CONFORMATION OF 5-BROMO-URACIL-ARABINOFURANOSIDE

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Summary

The structure of 5-bromo-uracil-arabinoside is studied by X-ray diffraction. The presence of $O_{(2')}$ and $O_{(1')}$ of the arabinofuranose keeps the compound in anti conformation.

Introduction

The spongosides were discovered in 1950 by Bergmann and Feeney (1) in highly differentiated cells of the sponge Cryptotethya crypta. These nucleosides were found to be 1-β-D-arabinofuranosides of thymine and uracil.

Since then many syntheses of arabinosides have been reported, especially since the discovery that these compounds had strong antibacterial, antiviral and cancerostatic effects. Although the mode of action of arabinosides is still poorly understood, it had been shown that they inhibit the synthesis of DNA and RNA (2,3).

The crystallographic literature contains numerous reports (4) on the structure of ribo-and deoxyribonucleosides, and their derivatives, but there had been no arabinosides examined by X-ray diffraction. In the present paper the X-ray diffraction study of 5-bromo-uracil-arabinoside will be reported.

Materials and Methods

The crystals of 5-bromo-uracil-arabinoside were prepared by Dr. M. Privat de Garilhe (Roussel-UCLAF, Paris). The nucleoside crystallises in very long prisms. The dimensions of the unit cell were determined on rotation and Weissenberg photographs (with Cu K_α radiation); the rotation axis was parallel to the longest crystal axis. The correction of absorption was omitted. The space group was found to be $P2_1$.

The parameters of the unit cell were determined as follows:

$a = 5.12 \pm 0.02$ Å $\quad b = 11.03 \pm 0.02$ Å $\quad c = 9.68 \pm 0.02$ Å

$\beta = 93°36' \quad Z = 2$

About 1190 reflections were collected by the multiple-film equi-incli-

nation Weissenberg technique and measured by a Huet microdensitometer. The intensities were corrected with the corresponding Lorentz-polarisation and Phillips correction factors. Furthermore, splitting of the α_1-α_2 doublet has been taken into account. The intensities were reduced to an absolute scale by the Wilson plot. The overall temperature factor was estimated to 2.2 $\mathring{A}^2$.

A Patterson synthesis has been calculated from the hOl data in order to determine the x and z coordinates of the bromine atom. The indeterminated y coordinate was arbitrarily set to zero.

The structure was resolved by the heavy atom method on a three-dimensional electron density map.

The structure factor calculation based on the parameters of all the atoms of the molecule reduced the initial R index of 0.35 to 0.22. After five further least squares cycles of refinement the final R index was 0.10.

Results and Discussion

The atomic parameters are listed in Table I. 5-bromo-uracil-arabinoside is in the anti conformation (Fig. 1) according to the definition of Donohue and Trueblood (5).

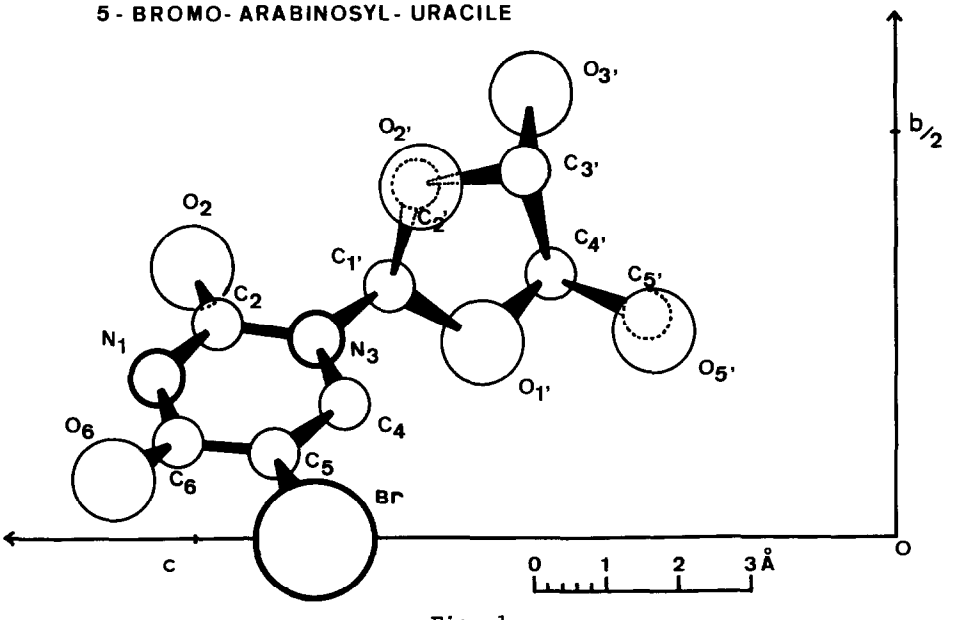

Fig. 1

This is actually the conformation found for all pyrimidine nucleosides studied so far by X-rays (4), except for 6-thiouridine (6). Furthermore, recent NMR and optical data (7,8) indicate a strong preference for the anti conformation in pyrimidine nucleosides in solution. In the case of pyrimi-

dine arabinosides, the 2'OH group will strongly reduce the free rotation around the glycosidic bond and will tend to keep the nucleoside in an extreme anti conformation. This is supported by recent ORD and CD work on arabinosides (9) where the highest optical activities for nucleosides have been so far observed. It has been suggested (9) that the freedom of rotation around the glycosidic bond was imperative for the recognition of the bases by the corresponding polymerases.

The results reported here confirm the conclusions based on optical measurements (9). 5-bromo-uracil-arabinoside is in an extreme anti conformation with $\phi_{CN} \neq -45°$.

The distances between $C_{(4)}$ and $O_{(2')}$, $C_{(4)}$ and $O_{(1')}$, are 3.19 Å and 2.8 Å respectively and clearly show that it is the $O_{(2')}$ that keeps the nucleoside in its particular conformation.

A detailed study of the structure of 5-bromo-uracil-arabinoside is under way and will be published elsewhere.

Table I

Atom	x/a	y/b	z/c	B(Å^2)
Br	0.66	0.50	0.82	3.3
N_1	0.18	0.70	1.05	2.4
C_2	0.02	0.76	0.96	1.7
N_3	0.07	0.75	0.82	1.6
C_4	0.25	0.67	0.78	1.1
C_5	0.40	0.61	0.88	1.3
C_6	0.38	0.62	1.02	1.9
$C_{1'}$	-0.09	0.81	0.72	1.2
$C_{2'}$	0.01	0.94	0.68	1.5
$C_{3'}$	-0.11	0.95	0.52	1.0
$C_{4'}$	-0.21	0.82	0.49	1.5
$C_{5'}$	-0.15	0.77	0.35	2.2
$O_{1'}$	-0.12	0.74	0.59	2.2
O_2	-0.14	0.83	1.00	3.2
$O_{3'}$	-0.31	1.03	0.51	1.9
$O_{2'}$	0.28	0.93	0.67	1.9
$O_{5'}$	0.11	0.75	0.34	2.5
O_6	0.51	0.57	1.11	3.5

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