Acta Cryst. (1982). B**38**, 1937–1942

Structural Studies of *S*-Cycloadenosine Derivatives. III. The Structure of 8,2′-Anhydro-8-mercapto-9-β-D-arabinofuranosyladenine 3′-Monophosphate (A^sp)*

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(*Received* 3 *September* 1981; *accepted* 24 *December* 1981)

Abstract

The crystal and molecular structure of 8,2′-anhydro-8-mercapto-9-β-D-arabinofuranosyladenine 3′-monophosphate (A^sp), $C_{10}H_{12}N_5O_6PS.2H_2O$, has been determined by X-ray methods and refined to an R value of 0·059 for 2779 non-zero reflections. A^sp crystallizes in space group $P2_1$ with four molecules per monoclinic unit cell of dimensions: $a = 11{\cdot}239$ (1), $b = 11{\cdot}564$ (1), $c = 13{\cdot}058$ (2) Å, and $\beta = 110{\cdot}25$ (1)°; $d_x = 1{\cdot}585$, $d_o = 1{\cdot}581$ (3) Mg m^{-3}. The conformations of the two independent A^sp molecules (*A* and *B*) in the asymmetric unit are similar except for the orientation of the phosphate group, which agrees well with the conformations observed in solution by NMR studies (T. Miyazawa, personal communication). The conformations of both A^sp molecules are as follows: χ_{CN} = 110·9 (8) (*A*) and 109·7 (8)° (*B*), both sugar puckerings are C(4′)-*endo*, the orientations of C(5′)–O(5′) are *gauche–trans* and the torsion angles φ' are 191·9 (6) (*A*) and 255·4 (7)° (*B*).

Introduction

The rigid cyclo-nucleosides or nucleotides in which the base–sugar orientation is fixed at a given region provide a good model for physicochemical solution studies such as NMR and CD (Ikehara, Kaneko, Muneyama & Tanaka, 1967) since the conformation in the solid state is maintained in solution. It was suggested that the cyclo-nucleoside and nucleotide in which the 8-position of the purine moiety and 2′-position of the sugar are connected by a covalent bond through the S atom, such as 8,2′-anhydro-8-mercapto-9-β-D-arabinofuranosyladenine (A^s), should have the high-*anti* conformation rather than the usual *anti* conformation. As a part of the study on the conformations of these compounds, we have already reported the crystal structure of 8,2′-anhydro-8-mercapto-9-β-D-arabinofuranosyladenine 5′-monophosphate (pA^s) (Tanaka, Fujii, Fujiwara & Tomita, 1979). The present paper describes the crystal and molecular structure of the 3′-monophosphate of A^s (A^sp). The chemical structure and the numbering of the A^sp molecule are shown in Fig. 1.

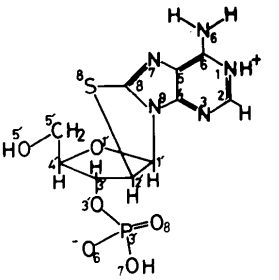

Fig. 1. Chemical structure and numbering of the A^sp molecule.

Experimental

The sample was kindly supplied by Professor M. Ikehara, Osaka University. The transparent thin crystals were obtained by slow evaporation of an aqueous solution of A^sp. The crystal system and space group were determined by Weissenberg photographs and then the cell dimensions were determined by least-squares refinement using the setting angles of 25 reflections measured by diffractometer ($\lambda_{CuK\alpha}$ = 1·5418 Å).

The intensities of 2859 independent reflections up to $2\theta = 135°$ were collected on a Rigaki Denki automatic four-circle diffractometer with Cu $K\alpha$ radiation. The ω–2θ scanning technique was employed at a rate of 1° min^{-1} in ω. The crystal size was 0·33 × 0·28 × 0·07 mm. The intensities of the three standard reflections were measured every 50 reflections of the data set and indicated no deterioration during the run. Lorentz–polarization corrections were applied to the intensities but no correction was made for absorption.

* (6a*S*,7*R*,8*R*,9a*R*)-4-Amino-6a,7,8,9a-tetrahydro-8-hydroxymethylfuro[2′,3′:4,5]thiazolo[3,2-*e*]purin-3-ium-7-yl phosphate.

0567-7408/82/071937-06$01.00

Structure determination and refinement

From the density measurement and the dimensions of the unit cell, it was found that two independent A^{s}p and a few solvent molecules should be contained in the asymmetric unit. The structure was solved by a combination of the direct method (*MULTAN* 78; Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978) and the Fourier technique. *MULTAN* showed one set of phases with a high value of the figure of merit to be correct. From an *E* map using these phases, we could assign the positions for almost all the atoms of the two A^{s}p molecules. Successive Fourier syntheses revealed the remaining non-H atoms including four water molecules of crystallization.

The refinement of positional and isotropic temperature parameters was carried out by the full-matrix least-squares method and further refinements with anisotropic parameters were by the block-diagonal least-squares method. All the H atoms appeared in a difference Fourier synthesis and their positional parameters were refined together with the anisotropic parameters of the non-H atoms. The final *R* value was 0·059 for 2779 non-zero reflections. Throughout the refinement, the intensity of each reflection was given a unit weight. The atomic scattering factors cited in *International Tables for X-ray Crystallography* (1974) were used. All computations with the *UNICS* (1973) program system were performed on an ACOS-700 computer at the Crystallographic Research Center, Institute for Protein Research, Osaka University.

Results and discussion

There are two independent A^{s}p molecules in the asymmetric unit, designated (*A*) and (*B*). They are both zwitterionic forms, in which N(1) is protonated by a proton released from the phosphate group. The final positional parameters for non-H atoms are listed in Table 1.* The bond lengths, angles and selected torsion angles are listed in Tables 2, 3 and 4, respectively.

(*a*) *Bond lengths and angles*

Some of the bond lengths and angles deviate somewhat from the standard values. This is due to the strain induced by the cyclization between the base and the C(2′)-position of the sugar such as is found in pA^s (Tanaka *et al.*, 1979). The length of C(8)–N(9) is normal in both the A^{s}p molecules, while in pA^s this length is unusually short (1·349 Å).

* Lists of structure factors, anisotropic thermal parameters for non-H atoms and positional and thermal parameters for H atoms have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36701 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Final atomic coordinates and isotropic parameters for non-*H *atoms* ($\times 10^4$) *with e.s.d.'s in parentheses*

	x	*y*	*z*	*B* (Å^2)
Molecule *A*				
N(1)	5664 (6)	8492 (6)	7539 (5)	2·2 (2)
C(2)	6503 (7)	8999 (7)	7129 (6)	2·6 (2)
N(3)	6435 (6)	8940 (6)	6114 (5)	2·4 (2)
C(4)	5427 (6)	8312 (7)	5490 (5)	2·0 (2)
C(5)	4523 (7)	7770 (7)	5822 (5)	1·9 (2)
C(6)	4653 (7)	7858 (6)	6909 (6)	2·0 (2)
N(6)	3898 (6)	7347 (6)	7373 (5)	2·3 (2)
N(7)	3642 (6)	7200 (6)	4952 (5)	2·0 (2)
C(8)	4025 (7)	7400 (7)	4119 (6)	2·0 (2)
N(9)	5101 (5)	8088 (6)	4409 (4)	2·1 (2)
C(1′)	5547 (7)	8443 (7)	3528 (6)	2·2 (2)
C(2′)	4726 (7)	7791 (7)	2488 (6)	2·1 (2)
C(3′)	4224 (7)	8748 (8)	1653 (6)	2·3 (2)
C(4′)	4294 (7)	9825 (7)	2329 (7)	2·1 (2)
C(5′)	3072 (7)	10061 (8)	2577 (7)	2·7 (2)
O(1′)	5366 (5)	9638 (5)	3333 (4)	2·3 (2)
S(8)	3434 (2)	6992 (2)	2766 (1)	2·5 (1)
O(3′)	5138 (5)	8940 (6)	1114 (4)	2·6 (2)
O(5′)	3233 (6)	11034 (5)	3284 (5)	2·8 (2)
P(3′)	5194 (2)	8125 (2)	137 (2)	2·6 (1)
O(6)	5942 (6)	8829 (6)	−414 (5)	3·4 (2)
O(7)	5953 (6)	7039 (7)	731 (6)	4·4 (2)
O(8)	3885 (5)	7779 (6)	−559 (4)	3·5 (2)
Molecule *B*				
N(1)	10776 (6)	8599 (6)	7707 (5)	2·3 (2)
C(2)	11605 (7)	9115 (7)	7281 (6)	2·5 (2)
N(3)	11547 (6)	9046 (6)	6279 (5)	2·3 (2)
C(4)	10559 (7)	8403 (7)	5650 (6)	1·9 (2)
C(5)	9661 (7)	7850 (7)	5990 (6)	2·0 (2)
C(6)	9771 (7)	7948 (7)	7077 (6)	2·1 (2)
N(6)	9021 (6)	7457 (6)	7542 (5)	2·4 (2)
N(7)	8790 (6)	7258 (6)	5130 (5)	2·2 (2)
C(8)	9178 (7)	7447 (7)	4298 (6)	2·3 (2)
N(9)	10243 (5)	8147 (6)	4577 (4)	2·0 (2)
C(1′)	10678 (7)	8515 (7)	3691 (6)	2·2 (2)
C(2′)	9860 (7)	7844 (7)	2652 (6)	2·2 (2)
C(3′)	9334 (7)	8791 (7)	1799 (6)	2·1 (2)
C(4′)	9382 (7)	9855 (7)	2477 (6)	2·0 (2)
C(5′)	8145 (8)	10060 (8)	2713 (7)	2·8 (2)
O(1′)	10453 (5)	9704 (5)	3487 (4)	2·4 (1)
S(8)	8597 (2)	7035 (2)	2947 (1)	2·6 (1)
O(3′)	10266 (5)	8928 (6)	1256 (4)	3·0 (2)
O(5′)	8299 (6)	10983 (5)	3471 (5)	2·8 (2)
P(3′)	9833 (2)	9228 (2)	10 (2)	2·3 (1)
O(6)	11032 (5)	9247 (6)	−269 (4)	3·0 (2)
O(7)	9366 (6)	10518 (7)	−51 (7)	4·5 (2)
O(8)	8802 (5)	8432 (6)	−617 (4)	3·2 (2)
Water				
O(*W*1)	7940 (8)	6507 (7)	255 (9)	5·1 (3)
O(*W*2)	2963 (7)	5953 (7)	303 (8)	4·7 (3)
O(*W*3)	6732 (6)	5589 (7)	4566 (6)	4·1 (2)
O(*W*4)	1706 (6)	5465 (7)	4464 (6)	3·8 (2)

(*b*) *Molecular conformation*

The molecular conformations of A^{s}p(*A*) and A^{s}p(*B*) are shown in Fig. 2. The nucleoside portions (A^s) of both A^{s}p molecules as well as pA^s have a similar conformation. The torsion angles, χ_{CN}, defining the

Table 2. *Bond lengths* (Å) *with their e.s.d.'s in parentheses*

	Molecule *A*	Molecule *B*		Molecule *A*	Molecule *B*
N(1)–C(2)	1·367 (11)	1·375 (11)	N(1)–C(6)	1·363 (11)	1·369 (10)
C(2)–N(3)	1·303 (11)	1·291 (11)	N(3)–C(4)	1·355 (11)	1·353 (10)
C(4)–C(5)	1·385 (11)	1·390 (11)	C(4)–N(9)	1·355 (11)	1·353 (10)
C(5)–C(6)	1·379 (11)	1·387 (11)	C(5)–N(7)	1·389 (10)	1·388 (10)
C(6)–N(6)	1·340 (10)	1·325 (11)	N(7)–C(8)	1·321 (10)	1·321 (11)
C(8)–N(9)	1·386 (11)	1·386 (11)	C(8)–S(8)	1·724 (8)	1·723 (9)
N(9)–C(1′)	1·464 (11)	1·467 (11)	C(1′)–C(2′)	1·548 (12)	1·557 (12)
C(1′)–O(1′)	1·406 (10)	1·407 (10)	C(2′)–C(3′)	1·520 (12)	1·527 (12)
C(2′)–S(8)	1·859 (9)	1·849 (9)	C(3′)–C(4′)	1·512 (12)	1·505 (12)
C(3′)–O(3′)	1·448 (11)	1·462 (11)	C(4′)–C(5′)	1·541 (13)	1·542 (13)
C(4′)–O(1′)	1·457 (10)	1·456 (10)	C(5′)–O(5′)	1·427 (12)	1·425 (11)
O(3′)–P(3′)	1·606 (7)	1·568 (8)	P(3′)–O(6)	1·519 (8)	1·512 (8)
P(3′)–O(7)	1·565 (9)	1·575 (9)	P(3′)–O(8)	1·491 (8)	1·485 (8)

Table 3. *Bond angles* (°) *with their e.s.d.'s in parentheses*

	Molecule *A*	Molecule *B*		Molecule *A*	Molecule *B*
C(2)–N(1)–C(6)	122·5 (7)	122·0 (7)	N(1)–C(2)–N(3)	124·8 (8)	125·4 (8)
C(2)–N(3)–C(4)	112·4 (7)	113·1 (7)	N(3)–C(4)–C(5)	127·3 (7)	126·4 (7)
N(3)–C(4)–N(9)	126·7 (7)	127·9 (7)	C(5)–C(4)–N(9)	106·1 (7)	105·7 (7)
C(4)–C(5)–C(6)	117·5 (7)	118·2 (7)	C(4)–C(5)–N(7)	110·5 (7)	110·8 (7)
C(6)–C(5)–N(7)	132·0 (7)	131·0 (7)	N(1)–C(6)–C(5)	115·5 (7)	115·0 (7)
N(1)–C(6)–N(6)	119·4 (7)	118·9 (7)	C(5)–C(6)–N(6)	125·1 (7)	126·1 (7)
C(5)–N(7)–C(8)	104·3 (6)	104·1 (7)	N(7)–C(8)–N(9)	112·2 (7)	112·4 (7)
N(7)–C(8)–S(8)	132·5 (6)	132·9 (7)	N(9)–C(8)–S(8)	115·3 (6)	114·7 (6)
C(4)–N(9)–C(8)	106·9 (7)	107·1 (7)	C(4)–N(9)–C(1′)	136·2 (7)	135·5 (7)
C(8)–N(9)–C(1′)	116·8 (7)	117·1 (7)	N(9)–C(1′)–C(2′)	106·8 (7)	106·6 (7)
N(9)–C(1′)–O(1′)	110·5 (7)	110·2 (7)	C(2′)–C(1′)–O(1′)	108·3 (7)	107·9 (7)
C(1′)–C(2′)–C(3′)	103·6 (7)	104·0 (7)	C(1′)–C(2′)–S(8)	109·9 (6)	109·6 (6)
C(3′)–C(2′)–S(8)	112·4 (6)	112·5 (6)	C(2′)–C(3′)–C(4′)	104·4 (7)	103·4 (7)
C(2′)–C(3′)–O(3′)	108·1 (7)	105·6 (7)	C(4′)–C(3′)–O(3′)	104·8 (7)	108·1 (7)
C(3′)–C(4′)–C(5′)	113·5 (7)	113·1 (7)	C(3′)–C(4′)–O(1′)	105·2 (7)	106·5 (7)
C(5′)–C(4′)–O(1′)	110·9 (7)	110·9 (7)	C(4′)–C(5′)–O(5′)	110·7 (7)	110·7 (7)
C(1′)–O(1′)–C(4′)	109·4 (6)	109·1 (6)	C(8′)–S(8′)–C(2′)	90·8 (4)	91·6 (4)
C(3′)–O(3′)–P(3′)	121·7 (6)	120·7 (4)	C(3′)–P(3′)–O(6)	104·0 (4)	105·7 (4)
O(3′)–P(3′)–O(7)	104·0 (4)	103·9 (4)	O(3′)–P(3′)–O(8)	109·9 (4)	109·7 (4)
O(6)–P(3′)–O(7)	111·7 (4)	106·5 (5)	O(6)–P(3′)–O(8)	116·5 (4)	117·8 (4)
O(7)–P(3′)–O(8)	109·9 (5)	112·1 (5)			

Table 4. *Torsion angles* (°) *of* A^sp *and* pA^s *molecules with their e.s.d.'s in parentheses*

Notation	Designation	A^sp Molecule *A*	A^sp Molecule *B*	pA^{s*}
χ_{CN}	C(8)–N(9)–C(1′)–O(1′)	110·9 (8)	109·7 (8)	118·6 (6)
ψ'	O(3′)–C(3′)–C(4′)–C(5′)	155·5 (7)	156·9 (7)	
τ_0	C(4′)–O(1′)–C(1′)–C(2′)	11·6 (8)	10·4 (8)	19·4 (6)
τ_1	O(1′)–C(1′)–C(2′)–C(3′)	7·8 (9)	8·9 (8)	2·0 (6)
τ_2	C(1′)–C(2′)–C(3′)–C(4′)	−23·0 (8)	−23·6 (8)	−20·5 (6)
τ_3	C(2′)–C(3′)–C(4′)–O(1′)	30·4 (8)	30·7 (8)	32·2 (6)
τ_4	C(3′)–C(4′)–O(1′)–C(1′)	−26·5 (8)	−26·2 (8)	−33·1 (6)
ψ_{CO}	C(3′)–C(4′)–C(5′)–O(5′)	175·6 (7)	172·3 (7)	163·2 (5)
ψ_{OO}	O(1′)–C(4′)–C(5′)–O(5′)	57·4 (9)	52·7 (9)	45·4 (7)
φ'	C(4′)–C(3′)–O(3′)–P(3′)	191·9 (6)	255·4 (7)	
ω'_1	C(3′)–O(3′)–P(3′)–O(6)	162·3 (6)	182·5 (6)	
ω'_2	C(3′)–O(3′)–P(3′)–O(7)	279·4 (7)	70·5 (7)	
ω'_3	C(3′)–O(3′)–P(3′)–O(8)	36·9 (8)	310·5 (8)	

* Tanaka *et al.* (1979).

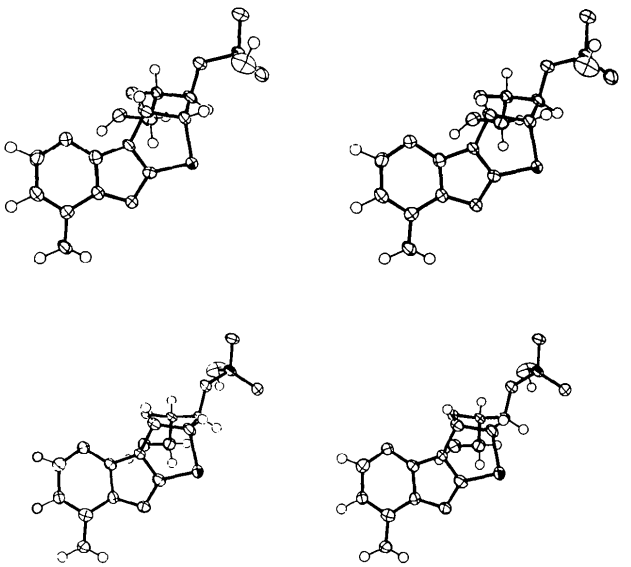

Fig. 2. Stereographic representation of the molecular conformation of A^{s}p(*A*) (upper) and A^{s}p(*B*).

base–sugar orientation, are 110·9 (8) for (*A*), 109·7 (8) for (*B*) and 118·8 (6)° for pA^s, which are all in the high-*anti* region. The sugar rings have a C(4′)-*endo* conformation in which atom C(4′) is displaced by 0·42 (1) for (*A*), by 0·41 (2) for (*B*) and by 0·48 (1) Å for pA^s from the best plane including C(3′)–C(2′)–C(1′)–O(1′) as listed in Table 5. As shown in Table 4, the pA^s molecule has a smaller τ_1 value (2·0°) compared with the A^{s}p molecules, indicating that the sugar puckering in the pA^s molecule is a more ideal envelope form. On the other hand, the τ_1 values in the A^{s}p molecules are slightly larger (7·8 and 8·9°) because the envelope forms are probably distorted by strong hydrogen bonds, as described later. This distortion could also explain the displacement of atom C(1′) from the base plane: 0·10 (1) for (*A*) and 0·12 (1) Å for (*B*) which are somewhat larger than 0·01 (1) Å in the case of pA^s. The orientation of the C(5′)–O(5′) bond is *gauche–trans* in both molecules.

(*c*) *Phosphate group*

A significant difference between the two independent A^{s}p molecules is found in the orientation of the phosphate group. The torsion angle, φ', is 191·9 (6) for (*A*) and 255·4 (7)° for (*B*). Pattabiraman, Rao & Sasisekharan (1980) had reported that the flexibility of the phosphate group in the 3′-nucleotides is related to the sugar puckering. In the case of ribose, they found an energy minimum at $\varphi' \simeq 280°$ for the C(2′)-*endo* form, while in the case of deoxyribose, unlike ribose, there are local minima at $\varphi' \simeq 190°$ and $\varphi' \simeq 280°$ for the C(2′)-*endo* form. This additional conformation is prohibited for ribose because of short contacts between the OH group at C(2′) of the sugar and the atoms in the phosphate group, these contacts being relieved to some extent in deoxyribose, in which only an H atom is attached at C(2′). The A^{s}p molecule has an S atom attached at the C(2′)-position in the reverse direction to the phosphate group, and therefore the molecule has the deoxyribose-type sugar ring with the C(4′)-*endo* conformation which is similar to C(2′)-*endo*. The two different orientations of the phosphate group found in this crystal are quite reasonable. In fact, the distance between H(2′) and O(7) of the phosphate group is 2·31 Å for the A^{s}p(*A*) molecule having $\varphi' = 191·9°$ and this value is just the sum of the van der Waals contacts.

Table 5. *Deviations* (Å) *of atoms from best planes through several parts of the molecules*

x, *y* and *z* refer to the orthogonal coordinate system (Å) with *x* along **a**, *y* along **b** and *z* along **c***. An asterisk indicates an atom included in the calculation of the best plane.

(*a*) Purine moiety

	A^{s}p		pA^s†
	Molecule *A* Plane (I)	Molecule *B* Plane (II)	
N(1)*	−0·00 (1)	−0·01 (1)	−0·03 (1)
C(2)*	−0·00 (1)	−0·00 (1)	−0·00 (1)
N(3)*	0·00 (1)	0·00 (1)	0·02 (1)
C(4)*	0·00 (1)	0·01 (1)	0·00 (1)
C(5)*	0·01 (1)	0·01 (1)	0·00 (1)
C(6)*	−0·00 (1)	−0·00 (1)	0·02 (1)
N(7)*	0·00 (1)	0·01 (1)	0·01 (1)
C(8)*	−0·02 (1)	−0·02 (1)	−0·01 (1)
N(9)*	0·00 (1)	−0·00 (1)	−0·01 (1)
N(6)	−0·06 (1)	−0·03 (1)	0·07 (1)
C(1′)	0·10 (1)	−0·12 (1)	0·01 (1)
C(2′)	−0·02 (1)	0·01 (1)	−0·04 (1)
S(8)	−0·03 (1)	−0·01 (1)	−0·04 (1)

Equations of the planes

(I) $-0·5230X + 0·8262Y - 0·2094Z - 4·6361 = 0·0$
(II) $-0·5315X + 0·8163Y - 0·2260Z - 1·4074 = 0·0$

(*b*) Sugar moiety

	A^{s}p		pA^s†
	Molecule *A* Plane (III)	Molecule *B* Plane (IV)	
C(1′)*	−0·05 (1)	−0·05 (1)	−0·01 (1)
C(2′)*	0·04 (1)	0·05 (1)	0·01 (1)
C(3′)*	−0·03 (1)	−0·03 (1)	−0·01 (1)
C(4′)	0·42 (1)	0·41 (2)	0·48 (1)
C(5′)	1·93 (1)	1·93 (1)	1·99 (1)
O(1′)*	0·01 (1)	0·02 (1)	0·01 (1)

Equations of the planes

(III) $0·9647X - 0·0115Y - 0·2631Z - 3·1766 = 0·0$
(IV) $0·9648X + 0·0123Y - 0·2627Z - 8·8480 = 0·0$

† Tanaka *et al.* (1979).

It is interesting to note that the two orientations around the C(3′)—O(3′) bond actually coexist in the crystalline state and the conformational energy levels of two such conformers should be almost the same. The cyclo-dinucleoside monophosphates, 8,2′-*S*-cyclo-2′-thioadenylyl(3′-5′)-8,2′-*S*-cyclo-2′-thioadenosine (A^spA^s) (Fujii, Hamada, Miura, Uesugi, Ikehara & Tomita, 1982) and 8,2′-anhydro-8-mercapto-9-β-D-arabinofuranosylhypoxanthylyl(3′-5′)-8,2′-anhydro-8-mercapto-9-β-D-arabinofuranosyladenine (I^spA^s) (Hamada, Matsuo, Miyamae, Fujii & Tomita, 1982), also have the C(2′)-*endo*-like conformation with $\varphi' = 209{\cdot}0$ and 209·8° for the two independent A^spA^s molecules and $\varphi' = 211{\cdot}9°$ for I^spA^s. It is important that the conformer with $\varphi' \simeq 200$ and C(4′)-*endo* is certainly stable and the φ' value is restricted to the narrow region around 200°.

(*d*) *Packing and hydrogen bonds*

Figs. 3 and 4 show the molecular packing viewed along the *b* and *c* axes, respectively. The *A* molecules lie along $a = \frac{1}{2}$ and the *B* molecules along $a = 0$, and their packings are very similar to each other; therefore they could be fitted to another with a half-cell translation in the *a*-axis direction as shown in Fig. 4.

The hydrogen-bond distances are listed in Table 6. All the H atoms having the ability to establish hydrogen bonds participate in hydrogen-bond formation. A hydrogen bond between N(1) and O(6) of the adjacent molecule, N(1)(*A*)—H···O(6)(*A*) or N(1)(*B*)—H···O(6)(*B*), with a distance of 2·610 (10) or 2·666 (10) Å, is strong, because the N(1) atom has a positive charge and the O(6) atom has a negative charge, the extra Coulomb interaction strengthening the hydrogen bond. It is worth noting that the amino N(6) of each independent molecule participates in a hydrogen bond with the phosphate O(8) of the equivalent molecule and the cyclic hydrogen-bonding pair is formed together with the N(1)—H···O(6) hydrogen bond between the base and the adjacent phosphate group.

Another strong hydrogen bond is formed between O(7) and the two water molecules which have similar environments, *i.e.* O(7)(*A*)—H···O(*W*1) [2·591 (14)] and O(7)(*B*)—H···O(*W*2) [2·572 (13) Å]. These two water molecules, *W*(1) and *W*(2), also contribute to form hydrogen bonds with other O atoms [O(6) and O(8)] of the phosphate group and play important roles in the hydrogen-bond network with the other water molecules, *W*(3) and *W*(4), as shown in Table 6.

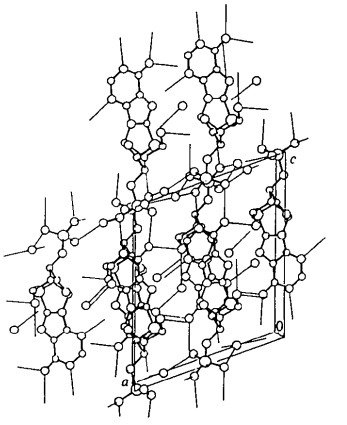

Fig. 3. Molecular packing along the *b* axis. The thin lines indicate the hydrogen bonds.

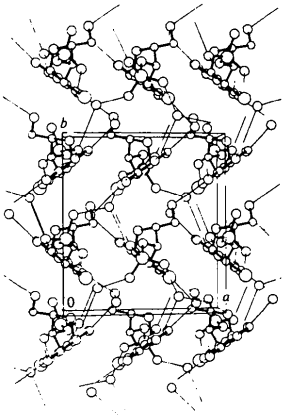

Fig. 4. Molecular packing along the *c* axis. The thin lines indicate the hydrogen bonds.

Table 6. *Hydrogen-bond distances* (Å) *with their e.s.d.'s in parentheses*

Donor	Acceptor		Donor	Acceptor		Donor	Acceptor	
N(1)(*A*)	O(6)(A^{ii})	2·610 (10)	O(5′)(*A*)	O($W3^{iv}$)	2·841 (10)	O(*W*2)	O(6)(A^{vii})	2·729 (12)
N(1)(*B*)	O(6)(B^{ii})	2·666 (10)	O(5′)(*B*)	O($W4^{iv}$)	2·764 (10)	O(*W*2)	O(8)(A^{i})	2·757 (12)
N(6)(*A*)	O(8)(A^{ii})	2·751 (10)	O(7)(*A*)	O($W1^{i}$)	2·591 (14)	O(*W*3)	N(3)(B^{viii})	3·102 (11)
N(6)(*A*)	O(5′)(B^{iii})	2·813 (10)	O(7)(*B*)	O($W2^{v}$)	2·572 (13)	O(*W*3)	N(7)(B^{i})	2·905 (11)
N(6)(*B*)	O(8)(B^{ii})	2·744 (10)	O(*W*1)	O(6)(B^{vi})	2·855 (13)	O(*W*4)	N(3)(A^{iii})	3·022 (11)
N(6)(*B*)	O(5′)(A^{iii})	2·898 (10)	O(*W*1)	O(8)(B^{i})	2·820 (13)	O(*W*4)	N(7)(A^{i})	2·864 (10)

Symmetry code: (i) x,y,z; (ii) $x, y, 1+z$; (iii) $1-x, -0{\cdot}5+y, 1-z$; (iv) $1-x, 0{\cdot}5+y, 1-z$; (v) $1-x, 0{\cdot}5+y, -z$; (vi) $2-x, -0{\cdot}5+y, -z$; (vii) $1-x, -0{\cdot}5+y, -z$; (viii) $2-x, -0{\cdot}5+y, 1-z$.

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The Charge Density in Polymorph II of 5,5-Diethylbarbituric Acid (Barbital) at 198 K

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(*Received* 6 *July* 1981; *accepted* 6 *January* 1982)

Abstract

The charge density in barbital II ($C_8H_{12}N_2O_3$) at 198 K has been determined from 3220 X-ray reflections (Mo $K\alpha$ radiation) having $\sin\theta/\lambda < 1{\cdot}08$ Å^{-1} and $|F_{obs}| > 3\sigma$. Atomic positional parameters and H-atom thermal parameters were given fixed values determined in a previous neutron structure determination. Other parameters, including electron population parameters, and third-order temperature factors, were obtained by least-squares refinement, assuming Stewart's rigid pseudoatom formalism. Results show that in chains of four C atoms there appears to be an alternation of atomic charges which may represent an inductive effect. The H atom which is H-bonded is significantly depleted of electronic charge (~0·2 e) compared with methyl or methylene H atoms. There is a polarization of charge density in C—N and C—O bonds. Carbonyl O atoms have paired lobes of excess electron density (~1·2 e Å^{-3}) above and below the amide plane. It has not been explained why these lobes are found in various orientations in amide crystal structures. The calculated molecular dipole moment is 0·7 (1·2) debye (1 debye = 3·336 × 10^{-30} C m) with negative charge displacement towards atom C(5) and positive towards O(2).

Introduction

The barbiturate drugs act primarily on the central nervous system, producing sleep, hypnosis, anesthesia or death. They have both pre- and postsynaptic effects (Nicoll, 1978). The principal postsynaptic effect of barbiturates is to antagonize the excitatory action of neurotransmitters such as acetylcholine and amino acids. Presynaptic effects are poorly understood, but these may include modification of the rate of transmitter release. Barbiturate receptor sites have not yet been identified at the molecular level. Postsynaptic activity seems to be insensitive to the molecular structure of the barbiturate and may occur through nonspecific membrane interactions. Other interactions must involve considerable stereoselectivity, since there are significant differences in the duration of sleep induced by *R*(+)- and *S*(−)-pentobarbital, or secobarbital (Freudenthal & Martin, 1975).

In order for barbiturates to have potent hypnotic activity, they must have amphiphilic properties which are derived from a polar ring system (typically a trioxopyrimidine moiety) and two non-polar C(5) substituents (typically containing a total of from four to eight C atoms). They are weak acids ($pK_a \sim 7{\cdot}5$) which are partially dissociated at pH values corresponding to those of most body fluids.

There have been extensive crystal structure determinations of the barbiturate drugs, which have given a better understanding of their tautomeric form and conformation (Craven, Vizzini & Rodrigues, 1969; Bideau, Leroy & Housty, 1969; Williams, 1974; Voet, 1972), their metal binding (Wang & Craven, 1971) and their characteristic crystal polymorphism (Craven & Vizzini, 1971). The barbiturate drugs are remarkable in

0567-7408/82/071942-11$01.00