

CONFORMATIONAL DIFFERENCE BETWEEN 8-BROMO-2'-O-TRIISOPROPYL-  
BENZENESULFONYL-ADENOSINE AND ITS 3'-ISOMER DETERMINED BY  
X-RAY METHOD

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**SUMMARY:** The crystal structures of 8-bromo-2'-O-triisopropylbenzenesulfonyl-adenosine and its 3'-isomer have been determined by X-ray diffraction method. In the former crystal, an intramolecular stacked conformation between adenine- and benzene-ring was found and there exist two modes of dimer formation: an intermolecular stacked dimer and a hydrogen-bonded one. On the other hand, the 3'-isomer, 8-bromo-3'-O-triisopropylbenzenesulfonyl-adenosine, has a similar elongated non-stacked conformation as puromycin.

It has been recognized that the stacking interaction between adjacent bases as well as the base-pairing hydrogen bond makes a substantial contribution to the stability of regular conformation of DNA and RNA.

M.Ikehara et al.<sup>1)</sup> have reported that the molecular conformation of 8-bromo-2'-O-triisopropylbenzenesulfonyl-adenosine (abbr.: 8-Br-2'-O-TPS-ads., see Fig.1) should retain a more folded form than that of 3'-isomer, 8-bromo-3'-O-triisopropylbenzenesulfonyl-adenosine (abbr.: 8-Br-3'-O-TPS-ads.) as the results of the precise analyses of NMR spectra, Rf values in TLC and the differences of extinction coefficient in acidic and neutral solution. In order to confirm these considerations, we have investigated the crystal and molecular structures of these isomers by X-ray diffraction technique.

Single crystals of 8-Br-2'-O-TPS-ads. were grown by slow evaporation from n-propanol solution as colorless prismatic needles and 3'-isomer from ethanol solution as colorless prisms. Crystal data for these isomers and puromycin<sup>2)</sup> are listed in Table I, in which 8-Br-2'-O-TPS-ads. is shown to contain two

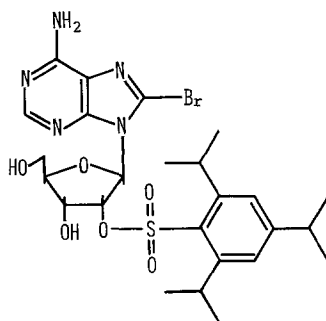


Fig.1 8-Br-2'-O-TPS-adenosine

Table I Crystal Data

Compound	8-Bromo-2'-O-TPS-adenosine	8-Bromo-3'-O-TPS-adenosine	Puromycin (Ref. 2)
Chemical Formula	$C_{25}H_{34}N_5O_6SBr$	$C_{25}H_{34}N_5O_6SBr \cdot H_2O$	$C_{22}H_{29}N_7O_5 \cdot 2HCl \cdot 5H_2O$
Mol. Wt.	612.6	630.6	634.5
m.p. ( $^{\circ}C$ )	217 - 218	185 - 186	175.5 - 176.5
a (Å)	$21.58 \pm 0.02$	$27.53 \pm 0.04$	$28.642 \pm 0.004$
b (Å)	$27.63 \pm 0.05$	$12.36 \pm 0.02$	$13.211 \pm 0.002$
c (Å)	$9.57 \pm 0.02$	$8.61 \pm 0.02$	$7.836 \pm 0.001$
Crystal System	orthorhombic	orthorhombic	orthorhombic
Space Group	$P2_12_12$	$P2_12_12_1$	$P2_12_12_1$
Z	8	4	4
$D_o$ ( $g \cdot cm^{-3}$ )	1.43	1.43	1.421
$D_c$ ( $g \cdot cm^{-3}$ )	1.43	1.43	1.418

molecules ( Mol.I and Mol.II ) in the asymmetric unit. The structures of these isomers were solved by the heavy atom method and the refinements by a block-diagonal least-squares method are now in progress.

As shown in Fig.2, the conformations around the glycosidic bond of these molecules ( Mol.I, Mol.II and 3'-isomer ) are all syn conformations with an intramolecular hydrogen bond ( dashed lines in Fig.2 ) between 5'-oxygen atom of the ribose and N(3) atom of the base, the torsion angle  $\chi$  as defined by Sundaralingam<sup>3)</sup> being  $235^{\circ}$  (Mol.I) ,  $246^{\circ}$  (Mol.II) and  $239^{\circ}$  (3'-isomer). C(2') atom of the ribose ring is puckered out on the

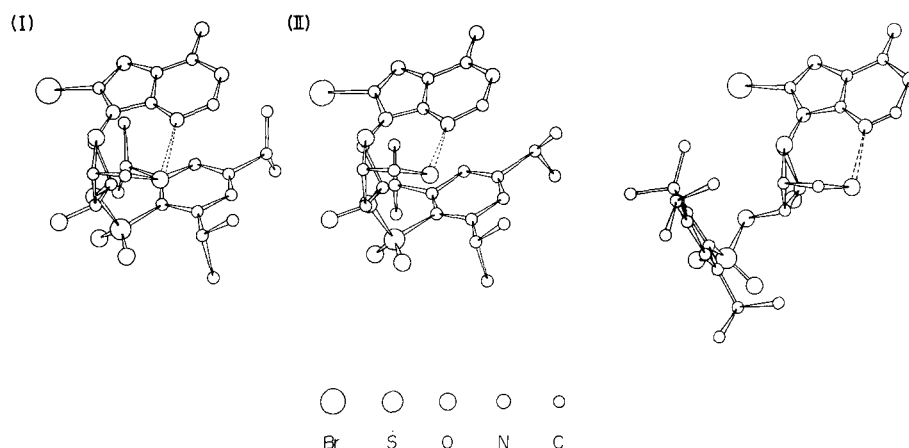


Fig.2

8-Br-2'-O-TPS-adenosine

8-Br-3'-O-TPS-adenosine

same side as C(5') atom by 0.59 Å(Mol.I), 0.67 Å(Mol.II) and 0.57 Å(3'-isomer) from the plane formed by the other four atoms; that is, C(2')-endo conformation. On the other hand, puromycin has anti conformation around the glycosidic bond and C(3')-endo as the ribose conformation.

One of the most interesting features is the difference in the intramolecular conformation between purine- and benzene-ring in 2'- and 3'-isomer as seen in Fig.2. 2'-isomer displays the intramolecular stacked conformation and the spacings between two rings are about 4.10 Å(Mol.I) and 3.97 Å(Mol.II). In the crystal of A2'p5'U<sup>4)</sup>, it was also found to have the intramolecular stacked form between bases. 8-Br-2'-O-TPS-ads. is, however, the first one in purine nucleoside derivatives which has the syn conformation and the intramolecular stacking in solid state. Moreover, the outstanding feature of molecular packing in 2'-isomer is the two modes of intermolecular association between two adjacent molecules related by two fold rotation axis; one is the intermolecular stacked dimer between purine-rings (Mol.I), in which the six-membered rings of purine base overlap in one pair such as bromine atoms keep away one another and the spacing between adjacent purine-rings is about 3.56 Å. The second one is the hydrogen bonded base-pairing dimer (Mol.II), in which the two base-planes jointed by two N-H---N hydrogen bonds are tilted one another. This suggests that the intermolecular stacking may exist in solution as well as the hydrogen bonded base-pairing.

On the other hand, considering the similarities of the crystal system, cell constants and space group between 8-Br-3'-O-TPS-ads. and puromycin (see Table I), it seems likely that the molecular conformation of 3'-isomer might be a non-stacked and elongated one as well as that of puromycin. In fact, there is no intramolecular stacking between benzene- and purine-ring as shown in Fig.2. Although the conformation around the glycosidic bond and the ribose-puckering of 8-Br-3'-O-TPS-ads. are very different from those of puromycin, it seems to be quite interesting to compare the biochemical or physiological activity of both compounds from the analogy of molecular shape.

In solution, these isomers might retain the similar conformation as those in solid state, for the profile of CD spectrum of 3'-isomer in ethanol solution exhibits a single negative Cotton effect at near 274m $\mu$  as similar as one of 8-bromoadenosine, while the CD spectrum of 2'-isomer in ethanol solution shows three large positive Cotton effects at near 287m $\mu$ , 255m $\mu$  and 247m $\mu$  which might be explainable as a result of the stacking interaction between purine- and benzene-ring.

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