The Crystal Structure of the Intermolecular Complex between 9-Ethyladenine and Indole

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(Received February 12, 1976)

The crystal structure of a 1 : 1 complex of 9-ethyladenine and indole has been determined by the X-ray method. The crystal system is monoclinic with the space group of $P2_1/c$. The cell dimensions are $a=15.712(2)$, $b=8.098(1)$, $c=11.838(1)$Å, and $\beta=103.90(1)$°. Adenines form walls made of double layer. An overlap of adenines is found between layers. The adenine molecule in the front layer is found to be joined by the hydrogen bond with the molecule in the back layer. An intermolecular hydrogen bond is found between adenine and indole rings. The significance of these observations in the interaction of adenine with tryptophan in biological systems is discussed.

The crystal structures of adenine derivatives and its complexes with uracil or thymine have been studied in order to find the intermolecular forces between DNA bases and other related molecules.[1–6] Adenine is also important as a constituent of many biologically significant molecules such as ATP, NAD and FAD. Voet and Rich,[7–9] and Tomita and his group[10] studied the structure of intermolecular complexes between adenine with other molecules such as riboflavin, barbiturate and nicotinic acid derivatives. The aim of these investigations is to find a specific interaction in enzymatic or biological reactions involving adenine group.

Helene and his co-workers[11–14] studied the interaction of aromatic residues of proteins with nucleic acids and their model system spectroscopically, and suggested the formation of complexes between purine or pyrimidine with aromatic amino acids, *e.g.*, adenosine with tryptophan. Morita *et al.*[15–17] studied a specific interaction between ATP with an enzyme, myosine-ATPase, and its model system by the UV absorption measurement. They suggested that a charge transfer force exists between adenine and indole rings through the stacking of molecules. The charge transfer force may be important between the donor and acceptor molecules. However, no such interaction has been confirmed in the crystal of the complex composed of adenine and indole. An X-ray study is desirable on the complex of these molecules.

In the present paper we give the crystal structure of a 1 : 1 9-ethyladenine-indole complex. It was found that the hydrogen bonding is most important as an intermolecular force between adenine and indole rings as well as between adenines.

Experimental

Equimolar amounts of 9-ethyladenine and indole were dissolved in methanol. Pale yellow crystals were obtained by slow evaporation at room temperature. The ultraviolet spectrum of the dissolved crystals shows that they contain approximately equimolar amounts of 9-ethyladenine and indole.

The space group was determined from oscillation and Weissenberg photographs. The density was measured by the flotation method in the mixed solution of cyclohexane and carbon tetrachloride. The cell dimensions were determined by the least-squares method, using twelve reflections carefully measured on a Hilger-Watts four circle diffractometer with Zr-filtered Mo*K*α radiation ($\lambda=0.71069$ Å). The crystal was found to be not so unstable while being left to stand in the air, but the color changed to light brown. It was therefore mounted in a glass capillary for the X-ray measurements. Intensity data were collected with the same diffractometer in the ω-2θ scanning mode ($2\theta\leqq52°$) with the same radiation. The size of the crystal used was $0.3\times0.3\times0.2$ mm. No absorption or extinction correction was made because of the smallness of the crystal. In order to confirm the stability of the crystal and the counter system, the intensities of three standard reflections were measured every 50 reflections. The fluctuation and the decay of standard reflections was within 5%. The crystal data are given in Table 1.

TABLE 1. CRYSTAL DATA

$C_7H_9N_5\cdot C_8H_7N$
F.W.: 280.33
Crystal system: monoclinic
Space group: $P2_1/c$
$a=15.712$ (2), $b=8.098$ (1),
$c=11.838$ (1) Å; $\beta=103.90$ (1)°,
$D_m=1.274$, $D_c=1.273$ g·cm^{-3}
$\mu=1.05$ cm^{-1} (for Mo*K*α radiation).

Determination and Refinement of the Structure

The structure was solved by the direct method with the program MULTAN[18] using 415 reflections with $|E|\geqq1.20$. An E-map computed from the phase set with the highest figures of merit ($FOM=1.448$) revealed the positions of non-hydrogen atoms. The block-diagonal least-squares method was applied to the refinement of the structure parameters by using 1106 independent reflections with $|F°|\geqq5\sigma$. An R-index was reduced to 0.107. At this stage, a difference Fourier synthesis was performed. Two other peaks could be assigned to the disordered ethyl group of 9-ethyladenine, and eleven hydrogen atoms, other than those belonging to the ethyl groups, were found in this map. The occupancies for the differently oriented ethyl groups were also refined as a group by the least-squares method to be 0.65 and 0.35, respectively. Subsequent refinement was carried out with anisotropic thermal parameters for non-hydrogen atoms, and with isotropic ones for hydrogen atoms. The final R-index converged to 0.074 with an equal weight for each reflection.

The atomic scattering factors were taken from the work of Stewart, Davidson and Simpson[19] for the

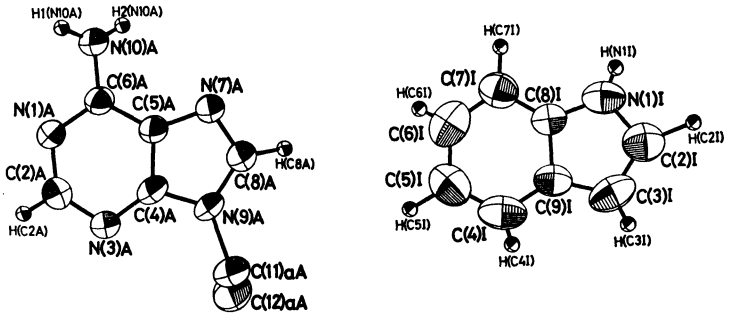

Fig. 1. The atomic labelings of 9-ethyladenine and indole. Nonhydrogen atoms are represented as thermal ellipsoids of a size such that the vibrating atoms have a 50% probability of being found within them. Hydrogen atoms are represented as spheres that are defined by the artificial isotropic thermal factor B of 1.0 Å^2.

hydrogen atom and from the International Tables for X-ray Crystallography[20] for other atoms. The program HBLS-IV coded by Ashida and the program written by Katayama and Wada were utilized for the block-diagonal least-squares refinements. The program ORTEP coded by Johnson was utilized for the drawings in Figs. 1, 4 and 5. All the computations were performed on a FACOM 230-60 computer at the Nagoya University Computation Center. The observed and calculated structure factors are listed in Table 2.[21]

Results and Discussion

The atomic labelings and thermal ellipsoids are shown in Fig. 1. The 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 for those belonging to ethyl groups, are given in Table 5.

Molecular Structure. The bond distances and bond angles with their standard deviations involving only heavy atoms are given in Tables 6 and 7, respectively. The covalent bond distances and angles of 9-ethyladenine are in good agreement with values found in other crystals.[2,8] The bond distances and angles around the disordered ethyl groups show somewhat abnormal values because of the disordered structure. The adenine molecule is highly planar with a maximum deviation of 0.028 Å for C(5)A from the least-squares plane (Table 8).

The bond distances and angles of indole agree with values found in crystals of L-tryptophan hydrobromide,[24] tryptamine picrate and D,L-tryptophan picrate.[25] The only exception is in the C(7)I–C(8)I bond distance, which is smaller by *ca.* 0.06 Å as compared with the values in the literature.[24,25] The indole molecule is also highly planar with a maximum deviation of 0.011 Å for C(5)I from the least-squares plane.

Crystal Structure. The crystal structure projected along the b axis is shown in Fig. 2. Adenines form walls consisting of a double layer. An overlap of adenines, related to a center of symmetry, is observed between the layers. Four hydrogen bonds are found between adenine molecules which connect the molecule in the front layer with the molecule in the back one (Fig. 3).

TABLE 3. ATOMIC COORDINATES AND THEIR STANDARD DEVIATIONS OF HEAVY-ATOMS

	x	y	z
N(1)A	0.5394 (4)	−0.2711 (8)	0.3944 (6)
C(2)A	0.5873 (5)	−0.3077 (11)	0.5023 (8)
N(3)A	0.6376 (4)	−0.2102 (9)	0.5798 (6)
C(4)A	0.6358 (4)	−0.0550 (11)	0.5389 (7)
C(5)A	0.5893 (4)	0.0019 (10)	0.4320 (7)
C(6)A	0.5396 (4)	−0.1149 (10)	0.3558 (7)
N(7)A	0.6055 (4)	0.1677 (9)	0.4186 (6)
C(8)A	0.6601 (6)	0.2075 (12)	0.5180 (9)
N(9)A	0.6811 (5)	0.0773 (10)	0.5925 (7)
N(10)A	0.4945 (4)	−0.0801 (8)	0.2478 (6)
C(11)aA[a]	0.727 (1)	0.087 (2)	0.731 (1)
C(11)bA[a]	0.774 (1)	0.070 (3)	0.683 (2)
C(12)aA[a]	0.817 (1)	0.033 (2)	0.720 (1)
C(12)bA[a]	0.729 (2)	0.081 (5)	0.794 (2)
N(1)I	0.7783 (4)	−0.3929 (9)	0.7547 (7)
C(2)I	0.7949 (5)	−0.4117 (14)	0.8741 (9)
C(3)I	0.8688 (5)	−0.5067 (13)	0.9058 (8)
C(4)I	0.9681 (4)	−0.6378 (12)	0.7841 (9)
C(5)I	0.9789 (5)	−0.6512 (13)	0.6727 (10)
C(6)I	0.9168 (5)	−0.5753 (14)	0.5837 (9)
C(7)I	0.8473 (5)	−0.4849 (12)	0.6014 (8)
C(8)I	0.8399 (4)	−0.4743 (10)	0.7120 (7)
C(9)I	0.8990 (4)	−0.5481 (11)	0.8064 (8)

a) The symbols a and b were used for the disordered carbons, C(11) and C(12), to discriminate the major and the minor sites.

The hydrogen bond network is developed along the b axis. All the amino NH bonds participate in hydrogen bonds, N(10)A-H···N(7)A($1-x$, $1/2+y$, $1/2-z$) and N(10)A-H···N(1)A($1-x$, $-1/2+y$, $1/2-z$). The intermolecular distances and angles for the hydrogen bonds are given in Table 9. The overlapping mode of adenine molecules is shown in Fig. 4. The interplanar distance between adenine rings is 3.50 Å. A more extensive overlapping of adenine rings is found in 9-methyladenine,[1] ATP,[6] and (9-ethyladenine)-(1-methyl-5-fluorouracil) complex.[3] The interplanar distance is 3.31—3.40 Å.

The stacking and hydrogen bondings may influence the conformation of the ethyl group, namely the structure of methylene carbons. C(11)aA and C(11)bA bend

Table 4. Anisotropic thermal factors* ($\times 10^4$) and their standard deviations of heavy-atoms

	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
N(1)A	65 (4)	135 (12)	82 (6)	−9 (12)	−28 (8)	−6 (15)
C(2)A	68 (6)	162 (17)	94 (9)	−46 (17)	1 (11)	39 (21)
N(3)A	66 (4)	151 (14)	87 (6)	−21 (13)	−35 (8)	27 (16)
C(4)A	51 (5)	173 (17)	79 (7)	−14 (14)	−32 (9)	−18 (19)
C(5)A	44 (4)	133 (14)	78 (7)	13 (13)	−13 (8)	0 (18)
C(6)A	43 (4)	139 (15)	72 (7)	25 (13)	1 (8)	−17 (17)
N(7)A	64 (4)	146 (13)	105 (7)	−21 (13)	−61 (9)	35 (16)
C(8)A	102 (8)	170 (19)	140 (11)	−72 (20)	−118 (15)	71 (25)
N(9)A	105 (6)	182 (15)	111 (8)	−68 (17)	−124 (11)	14 (19)
N(10)A	67 (4)	139 (12)	80 (6)	3 (13)	−33 (8)	7 (16)
C(11)aA	66 (8)	231 (30)	90 (12)	2 (27)	−24 (16)	2 (33)
C(11)bA	38 (12)	128 (41)	61 (21)	10 (39)	−36 (26)	−4 (53)
C(12)aA	44 (7)	264 (34)	147 (16)	−7 (26)	−3 (17)	10 (39)
C(12)bA	121 (25)	448 (96)	15 (20)	48 (84)	16 (36)	−54 (74)
N(1)I	67 (5)	184 (16)	119 (8)	−6 (15)	−7 (9)	36 (18)
C(2)I	66 (6)	261 (23)	133 (11)	−29 (21)	30 (13)	10 (28)
C(3)I	85 (7)	261 (23)	97 (9)	−89 (22)	6 (12)	73 (25)
C(4)I	62 (6)	208 (20)	148 (11)	−38 (18)	−22 (13)	58 (26)
C(5)I	60 (6)	240 (22)	166 (13)	−6 (19)	18 (14)	−92 (28)
C(6)I	90 (7)	248 (23)	120 (10)	−116 (22)	51 (14)	−71 (26)
C(7)I	58 (5)	211 (20)	125 (10)	0 (18)	18 (12)	−1 (24)
C(8)I	49 (5)	163 (16)	88 (8)	−16 (14)	17 (9)	13 (19)
C(9)I	47 (5)	174 (17)	103 (8)	−21 (15)	7 (10)	23 (20)

* The anisotropic thermal factors are of the form $\exp\{-(h^2B_{11}+k^2B_{22}+l^2B_{33}+hkB_{12}+hlB_{13}+klB_{23})\}$.

Table 5. Hydrogen atom parameters and their standard deviations

	x	y	z	B
H(C2A)	0.568 (3)	−0.406 (9)	0.534 (6)	5.2 (18)
H(C8A)	0.716 (5)	0.307 (14)	0.499 (9)	13.2 (35)
H1(N10A)	0.437 (5)	−0.137 (16)	0.227 (10)	16.2 (42)
H2(N10A)	0.507 (4)	0.004 (10)	0.225 (7)	6.7 (21)
H(N1I)	0.740 (4)	−0.343 (11)	0.727 (7)	7.3 (23)
H(C2I)	0.735 (4)	−0.347 (11)	0.912 (7)	8.5 (25)
H(C3I)	0.889 (4)	−0.530 (11)	0.972 (7)	7.5 (24)
H(C4I)	0.991 (4)	−0.677 (11)	0.843 (7)	7.4 (23)
H(C5I)	1.038 (5)	−0.704 (13)	0.655 (8)	10.5 (30)
H(C6I)	0.930 (4)	−0.568 (10)	0.522 (7)	6.6 (21)
H(C7I)	0.802 (4)	−0.430 (11)	0.541 (7)	7.7 (23)

Table 6. Bond lengths and their standard deviations

9-Ethyladenine		Indole	
N(1)A–C(2)A	1.35 (1) Å	N(1)I–C(2)I	1.38 (1) Å
N(1)A–C(6)A	1.35 (1)	N(1)I–C(8)I	1.36 (1)
C(2)A–N(3)A	1.32 (1)	C(2)I–C(3)I	1.37 (1)
N(3)A–C(4)A	1.34 (1)	C(3)I–C(9)I	1.41 (1)
C(4)A–C(5)A	1.38 (1)	C(4)I–C(5)I	1.37 (2)
C(4)A–N(9)A	1.36 (1)	C(4)I–C(9)I	1.38 (1)
C(5)A–C(6)A	1.41 (1)	C(5)I–C(6)I	1.39 (1)
C(5)A–N(7)A	1.38 (1)	C(6)I–C(7)I	1.37 (1)
C(6)A–N(10)A	1.33 (1)	C(7)I–C(8)I	1.34 (1)
N(7)A–C(8)A	1.32 (1)	C(8)I–C(9)I	1.40 (1)
C(8)A–N(9)A	1.36 (1)		
N(9)A–C(11)aA	1.62 (1)		
N(9)A–C(11)bA	1.59 (2)		
C(11)aA–C(12)aA	1.51 (2)		
C(11)bA–C(12)bA	1.64 (4)		

Table 7. Bond angles and their standard deviations

9-Ethyladenine		Indole	
N(1)A–C(2)A–N(3)A	129.1 (8)°	N(1)I–C(2)I–C(3)I	106.3 (9)°
N(1)A–C(6)A–C(5)A	117.4 (6)	N(1)I–C(8)I–C(7)I	128.8 (7)
N(1)A–C(6)A–N(10)A	118.7 (6)	N(1)I–C(8)I–C(9)I	107.7 (7)
C(2)A–N(1)A–C(6)A	118.8 (6)	C(2)I–N(1)I–C(8)I	110.5 (7)
C(2)A–N(3)A–C(4)A	110.6 (7)	C(2)I–C(3)I–C(9)I	109.8 (8)
N(3)A–C(4)A–C(5)A	127.1 (7)	C(3)I–C(9)I–C(8)I	105.8 (7)
C(4)A–C(5)A–C(6)A	117.0 (7)	C(4)I–C(5)I–C(6)I	117.7 (9)
C(4)A–C(5)A–N(7)A	111.0 (6)	C(4)I–C(9)I–C(8)I	118.1 (8)
C(4)A–N(9)A–C(8)A	106.9 (7)	C(5)I–C(4)I–C(9)I	120.6 (8)
C(4)A–N(9)A–C(11)aA	124.5 (8)	C(5)I–C(6)I–C(7)I	123.9 (10)
C(4)A–N(9)A–C(11)bA	125.2 (11)	C(6)I–C(7)I–C(8)I	116.2 (8)
C(5)A–C(4)A–N(9)A	105.5 (7)	C(7)I–C(8)I–C(9)I	123.5 (7)
C(5)A–C(6)A–N(10)A	123.9 (7)		
C(5)A–N(7)A–C(8)A	103.5 (7)		
C(6)A–C(5)A–N(7)A	131.9 (7)		
N(7)A–C(8)A–N(9)A	113.1 (8)		
C(8)A–N(9)A–C(11)aA	126.4 (9)		
C(8)A–N(9)A–C(11)bA	120.5 (11)		
N(9)A–C(11)aA–C(12)aA	95.7 (10)		
N(9)A–C(11)bA–C(12)bA	92.2 (13)		

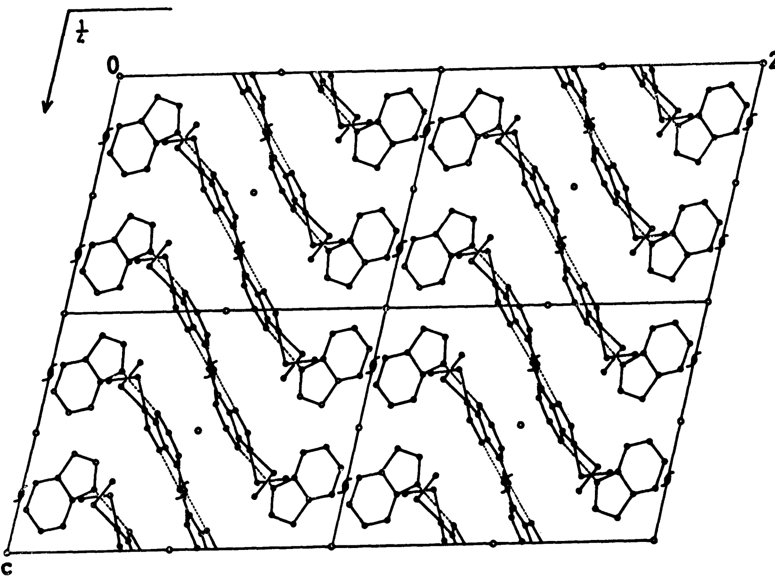

Fig. 2. Projection of the crystal structure along the b axis. Carbon atoms are depicted as open circles and nitrogen atoms as filled circles. Hydrogen bonds are represented with both dotted and broken lines. The atoms of 9-ethyladenines in both ends of the dotted line are related by the symmetry code (ii), and those of broken line are related by the symmetry code (iii) in Table 9.

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

9-Ethyladenine plane[a]		Indole plane[b]	
N(1)A	0.012 Å	N(1)I	0.003 Å
C(2)A	0.001	C(2)I	0.004
N(3)A	−0.002	C(3)I	0.000
C(4)A	−0.017	C(4)I	−0.006
C(5)A	−0.028	C(5)I	0.011
C(6)A	0.009	C(6)I	−0.003
N(7)A	0.002	C(7)I	0.000
C(8)A	0.008	C(8)I	−0.006
N(9)A	0.015	C(9)I	−0.003
N(10)A[c]	0.064		
C(11)aA[c]	−0.32		
C(11)bA[c]	0.71		

a) Equation of the plane: $0.8971X-0.2178Y-0.3844Z'-5.320=0$. b) Equation of the plane: $0.5484X+0.8270Y+0.1244Z'-3.975=0$. c) Atoms not included in the least-squares calculation.

away to the opposite side from the adenine plane by 0.32 and 0.71 Å, respectively. A similar deviation from the plane of the adenine ring is observed for the carbon atoms of glycosidic bonds in adenosine-5′-phosphate[22] and deoxyadenosine[23] crystals, where the hydrogen bond network is developed extensively and the molecular packing is favorable to the bent conformation. Hydrogen bonds are also formed in the present crystal, the region around the disordered ethyl groups being crowded by the neighboring molecules. The distance between the terminal methyl carbon (C(12)aA) and the atoms of indole rings (C(4)I and C(5)I) is *ca.* 3.50 Å, and that between C(12)bA and hydrogen atoms of adenine rings, (H1(N10A) and H(C8A)), is *ca.* 2.60 Å (Table 9).

Indole molecules are sandwiched by the adenine walls, sticking to the wall by the hydrogen bonding. A stereoscopic view along the a axis is shown in Fig. 5. No stacking interaction is found between indoles, nor between adenine and indole. Their arrangement in the crystal may be favored by the hydrogen bonding and the dipole-dipole interaction between neighboring molecules.

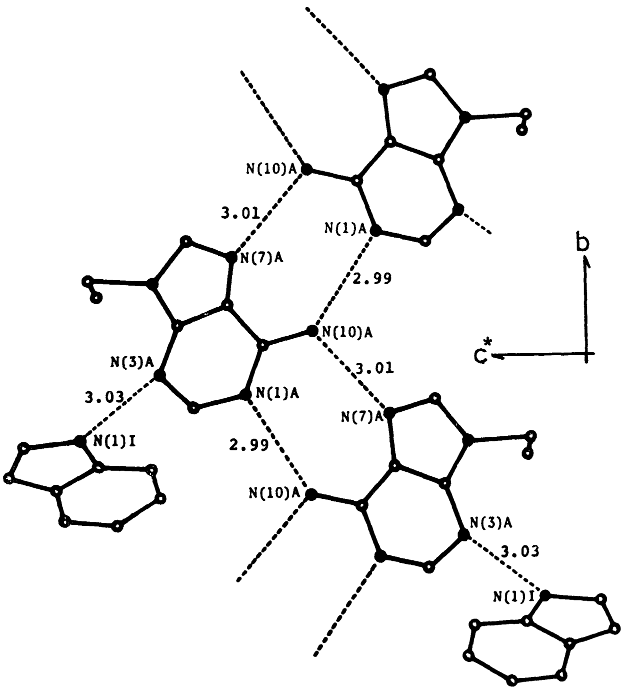

Fig. 3. Hydrogen bond network viewed along the a axis.

The most interesting feature of the crystal structure is the hydrogen bonding between adenine and indole. The N(1)I–H···N(3)A distance is 3.03 Å, which is not

Table 9. Hydrogen bonds and short van der Waals contacts
Roman numerals represent symmetry operators relevant to the atoms listed second.

Hydrogen bonds

Donor	Acceptor	Distance D···A	Distance H···A	Angle D—H···A
N(1)I —H (N1I)	···N(3)A$^{\text{i)}}$	3.03 (1) Å	2.33 (7) Å	159 (9)°
N(10)A—H1(N10A)	···N(7)A$^{\text{ii)}}$	3.01 (1)	2.32 (12)	126 (9)
N(10)A—H2(N10A)	···N(1)A$^{\text{iii)}}$	2.99 (1)	2.31 (8)	147 (6)

Short van der Waals contacts

Contact	Distance	Contact	Distance
C(4)A···C(6)A$^{\text{iv)}}$	3.56 (1) Å	N(10)A···C(12)bA$^{\text{iv)}}$	3.43 (3) Å
C(4)A···C(2)I$^{\text{v)}}$	3.53 (1)	C(4)I ···C(12)aA$^{\text{vii)}}$	3.53 (2)
C(5)A···C(5)A$^{\text{iv)}}$	3.55 (1)	C(5)I ···C(12)aA$^{\text{viii)}}$	3.49 (1)
C(5)A···C(2)I$^{\text{v)}}$	3.54 (1)	C(11)aA···H1(N10A)$^{\text{iv)}}$	2.8 (1)
N(7)A···C(12)bA$^{\text{vi)}}$	3.39 (3)	C(12)aA···H(C5I)$^{\text{ix)}}$	3.1 (1)
C(8)A···C(12)bA$^{\text{vi)}}$	3.54 (3)	C(12)bA···H1(N10A)$^{\text{iv)}}$	2.6 (1)
N(10)A···C(11)aA$^{\text{iv)}}$	3.55 (1)	C(12)bA···H(C8A)$^{\text{x)}}$	2.6 (1)

Symmetry code

Symmetry code superscript	Symmetry operator			Symmetry code superscript	Symmetry operator		
i)	x	y	z	vi)	x	$1/2-y$	$-1/2+z$
ii)	$1-x$	$1/2+y$	$1/2-z$	vii)	x	$-1+y$	z
iii)	$1-x$	$-1/2+y$	$1/2-z$	viii)	$2-x$	$-1/2+y$	$3/2-z$
iv)	$1-x$	$-y$	$1-z$	ix)	$2-x$	$1/2+y$	$3/2-z$
v)	x	$-1/2-y$	$-1/2+z$	x)	x	$1/2-y$	$1/2+z$

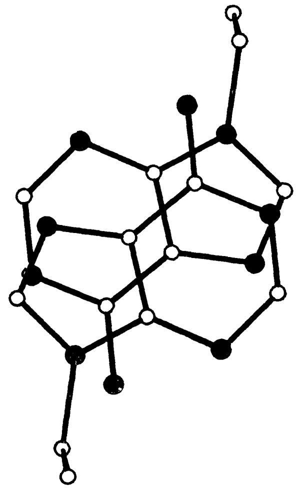

Fig. 4. A stacking pattern of the 9-ethyladenine pair. Carbon atoms are depicted as open circles and nitrogen atoms are filled circles.

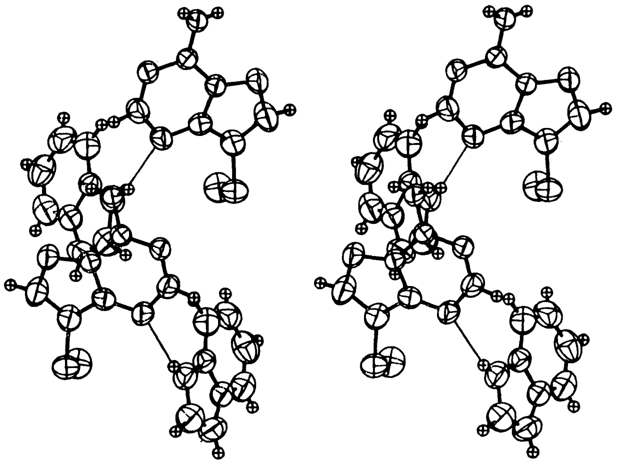

Fig. 5. A stereoscopic view of the 9-ethyladenine-indole pair. The criterion to thermal ellipsoids of nonhydrogen atoms and that of hydrogen atoms are the same in Fig. 1. The hydrogen bond between H(N1I) and N(3)A is represented in a thin solid line.

particularly small as compared with other NH···N hydrogen bond distances.[9] The molecular plane of indole tilts to that of the adenine ring with a dihedral angle of 74.7°. No particular stacking of adenine-indole pair is found in the crystal. It is therefore unlikely that the molecular association for this pair occurs through the overlapping of two rings.

The result is biologically significant in that the same mode of interaction is expected to exist between adenine and tryptophan in the biological system. It can be suggested that the hydrogen bonding is more important than the stacking of two rings in the pair. This seems reasonable since both molecules have an electron donating character contrary to the case in which one is electron donating and the other accepting. An alternative interpretation on the spectral change found in model biological systems should be worth considering by the result in this study.

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