Structural Studies of the Interaction between Indole Derivatives and Biologically Important Aromatic Compounds. II. The Crystal and Molecular Structure of the Tryptamine–Phenylacetic Acid (1: 1) Complex

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The title complex crystallizes in the monoclinic space group of $P2_1/c$. The unit-cell dimensions are $a=6.673(4)$, $b=19.017(8)$, $c=13.394$ (7) Å, and $\beta=110.54(2)°$. The crystal structure was solved by a direct method. By block-diagonal least-squares refinements, the R-value converged to 0.062. In this complex, a salt bridge is found between the anionic carboxyl group of phenylacetic acid (PAA) and the cationic amino group of tryptamine (TPA). All the hydrogen atoms attached to the nitrogen atoms participate in the hydrogen bonding. The two complex molecules are hydrogen-bonded around a center of symmetry to form one unit, which is held together by van der Waals contacts in the b- and c-directions. Each unit is also stabilized by forming a hydrogen bond with the unit of the neighboring cell translated in the a-direction.

The 1: 1 molecular complex of tryptamine (TPA) and phenylacetic acid (PAA) was crystallized, and its structure was determined in order to investigate the interaction between the benzene and indole rings, because the existence of interaction between tyrosine and tryptophan residue has been indicated by fluorescence studies.[1–4)]

Experimental

Equimolar amounts of TPA and PAA were dissolved in a 50% ethanol aqueous solution. After evaporation at room temperature, transparent platelet crystals were obtained. Preliminary oscillation and Weissenberg photographs indicated the crystal to be monoclinic and the space group to be $P2_1/c$, judging from the systematic absent spectra.

Table 1. Crystal data

$C_8H_8O_2 \cdot C_{10}H_{12}N_2$	
$a=6.673(4)$Å	$F.W.$ 296.35
$b=19.017(8)$	Space group $P2_1/c$
$c=13.394(7)$	$Z=4$
$\beta=110.54(2)°$	$V=1591.7$Å^3
$D_m=1.230$ g cm^{-3}	μ(Cu $K\alpha$) $=7.61$ cm^{-1}
$D_x=1.237$	

The crystallographic data are shown in Table 1. The density was measured by the floatation method in a benzene-carbon tetrachloride mixture. The three-dimensional intensity data were collected with a computer-controlled four-circle diffractometer using Ni-filtered Cu $K\alpha$ radiation. By means of the ω-2θ scan technique, the intensities of a total of 2108 independent reflections within $\sin\theta/\lambda$ less than 0.54 Å^{-1} were collected and corrected for the Lorentz and polarization factors, but not for the absorption. Standard reflections measured for every 50 reflections of the data set showed no decrease in intensity during the run. The scan speed was 4°/min, and the backgrounds were measured in 5 s. All the numerical calculations were carried out on an NEAC 2200-700 computer of the Computation Center of Osaka University using the "UNICS" program (1973).[5)] The atomic scattering factors used were in "International Tables for X-Ray Crystallography," Vol. 4 (1974).[6)]

Determination and Refinement of the Structure

The phases of 331 reflections ($E \geqq 1.2$) were determined by the symbolic addition method, and the following three-dimensional E-map revealed reasonable peaks corresponding to the heavy atoms.

The structure was refined by the least-squares method, and a difference map revealed the positions of all twenty hydrogen atoms (peak height: 0.35—0.45 e Å^{-3}). The final least-squares refinement, including hydrogen atoms with isotropic temperature factors, was performed with a weighting scheme of this form: $w=1.26$ for $F_o=0$, $w=1.0$ for $0<F_o \leqq 28$, and $w=\{1.0+2.0(F_o-28.0)\}^{-1}$ for $F_o>28.0$. In the last cycle of refinement, no parameters shifted more than one-fifth of the estimated deviation. The final R-value was 0.062, including $F_o=0$.

The residual fluctuations in the difference Fourier map were within the range from -0.3 to 0.3 e Å^{-3}. The observed and final calculated structure factors are listed in Table 2.[7)]

Results and Discussion

The perspective view of the component molecule with the atomic numbering and the a-axis projection

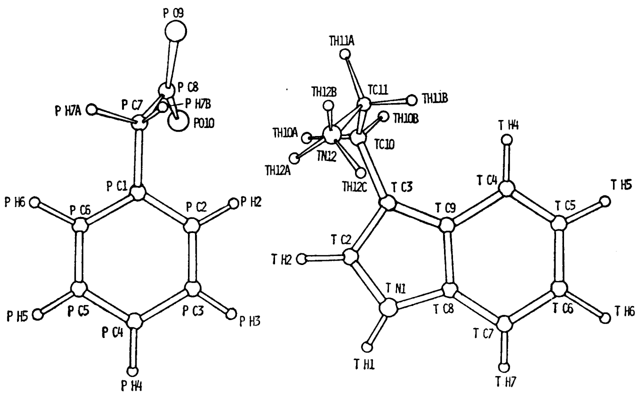

Fig. 1. The perspective view of PAA and TPA molecules with the atomic numbering.

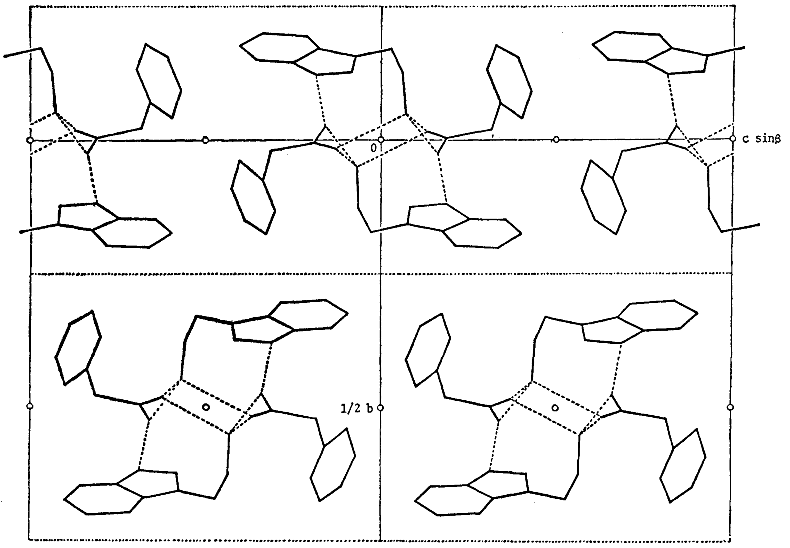

Fig. 2. Molecular packing of TPA–PAA viewed down the a-axis.

of the molecular packing are presented in Figs. 1 and 2 respectively, where the dotted lines indicate the hydrogen bonds. The atomic coordinates and thermal parameters, with their estimated standard deviations for non-hydrogen atoms, are given in Tables 3 and 4. The coordinates with isotropic thermal parameters for hydrogen atoms are shown in Table 5.

The Molecular Structure. Tables 6 and 7 show the bond lengths and angles, with their standard deviations. The equations of the least-squares planes for the benzene ring, the carboxyl group, the indole ring, and the aminoethyl group, and the deviations of the individual atoms from these planes are listed in Table 8.

PAA Molecule: The planarity of the benzene ring including the PC7 atom is good, and the bond lengths within the benzene ring are in the range of 1.377 to 1.387 Å (average value: 1.380 Å), significantly shorter than in the standard aromatic ring (1.395±0.003 Å)[8] as well as the smaller PC1–PC7 bond length (1.509 Å). The carbon-oxygen bond lengths in the carboxyl group are both short, but are nearly identical, and the PC7–PC8 bond length (1.521 Å) is close to that of the normal C(sp^3)–C(sp^2) single bond.[9] The torsional angles, χ(PC2–PC1–PC7–PC8) and ϕ(PC1–PC7–PC8–PO9), are 64.8° and −168.1° respectively. As these values are similar to those in β-phenethylamine ($\chi=72.6°$, $\phi=-171.1°$),[10] the precursor of PAA in a living body, both conformations might be fixed in their metabolic

TABLE 3. ATOMIC COORDINATES (×10^4) AND THEIR STANDARD DEVIATIONS OF HEAVY ATOMS

Atom	x	y	z
PC1	1681(4)	660(1)	6640(2)
PC2	2023(5)	1351(1)	6990(2)
PC3	3469(5)	1769(2)	6737(2)
PC4	4577(5)	1508(2)	6121(2)
PC5	4203(5)	827(2)	5752(3)
PC6	2776(5)	408(1)	6011(2)
PC7	105(4)	202(2)	6919(2)
PC8	664(4)	39(1)	8097(2)
PO9	−776(3)	−234(1)	8363(1)
PO10	2499(3)	171(1)	8732(1)
TN1	4106(4)	1205(1)	1870(2)
TC2	3888(4)	1277(1)	820(2)
TC3	5661(4)	1574(1)	729(2)
TC4	9170(4)	1969(2)	2225(2)
TC5	10138(5)	2005(2)	3308(3)
TC6	9087(5)	1782(2)	3984(2)
TC7	7056(5)	1500(1)	3594(2)
TC8	6083(4)	1456(1)	2490(2)
TC9	7108(4)	1690(1)	1795(2)
TC10	5979(5)	1741(1)	−298(2)
TC11	7526(4)	1265(1)	−572(2)
TN12	6822(3)	516(1)	−667(2)

TABLE 4. ANISOTROPIC THERMAL PARAMETERS (×10^4) AND THEIR STANDARD DEVIATIONS OF HEAVY ATOMS

Atom	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
PC1	215(7)	27(1)	46(2)	−6(4)	50(5)	11(2)
PC2	338(9)	28(1)	61(2)	−4(4)	123(7)	2(2)
PC3	413(10)	26(1)	75(2)	−40(5)	105(8)	4(2)
PC4	322(9)	36(1)	88(2)	−36(5)	132(8)	23(3)
PC5	353(10)	35(1)	107(3)	12(5)	231(9)	16(3)
PC6	322(9)	26(1)	80(2)	6(4)	156(7)	7(2)
PC7	214(7)	40(1)	58(2)	−43(4)	57(6)	9(2)
PC8	184(6)	21(1)	62(2)	−4(3)	111(5)	−3(2)
PO9	235(5)	35(1)	84(1)	−41(3)	181(5)	−8(2)
PO10	204(5)	39(1)	53(1)	−52(3)	48(4)	13(1)
TN1	259(6)	30(1)	95(2)	−40(4)	187(6)	−14(2)
TC2	202(7)	29(1)	82(2)	−12(4)	105(6)	−19(2)
TC3	208(7)	21(1)	68(2)	7(4)	105(6)	2(2)
TC4	225(7)	29(1)	93(2)	−27(4)	93(7)	−9(2)
TC5	300(9)	37(1)	95(3)	−14(5)	30(8)	−17(3)
TC6	435(11)	33(1)	75(2)	37(5)	30(8)	−13(2)
TC7	470(11)	24(1)	77(2)	33(5)	190(8)	1(2)
TC8	279(8)	19(1)	71(2)	1(4)	139(6)	−2(2)
TC9	198(6)	18(1)	70(2)	−3(3)	104(6)	0(2)
TC10	331(9)	28(1)	73(2)	16(4)	128(7)	14(2)
TC11	266(8)	30(1)	73(2)	−27(4)	145(7)	7(2)
TN12	189(5)	29(1)	58(1)	−12(3)	104(5)	1(2)

Table 5. Hydrogen atom coordinates ($\times 10^3$) and isotropic temperature factors, with their standard deviations

Atom	x	y	z	B(Å)
PH2	119(5)	154(2)	743(2)	3.8(7)
PH3	380(5)	228(2)	704(3)	4.8(8)
PH4	564(5)	183(2)	593(2)	4.0(7)
PH5	507(5)	64(2)	527(3)	5.0(8)
PH6	256(5)	−11(2)	569(2)	4.0(7)
PH7A	−8(5)	−28(2)	649(2)	4.2(7)
PH7B	−139(5)	43(2)	665(3)	5.1(8)
TH1	298(6)	90(2)	193(3)	6.1(9)
TH2	254(5)	113(2)	16(2)	3.4(7)
TH4	1008(5)	214(2)	176(3)	5.3(8)
TH5	1174(5)	221(2)	366(2)	4.5(7)
TH6	986(5)	180(2)	486(3)	4.7(8)
TH7	628(5)	135(2)	408(2)	4.3(7)
TH10A	447(4)	171(2)	−93(2)	3.2(6)
TH10B	661(5)	223(2)	−23(3)	4.7(8)
TH11A	768(4)	140(2)	−130(2)	2.9(6)
TH11B	900(4)	129(2)	3(2)	3.1(6)
TH12A	528(5)	41(2)	−98(2)	4.3(7)
TH12B	763(5)	23(2)	−99(2)	3.6(7)
TH12C	716(5)	28(2)	8(2)	3.9(7)

Table 6. Bond lengths and their standard deviations

	PAA		
PC1–PC2	1.387(4)Å	PC1–PC6	1.381(4)Å
PC1–PC7	1.509(4)	PC2–PC3	1.381(5)
PC3–PC4	1.379(5)	PC4–PC5	1.377(5)
PC5–PC6	1.377(5)	PC7–PC8	1.521(4)
PC8–PO9	1.248(3)	PC8–PO10	1.247(3)
	TRP		
TN1 –TC2	1.369(4)	TN1 –TC8	1.375(4)
TC2 –TC3	1.355(4)	TC3 –TC9	1.432(4)
TC3 –TC10	1.497(4)	TC4 –TC5	1.368(5)
TC4 –TC9	1.396(4)	TC5 –TC6	1.392(5)
TC6 –TC7	1.378(5)	TC7 –TC8	1.393(4)
TC8 –TC9	1.407(4)	TC10–TC11	1.512(4)
TC11–TN12	1.491(3)		

Table 7. Bond angles and their standard deviations

PAA	
PC2–PC1–PC6	118.4(3)°
PC6–PC1–PC7	121.0(2)
PC2–PC3–PC4	120.5(3)
PC4–PC5–PC6	120.6(3)
PC1–PC7–PC8	115.8(2)
PC7–PC8–PO10	119.4(2)
PC2–PC1–PC7	120.6(2)
PC1–PC2–PC3	120.6(3)
PC3–PC4–PC5	119.0(3)
PC5–PC6–PC1	120.9(3)
PC7–PC8–PO9	116.6(2)
PO9–PC8–PO10	123.9(2)
TRP	
TC2 –TN1 –TC8	108.6(2)
TC2 –TC3 –TC9	106.2(2)
TC9 –TC3 –TC10	128.3(2)
TC4 –TC5 –TC6	121.1(3)
TC6 –TC7 –TC8	117.2(3)
TC7 –TC8 –TC9	121.9(3)
TC8 –TC9 –TC3	107.2(2)
TC3 –TC9 –TC4	133.8(3)
TC10–TC11–TN12	111.8(2)
TN1 –TC2 –TC3	110.7(3)
TC2 –TC3 –TC10	125.5(3)
TC5 –TC4 –TC9	119.1(3)
TC5 –TC6 –TC7	121.7(3)
TC7 –TC8 –TN1	130.8(3)
TN1 –TC8 –TC9	107.3(2)
TC8 –TC9 –TC4	119.0(3)
TC3 –TC10–TC11	115.2(3)

process.[11]

The dihedral angle between the benzene ring and the carboxyl group is 110.1°.

TPA Molecule: Three hydrogen atoms found in the difference map are tetrahedrally bound to the nitrogen atom of the aminoethyl side chain, indicating the amino group to be in a cationic form, $-NH_3^+$.

The bond length of TC11–TN12, 1.491 Å, is similar to the normal values reported previously.[12–14] The bond lengths and angles of the indole moiety are normal, in the range found in the crystal structures of indole derivatives.[11] The planarity of the indole ring is better than those of the other tryptamine derivatives.[12,13,15]

The TH1 atom deviates significantly from the indole ring plane, causing the TN1–TN1H···PO9 angle to be 163.0°. The conformation of the tryptamine molecule found in this complex, (χ(TC2–TC3–TC10–TC11)$=$107.2° and ϕ(TC3–TC10–TC11–TN12)$=-59.8°$), is a stable one according to the energy calculation by Pullman *et al.*[16]

Although it is influenced by the various crystal-packing forces, it is noteworthy that a similar conformation is also found in the tryptamine hydrochloride[15] and tryptamine picrate[13] crystals, suggesting that this conformation is intrinsic and the most probable one for the tryptamine molecule. The dihedral angle between the indole ring and the aminoethyl group is 77.8°

The Crystal Structure. In the TPA-PAA complex, a salt bridge is formed between the anionic carboxyl group of PAA and the cationic amino group of TPA. The possible hydrogen bonds and the short contacts less than 3.5 Å are given in Table 9. All the hydrogen atoms attached to either an oxygen or nitrogen atom participate in the hydrogen bondings, forming infinite chains along the a-axis, as is shown in Fig. 3. There is no possibility of indole ring-benzene ring interaction, the dihedral angle between these planes being 119.3°.

However, the carboxyl plane of PAA lies fairly parallel to the plane of the indole ring of TPA (dihedral angle, 9.4°), with a 3.52 Å separation on the average, as is shown in Fig. 4. Even though these contact distances are slightly longer than the van der Waals separation, the possibility can not be discarded of the interaction

TABLE 8. DEVIATIONS OF ATOMS FROM THE LEAST-SQUARES PLANES

Equations of the best planes with the $m_1X+m_2Y+m_3Z=d$ formula in an orthogonal space

Plane	m_1	m_2	m_3	d
Benzene ring	0.4760	−0.3310	0.8226	5.5000
Carboxyl group	−0.3829	0.9116	0.1494	2.8673
Indole ring	0.4094	−0.9123	0.0129	−1.3037
Aminoethyl group	0.1825	−0.1360	0.9738	−0.0603

Deviations (in Å) from the best planes

PAA		TRP	
Benzene ring		Indole ring	
PC1*	−0.010	TN1*	0.006
PC2*	0.008	TC2*	0.006
PC3*	0.000	TC3*	−0.009
PC4*	−0.008	TC4*	0.000
PC5*	0.006	TC5*	0.012
PC6*	0.002	TC6*	−0.007
PC7	−0.004	TC7*	−0.005
PH2	0.032	TC8*	0.001
PH3	−0.043	TC9*	−0.004
PH4	−0.001	TC10	−0.030
PH5	0.009	TH1	0.225
PH6	0.021	TH2	0.009
Carboxyl group		TH4	0.026
PC7*	0.001	TH5	0.025
PC8*	−0.005	TH6	0.015
PO9*	0.002	TH7	−0.043
PO10*	0.002	Aminoethyl group	
PC1	−0.287	TC10*	0.0
		TC11*	0.0
		TN12*	0.0
		TC3	1.171

Atoms with asterisks define the plane.

TABLE 9. HYDROGEN BONDS AND SHORT CONTACTS LESS THAN 3.5Å

Superscribed numbers represent symmetry operators.

Hydrogen bonds

Donor	Acceptor	Distance D···A	Distance H···A	Angle D-H···A
TN1$^{1)}$	PO9$^{5)}$	2.821(3)Å	1.87(4)Å	163(3)°
TN12$^{1)}$	PO9$^{4)}$	2.784(3)	1.83(3)	175(3)
TN12$^{1)}$	PO10$^{2)}$	2.788(3)	1.81(3)	168(3)
TN12$^{1)}$	PO10$^{3)}$	2.793(3)	1.75(3)	174(3)

Short contacts

TC2$^{1)}$	PO10$^{2)}$	3.359(3)Å
TN12$^{1)}$	PO9$^{3)}$	3.326(3)
TN12$^{1)}$	PC8$^{3)}$	3.424(3)
TC2$^{1)}$	PO9$^{5)}$	3.323(3)

Symmetry code

Superscript	Symmetry operator		
1)	x	y	z
2)	x	y	$-1+z$
3)	$1-x$	$-y$	$1-z$
4)	$1+x$	y	$-1+z$
5)	$-x$	$-y$	$1-z$

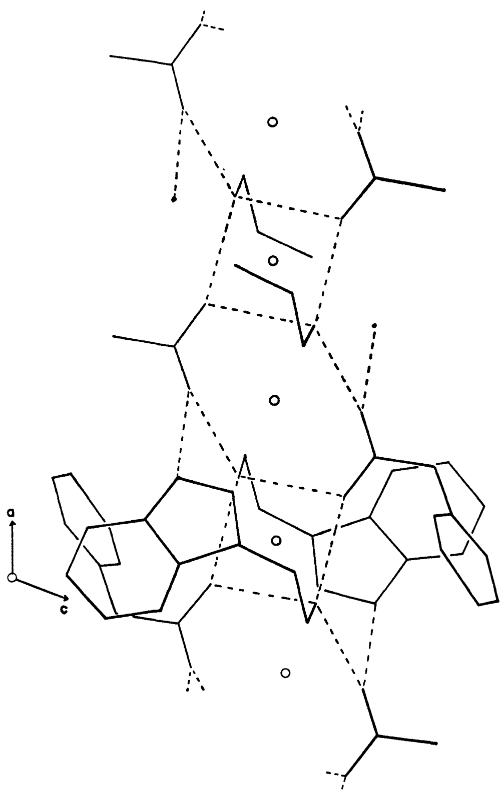

Fig. 3. The hydrogen bond network on the ac-plane found in this complex.

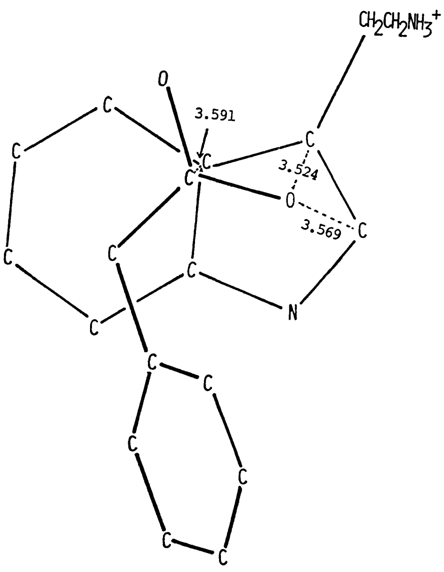

Fig. 4. Geometry of the stacked indole ring and carboxyl group projected to the indole ring plane.

between the polarizable π-electron system and the polar carbonyl group being similar to those in serotonin picrate,[14] tryptophan picrate, and tryptamine picrate.[13] As a whole, each of the two complex molecules is hydrogen-bonded around a center of symmetry to form one unit (two TPA and two PAA), and each is stabilized by forming a hydrogen bond with the unit of the neighboring cell, translated in the a-direction (see Figs. 2 and 3), a structure which is held together by van der Waals contact in the b- and c-directions.

In this hydrogen-bonding mode, as a complex of 5-methoxytryptamine–5-methoxyindole-3-acetic acid and 5-methoxytryptamine–indole-3-acetic acid,[12)] one of the carboxyl oxygen atoms forms two hydrogen bonds with two neighboring NH_3^+-groups. The other participates in two hydrogen bonds with a neighboring NH_3^+-group and a nitrogen atom in the indole ring, which may strengthen the hydrogen bond between anionic COO^- and cationic NH_3^+.

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