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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 $a=3{\cdot}683$ (1), $b=14{\cdot}685$ (3), $c=10{\cdot}318$ (2) Å, $\beta=97{\cdot}47$ (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 anticancer 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 ($\lambda=1{\cdot}5418$ Å) up to $2\theta_{max}=127°$. The crystal

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Table 1. *Crystal data*

Formula	$C_5H_4N_4O$
Space group	$P2_1/c$
a	3·683 (1) Å
b	14·685 (3)
c	10·318 (2)
β	97·47 (2)°
d_{obs}	1·635 g.cm^{-3} (by flotation in $CCl_4/CHBr_3$)
d_{calc}	1·635 g.cm^{-3}

was mounted with the a axis parallel to the φ axis of the diffractometer and 904 reflections were recorded. The intensities were corrected for the fluctuations in the standard reflections, and for the usual Lorentz and polarization factors. A reflection was considered observed if $I > 1{\cdot}5\sigma(I)$, where the standard deviation $\sigma(I)$ was computed using counting statistics and an electronic-instability factor of 0·02 (Stout & Jensen, 1968). 647 reflections were considered to be observed and these were used in the structure analysis.

Structure determination

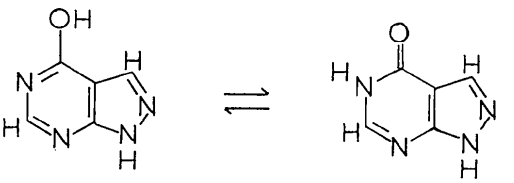
The structure was solved by means of direct methods using Long's (1965) computer program. The phases of 132 reflections with E's $> 1{\cdot}5$ were obtained through reiterative application of Sayre's (1954) equation. The four initial reflections ($\bar{1}02, 195, 063, 1,10,4$) produced 16 possible solutions. The solution chosen was that which converged in the least number of cycles and which gave the highest consistency index

$$C = \langle |E_A \Sigma E_B E_C| \rangle / \langle |E_A| \Sigma |E_B| |E_C| \rangle$$

where the sum is over all the terms in the Sayre equations. A three-dimensional E map revealed the entire structure with the 10 nonhydrogen atoms giving rise to the 10 strongest peaks.

Structure refinement

The coordinates of the 10 nonhydrogen atoms were subjected to two cycles of isotropic refinement using the full-matrix least-squares program *ORFLS* (Busing, Martin & Levy, 1964) modified for use on the UNIVAC 1108 computer (Rao, 1969). The agreement index R

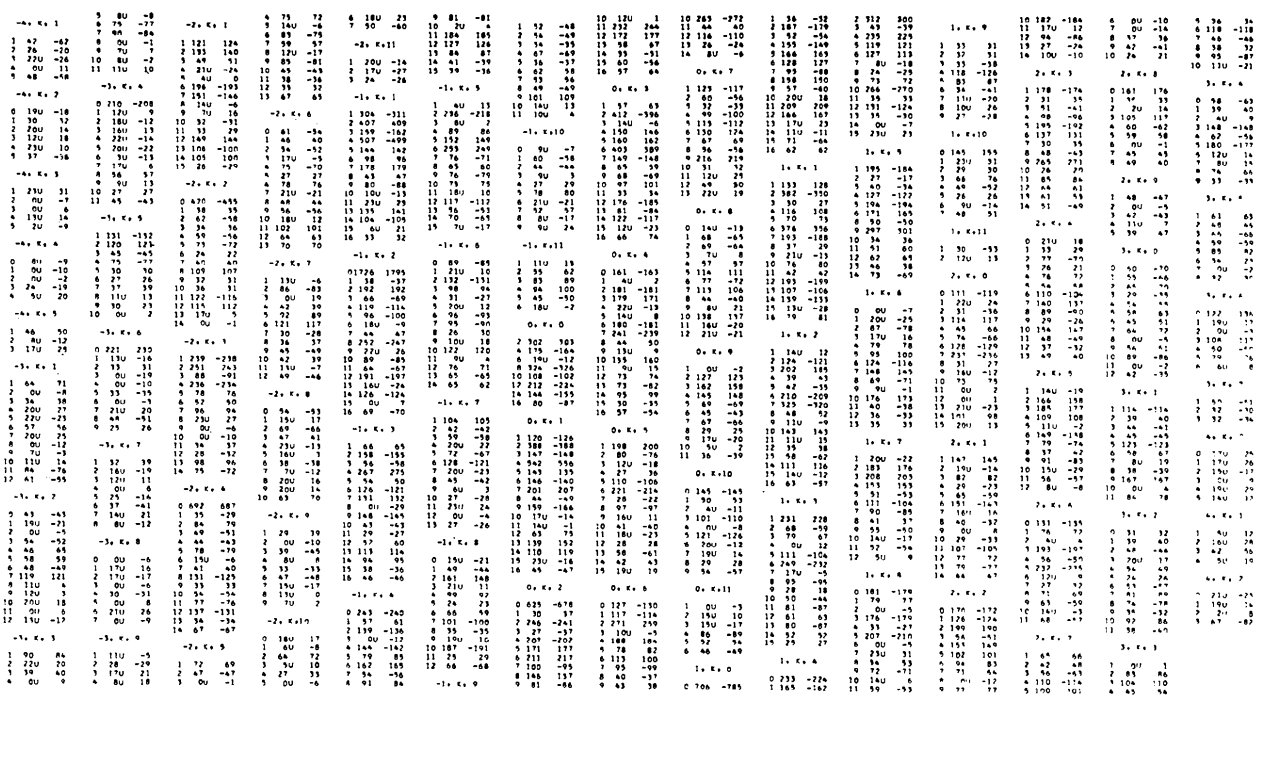


I II

Fig. 1. Two possible tautomeric forms of allopurinol. I: enol form, II: keto form.

Table 2. *Observed and calculated structure factors*

The columns are k, $10|F_{obs}|$, and $10|F_{calc}|$. Signs attached to $|F_{calc}|$ correspond to the phase angle.



dropped from an initial value of 0·20 to 0·12. Two cycles of anisotropic refinement of the nonhydrogen atoms lowered the R value to 0·072. A difference Fourier map revealed all four hydrogen atoms in the structure. An additional two cycles of anisotropic refinement of the nonhydrogen atoms along with two cycles of isotropic refinement of the hydrogen atoms gave a final R value of 0·045. The average shift/σ ratio in the positional and thermal parameters was 0·116 with a maximum ratio of 0·680.

During the final two cycles of refinement a Hughes-type weighting scheme was employed where $1/\sqrt{w}=\sigma(F_{obs})=3{\cdot}35$ for $|F_{obs}|<57{\cdot}12$ and $\sigma(F_{obs})=2{\cdot}85+0{\cdot}0085|F_{obs}|$ for $|F_{obs}|>57{\cdot}12$. The scattering factors for C, N, and O atoms used throughout the analysis were those of Cromer & Waber (1965), while those for H were from Stewart, Davidson & Simpson (1965).

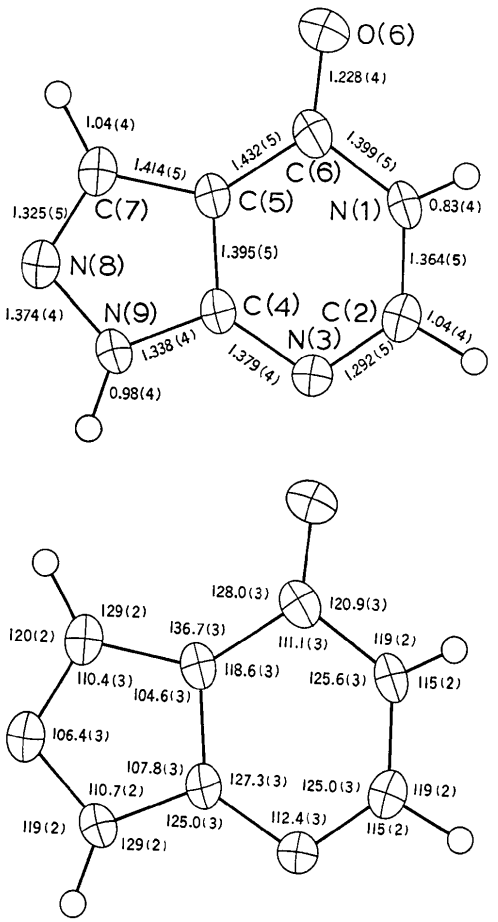


Fig. 2. Bond distances (Å) and bond angles (°) in allopurinol.

Results and discussion

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 0·003 Å for O, N and C, and 0·04 Å for H. The bond distances and angles are shown in Fig. 2.

Bond distances and angles

The bond distances and angles in the pyrimidine portion of the allopurinol ring are generally similar to the values found for hypoxanthine (Sletten & Jensen, 1969). The five-membered ring portion of the base has two neighboring nitrogen atoms at positions (8) and (9) forming a diazole ring. The N(9)–N(8) distance is in agreement with the value found in 8-azaguanine monohydrate, which has a triazole ring (Sletten, Sletten & Jensen, 1968), and to the distance found in the diazole ring of formycin (Prusiner, Brennan & Sundaralingam, 1971). All the diazole ring systems examined to date tend to exhibit considerable distortions of bond angles when compared to imidazole rings. Specifically, formycin, 8-azaguanine and allopurinol exhibit an increase in the endocyclic angles C(5)–N(7) [C(7)]–N(8) and C(4)–C(9) [N(9)]–N(8) which is accompanied by a decrease in the N(7) [C(7)]–N(8)–C(9) [N(9)] angle.

Table 3. *Positional and thermal parameters of atoms in allopurinol*

Positional parameters are $\times 10^4$ for heavy atoms, and $\times 10^3$ for hydrogen atoms. The β_{ij}'s are $\times 10^4$. Standard deviations refer to the least significant digits. The anisotropic temperature factor is of the form:

$$\exp\left[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)\right].$$

	X	Y	Z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
N(1)	4896 (9)	7086 (2)	2412 (3)	715 (29)	16 (1)	82 (3)	−8 (5)	−36 (8)	−3 (2)
C(2)	2837 (11)	6904 (2)	1245 (4)	644 (34)	25 (2)	72 (4)	6 (6)	−34 (9)	2 (2)
N(3)	1884 (8)	6100 (2)	820 (3)	691 (27)	24 (1)	68 (3)	0 (5)	−48 (7)	1 (1)
C(4)	3250 (9)	5432 (2)	1675 (3)	576 (30)	19 (1)	62 (3)	5 (5)	−2 (8)	−1 (2)
C(5)	5368 (9)	5533 (2)	2887 (3)	551 (31)	22 (1)	64 (4)	−4 (5)	−20 (8)	0 (2)
C(6)	6335 (10)	6435 (2)	3329 (4)	589 (31)	26 (2)	75 (4)	−6 (6)	2 (9)	−4 (2)
O(6)	8193 (8)	6665 (2)	4351 (3)	947 (28)	35 (1)	84 (3)	−29 (5)	−103 (7)	−8 (2)
C(7)	6031 (10)	4636 (2)	3358 (4)	690 (34)	23 (2)	76 (4)	−1 (6)	−23 (9)	4 (2)
N(8)	4455 (9)	4036 (2)	2505 (3)	790 (30)	20 (1)	77 (3)	13 (5)	−24 (8)	5 (2)
N(9)	2755 (8)	4530 (2)	1468 (3)	705 (28)	20 (1)	68 (3)	0 (5)	−42 (7)	−1 (1)
H(1)	550 (10)	763 (3)	253 (4)	2·7 (8)					
H(2)	179 (11)	744 (3)	65 (4)	4·2 (9)					
H(7)	756 (11)	441 (3)	422 (4)	3·6 (8)					
H(9)	115 (11)	421 (3)	77 (4)	4·2 (9)					

Least-squares planes

Table 4 shows the deviations of the atoms from the least-squares plane through the 9 atoms of the purine ring and through the entire base. The ring is planar within experimental error.

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

Plane I: $0{\cdot}895X - 0{\cdot}045Y - 0{\cdot}444Z = -0{\cdot}241$ Å
Plane II: $0{\cdot}896X - 0{\cdot}044Y - 0{\cdot}442Z = -0{\cdot}233$
Atoms not defining the plane are marked with *.

	Plane I	Plane II
N(1)	0·005 Å	0·007 Å
C(2)	0·008	0·007
N(3)	−0·009	−0·010
C(4)	−0·005	−0·006
C(5)	−0·010	−0·009
C(6)	−0·005	−0·001
O(6)	0·006	0·011*
C(7)	−0·004	−0·002
N(8)	0·006	0·006
N(9)	0·009	0·007
rms Δ	0·007	0·007

Hydrogen bonding

The hydrogen bonding as viewed along the a^* axis is shown in Fig. 3. Each base ring is surrounded in the same plane by six bases but forms hydrogen bonds with only five of them. The four ring nitrogens, O(6), and C(2) are involved in hydrogen bonding. The only hydrogen atom not involved in hydrogen bonding is that attached to C(7). N(8) is hydrogen-bonded with N(1) of a screw-related base. The exocyclic angles N(9)–N(8)···H(1) and C(7)–N(8)···H(1) are 121 and 132° respectively. N(3) and N(9) are involved in a hydrogen-bonded pair with an inversion center related molecule. The exocyclic angles C(4)–N(3)···H(9) and C(2)–N(3)···H(9) are 119 and 127 respectively. The carbonyl oxygen O(6) is involved in a C–H···O hydrogen bond with C(2) of a glide plane related base. The exocyclic angle C(6)–O(6)···H(2) is 156°. C–H···O hydrogen-bonding is commonly observed at the C(8) position in several other purine systems (Sutor, 1963; Sundaralingam, 1966; Shefter, Barlow, Sparks & Trueblood, 1969; Prusiner & Sundaralingam, 1972). Apparently a carbon atom flanked on both sides by nitrogen atoms is electronegative enough to donate its hydrogen to an acceptor atom.

Molecular packing and base stacking

The molecular packing viewed normal to the plane of the base is shown in Fig. 4. Each base is surrounded by 8 other bases. Five of the six base rings in the plane are involved in hydrogen bonding whereas the two base rings above and below are involved in van der Waals interactions. The packing consists of stacks of parallel hydrogen-bonded sheets of bases with partial overlap of the rings. The interplanar spacing between the bases is 3·301 Å. The shorter contacts between

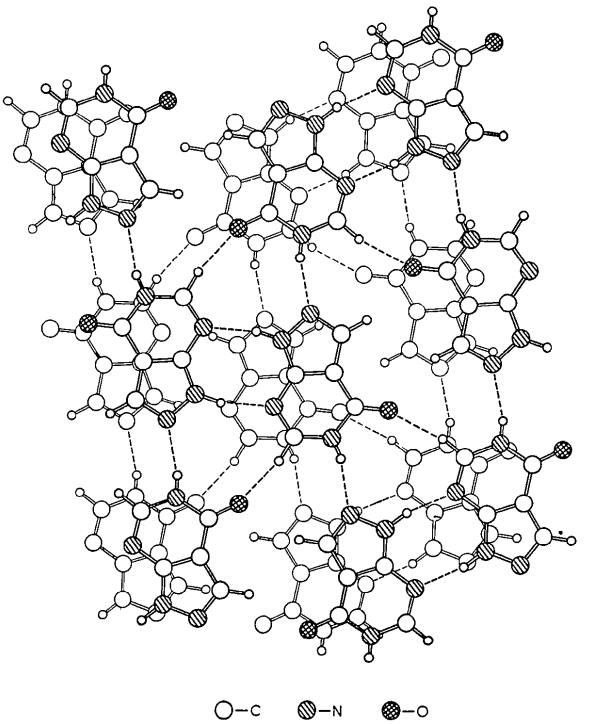


Fig. 4. A view normal to the top central base plane from a finite viewing distance with the origin point at C(4) of the top central base. The hetero atoms are denoted by shading in the top layer with the bottom layer unshaded.

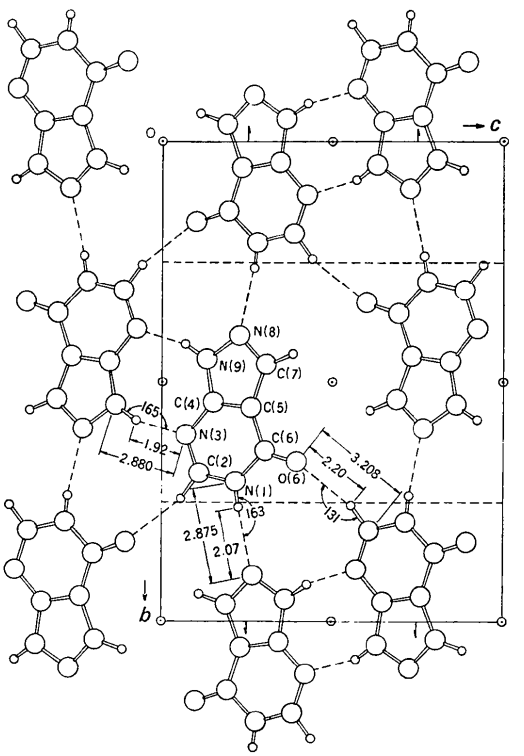


Fig. 3. A view along the a^* axis showing the hydrogen-bonding. The hydrogen-bond distances (Å) and angles (°) are shown.

atoms of overlapping bases are: O(6)···C(6) = 3·323, N(1)···O(6) = 3·430, N(9)···N(8) = 3·445, and N(8)···C(7) = 3·448 Å; all other contacts are greater than 3·500 Å. The sheets are tilted approximately 32° from the *bc* plane and lie approximately parallel to the ($\bar{1}$02) plane. Consequently, the largest $|E|$ value was that of the $\bar{1}$02 reflection.

Both of the tautomeric structures shown in Fig. 1 can be proposed for allopurinol. The present X-ray structure analysis has revealed that the keto form (II) is the preferred tautomer in the crystal. It is entirely possible that the molecule might assume the enol form during certain chemical reactions. Allopurinol and hypoxanthine are both substrates for xanthine oxidase. Hypoxanthine is oxidized to xanthine with is further oxidized to uric acid. The latter compound is then released from the active site of the enzyme. However, allopurinol is oxidized to oxoallopurinol which is retained at the active site of the enzyme. The crystalline structure of allopurinol has revealed that in addition to other sites on the base, N(8) is engaged in strong hydrogen bonding. Since N(8) cannot be oxidized by the enzyme, it may be involved in hydrogen bonding to a neighboring amino acid side chain or the main chain at the active site. The latter hydrogen-bonding potential of allopurinol probably makes it a potent inhibitor of xanthine oxidase.

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The Crystal Structure of *p*-Iodotoluene

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p-Iodotoluene, C_7H_7I, is orthorhombic, space group $P2_12_12_1$, with cell dimensions $a = 7{\cdot}46(1)$, $b = 16{\cdot}50(2)$, and $c = 6{\cdot}11(1)$ Å; $Z = 4$. The structure was determined from precession, Weissenberg, and diffractometer data by means of a Patterson synthesis and least-squares refinement to a final discrepancy index of $R = 0{\cdot}059$. In spite of some disorder, the molecular structure is as expected, with an average C–C distance of 1·389 Å in the benzene ring and C–I = 2·06 Å. The iodine atoms form a zigzag chain around 2_1 along *c*, with an I···I distance of 4·06 Å; the arrangement suggests weak bonding between molecules.

Introduction

The existence of short intermolecular contacts in many interhalogen compounds, polyhalide ions, and organic molecule–halogen molecule addition compounds is well known. They occur, for example, in IBr (Swink & Carpenter, 1968), CsI_3 (Tasman & Boswijk, 1955), and 2:1 methanol–bromine (Groth & Hassel, 1964). Studies of simple organic halides, such as *p*-diiodobenzene (Lyan & Struchkov, 1959) and *p*-dibromobenzene (Bezzi & Croatto, 1942), also show these short

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