ring (5-MT) and indole ring (acid)	87·93	90·41
Between C(6*B*)···C(3*B*) and indole ring (acid)	51·36	49·46
Between C(10*B*)···C(7*B*) and indole ring (acid)	53·54	52·06
Between C(6*A*)···C(3*A*) and indole ring (5-MT)	46·25	45·18
Between C(10*A*)···C(7*A*) and indole ring (5-MT)	48·11	47·52

* Quarles, Templeton & Zalkin (1974).
† Karle, Britts & Gum (1964).
‡ Sakaki, Wakahara, Fujiwara & Tomita (1975).

The intermolecular dihedral angles for each complex are also given in Table 8 and show little difference between the two complexes.

Therefore, the major factors determining the molecular packing of the crystal complexes might be the hydrogen-bonding mode and the relative position of the indole ring around the twofold screw axis. In order to compare the molecular conformations of the two complexes, relevant torsion angles of the side chains are listed in Table 9 with those found in each component molecule. In the case of IAA:5-MT, the overall conformation of each component molecule is the same as that of free 5-MT or IAA. On the other hand, the torsion angles in the 5-MIAA:5-MT complex differ considerably from those of each free component (Fig. 6).

It seems important to discuss the reason why 5-MT, in spite of its activity as a biogenic monoamine, exists in the living body or is excreted into urine without enzymatic degradation.

When 5-MT is metabolized to 5-MIAA by monoamine oxidase (MAO) and aldehyde oxidase, the amino side chain needs to be recognized by MAO. If 5-MT forms a molecular complex with 5-MIAA, its final

Table 9. *Torsion angles* (°)

The torsion angle is as defined by Klyne & Prelog (1960).

5-MT

Bond sequence	5-MT[a]	5-MT in IAA:5-MT	5-MT in 5-MIAA:5-MT
C(10)–C(3)–C(2)–C(1)	116·3 (anticlinal)	106·1 (anticlinical)	11·8 (synperiplanar)
C(3)–C(2)–C(1)–N(1)	−53·9 [(−)synclinal]	−64·4 [(−)synclinal]	70·7 (synclinal)

Acids

Bond sequence	IAA[b]	IAA in IAA:5-MT	5-MIAA[c]	5-MIAA in 5-MIAA:5-MT
C(10)–C(3)–C(2)–C(1)	97·7 (anticlinal)	113·4 (anticlinal)	6·0 (synperiplanar)	125·6 (anticlinal)
C(3)–C(2)–C(1)–O(1)	173·6 (antiperiplanar)	148·5 (anticlinal)	119·2 (anticlinal)	165·7 (antiperiplanar)
C(3)–C(2)–C(1)–O(2)	−11·7 (synperiplanar)	−29·4 (synperiplanar)	−61·9 [(−)synclinal]	−9·6 (synperiplanar)
C(11)–O(3)–C(6)–C(5)	–	–	−1·1 (synperiplanar)	27·0 (synperiplanar)

(*a*) Quarles, Templeton & Zalkin (1974). (*b*) Karle, Britts & Gum (1964). (*c*) Sakaki, Wakahara, Fujiwara & Tomita (1975).

metabolite, or with IAA, a final tryptamine metabolite, the aminoethyl side chain of 5-MT becomes interior, surrounded by hydrophobic indole rings. Therefore, 5-MT in a molecular complex would not be recognized by MAO, and it might be preserved in the living body or in urine. Moreover, provided that the side-chain conformation of the 5-MT crystal binds stereospecifically to MAO as a substrate, it seems that the conformation of 5-MT, when complexed with 5-MIAA, differs from that recognizable by MAO.

Further to these ideas, therefore, a structure analysis of the molecular complex between tryptamine and its final metabolite, IAA, is also of interest.

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