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The Structure of 8-Thioxoadenosine Monohydrate

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Abstract

The structure of 8-thioxoadenosine monohydrate, $C_{10}H_{13}N_5O_4S.H_2O$, has been determined. The crystals are monoclinic, space group $P2_1$, with $a = 8.758$ (1), $b = 6.717$ (1), $c = 11.462$ (2) Å, $\beta = 95.22$ (1)°, $Z = 2$. The structure was refined to $R = 0.048$. The conformation about $C(4')-C(5')$ is *gauche–trans*, and the puckering of the ribose is $C(2')$-*endo*–$C(3')$-*exo*. The molecule exhibits a *syn* conformation about the glycosyl bond in spite of the absence of an intramolecular $O(5')-H\cdots N(3)$ hydrogen bond. The bases are stacked into columns, overlapping mainly at the S substituents of adjacent molecules. All the donor atoms are involved in hydrogen bonds, while the S atom acts as a hydrogen-bond acceptor.

Introduction

It is generally accepted that in purine nucleosides bulky substituents at the 8 position of the purine bases lead to a *syn* conformation about the glycosyl bond for steric reasons. This has been found in a number of crystal structures of such analogs (Yasuniwa *et al.*, 1979; Birnbaum & Shugar, 1978).

The title compound could form the thioketo structure rather than the alternative tautomeric structure. Therefore, it is of considerable interest to study the influence of a geometrical change in the imidazole portion of the adenine base and the steric effect of the thioxo substituent on the overall conformation of the molecule. It is also of interest to estimate the effects of the thioxo substituent on the base stacking and hydrogen bonding.

Experimental

The title compound was synthesized (Ikehara & Yamada, 1971), and crystallized from aqueous solution as greenish-yellow prisms. The crystals belong to the space group $P2_1$. The cell constants were determined from a least-squares refinement of the setting angles of 20 medium-angle reflections measured on a Rigaku–Denki automated diffractometer. The density was measured by flotation. Crystallographic data are given in Table 1. Intensity data were collected on the diffractometer with Ni-filtered Cu $K\alpha$ radiation, employing the $\omega-2\theta$ scan mode. There were 939 unique reflections up to $2\theta = 110°$, of which 931 were considered as observed. The intensities were corrected for Lorentz and polarization factors but not for absorption.

The structure was determined by the heavy-atom method and the parameters of the nonhydrogen atoms were refined by block-diagonal least squares with anisotropic temperature parameters. All H atoms were located on difference Fourier maps and refined with isotropic temperature parameters. The final R value was 0.048. Tables 2 and 3 list the final positional

Table 1. *Crystal data*

$C_{10}H_{13}N_5O_4S.H_2O$	$M_r = 317.33$
Monoclinic	Space group $P2_1$
$a = 8.758$ (1) Å	$Z = 2$
$b = 6.717$ (1)	$F(000) = 332$
$c = 11.462$ (2)	$V = 671.5$ (1) Å^3
$\beta = 95.22$ (1)°	$D_m = 1.566$ Mg m^{-3}
$\lambda(\text{Cu }K\alpha) = 1.5418$ Å	$D_x = 1.569$
$\mu = 2.40$ mm^{-1}	

Table 2. *Final positional parameters for the non-hydrogen atoms* ($\times 10^4$), *with e.s.d.'s in parentheses*

	x	y	z
S	12068 (1)	7 (3)	3764 (1)
O(1')	8079 (4)	1526 (5)	2191 (3)
O(2')	7926 (3)	−3831 (5)	2294 (3)
O(3')	8053 (4)	−1437 (6)	261 (3)
O(5')	5395 (4)	4108 (5)	1633 (3)
N(1)	6510 (4)	−56 (8)	6710 (3)
N(3)	6403 (4)	−130 (9)	4617 (3)
N(6)	8775 (4)	5 (9)	7920 (3)
N(7)	10348 (4)	−23 (8)	5596 (3)
N(9)	8947 (3)	−182 (7)	3899 (3)
C(2)	5800 (5)	−111 (11)	5635 (4)
C(4)	7942 (5)	−105 (9)	4777 (4)
C(5)	8786 (4)	−22 (9)	5827 (3)
C(6)	8058 (5)	−35 (9)	6848 (4)
C(8)	10442 (4)	−63 (9)	4415 (3)
C(1')	8580 (5)	−345 (8)	2658 (4)
C(2')	7317 (5)	−1811 (8)	2240 (4)
C(3')	6887 (5)	−1052 (8)	1024 (4)
C(4')	6874 (5)	1167 (8)	1241 (4)
C(5')	5350 (6)	1933 (8)	1583 (4)
O(W)	11423 (4)	−147 (8)	609 (3)

Table 3. *Final positional parameters for the hydrogen atoms* ($\times 10^3$), *with e.s.d.'s in parentheses*

Overall isotropic temperature factors are 3·14 Å².

	x	y	z
H(N61)	824 (6)	−15 (10)	868 (4)
H(N62)	988 (5)	−9 (11)	796 (4)
H(N7)	1108 (6)	−15 (11)	615 (4)
H(C2)	454 (6)	−31 (10)	564 (4)
H(C1')	967 (6)	−94 (10)	239 (5)
H(C2')	643 (6)	−162 (9)	276 (5)
H(C3')	580 (6)	−171 (10)	63 (4)
H(C4')	699 (6)	214 (10)	49 (4)
H(C5'1)	450 (6)	144 (11)	86 (5)
H(C5'2)	510 (6)	134 (11)	236 (4)
H(O2')	708 (6)	−465 (10)	205 (5)
H(O3')	814 (6)	−293 (11)	3 (5)
H(O5')	522 (6)	426 (9)	236 (5)
H(W1)	1029 (6)	−18 (12)	32 (4)
H(W2)	1172 (6)	−34 (9)	147 (4)

parameters.* All numerical calculations were carried out on an ACOS Series 77 NEAC ACOS 700 computer at the Crystallographic Research Center, Institute for Protein Research, Osaka University, with programs of *The Universal Crystallographic Computing System* (1973).

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* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35022 (6 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.
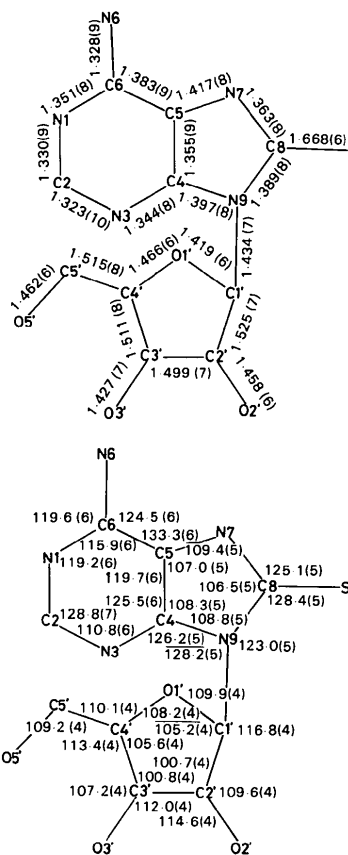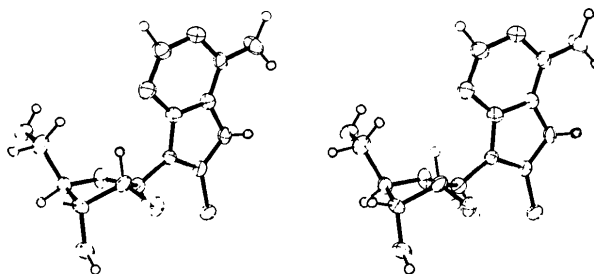

Fig. 1. Bond distances (Å) and angles (°). Standard deviations are given in parentheses.

Fig. 2. A stereoscopic view of the molecule.

Results and discussion

Geometry of the adenine base

The bond distances and angles are shown in Fig. 1, while a stereoscopic view of the molecule showing each atom as an ellipsoid (Johnson, 1965) is presented in Fig. 2.

Table 4. *Deviations (Å) of the atoms from the least-squares planes through several parts of the molecule*

E.s.d.'s in the atom deviations are ca 0·005 Å.

(a) Base

Plane (I) $0.019X - 0.999Y + 0.036Z = 0.399$
Plane (II) $0.018X - 1.000Y + 0.022Z = 0.299$
Plane (III) $0.021X - 1.000Y + 0.047Z = 0.475$

	Plane (I)	Plane (II)	Plane (III)
N(1)	−0·006*	0·003*	−0·027
C(2)	0·010*	0·002*	0·005
N(3)	0·027*	0·004*	0·035
C(4)	0·012*	−0·007*	0·015*
C(5)	0·014*	0·011*	0·002*
C(6)	−0·023*	−0·011*	−0·047
N(7)	−0·004*	−0·009	−0·015*
C(8)	0·014*	−0·010	0·017*
N(9)	−0·022*	−0·054	−0·009*
N(6)	−0·049	−0·020	−0·089
S	0·059	0·027	0·069
C(1′)	−0·077	−0·129	−0·047

(b) Sugar

Plane (IV) $0.754X - 0.044Y - 0.655Z = 3.480$

	Plane (IV)		Plane (IV)
O(1′)	0·000*	C(4′)	0·000*
C(1′)	0·000*	C(5′)	1·312
C(2′)	0·445	N(9)	0·788
C(3′)	−0·253		

* Atoms included in the calculations of the planes.

Table 5. *Torsion angles (°)*

Glycosyl angle	χ	257·5 (6)
Sugar ring torsion angles	τ_0	−17·6 (5)
	τ_1	38·4 (5)
	τ_2	−42·9 (5)
	τ_3	33·6 (5)
	τ_4	−10·0 (5)
Backbone torsion angles	ψ'	155·7 (4)
	ψ_{OC}	186·8 (4)
	ψ_{OO}	68·8 (5)
Sugar puckering	C(2′)-endo–C(3′)-exo ($^2T_3$)	
Conformation about C(4′)–C(5′)	gauche–trans	

The base was found to exist in the thioxo form (C=S) with N(7) protonated, rather than the alternative tautomeric form (C—SH). A similar thioxo form was observed in 2-thioxo-1-(β-D-ribofuranosyl)-3H-benz-imidazole (TRB) (Prusiner & Sundaralingam, 1973). Compared to TRB, the C(8)=S bond distance is shorter by 0·025 Å while the N(7)—C(8) bond distance is longer by 0·019 Å, indicating more thioketo character in the present structure. The observation of an unexpectedly short C(4)—C(5) distance indicates considerable double-bond character, which may origi-nate from the smaller degree of conjugation in the imidazole ring system compared to that in natural purine nucleosides. On the other hand, the bond

distances and angles in the pyrimidine moiety are generally in good agreement with those in adenosine (Lai & Marsh, 1972) except for the C(4)—C(5) distance referred to above.

Deviations of the atoms from the least-squares planes through several parts of the molecule are given in Table 4. The pyrimidine ring is essentially planar. The atoms of the imidazole ring, however, show somewhat larger deviations from planarity, especially C(8) bonded to the S atom. The nine atoms of the purine ring are therefore not planar.

Sugar conformation

Deviations of the out-of-plane atoms of the ribose ring (Table 4) show C(2′)-*endo*—C(3′)-*exo* ($^2T_3$) puck-ering. The torsion angles are shown in Table 5. The *syn* conformation is unavoidable even in the case of the thioxo substituent, where the van der Waals radius of S is the smallest (1·75–1·85 Å) of the many substituents at the 8 position of purine nucleosides so far examined by X-ray crystallography.

The conformation about the exocyclic C(4′)—C(5′) bond is *gauche–trans*. The O(5′)H atom is not involved in an intramolecular hydrogen bond with N(3), which is commonly found in purine nucleosides having C(2′)-*endo* pucker, *gauche–gauche* and *syn* conformations. It is of interest to note that such an intramolecular hydrogen bond was observed in formycin hydro-bromide (Koyama, Umezawa & Iitaka, 1974), whose conformational parameters, *viz syn* ($\chi = 210.7°$), C(2′)-*endo*—C(3′)-*exo* and *gauche–trans* ($\psi_{OO} = 46.6°$ and $\psi_{OC} = 162.4°$), are similar to the corresponding values in the present structure; $\Delta\chi$ (46·8°) shows the largest difference between the corresponding torsion angles of the two structures. This indicates that a substantial degree of rotation, mainly about the glycosyl bond, could lead to the formation of an intramolecular hydrogen bond even in the *gauche–trans* exocyclic conformation.

Hydrogen bonding and molecular packing

All protons attached to O and N atoms are involved in hydrogen bonds (Table 6), forming an extensive intermolecular network (Fig. 3). S atoms in thioxo-purines or thioxopyrimidines act as potential hydrogen-bond acceptors in the crystals (Thewalt & Bugg, 1972; Lin, Sundaralingam & Arora, 1971). In fact, the S atom in the present structure accepts a proton from the water molecule. Although the S···H distance of 2·62 Å indicates a weak hydrogen bond, the S···H—O(W) angle of 169·4° is geometrically preferable.

The 8-thioxoadenosine moieties lie nearly parallel to the *ac* plane, as shown in Fig. 3, forming a stacked column around the screw axis passing through (0,0,$\frac{1}{2}$); the base moieties are overlapped mainly at the S sub-

Table 6. *Hydrogen-bond distances*

Estimated standard deviations are given in parentheses.

Donor (D)	Acceptor (A)	Distance (Å) D—A	H—A	Symmetry operation on A
N(6)	O(3')	2·974 (7)	2·03 (7)	$(x, y, 1 + z)$
N(6)	O(2')	3·024 (7)	2·15 (8)	$(2 - x, 0·5 + y, 1 - z)$
N(7)	O(2')	2·848 (6)	2·10 (7)	$(2 - x, 0·5 + y, 1 - z)$
O(2')	O(5')	2·664 (5)	1·72 (7)	$(x, -1 + y, z)$
O(3')	O(W)	2·738 (7)	1·72 (7)	$(2 - x, -0·5 + y, -z)$
O(5')	N(1)	2·697 (6)	1·99 (6)	$(1 - x, 0·5 + y, 1 - z)$
O(W)	O(3')	3·068 (6)	2·13 (8)	(x, y, z)
O(W)	S	3·610 (5)	2·62 (6)	(x, y, z)
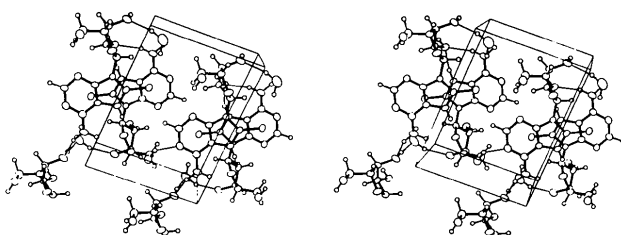
Fig. 3. A stereoscopic view of the crystal packing. Thin lines represent hydrogen bonds.

Fig. 4. Base-stacking patterns in crystals of (a) 8-thioxoadenosine and (b) 2-thioxo-1-(β-D-ribofuranosyl)-3H-benzimidazole (TRB), as viewed normal to the upper base (darker lines).

stituents of adjacent bases with an interplanar base separation of 3·34 Å and a dihedral angle of 1·4 (2)°. This stacking pattern is apparently a general feature found in the crystal structures of thioxonucleosides (Thewalt & Bugg, 1972). However, in the crystal structure of TRB (Prusiner & Sundaralingam, 1973), an analog of 8-thioxoadenosine, the S atoms are precluded from overlapping with adjacent bases. Fig. 4 shows an interesting contrast between the two crystals.

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