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Stereochemistry of Nucleic Acids and Their Constituents. XXV. Crystal and Molecular Structure of Adenine N^1 -Oxide-Sulfuric Acid Complex*

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Adenine N^1 -oxide is an oxidation product of adenine. Current interest in the N -oxide derivatives of purines stems from the fact that they possess spontaneous cancer induction properties. Crystals of the sulfuric acid complex of adenine N^1 -oxide belong to the orthorhombic space group $P2_12_12_1$, with four molecules in the unit cell of dimensions: $a = 10.224$ (1), $b = 14.944$ (2), $c = 5.639$ (1) Å; $D_{\text{calc}} = 1.921$, $D_{\text{obs}} = 1.910$ g.cm⁻³. The tangent method for noncentrosymmetric crystals was used to obtain the structural solution with initial phasing on the sulfur atom. The structure was refined to a final R value of 0.042 using 838 reflections collected on a diffractometer. The protonated sites in the base are O(1), N(9) and N(7). The bond distances and bond angles, with average standard deviations of 0.005 Å and 0.3°, are in good agreement with other protonated adenine derivatives. The O(1) of the base is involved in a possible symmetric hydrogen bond to O(4) of the sulfate, of 2.54 Å. The compound provides an example of a C-H...O interaction involving the C(8) position of the base and a sulfate oxygen. Other hydrogen bonds involve the N(7), N(9), and the amino group of the base and the sulfate. The S-O bond distances range from 1.455 to 1.494 Å and are correlated with the strengths of the hydrogen bonds involving the sulfate oxygen atoms. The crystal packing arrangement consists of seven negatively charged sulfate groups surrounding each positively charged base, and *vice versa*.

Introduction

The crystal structure of the adenine N^1 -oxide-sulfuric acid complex has been determined as part of a program of research in our laboratory on the molecular structures of the nucleic acid constituents and their derivatives. Our attention was focused on adenine N^1 -oxide (1) when it was shown by Cramer, Doepner, Haar, Schlimme & Seidel (1968) that the exposed ade-

nine bases in transfer ribonucleic acid (tRNA) can be selectively oxidized by monopero-phthalic acid. Weiss & Venner (1969) had reported that 1 forms crystalline metal complexes. We felt, therefore, that these experiments would be suited to the preparation of isomorphous heavy-atom derivatives of tRNA which would then serve in the solution of its crystallographic 'phase problem'. In this connection we were initially interested in the copper perchlorate complex of 1. Our X-ray study of the complex revealed that 1 had undergone degradation with the expulsion of carbon C(2) and the resulting product served as the ligand in the complexing with copper (Sundaralingam, Stout & Hecht, 1971). Apparently, the highly acidic conditions

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and the prolonged heat treatment employed by Weiss & Venner (1969) were sufficient to degrade 1. A plausible mechanism for the degradation of 1 has been given (Sundaralingam *et al.*, 1971). We were interested in studying the effect of sulfuric acid alone without prolonged heating and also the protonation sites in 1. Colorless crystals of the complex were readily obtained by adding $\sim 0.01N$ sulfuric acid to 1 and in this paper we report its crystal structure.

Apparently, 1 forms metal complexes only at neutral pH's (Perrin, 1960), but as yet we have not been successful in isolating such complexes.

Experimental

Crystals of the sulfuric acid complex of adenine N^1 -oxide were obtained by the addition of H_2SO_4 and $CuSO_4$ to an aqueous solution of adenine N^1 -oxide. Large clear crystals ($0.10 \times 0.20 \times 0.25$ mm) were easily obtained after several days of slow evaporation at room temperature. Weissenberg and oscillation pictures established that the crystals were orthorhombic. The systematic absences $h00$, $h = 2n + 1$; $0k0$, $k = 2n + 1$; and $00l$, $l = 2n + 1$ indicated the space group to be $P2_12_12_1$. The cell dimensions were determined by a least-squares refinement of the angles 2θ , ω and χ of 12 reflections measured in the 2θ range 40–60 on a Picker FACS-I diffractometer and are given in Table 1 together with other crystal data. The measured and calculated densities of the crystal were in agreement with the presence of a 1:1 mixture of adenine N^1 -oxide and sulfuric acid.

Table 1. *Crystal data for adenine N^1 -oxide-sulfuric acid complex*

Formula	$[C_5H_7N_5O]^{2+} \cdot SO_4^{2-} \rightleftharpoons [C_5H_6N_5O]^+ \cdot HSO_4^-$
Molecular weight	249.22
Space group	$P2_12_12_1$
<i>a</i>	10.224 ± 0.001 Å
<i>b</i>	14.944 ± 0.002
<i>c</i>	5.639 ± 0.001
Volume	861.57 Å ³
D_{obs}	1.910 g.cm ⁻³ (by flotation in $CCl_4/CHBr_3$)
D_{calc}	1.921 g.cm ⁻³
μ	35.1 cm ⁻¹

Three-dimensional intensity data were collected up to $2\theta = 127^\circ$ employing the θ - 2θ scan technique and using Ni-filtered Cu $K\alpha$ radiation. The crystal was mounted parallel to the *c* axis and 853 reflections were recorded. A reflection was considered unobserved if $I < 1.5\sigma(I)$ where the standard deviation $\sigma(I)$ was computed using counting statistics and an electronic instability factor of 0.02 (Stout & Jensen, 1968). A total of 838 reflections were considered observed using this criterion and these were used in the structure analysis, after making Lorentz and polarization corrections.

Structure determination

The structure was solved by a combination of the heavy atom technique and the application of the tangent formula (Karle & Hauptman, 1956). A three-dimensional electron density map was calculated using the position of the heavy atom determined from the Patterson map in the phasing. The resultant peaks in the map did not give a clear picture of the molecular structure, so the tangent formula was employed to refine the phases of 218 reflections with E 's > 1.4 , using the heavy-atom position as the phasing model. The Direct Phasing Methods Program UWAC-17 (Hall, 1968) was used to carry out the refinement. The resulting E map clearly revealed all the 16 nonhydrogen atoms of the structure.

Structure refinement

The coordinates of the 16 nonhydrogen atoms were subjected to two cycles of isotropic refinement using the full-matrix least-squares program (Busing, Martin & Levy, 1962) modified for use on the UNIVAC 1108 Computer (Rao, 1969). The agreement index $R = \sum ||F_o| - |F_c|| / \sum |F_o|$ dropped from an initial value of 0.26 to 0.08. This was followed by two cycles of anisotropic refinement of the nonhydrogen atoms and R dropped to 0.055. A difference Fourier map revealed all 7 hydrogen atoms in the structure. Two cycles of isotropic refinement of the hydrogen atoms keeping the nonhydrogen atoms fixed lowered the R value to 0.044. Two additional cycles on the nonhydrogen atoms, keeping the hydrogen atoms fixed, gave a final R of 0.043. The average shift/ σ ratio in the positional and thermal parameters was 0.03, with a maximum of 0.12.

During the refinement the hydrogen atom H(O1) was initially placed at a position of 1.0 Å from O(1) of the adenine N^1 -oxide, but it refined to the position given in Table 3 with a O(1)–H distance of 1.23 Å. H(O1) was also placed 1 Å from the sulfate oxygen atom O(4) and three cycles of isotropic refinement moved it to a position of 1.28 Å from O(4). The above suggests that the hydrogen atom H(O1) is probably shared equally by the sulfate and the N -oxide. The average shift/ σ ratio in its coordinates was 0.30 (see discussion below).

The Cruickshank (1961) type weighting scheme where $1/w = \sigma(F_o)^2 = 4.47 + 0.0028|F_o| + 0.000054|F_o|^2$ was used in the refinement. The scattering factors for S, O, N and C atoms used throughout the analysis were those of Cromer & Waber (1965), while that of H was from Stewart, Davidson & Simpson (1965).

Results

The observed and calculated structure amplitudes are listed in Table 2. The atomic coordinates are given in Table 3. The average estimated standard deviations in the atomic positions are S = 0.001 Å, O = N = C = 0.004 Å

Table 2. The calculated and observed structure factors $\times 10$ for adenine N^1 -oxide-sulfuric acid complex

[A large table containing calculated and observed structure factors for the adenine N1-oxide-sulfuric acid complex. The table is organized into columns for different hkl reflections and their corresponding structure factor values. It includes both calculated and observed values for various reflections, such as 2 268 260, 4 1370 1370, etc., up to 18 37 52.]

Table 3. Atomic parameters

(a) Positional parameters and anisotropic thermal parameters of the nonhydrogen atoms

All parameters for nonhydrogen atoms and their e.s.d.'s given in parentheses have been multiplied by 10^4 . The temperature factor is of the form $\exp[-(B_{11}h^2 + \dots + 2B_{12}hk + \dots)]$.

	x	y	z	B ₁₁	B ₂₂	B ₃₃	B ₁₂	B ₁₃	B ₂₃
S	5525 (1)	3283 (1)	-563 (2)	14 (1)	14 (0)	127 (4)	0 (1)	3 (2)	10 (1)
O(2)	4668 (4)	2511 (3)	-314 (7)	63 (4)	27 (1)	261 (14)	-20 (2)	25 (7)	3 (4)
O(3)	4904 (3)	4088 (2)	423 (7)	42 (3)	22 (1)	281 (13)	7 (2)	36 (6)	9 (4)
O(4)	6747 (3)	3098 (2)	808 (7)	36 (3)	32 (2)	239 (13)	8 (2)	-40 (6)	9 (4)
O(5)	5871 (3)	3422 (3)	-3044 (7)	45 (3)	40 (2)	152 (11)	-3 (2)	13 (5)	14 (4)
O(1)	2667 (3)	556 (2)	6984 (7)	23 (3)	29 (2)	246 (13)	-8 (2)	7 (6)	-10 (4)
N(1)	4003 (4)	725 (3)	7000 (8)	26 (3)	16 (1)	161 (13)	-3 (2)	7 (6)	-5 (4)
C(2)	4705 (5)	379 (3)	8820 (10)	46 (5)	15 (2)	213 (18)	-6 (3)	21 (9)	-4 (5)
N(3)	5977 (4)	471 (3)	9004 (8)	46 (4)	20 (2)	156 (14)	1 (2)	-15 (7)	4 (5)
C(4)	6501 (5)	935 (3)	7196 (9)	35 (4)	16 (2)	174 (17)	0 (2)	-4 (8)	-7 (5)
C(5)	5846 (4)	1287 (3)	5265 (9)	26 (4)	15 (2)	166 (16)	1 (2)	2 (7)	-4 (5)
C(6)	4479 (4)	1188 (3)	5101 (8)	34 (4)	10 (2)	157 (16)	2 (3)	0 (7)	-13 (4)
N(6)	3704 (4)	1485 (3)	3426 (8)	33 (4)	24 (2)	165 (14)	-1 (2)	-13 (6)	11 (4)
N(7)	6770 (4)	1701 (3)	3851 (8)	45 (4)	21 (2)	161 (13)	-1 (2)	10 (6)	7 (4)
C(8)	7928 (4)	1608 (3)	4914 (9)	26 (4)	19 (2)	209 (18)	-1 (2)	7 (7)	-10 (5)
N(9)	7799 (4)	1143 (3)	6922 (8)	29 (3)	22 (2)	199 (15)	2 (2)	-12 (7)	-4 (5)

Table 3 (cont.)

(b) Positional and isotropic thermal parameters of the hydrogen atoms

All positional parameters for hydrogen atoms and their e.s.d.'s have been multiplied by 10^3 .

	x	y	z	B(Å ²)
H(01)	208 (8)	111 (5)	820 (15)	8.5 (22)
H(2)	420 (4)	-3 (3)	996 (8)	1.2 (09)
H(61)	277 (5)	125 (4)	348 (11)	3.3 (12)
H(62)	404 (4)	191 (3)	255 (9)	1.1 (10)
H(7)	679 (7)	211 (5)	258 (13)	5.0 (20)
H(8)	876 (4)	177 (3)	401 (9)	1.4 (09)
H(9)	856 (5)	104 (3)	772 (10)	2.0 (10)

and $H=0.05 \text{ \AA}$. The ellipsoids of vibration drawn using the program of Johnson (1965) are shown in Fig. 1.

Discussion of structure

The adenine N^1 -oxide molecule can possess the tautomeric structures I or II shown in Fig. 2. Since here we are dealing with the protonated form of adenine N^1 -oxide it will not be possible to establish the site of the original hydrogen atom on the imidazole ring in an obvious manner.

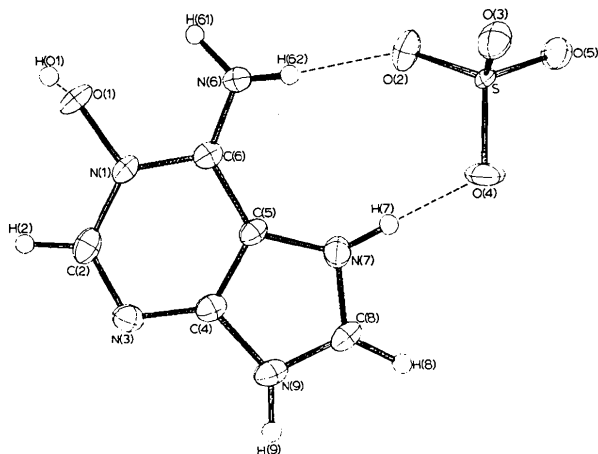


Fig. 1. Illustration showing the thermal ellipsoids for the non-hydrogen atoms, drawn using ORTEP (Johnson, 1965).

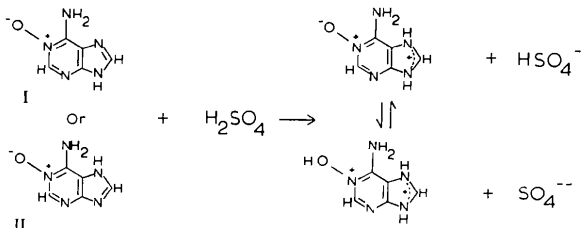


Fig. 2. Scheme of the reaction between adenine N^1 -oxide (I) and sulfuric acid. I and II represent the two tautomeric forms of adenine N^1 -oxide.

Bond distances and bond angles

The bond distances and bond angles are shown in Fig. 3. The bond distances and bond angles in the pyrimidine portion of the adenine N^1 -oxide cation are similar to the values found in the protonated adenine derivatives (Sundaralingam, 1966, Rao & Sundaralingam, 1970). The values in the imidazole portion are similar to the values found in other purine systems where both N(7) and N(9) are protonated, e.g. guanine-copper chloride complex (Carrabine & Sundaralingam, 1970), isoguanine sulfate monohydrate (Subramanian & Marsh, 1971). The N(1)–O(1) bond distance of 1.389 Å compares favorably with that found for pyridine N -oxide (Golic, Hadzi & Lazarini, 1971). The exocyclic angle at C(6) [N(1)–C(6)–N(6)] adjacent to the N(1)–O(1) bond is about 6° smaller than the angle N(6)–C(6)–C(5).

The dimensions of the sulfate group are comparable to the values found in other sulfates; e.g. isoguanine sulfate monohydrate (Subramanian & Marsh, 1971). The O–S–O angles range from 107.9–110.6° while the S–O bond distances range from 1.455 to 1.494, Fig. 3. The longest S–O bond is associated with the shortest hydrogen bond in the structure (see below). Likewise the next largest S–O bond is involved in the next shortest hydrogen bond. These observations suggest that significant variations in the bond distances can result from differences in hydrogen bonding strengths.

The determination of the hydrogen atom positions has revealed that the exocyclic angles involving the

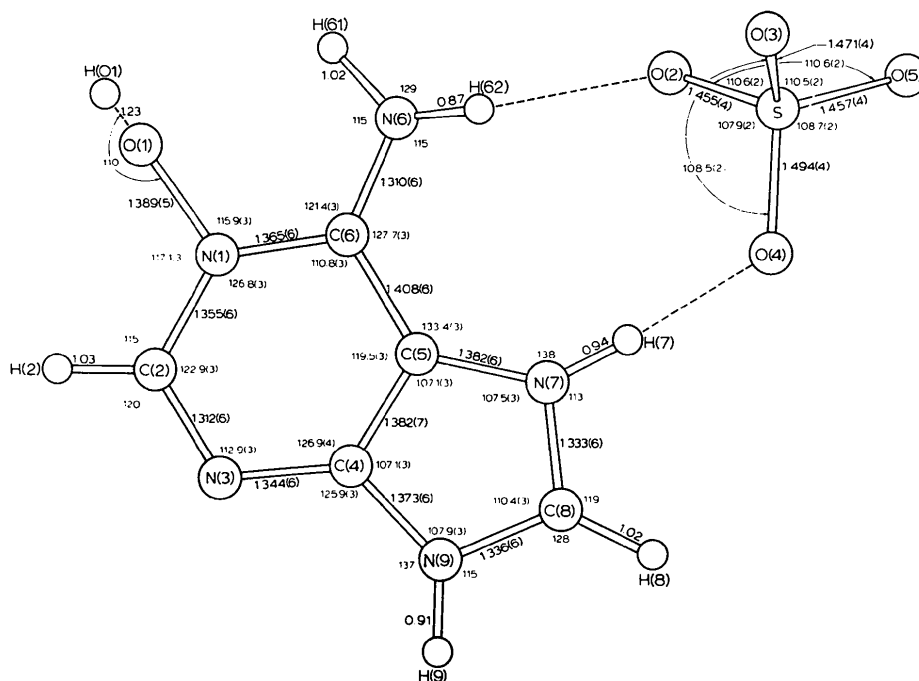


Fig. 3. The bond lengths and bond angles in the asymmetric unit. The e.s.d.'s are given in parentheses and correspond to the last digit in the given distances and angles.

imidazole ring atoms N(7), C(8) and N(9) show considerable departure from equality.

Least-squares planes

Table 4 shows the deviations of the atoms from the least-squares plane through the entire base (plane I) and the 9 base ring atoms (plane II). The ring generally appears to be coplanar (plane II) with the possible exception of N(1). The substituent O(1) is displaced significantly on the opposite side of N(1).

Hydrogen bonding scheme

The hydrogen bond distances and angles are shown in the *c* projection in Fig. 4. Each sulfate group, although surrounded by seven bases (cations), is hydrogen bonded to 5 neighboring bases (see also Fig. 5).

Table 4. *Least-squares planes for the base and deviations of the atoms from the planes*

Atoms not defining the plane are marked with asterisks.

Plane I, $0.135X - 0.852Y - 0.505Z = -2.346$

Plane II, $0.134X - 0.854Y - 0.504Z = -2.350$

	Deviation from Plane I (Å)	Deviation from Plane II (Å)
O(1)	0.015	0.021*
N(1)	-0.020	-0.016
C(2)	-0.000	0.004
N(3)	0.004	0.008
C(4)	0.001	0.002
C(5)	0.013	0.012
C(6)	-0.004	-0.003
N(6)	-0.010	-0.010*
N(7)	0.016	0.013
C(8)	-0.009	-0.013
N(9)	-0.006	-0.007
r.m.s. ^d	0.011	0.010

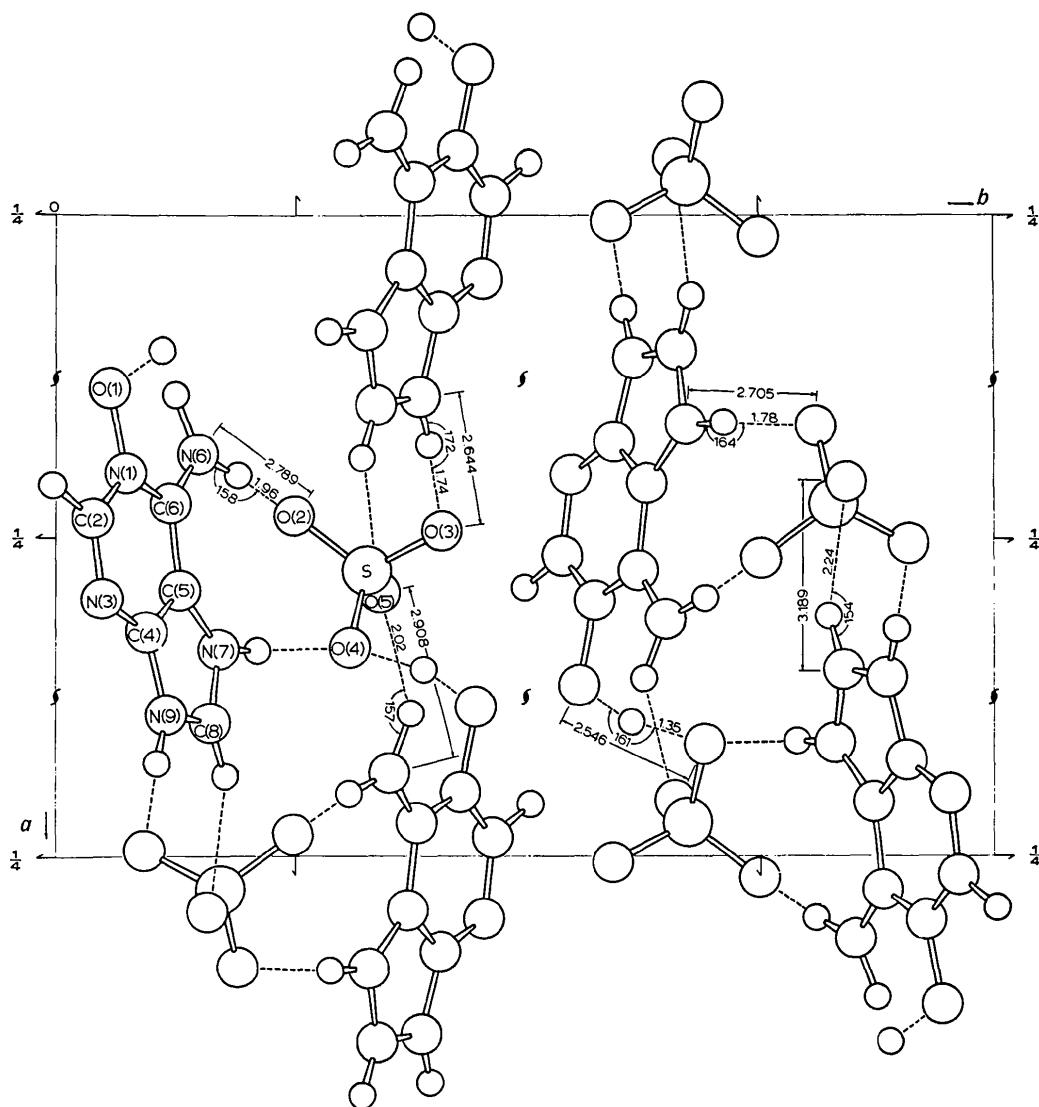


Fig. 4. The molecular packing and hydrogen bonding distances and angles viewed down the *c* axis.

The sulfate oxygen atoms O(2) and O(4) form a hydrogen-bonded pair with N(6) and N(7) of the cation (Fig. 2). Similar hydrogen-bonded pairing has been observed between the phosphate and the protonated adenine base in the nucleotides (Hecht & Sundaralingam, 1972). A rather common mode of base-phosphate interaction involves the pairing of N(6) and N(1) sites of the adenine base and the phosphate (Sundaralingam, 1966). The sulfate O(4) is also hydrogen bonded to the O(1) atom of the cation. The angle $H(7)\cdots O(4)\cdots H(O1)$ is 119° . The least-squares refinement studies suggest that the hydrogen atom H(O1) is probably shared equally by the sulfate and the *N*-oxide. The distance $O(1)\cdots O(4)$ of 2.546 \AA is the shortest hydrogen bond in the structure. The above observations suggest that H(O1) is probably involved in a symmet-

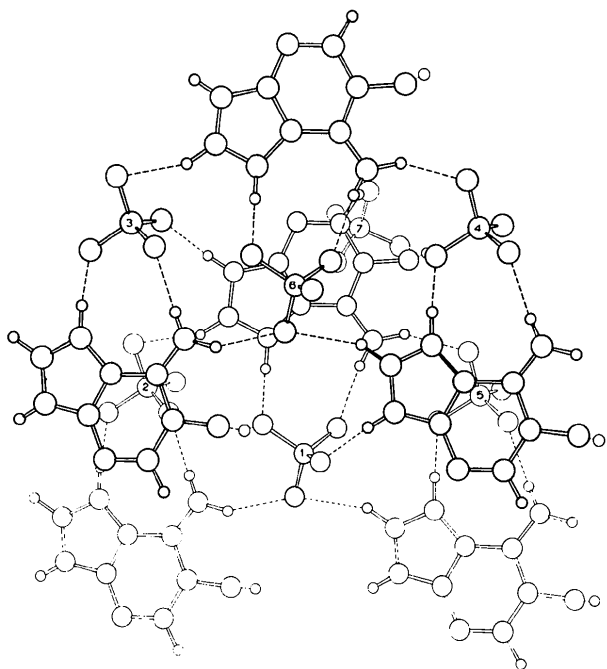


Fig. 5. The molecular packing and hydrogen bonding scheme viewed normal to the plane of the purine ring.

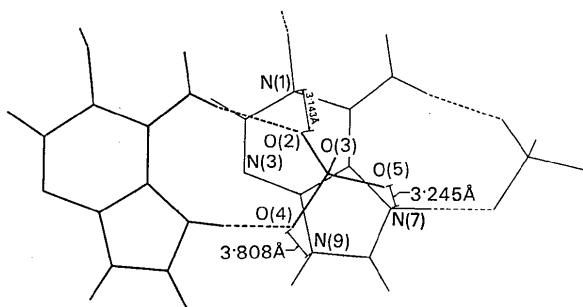


Fig. 6. A view normal to the plane of the purine ring showing two asymmetric units separated by a translation along *c*. The shorter distances between the anion and cation are shown.

rical hydrogen bond. A similar possible symmetrical hydrogen bond has been observed in the hydrogen-bonded adduct of pyridine *N*-oxide with trichloroacetic acid (Golic, Hadzi & Lazarini, 1971), where an $O\cdots O$ distance of 2.411 \AA was observed between the *N*-oxide and trichloroacetic acid. A survey of structures with short $O\cdots O$ hydrogen bonds has been presented elsewhere (Hamilton & Ibers, 1968; Putkey, 1969).

The sulfate O(5) hydrogen bonds with H(61) and H(8) of two symmetry related bases as shown in Fig. 4. The angle $H(61)\cdots O(5)\cdots H(8)$ is 158° . $C-H\cdots O$ interactions involving the C(8) group is highly preferred when the base occurs as a cation. Other examples of this type of hydrogen bonding involving purine systems are: adenosine 3'-phosphate dihydrate (Sundaralingam, 1966), adenosine 2',5'-uridine phosphate (Shefter, Barlow, Sparks & Trueblood, 1969), cyclic 3',5'-adenosine monophosphonate monohydrate (Sundaralingam & Abola, 1972).

Molecular packing

There is no base stacking in this structure. The sulfate group seems to dictate the packing arrangement in the crystal lattice. Fig. 5 shows the molecular packing arrangement viewed normal to the plane of the purine ring. Each ring is surrounded by seven sulfate groups. Five of the surrounding sulfates (nos. 1–5) are involved in hydrogen bonding as shown in Figs. 4 and 5, whereas the other two sulfates (nos. 6–7) above and below the plane of the ring are involved in ionic interactions. Fig. 6 shows two asymmetric units separated by a translation along *c* and viewed normal to the plane of the base. The distances between the negatively charged oxygens of the sulfate and the positively charged nitrogens of the purine ring vary from 3.143 to 3.808 \AA .

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Stereochemistry of Nucleic Acids and Their Constituents. XXIX.* Crystal and Molecular Structure of Allopurinol, a Potent Inhibitor of Xanthine Oxidase

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The crystalline structure of allopurinol, a potent inhibitor of xanthine oxidase, has been determined using three-dimensional X-ray data, measured on a diffractometer. The compound was found to crystallize in the monoclinic space group $P2_1/c$ with cell constants $a = 3.683$ (1), $b = 14.685$ (3), $c = 10.318$ (2) Å, $\beta = 97.47$ (2)°. The structure was solved using direct methods and was refined by full-matrix least-squares methods to an R value of 0.045. The bases are hydrogen-bonded in sheets parallel to the $(\bar{1}02)$ plane. Layers of these sheets are stacked with a staggered overlap of the base rings. All ring nitrogen atoms, O(6), and C(2) are involved in hydrogen bonding.

Introduction

The crystal structure of allopurinol (II in Fig. 1) has been determined in our laboratory as part of a program of research on the molecular structures of nucleic acid constituents and their derivatives. Allopurinol is known to be a potent inhibitor of xanthine oxidase and is used extensively for the treatment of gout (Rundles, Wyngaarden, Hitchings, Elion & Silberman, 1963). The compound has also been used in conjunction with anti-cancer drugs which impede RNA biosynthesis and as adjunct therapy in conjunction with 6-mercaptopurine in the treatment of leukemia (Elion, Callahan, Hitchings, Rundles & Laszlo, 1962).

Experimental

Crystals of allopurinol were obtained by dissolving the compound in a 1:1 mixture of acetone and water. After several days of slow evaporation small crystals were obtained. Weissenberg and oscillation photographs show that the crystals are monoclinic. The systematic absences $h0l$, $l = 2n + 1$; $0k0$, $k = 2n + 1$ indicate the space group to be $P2_1/c$. The cell dimensions are given in Table 1 together with other crystal data. They were determined by a least-squares refinement of the angles 2θ , ω , and χ values for 12 reflections measured in the 2θ range of 40–60° on a Picker FACS 1 diffractometer. The measured and calculated densities of the crystal are in agreement with the presence of four molecules of allopurinol per unit cell.

Three-dimensional intensity data were collected using the θ - 2θ scan technique with Ni-filtered copper radiation ($\lambda = 1.5418$ Å) up to $2\theta_{\max} = 127^\circ$. The crystal

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