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# X-Ray Structural Studies of the Interactions between the Components of Protein and Nucleic Acid. II.[1] Crystal Structure of the Adenin-9-ylethylamine: Phenylacetic Acid (1: 1) Complex

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The crystal structure of a 1: 1 complex of adenin-9-ylethylamine and phenylacetic acid, $C_7H_{10}N_6 \cdot C_8H_8O_2$, has been determined by the X-ray method. The crystal is orthorhombic, space group $P2_12_12_1$, with unit-cell dimensions of $a=7.050(2)$, $b=11.835(4)$ and $c=18.711(7)$ Å. The structure was solved by the direct method and refined by the block-diagonal least-squares method to give a final $R$ value of 0.037. In this complex, a salt bridge exists between the anionic carboxyl group of phenylacetic acid and the cationic amino group of adenin-9-ylethylamine. No specific interaction between the adenine and benzene rings was observed. The component molecules are held together by a three-dimensional framework of hydrogen bonds around the twofold screw axis to form an infinite helical array in the $a$ direction.

**Keywords**——adenin-9-ylethylamine; phenylacetic acid; X-ray analysis; salt bridge formation; hydrogen bonds

## Introduction

The mutual recognition between proteins and nucleic acids is one of the most important and fundamental steps involved in the transmission and expression of genetic information. The geneic reactions are achieved by the accurate recognition of nucleic acids by enzymes. This specific recognition requires direct interactions among the chemical groups constituting each of the two macromolecules.

While an amino acid having a basic or acidic group such as aspartic acid, glutamic acid, lysine or arginine provides specificity in the selective recognition of nucleic base sequences by hydrogen bonding or electrostatic interactions,[2-4] an aromatic amino acid such as tryptophan, tyrosine or phenylalanine may play a specific role in the recognition by means of stacking interactions with nucleic acid bases.[5-7]

Since it would appear to be of interest to establish the stereochemistry of these interactions at the atomic level, we are investigating the X-ray crystal structures of complexes containing both amino acids and nucleic bases,[8-14] which may serve as models for the contacts occurring in protein–nucleic acid interactions.

The present report deals with an X-ray diffraction analysis of the crystal structure of the 1:1 complex of adenin-9-ylethylamine (AA) and phenylacetic acid (PAA). This complex may constitute a model for the interaction between the nucleic acid base adenine and the amino acid phenylalanine. It has already been reported that these aromatic rings are mutually stacked in the gene 5 protein-oligodeoxynucleotides[15–17] and peptides-deoxyribonucleie acid (DNA) interactions.[18]

## Experimental

**Preparation of Complex Crystals**——AA was synthesized from adenine and aziridine according to the previously described method.[19] Transparent platelet crystals were obtained by slow evaporation of a 50% aqueous ethanol solution containing equimolar AA and PAA at room temperature. The ultraviolet (UV) spectra in water and thermal analysis of the crystals showed that they consist of equimolar quantities of AA and PAA, and do not contain solvent molecules.

**X-Ray Data Collection**——A single crystal with dimensions of approx. $0.4 \times 0.3 \times 0.6$ mm, was used for the X-ray study. Preliminary oscillation and Weissenberg photographs showed that the crystal belongs to the orthorhombic space group $P2_12_12_1$ from the systematic absences. The cell dimensions were determined on a Rigaku computer-controlled four-circle diffractometer using 20 high angle ($\theta$) reflections and refined by the least-squares method. The crystallographic data are given in Table I. The calculated density, with four formula units in a unit cell, is in good agreement with the experimental value obtained by the flotation method using benzene-carbon tetrachloride mixture. Three-dimensional intensity data were collected with the diffractometer using graphite-monochromated Cu $K\alpha$ radiation. By means of the $\theta/2\theta$ scanning mode, a total of 1555 independent reflections, within $\sin\theta/\lambda$ less than 0.588 Å$^{-1}$, were collected at a rate of 4°/min; the background was counted for 5s at the edges of the reflections. The intensities of four standard reflections, measured every 100 reflection intervals, did not change during the course of data collection, showing that no structural deterioration had occurred. Corrections were made for the Lorentz and polarization factors, but not for the absorption effects.

Table I. Crystal Data

| | |
|---|---|
| Chemical formula | $C_7H_{10}N_6 \cdot C_8H_8O_2$ |
| Molecular weight | 313.34 |
| Crystal system | Orthorhombic |
| Space group | $P2_12_12_1$ |
| Cell constant | |
| $a$/Å | 7.050 (2) |
| $b$/Å | 11.835 (4) |
| $c$/Å | 18.711 (7) |
| Volume/Å$^3$ | 1561.3 (9) |
| $Z$ | 4 |
| $D_m$/g·cm$^{-3}$ | 1.333 (1) |
| $D_x$/g·cm$^{-3}$ | 1.333 |
| $\mu$(Cu$-K_\alpha$)/cm$^{-1}$ | 7.784 |
| $F$ (0 0 0) | 664 |

**Structure Determination and Refinements**——The structure was solved by the direct method with the MULTAN78 program[20] using 300 reflections with $|E| \geqq 1.29$. An $E$-map computed with the phase set of the lowest $\Psi_0$ value revealed the positions of all nonhydrogen atoms, the parameters being refined by the block-diagonal least-squares method with anisotropic temperature factors. All the hydrogen atoms, found on the difference Fourier map, were then included in the refinements with isotropic thermal factors. The minimized quantity was $\sum w(|F_o| - |F_c|)$.[2] In the final refinement, the following weighting scheme was used: $w = 0.35$ for $F_o = 0.0$, $w = 1.0$ for $0.0 < F_o \leqq 11.0$, and $w = 1.0/[1.0 + 0.273\ (F_o - 11.0)]$ for $F_o > 11.0$. The final $R$ value was 0.037 including $F_o = 0.0$. The atomic scattering factors were taken from the literature.[21] All the numerical calculations were carried out at the Crystallographic Research Center, Institute for Protein Research, and at the Computing Center, of Osaka University, using the UNICS program.[22] The final atomic coordinates are given in Table II.

TABLE II. Fractional Coordinates($\times 10^4$ for C, N, O Atoms, $\times 10^3$ for H Atom) and Isotropic Temperature Factors ($\times 10$)

| Atom | $x$ | $y$ | $z$ | $B$ |
|---|---|---|---|---|
| AA molecule | | | | |
| N (1) | 6070(3) | 4810(2) | 3531(1) | 33(1) |
| C (2) | 7887(3) | 4969(2) | 3363(1) | 35(2) |
| N (3) | 8651(3) | 5598(2) | 2844(1) | 31(1) |
| C (4) | 7291(3) | 6098(2) | 2462(1) | 26(1) |
| C (5) | 5349(3) | 6018(2) | 2561(1) | 28(2) |
| C (6) | 4739(3) | 5341(2) | 3130(1) | 32(2) |
| N (6) | 2906(3) | 5175(2) | 3299(1) | 40(2) |
| N (7) | 4390(3) | 6691(2) | 2074(1) | 34(1) |
| C (8) | 5731(4) | 7145(2) | 1697(1) | 36(2) |
| N (9) | 7528(3) | 6826(2) | 1899(1) | 29(1) |
| C (10) | 9351(4) | 7198(2) | 1611(1) | 37(2) |
| C (11) | 10230(3) | 6379(2) | 1090(1) | 31(2) |
| N (12) | 9488(3) | 6511(2) | 355(1) | 25(1) |
| H (2) | 885(4) | 449(3) | 372(2) | 27(6) |
| H (6a) | 269(6) | 483(3) | 375(2) | 42(8) |
| H (6b) | 199(5) | 544(3) | 301(2) | 43(8) |
| H (8) | 556(5) | 773(3) | 126(2) | 40(8) |
| H (10a) | 1021(4) | 734(2) | 204(1) | 27(6) |
| H (10b) | 912(4) | 797(2) | 137(1) | 20(6) |
| H (11a) | 997(4) | 553(2) | 124(1) | 21(6) |
| H (11b) | 1156(4) | 646(2) | 105(2) | 29(7) |
| H (12a) | 823(5) | 638(3) | 29(2) | 40(8) |
| H (12b) | 1011(5) | 609(3) | 3(2) | 39(7) |
| H (12c) | 969(4) | 723(2) | 22(1) | 23(6) |
| PAA molecule | | | | |
| C (1) | 3802(4) | −955(2) | 4382(2) | 38(2) |
| C (2) | 2267(4) | −1144(2) | 4816(2) | 38(2) |
| C (3) | 614(5) | −1606(2) | 4557(2) | 55(3) |
| C (4) | 482(6) | −1880(3) | 3849(3) | 67(3) |
| C (5) | 2005(8) | −1697(4) | 3410(2) | 74(3) |
| C (6) | 3647(6) | −1235(3) | 3671(2) | 59(3) |
| C (7) | 5643(5) | −522(3) | 4671(2) | 56(3) |
| C (8) | 5681(3) | 653(2) | 4998(1) | 26(1) |
| O (9) | 4331(2) | 1308(1) | 4913(1) | 33(1) |
| O (10) | 7161(2) | 912(2) | 5335(1) | 34(1) |
| H (2) | 233(5) | −94(3) | 537(2) | 37(7) |
| H (3) | −50(6) | −172(3) | 490(2) | 68(11) |
| H (4) | −75(7) | −224(4) | 368(2) | 69(11) |
| H (5) | 190(7) | −190(4) | 284(2) | 75(12) |
| H (6) | 489(6) | −103(4) | 334(2) | 69(11) |
| H (7a) | 658(6) | −52(4) | 424(2) | 77(12) |
| H (7b) | 614(7) | −105(4) | 512(2) | 89(13) |

The $B$ values of nonhydrogen atoms are the equivalent isotropic temperature factors calculated from anisotropic thermal parameters using the equation $B = 4/3\ (B_{11}a^2 + B_{22}b^2 + B_{33}c^2 + 2B_{12}ab\ \cos\gamma + 2B_{13}ac\ \cos\beta + 2B_{23}bc\ \cos\alpha)$, where $B_{ij}$ are the principal components of the mean square displacement matrix B.

## Results and Discussion

### Molecular Structure

The bond lengths and angles for nonhydrogen atoms are given in Fig. 1, which also shows the molecular conformation projected onto the adenine or benzene ring, along with the atomic numbering used in this work. The estimated standard deviations are 0.003 to 0.007 Å for lengths and 0.2 to 0.5° for angles. The bonding parameters involving hydrogen atoms are given in Table III. The equations of the least-squares planes for the adenine, benzene and car-

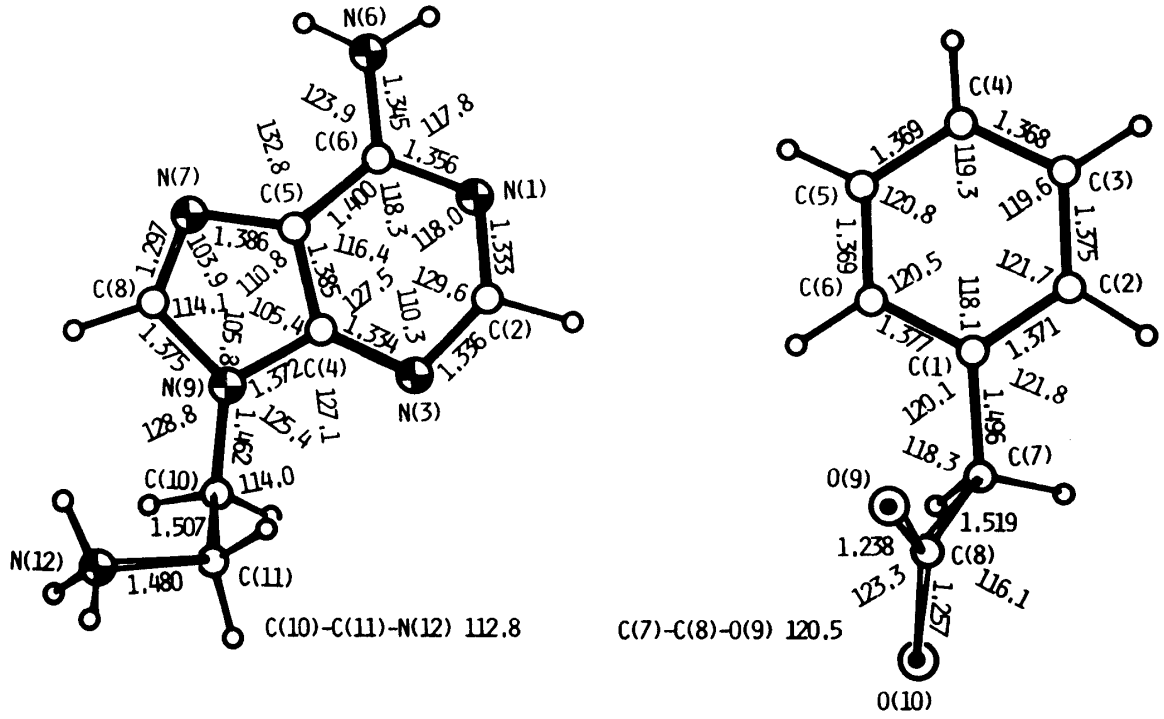


Fig. 1. The Bond Lengths (in Å) and Angles (in Degrees) of Nonhydrogen Atoms with Atomic Numbering

E.s.d's are 0.003 to 0.007 Å for lengths and 0.2 to 0.5° for angles. This figure also shows the molecular conformation projected onto the adenine or benzene ring.

TABLE III. Bond Lengths (in Å) and Angles (in Degrees) involving Hydrogen Atoms

| | | | |
|---|---|---|---|
| AA molecule | | | |
| C (2)-H (2) | 1.10(3) | N (6)-H (6a) | 0.95(4) |
| N (6)-H (6a) | 0.89(4) | C (8)-H (8) | 1.08(4) |
| C (10)-H (10a) | 1.02(3) | C (10)-H (10b) | 1.04(3) |
| C (11)-H (11a) | 1.05(3) | C (11)-H (11b) | 0.95(3) |
| N (12)-H (12a) | 0.91(4) | N (12)-H (12b) | 0.90(4) |
| N (12)-H (12c) | 0.90(3) | | |
| N (1)-C (2)-H (2) | 112(2) | N (3)-C (2)-H (2) | 118(2) |
| C (6)-N (6)-H (6a) | 115(2) | C (6)-N (6)-H (6a) | 120(2) |
| H (6a)-N (6)-H (6b) | 124(3) | N (7)-C (8)-H (8) | 127(2) |
| N (9)-C (8)-H (8) | 119(2) | N (9)-C (10)-H (10a) | 106(2) |
| N (9)-C (10)-H (10b) | 107(2) | C (11)-C (10)-H (10a) | 112(2) |
| C (11)-C (10)-H (10b) | 110(2) | H (10a)-C (10)-H (10b) | 107(2) |
| C (10)-C (11)-H (11a) | 112(2) | C (10)-C (11)-H (11b) | 113(2) |
| N (12)-C (11)-H (11a) | 106(2) | N (12)-C (11)-H (11b) | 105(2) |
| H (11a)-C (11)-H (11b) | 107(2) | C (11)-N (12)-H (12a) | 117(2) |
| C (11)-N (12)-H (12b) | 113(2) | C (11)-N (12)-H (12c) | 108(2) |
| H (12a)-N (12)-H (12b) | 107(3) | H (12a)-N (12)-H (12c) | 106(3) |
| H (12b)-N (12)-H (12c) | 105(3) | | |
| PAA molecule | | | |
| C (2)-H (2) | 1.06(4) | C (3)-H (3) | 1.03(5) |
| C (4)-H (4) | 1.02(5) | C (5)-H (5) | 1.08(5) |
| C (6)-H (6) | 1.10(6) | C (7)-H (7a) | 1.04(5) |
| C (7)-H (7b) | 1.10(5) | | |
| C (1)-C (2)-H (2) | 120(2) | C (3)-C (2)-H (2) | 118(2) |
| C (2)-C (3)-H (3) | 118(3) | C (4)-C (3)-H (3) | 122(3) |
| C (3)-C (4)-H (4) | 117(3) | C (5)-C (4)-H (4) | 123(3) |
| C (4)-C (5)-H (5) | 120(3) | C (6)-C (5)-H (5) | 120(3) |
| C (5)-C (6)-H (6) | 124(2) | C (1)-C (6)-H (6) | 115(2) |
| C (1)-C (7)-H (7a) | 106(3) | C (1)-C (7)-H (7b) | 111(3) |
| C (8)-C (7)-H (7a) | 107(3) | C (8)-C (7)-H (7b) | 102(3) |
| H (7a)-C (7)-H (7b) | 112(4) | | |

Table IV. The Least-Squares Planes of the Adenine Ring, Benzene Ring and Carboxyl Group, and the Deviations (in Å) of Atoms from Them

| | | | |
|---|---|---|---|
| (1) Adenine ring | | | |
| $0.03541X+0.78087Y+0.62369Z=8.70832$ | | | |
| N (1)* | 0.009(2) | N (6) | −0.004(3) |
| C (2)* | 0.006(3) | C (10) | 0.057(4) |
| N (3)* | 0.001(3) | H (2) | 0.00(3) |
| C (4)* | −0.017(3) | H (6a) | 0.21(4) |
| C (5)* | −0.024(3) | H (6b) | −0.12(4) |
| C (6)* | −0.001(3) | H (8) | 0.04(4) |
| N (7)* | 0.005(3) | | |
| C (8)* | 0.018(3) | | |
| N (9)* | 0.003(2) | | |
| (2) Benzene ring | | | |
| $0.34359X-0.91702Y+0.20252Z=3.61684$ | | | |
| C (1)* | −0.001(4) | C (7) | −0.087(6) |
| C (2)* | 0.001(4) | H (2) | −0.01(3) |
| C (3)* | −0.001(5) | H (3) | 0.01(4) |
| C (4)* | 0.001(6) | H (4) | −0.02(5) |
| C (5)* | −0.002(7) | H (5) | 0.02(5) |
| C (6)* | 0.002(5) | H (6) | 0.05(5) |
| (3) Carboxyl group | | | |
| $0.41484X+0.34862Y-0.84046Z=-5.92108$ | | | |
| C (7)* | −0.010(6) | C (1) | 0.253(6) |
| C (8)* | 0.008(3) | H (7a) | −0.96(5) |
| O (9)* | −0.002(2) | H (7b) | 0.76(5) |
| O (10)* | −0.002(3) | | |

In each of the equations of the planes, $X$, $Y$ and $Z$ are coordinates (Å) referred to the orthogonal axes. Atoms marked with asterisks were involved in the calculations of the least-squares planes.

Table V. Selected Torsion Angles

| | |
|---|---|
| AA molecule | |
| C (4)-N (9)-C (10)-C (11) | 83.0(3)° |
| C (8)-N (9)-C (10)-C (11) : $\chi$ | −100.0(3) |
| N (9)-C (10)-C (11)-N (12) : $\psi$ | 83.6(3) |
| PAA molecule | |
| C (2)-C (1)-C (7)-C (8) : $\phi$ | −64.3(5) |
| C (6)-C (1)-C (7)-C (8) | 119.4(4) |
| C (1)-C (7)-C (8)-O (9) | −12.8(5) |
| C (1)-C (7)-C (8)-O (10) : $\theta$ | 169.0(3) |

boxyl moieties and the deviation (in Å) of atoms from these planes are listed in Table IV. The selected torsion angles are listed in Table V.

The bond lengths and angles of the adenine ring are in good agreement with those found in the AA molecule of AA: 7,8-dimethylisoalloxazine-10-acetic acid complex[23] and related compounds.[24] The nine atoms in the adenine ring are almost planar with a maximum shift of −0.024 (3) Å for the C(5) atom from the least-squares plane, and the atoms attached to the ring lie essentially on the plane.

In order to avoid close atomic contacts, the C(11), H(10a) and H(10b) atoms are in a staggered orientation with respect to the C(4) and C(8) atoms, and consequently the torsion angle $\chi$ is close to a right angle (=−100.0 (3)°). Similarly, the N(12), H(11a) and H(11b) atoms orientate in the staggered form with respect to N(9), H(10a) and H(10b), and the torsion angle $\psi$ is 83.6 (3)°; the dihedral angle between the adenine ring and the plane of C(10), C(11) and N(12) atoms is 65.3 (2)°. A similar conformation was also observed in the AA molecule of the above mentioned complex[23] ($\chi=-119.9°$, $\psi=65.2°$), suggesting that this folded conformation is an energetically stable one for the AA molecule. Three hydrogen atoms, H (12a)-

H(12c), found in the difference map are tetrahedrally bound to the N(12) atom, indicating the amino group to be in a cationic $-NH_3^+$ form.

It is characteristic that the C(3), C(4) and C(5) atoms of the PAA molecule have relatively large thermal parameters, indicating that this moiety is more loosely packed in the crystal than the others. The benzene ring including the C(7) atom shows good planarity with deviations from −0.087 (6) Å for the C(7) atom to 0.05(5) Å for the H(6) atom. The bond distances and angles of the carboxyl group are the values of the ionized form. The slightly longer C(8)–O(10) bond length as compared with C(8)–O(9) shows that the negative charge is partially localized on the O(9) atom. The dihedral angle between the carboxyl group and the benzene ring is 110.3 (2)°, and the torsion angles $\phi$ and $\theta$ are −64.3 (5) and 169.0 (3)°, respectively, being very similar to those found in PAA: tryptamine[25] ($\phi = -64.8°$, $\theta = 168.1°$).

## Crystal Structure

A stereoscopic view projected along the *b*-axis is shown in Fig. 2. The intermolecular hydrogen bonds and short contacts (less than 3.5 Å) are given in Table VI.

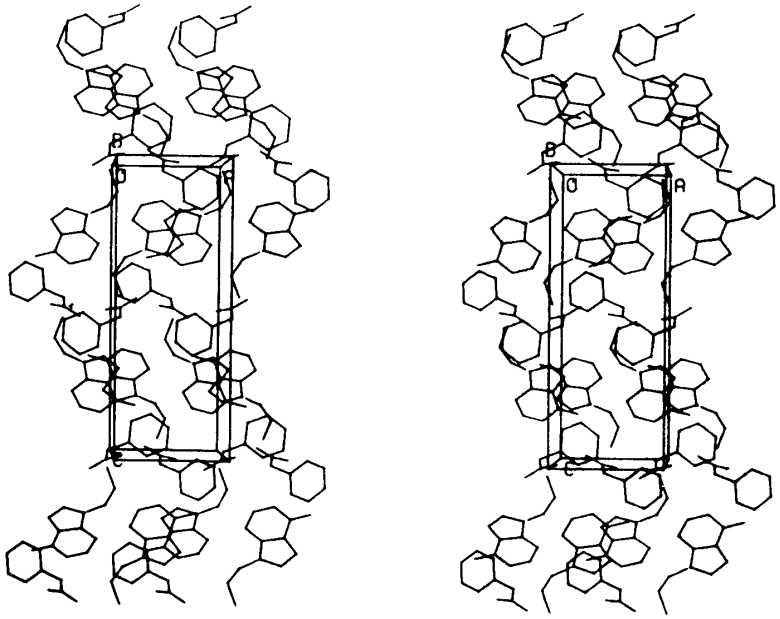


Fig. 2. A Stereoscopic Drawing viewed along the *b*-Axis

Table VI. Hydrogen Bonds and Short Contacts (less than 3.5 Å)

| Hydrogene bonds | | | | | |
|---|---|---|---|---|---|
| Donor | Acceptor | Distance/Å | | | Angle/° |
| | | D···A | | H···A | D—H···A |
| N(12) A[1] | O(9) P[2] | 2.835(3) | | 1.95(3) | 168(3) |
| N(12) A[1] | O(9) P[3] | 2.749(3) | | 1.85(4) | 172(3) |
| N(12) A[1] | O(10) P[4] | 2.784(3) | | 2.05(4) | 138(3) |
| N(6) A[1] | O(10) P[5] | 2.910(3) | | 1.96(4) | 178(4) |
| N(6) A[1] | N(3) A[6] | 3.158(3) | | 2.38(4) | 145(3) |
| Short contacts/Å | | | | | |
| C(10) A[1] | O(10) P[2] | 3.441(3) | N(12) A[1] | C(8) P[2] | 3.425(3) |
| N(12) A[1] | O(10) P[2] | 3.264(3) | C(8) A[1] | O(9) P[3] | 3.170(3) |
| C(8) A[1] | N(1) A[3] | 3.426(3) | N(12) A[1] | C(2) P[3] | 3.392(3) |
| C(11) A[1] | O(10) P[4] | 3.286(3) | N(7) A[1] | C(11) A[6] | 3.482(3) |

Symmetry code

1) $x, y, z$ 2) $3/2-x, 1-y, -1/2+z$
3) $1-x, 1/2+y, 1/2-z$ 4) $2-x, 1/2+y, 1/2-z$
5) $-1/2+x, 1/2-y, 1-z$ 6) $-1+x, y, z$

The suffixes A and P in the atom designations refer to AA and PAA molecules, respectively. Superscripts represent the symmetry operators.

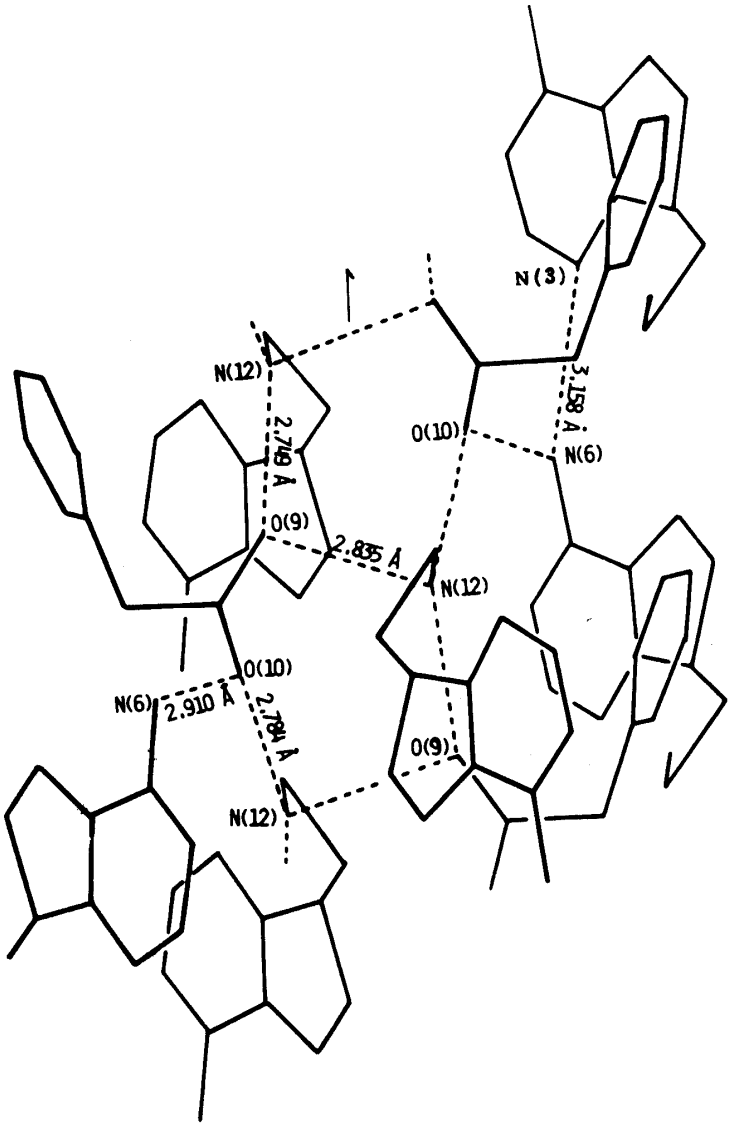


Fig. 3. Infinite Chains formed by the Hydrogen Bonding around the Twofold Screw Axis along the *a*-Axis

The dotted lines represent the hydrogen bonds.

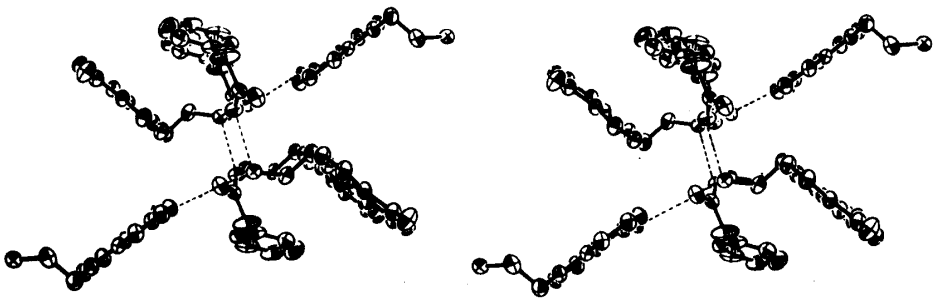

Fig. 4. The Stereoscopic View of the Crystal Packing around the Twofold Screw Axis Parallel to the *a*-Axis

In this crystal, the complex formation is mainly due to the salt bridge formation between the cationic amino group of AA and the anionic carboxyl group of PAA. The molecules are mutually linked around a twofold screw axis by hydrogen bonds between the amino nitrogen atom[N(12)] of AA and the carboxyl oxygen atoms [O(9) and O(10)] of PAA, forming an infinite chain along the *a*-axis, as shown in Fig. 3; one of the carboxyl oxygen atoms, O(9), forms two hydrogen bonds with two neighboring $NH_3^+$ groups (2.749(3) and 2.835(3) Å), and the other, O(10), participates in two hydrogen bonds with a neighboring $NH_3^+$ group (2.784(3) Å) and a neighboring nitrogen atom, N(6) (2.910(3) Å), which strengthens the hydrogen bonds between the carboxyl and amino groups. The N(6) atom is further hydrogen-bonded to the neighboring N(3) atom (3.158(3) Å), consequently connecting the AA molecules along the *a*-axis.

This packing mode, in which the complex molecules are packed around the twofold screw axis and form an infinite helical array with two complex pairs per turn (see Fig. 4), seems to be one of the most stable packing arrangements, and is frequently found in crystalline salts formed between amine and acid; *e.g.* tryptamine: adenin-9-ylacetic acid,[8] 5-methoxytryptamine:5-methoxyindole-3-acetic acid,[26] 5-methoxytryptamine: indole-3-acetic acid[26] and tryptamine: thymin-1-ylacetic acid.[10]

Fig. 5 shows a projection of AA and its nearest-neighboring PAA molecules onto the adenine ring. The dihedral angle between the adenine and benzene rings is 54.7(1)°, and the mean separation distance of the rings is 4.10 Å. Therefore, there is no specific interaction between the adenine and benzene rings in this complex, whereas stacking interactions of aromatinc rings were observed in protein–DNA interactions.[15–18] The hydrogen bonds between the acid and amine might be energetically preferable to any specific interaction of the adenine base and the benzene ring.

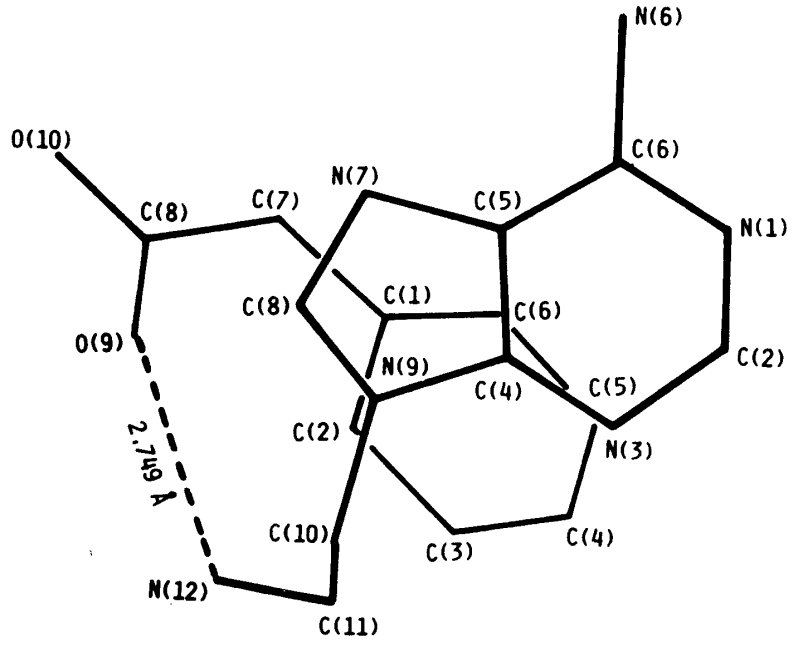


Fig. 5. The Overlapping Geometry of the Adenine Ring and Its Nearest Neighboring Benzene Ring, projected onto the Adenine Ring Plane

**References and Notes**

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