CRYSTAL AND MOLECULAR STRUCTURE OF A CYCLONUCLEOSIDE, 8,5'-ANHYDRO-2',3'-ISOPROPYLIDENE-8-MERCAPTOADENOSINE

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SUMMARY: The crystal and molecular structure of 8,5'-anhydro-2',3'-isopropylidene-8-mercaptoadenosine have been determined by X-ray diffraction methods. The relationship between the sugar-base torsion angle and sign and magnitude of the Cotton effect in purine cyclonucleosides is to be further considered.

It is very important to know the relative conformation between base and sugar components of the mononucleoside in order to elucidate the exact nature of polynucleotides in vivo and also in order to study the conformation of purine or pyrimidine mononucleoside in solution.

For this purpose, the cyclonucleoside[1] is very useful as a model compound in which the base plane is fixed to a certain angle on the furanose ring by anhydro-linkage. 8,5'-Anhydro-2',3'-isopropylidene-8-mercaptoadenosine (hereafter, S-cycloadenosine) was synthesized and characterized in its chemical and some physical nature; especially in optical rotatory dispersion study, it has been shown to have large positive Cotton effect around major absorption band of 280 mμ[2].

For X-ray analysis, this S-cycloadenosine was crystallized in butanol-saturated aqueous solution into colorless needle shape elongated along the c-axis, and it is hexagonal, space group $P6_3$, with cell dimensions a=b=20.42 ± 0.05 A, c=6.52 ± 0.01 A. Density was measured by flotation method with calcium chloride solution and it shows very good agreement with calculated density. Six molecules of S-cycloadenosine and two of water molecules are contained in the unit cell. Intensity data of 1542 independent reflections were collected by equi-inclination Weissenberg photographs around the c-axis ($\ell=0\sim5$) and the intensities were corrected with the Lorentz polarization factor. No absorption corrections were applied.

The usual heavy atom method was applied to find the sulfur atom position, and from the Patterson-Harker section (z=0 and z=1/2), the sulfur atom was easily located. Despite the fact that the z-parameter of the sulfur atom was arbitrarily chosen and pseudo mirror-plane symmetry in (001) plane was produced by this circumstance, it was possible to pick out the main features of S-cycloadenosine molecule from the three-dimensional Fourier map. The successive Fourier syntheses, started by only sulfur atom phase, were carried out.

From the inspection of molecular conformation, S-cycloadenosine could be in two forms, namely, exo type, in which the bridge sulfur atom situates in the side of the sugar lactol oxygen atom, and endo, in which the bridge sulfur atom situates in the side of the 2'- and 3'-hydrogen atoms.

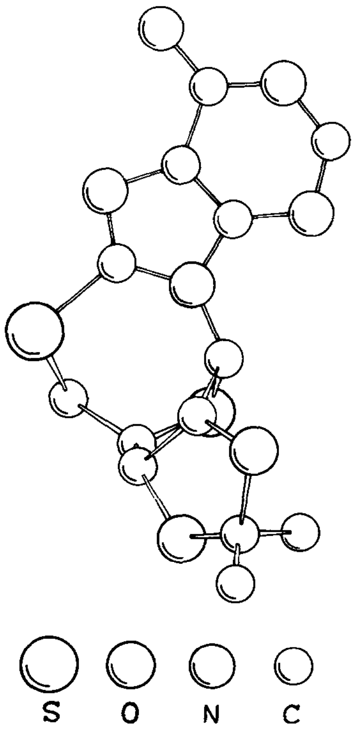

Fig. 1

Fig.1 shows the stereostructure of S-cycloadenosine, and it is clearly indicated that the molecular conformation is the endo-type, that is, the sulfur atom locates in the opposite side of the furanose oxygen atom, and not the exo-type which was predicted from ORD measurement[3].

The structure was refined by block-diagonal least squares method, and after five cicles refinement with anisotropic temperature factor to sulfur atom, the bond lengths and angles were converged to the reasonable values as shown in Fig.2. The descrepancy factor, R, dropped to 0.20 and the standard deviations of bond length and angle are around 0.03 A and 2°, respectively.

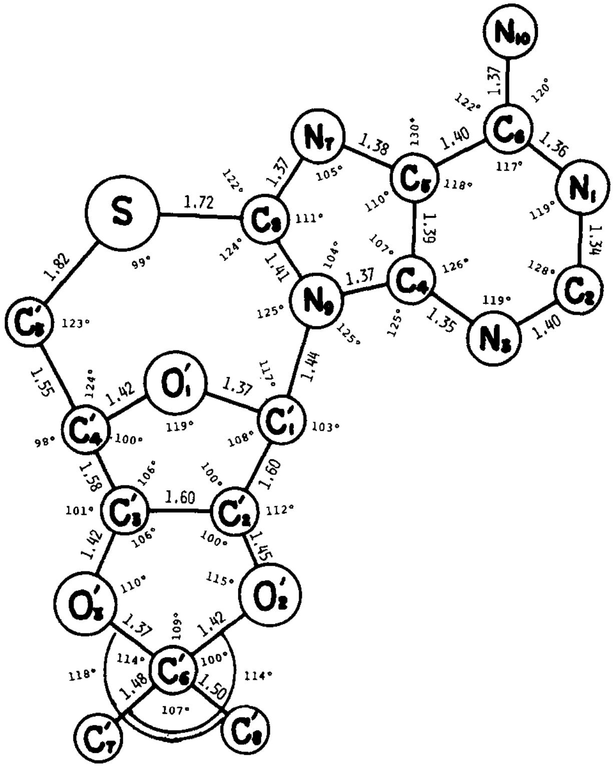

Fig. 2

In the crystal, the plane of the adenine part are stacked on each other parallel to (001) plane with a distance 3.26 A apart, and the sulfur atoms around three-fold axis contact each other with strong van der Waals force of 3.52 A. It seems likely to form weak hydrogen bonds between the amino nitrogen of adenine base and O_2' or O_3' of ribose in the neighboring molecule with a distance of around 3.2 A.

This crystal seems to consist of a so-called clathrate compound, that is, S-cycloadenosine molecule makes a clathrate lattice to result in a tunnel of 2.4 A radius along to the six-fold screw axis and the water molecule is on this six-fold screw axis as a clathrate molecule surrounded by hydrophobic methyl side-chain of isopropyl group. The water molecule itself has no three-fold symmetry, so that it seems to be very unusual that the oxygen atom of water molecule is situated on the six-fold screw axis. However, supposing either the free rotation of the water molecule or the existence of three orientations of water molecule at the point of the three-fold symmetry with same probability, it is possible to lie the water molecule on the six-fold screw axis.

This S-cycloadenosine has the anti-conformation and the sugar-base torsion angle, Φ_{CN}, proposed by Donohue and Trueblood[4] is about 60°. Recently, the relationship between the sign and magnitude of the long wave-length Cotton effect in the ORD of purine cyclonucleosides and their conformation is proposed and illustrated by means of a projection diagram[5]. Considering this projection diagram, S-cycloadenosine is indeed in the region of positive Cotton effect. However, $\Phi_{CN} = 60°$ in S-cycloadenosine is considerably deviated from that assumed in 8,5'-cyclo-8-hydroxyadenosine ($\Phi_{CN} = 30°$). Therefore, further theoretical consideration of a change either in the conformation or in the electronic transition and X-ray investigation of related cyclonucleosides should be required in order to elucidate the exact relationship between the conformation and sign and magnitude of the Cotton effect in purine cyclonucleosides.

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