Structural Studies of the Interaction between Indole Derivatives and Biologically Important Aromatic Compounds. IV. The Crystal and Molecular Structure of Tryptamine: Adenin-9-ylacetic Acid (1:1) Hemihydrate Complex

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The crystal structure of tryptamine: adenin-9-ylacetic acid (1: 1) hemihydrate complex has been determined by the X-ray method. The crystal is monoclinic, space group $P2_1/c$ with unit-cell dimensions: $a=9.164(2)$, $b=6.908(1)$, $c=29.524(4)$ Å and $\beta=110.98(2)°$. The structure was solved by application of MULTAN and refined by the block-diagonal least-squares method to give a final R-value of 0.064. No specific interaction between indole and adenine rings is observed. Both component molecules are held together by three-dimensional frameworks of hydrogen bonds around a twofold screw axis to form an infinite helical array along the b-direction. Two kinds of dimer formation around a center of symmetry are observed between adenin-9-ylacetic acid molecules.

In previous communications, reports were given on the crystal structures of 1-methyl-3-carbamoylpyridinium: indole-3-acetic acid (1: 1) complex[1)] and 7,8-dimethylisoalloxazine-10-acetic acid: tryptamine (1: 1) complex[2)] selected as suitable models for indole–NAD$^+$ and indole–FAD interaction, respectively.

Prominent stacking of indole–pyridinium or indole–isoalloxazine rings by charge-transfer interactions was observed. However, when we compare the spectroscopic data of these model complexes with those of indole–NAD$^+$ and the indole–FAD complexes, we see that there is a slight difference in the association constant and $\lambda_{\max}$ of charge-transfer band.

We thus synthesized the title complex. The present paper deals with crystal structure analysis of the complex which may provide further insight into intermolecular stacking interaction of indole–adenine rings suggested from spectroscopic studies.[3–12)]

Experimental

Potassium adenin-9-ylacetate was synthesized according to the reported procedure.[13)] Its aqueous solution was absorbed to the Amberlite-IRA-401 anion-exchange resin (OH-type) column, and eluted with an equimolar aqueous solution of tryptamine hydrochloride. Transparent platelet crystals were obtained by slow evaporation of the elute at room temperature.

The UV spectra and thermal analysis of the crystals indicated a one-to-one stoichiometry of adenin-9-ylacetic acid (AAA) and tryptamine (TPA) with a halfmolar water molecule.

Oscillation and Weissenberg photographs showed the space group to be $P2_1/c$. The density was measured by the floatation method in a benzene–carbon tetrachloride mixture. The cell dimensions were refined by the least-squares method, using 30 reflections measured on a Rigaku-Denki automatic four-circle diffractometer with Ni-filtered Cu $K\alpha$ radiation. The crystal data are given in Table 1.

Intensity data were collected on a diffractometer with the same radiation using $\omega/2\theta$ scanning technique within $\sin\theta/\lambda$ less than 0.55 Å^{-1} with scan speed 4°/min, and background being measured for 5s. A total of 2431 independent reflections were corrected for Lorentz and polarization factors, but not for absorption because of the smallness of the crystal (dimension: 0.3×0.3×0.4 mm). The intensities of three standard reflections, measured every 50 reflections, showed no deterioration during the course of data collection.

TABLE 1. CRYSTAL DATA OF TPA: AAA(1: 1) COMPLEX

Chemical formula	$C_{17}H_{19}N_7O_2 \cdot 1/2H_2O$
Molecular weight	362.39
Crystal system	Monoclinic
Space group	$P2_1/c$
Cell constant	
a/Å	9.164(2)
b/Å	6.908(1)
c/Å	29.524(4)
β/°	110.98(2)
Volume/Å^3	1745.1
Z	4
D_m/g·cm^{-3}	1.375(2)
D_x/g·cm^{-3}	1.379
μ(Cu $K\alpha$)/cm^{-1}	9.38

All the numerical calculations were carried out on an NEAC-2200-700 computer of the Computation Center of Osaka University using "UNICS" program (1973).[14)] Atomic scattering factors cited in "International Tables for X-Ray Crystallography"[15)] were used.

Determination and Refinement of the Structure

The structure was solved by the direct method with the program MULTAN[16)] using 493 reflections with $|E|\geqq 1.20$. An E-map computed with the phase set of the highest figure of merit (1.249) revealed the positions of all non-hydrogen atoms except a water molecule. At the stage $R=0.143$, a difference Fourier synthesis gave two peaks related by a center of symmetry at (0,1/2,0) which could be assigned to the disordered oxygen atoms of the water molecules (occupancy: 1/2 per one peak), and nineteen hydrogen atoms other than those of the water molecule. The final block-diagonal least-squares refinement was computed with the following weighting scheme: $w=0.30$ for $F_o=0.0$, $w=1.0$ for $0<F_o\leqq 21.0$ and $w=1.0/[1.0+0.263(F_o-21.0)]$ for $F_o>21.0$. In the last cycle of refinement, none of the positional parameters shifted more than one-fourth of

TABLE 3. ATOMIC COORDINATES ($\times 10^4$) AND THEIR STANDARD DEVIATIONS OF NON-HYDROGEN ATOMS

Atom	x	y	z	Atom	x	y	z
AN1	1303(3)	11380(4)	432(1)	TN1	6894(3)	293(3)	1882(1)
AC2	948(4)	10219(5)	741(1)	TC2	7413(3)	950(4)	2352(1)
AN3	1592(3)	8534(4)	929(1)	TC3	8184(3)	2663(4)	2388(1)
AC4	2702(3)	8021(4)	754(1)	TC4	8727(3)	4602(4)	1709(1)
AC5	3200(3)	9072(4)	442(1)	TC5	8549(4)	4547(5)	1227(1)
AC6	2458(3)	10850(4)	277(1)	TC6	7760(4)	3031(5)	931(1)
AN6	2860(3)	12029(4)	−18(1)	TC7	7133(3)	1536(5)	1111(1)
AN7	4377(3)	8095(3)	343(1)	TC8	7328(3)	1582(4)	1601(1)
AC8	4546(4)	6494(4)	599(1)	TC9	8131(3)	3091(4)	1909(1)
AN9	3570(3)	6360(3)	849(1)	TC10	8934(3)	3828(4)	2839(1)
AC10	3531(4)	4831(4)	1180(1)	TC11	8092(3)	5697(4)	2866(1)
AC11	4388(3)	5337(3)	1708(1)	TN12	6526(2)	5285(3)	2893(1)
AO12	4438(2)	4005(2)	2002(1)	O(H_2O)	517(7)	5120(8)	−130(2)
AO13	4961(2)	6976(3)	1820(1)				

TABLE 4. ANISOTROPIC THERMAL PARAMETERS ($\times 10^4$) AND THEIR STANDARD DEVIATIONS OF NON-HYDROGEN ATOMS

The anisotropic temperature factors are expressed in the form $\exp\{-(B_{11}h^2+B_{22}k^2+B_{33}l^2+B_{12}hk+B_{13}hl+B_{23}kl)\}$.

Atom	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
AN1	135(4)	188(6)	15(0)	49(8)	25(2)	−5(2)
AC2	144(5)	245(8)	16(0)	60(10)	41(3)	−1(3)
AN3	161(4)	237(7)	17(0)	60(9)	49(2)	9(3)
AC4	123(4)	178(7)	10(0)	12(8)	17(2)	−2(3)
AC5	115(4)	158(6)	10(0)	14(8)	19(2)	−3(2)
AC6	124(4)	156(6)	12(0)	25(8)	17(2)	−8(3)
AN6	184(4)	191(6)	19(0)	85(9)	52(2)	47(3)
AN7	140(4)	172(6)	13(0)	42(7)	34(2)	4(2)
AC8	153(5)	173(7)	12(0)	55(9)	26(2)	6(3)
AN9	154(4)	149(5)	11(0)	25(7)	26(2)	12(2)
AC10	190(5)	143(6)	12(0)	−59(9)	25(2)	4(3)
AC11	99(4)	105(5)	11(0)	−8(7)	28(2)	−2(2)
AO12	138(3)	112(4)	12(0)	−19(5)	35(1)	9(2)
AO13	156(3)	114(4)	13(0)	−78(6)	30(2)	−8(2)
TN1	116(4)	145(5)	24(1)	−66(7)	51(2)	−34(3)
TC2	111(4)	139(6)	22(1)	14(8)	60(3)	3(3)
TC3	86(4)	117(5)	16(0)	29(7)	38(2)	−1(3)
TC4	119(4)	158(6)	15(0)	−37(8)	25(2)	1(3)
TC5	151(5)	255(8)	16(1)	17(11)	32(3)	19(3)
TC6	151(5)	310(10)	15(1)	88(12)	30(3)	−9(4)
TC7	112(4)	257(8)	18(1)	48(10)	16(2)	−53(4)
TC8	87(4)	140(6)	18(0)	−14(8)	31(2)	−21(3)
TC9	77(3)	115(5)	15(0)	−4(7)	28(2)	−7(2)
TC10	104(4)	161(6)	14(0)	55(8)	30(2)	−2(3)
TC11	109(4)	127(6)	14(0)	−30(8)	32(2)	−13(3)
TN12	110(3)	113(5)	13(0)	22(6)	34(2)	−5(2)
O(H_2O)	267(11)	252(13)	33(1)	235(21)	80(6)	55(7)

the estimated standard deviations. The final R-value including $F_0=0.0$ is 0.064. The observed and calculated structure factors are given in Table 2.17) The final positional and thermal parameters with their standard deviations for non-hydrogen atoms are given in Tables 3 and 4, respectively. The coordinates and isotropic thermal parameters for hydrogen atoms except those of the water molecule are given in Table 5.

Results and Discussion

Molecular Structure. The bond distances and angles with their standard deviations for non-hydrogen atoms are shown in Fig. 1, with the atomic numbering used in this work. The least-squares planes of adenine, carboxyl, indole, and aminoethyl moieties are given in Table 6, together with the displacement of atoms from

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

Atom	x	y	z	B/Å^2
AH2	6(4)	1071(5)	86(1)	3.3(7)
AH6A	373(5)	1186(6)	−11(1)	5.0(9)
AH6B	214(5)	1298(6)	−19(1)	5.0(9)
AH8	534(4)	539(5)	61(1)	3.5(8)
AH10A	405(4)	360(5)	110(1)	3.6(8)
AH10B	239(4)	445(5)	114(1)	4.0(8)
TH1	627(4)	−81(5)	175(1)	3.0(7)
TH2	719(4)	20(5)	264(1)	2 6(7)
TH4	929(3)	570(4)	192(1)	2.1(6)
TH5	905(4)	563(5)	106(1)	4.5(9)
TH6	766(4)	306(5)	55(1)	3.2(7)
TH7	655(4)	36(5)	88(1)	4.0(8)
TH10A	1005(4)	424(5)	287(1)	2.5(7)
TH10B	907(4)	303(5)	316(1)	3.2(7)
TH11A	788(3)	651(4)	255(1)	2.0(6)
TH11B	872(4)	644(5)	318(1)	2.6(7)
TH12A	612(4)	650(5)	295(1)	2.5(7)
TH12B	636(5)	427(6)	309(1)	5.5(10)
TH12C	581(4)	482(5)	257(1)	2.7(7)

the planes. The torsion angles are given in Table 7. The bond lengths and angles of the adenine ring agree with those found in related compounds within their standard deviations.[18] The purine base is planar with a maximum deviation of 0.024 Å for AN3. The bond parameters for the carboxyl group are also within their expected ranges as having no hydrogen atom, the group being almost planar and at approximately right angles to the purine base (dihedral angle=78.0°). The molecular conformation of AAA with the torsion angle, τ and ω, is very similar to one of the same molecule determined by Voet[19] (τ=84.3°, ω=7.7°), both molecules lying in (+)clinal and synperiplanar for τ and ω, respectively.

The bond lengths and angles of the TPA molecule agree with the values found in the crystal structures of the other TPA molecules: TPA,[20] TPA picrate,[21] TPA hydrochloride,[22] TPA phenylacetate,[23] TPA thymine-1-ylacetate,[24] and TPA 7,8-dimethylisoalloxazine-10-acetate.[2] The indole ring is also planar with a maximum shift of 0.025 Å for TC8, the dihedral angle between the indole ring and the aminoethyl group being 74.6°. Three hydrogen atoms (TH12A—TH12C) found in the difference map are tetrahedrally bound to TN12, indicating the amino group to be in a cationic $-NH_3^+$ form. The conformation of the TPA molecule in this crystal is similar to the hitherto analysed TPA molecules except thymine-1-ylacetate. The conformation having the torsion angles, χ and ϕ, in (+)anticlinal and in (−)synclinal regions, respectively, is thought to be the most stable one.[20]

Crystal Structure. The crystal structure projected along the b-axis is shown in Fig. 2. The intermolecular distances and angles for the hydrogen bonds and the

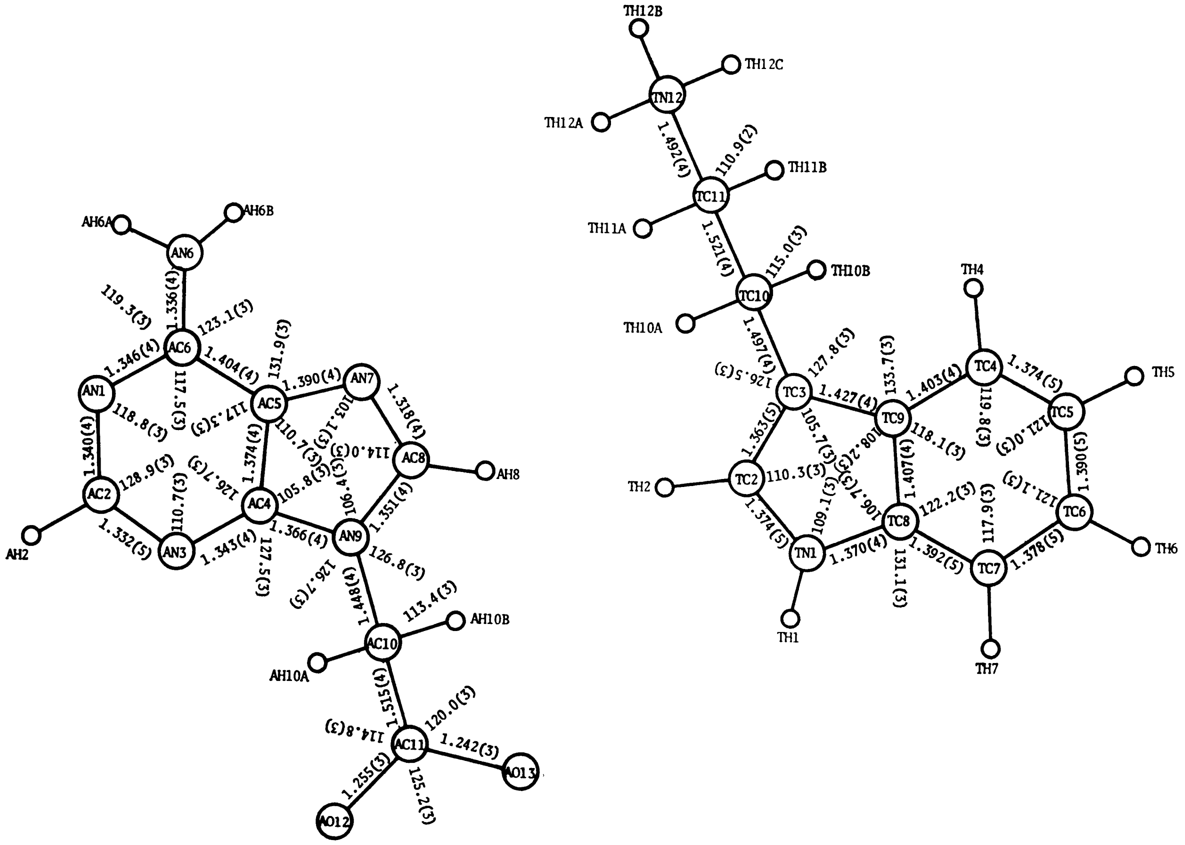

Fig. 1. Bond lengths and angles.

Table 6. Deviations of atoms from the least-squares planes

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

Plane	m_1	m_2	m_3	d
Purine ring	0.4328	0.4604	0.7750	4.8820
Carboxyl group	0.9435	−0.3247	−0.0658	0.5803
Indole ring	0.8419	−0.4977	0.2086	4.6306
Aminoethyl group	0.0555	−0.0222	0.9982	8.0422

Deviations (/Å) from the best planes:

AAA		TPA	
Purine ring		Indole ring	
AN1*	0.020	TN1*	0.005
AC2*	0.011	TC2*	−0.021
AN3*	−0.024	TC3*	−0.016
AC4*	−0.007	TC4*	0.018
AC5*	−0.014	TC5*	−0.016
AC6*	−0.009	TC6*	−0.021
AN7*	−0.004	TC7*	0.005
AC8*	0.009	TC8*	0.025
AN9*	0.018	TC9*	0.021
AN6	−0.049	TC10	−0.052
AC10	−0.036	TH1	0.062
AH2	0.014	TH2	−0.017
AH8	0.015	TH4	0.029
Carboxyl group		TH5	−0.081
AC10*	0.001	TH6	−0.055
AC11*	−0.004	TH7	−0.019
AO12*	0.001	Aminoethyl group	
AO13*	0.001	TC10*	0.0
AH10A	−0.821	TC11*	0.0
AH10B	0.853	TN12*	0.0
		TH10A	−0.125
		TH10B	−0.887
		TH11A	0.871
		TH11B	−0.859
		TH12A	−0.104
		TH12B	−0.536
		TH12C	0.904

Atoms with asterisks define the plane.

Table 7. Torsion angles (/°) of TPA and AAA molecules

AAA	
AC4–AN9–AC10–AC11	−76.5
AC8–AN9–AC10–AC11 ; τ	98.5
AN9–AC10–AC11–AO12	183.2
AN9–AC10–AC11–AO13 ; ω	3.9
TPA	
TC2–TC3–TC10–TC11 ; χ	108.5
TC9–TC3–TC10–TC11	−72.0
TC3–TC10–TC11–TN12 ; ϕ	−65.7

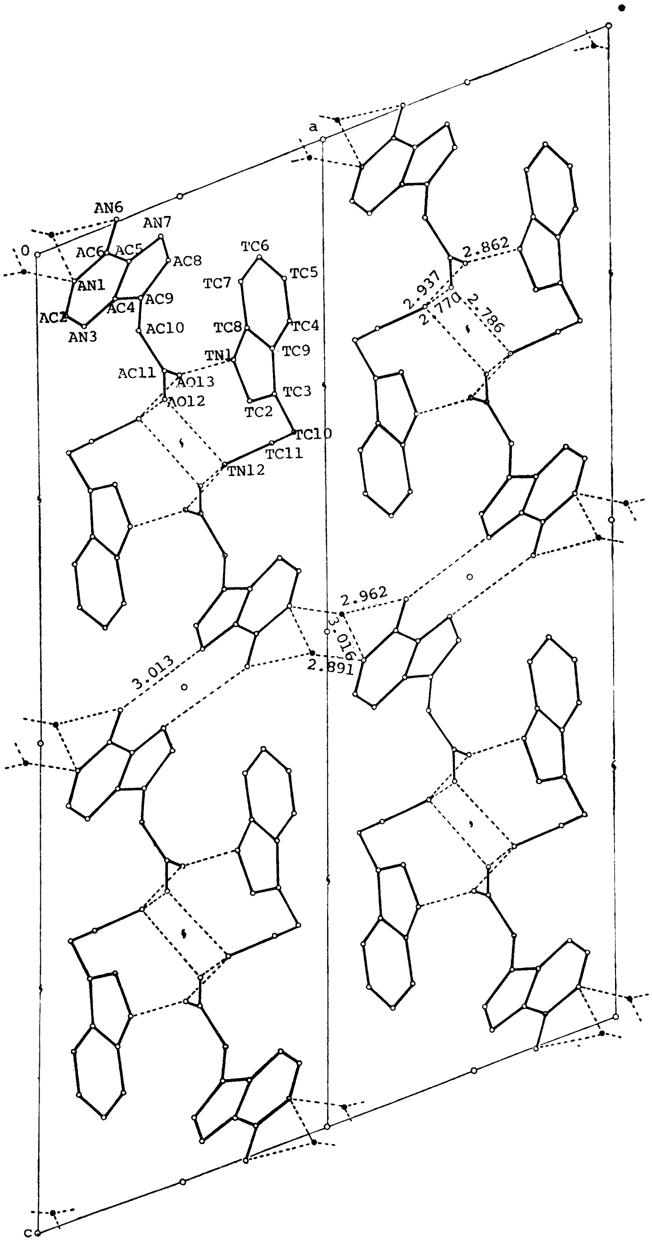

Fig. 2. The crystal structure viewed along the b-axis.

short contacts less than 3.5 Å are given in Table 8.

In the crystal, the complex formation is mainly due to the salt bridge between the amino and carboxyl groups. Both the molecules are linked by the hydrogen bonds of the amino nitrogen atom(TN12) to the carboxyl oxygen atom(AO12 and AO13), which are formed around a twofold screw axis, AO13 participating further in a hydrogen bond with TN1 of the indole ring, which may strengthen the salt bridge formation. The complex molecules form an infinite helical array with two complex pairs per turn (Fig. 3). The packing mode is found frequently in the crystal structures of the complex formed by a salt bridge between the acid and amine components, such as the 5-methoxytryptamine: 5-methoxyindole-3-acetic acid (1: 1) complex,[25] 5-methoxytryptamine: indole-3-acetic acid (1: 1) complex,[25] TPA: phenylacetic acid (1: 1) complex[23] and TPA: thymine-1-ylacetic acid (1: 1) complex.[24]

On the other hand, AAA molecule is further linked by two kinds of hydrogen-bonding schemes with the neighboring AAA molecules related by a center of symmetry. One is a linkage by two identical hydrogen bonds of AN6 to AN7. This kind of dimer formation is frequently observed in adenine derivatives.[19,26–29] The

Table 8. Hydrogen bonds and short contacts less than 3.5 Å
Superscribed numbers represent the symmetry operators.

Hydrogen bonds

Donor	Acceptor	Distance/Å D···A	Distance/Å H···A	Angle/° D-H···A
TN12$^{1)}$	AO12$^{1)}$	2.786(3)	1.79(3)	176(3)
TN12$^{2)}$	AO12$^{1)}$	2.770(3)	1.83(3)	170(3)
TN12$^{1)}$	AO13$^{2)}$	2.937(3)	2.07(5)	150(4)
TN1$^{3)}$	AO13$^{1)}$	2.862(4)	2.00(4)	150(3)
O(H_2O)$^{3)}$	AN1$^{1)}$	3.016(7)	—	—
O(H_2O)$^{1)}$	AN1$^{5)}$	2.891(7)	—	—
AN6$^{4)}$	AN7$^{1)}$	3.013(4)	2.07(4)	172(4)
AN6$^{1)}$	O(H_2O)$^{3)}$	2.962(7)	2.15(4)	144(8)

Short contacts

O(H_2O)$^{1)}$-AC4$^{1)}$	3.331(7)	O(H_2O)$^{1)}$-AN9$^{1)}$	3.335(7)
AC11$^{1)}$-TN12$^{1)}$	3.343(4)	AO12$^{1)}$-TC2$^{1)}$	3.307(4)
AO12$^{1)}$-TC3$^{1)}$	3.338(4)	AO13$^{1)}$-TC11$^{1)}$	3.493(4)
AO13$^{1)}$-TN12$^{1)}$	3.194(3)	AO13$^{1)}$-AN9$^{1)}$	2.723(3)
AO12$^{1)}$-TC11$^{2)}$	3.376(4)	TN1$^{1)}$-TN12$^{2)}$	3.429(4)
TC2$^{1)}$-AO12$^{2)}$	3.261(4)	TC2$^{1)}$-TN12$^{2)}$	3.449(4)
TN12$^{1)}$-AN3$^{2)}$	3.498(4)	AN1$^{1)}$-AC10$^{3)}$	3.390(4)
AC6$^{1)}$-O(H_2O)$^{3)}$	3.432(7)	AN1$^{1)}$-AN1$^{5)}$	3.389(5)

Symmetry code

1) x, y, z 2) $1-x, -1/2+y, 1/2-z$ 3) $x, 1+y, z$ 4) $1-x, 2-y, -z$ 5) $-x, 2-y, -z$

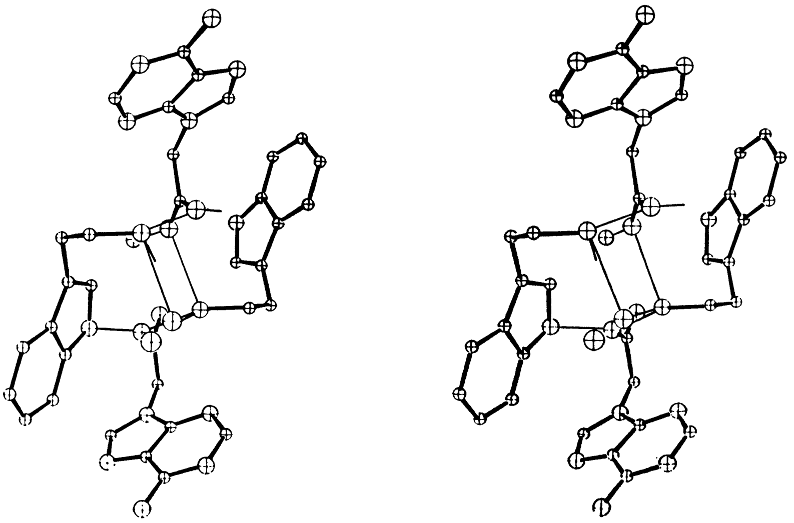

Fig. 3. The stereoscopic view of two complex pairs around a twofold screw axis.

other is the bond to the disordered crystal water (AN1···O(H_2O)). The water molecule is not located on a center of symmetry, but found at two equally disordered positions separated from a center of symmetry by 0.715 Å. The water molecule is further hydrogen bonded to AN6.

The dihedral angle between the indole and adenine rings is at approximately right angles (72.7°). Neither hydrogen bond nor short contacts less than 3.5 Å exist between both rings. Contrary to our expectation, there is no specific interaction between the indole and adenine rings in this complex, whereas the interaction through the hydrogen bond is observed in the related crystal structures.[30,31] The hydrogen bonds between the carboxyl and amino groups might be preferable to any specific interaction of indole–adenine rings.

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