CRYSTAL AND MOLECULAR STRUCTURE OF 3′-*O*-ACETYL-2′-DEOXY-4-THIOTHYMIDINE

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1. Introduction

When deoxy-4-thiothymidine-5′-triphosphate (ds^{4}TTP) was substituted for deoxythymidine-5′-triphosphate (dTTP) in the enzymatic synthesis of poly d (A-T) by DNA-polymerase the formation of poly d (A-s^{4}T) could be demonstrated [1]. Poly d (A-s^{4}T) was a poor primer for the synthesis of poly d (A-T) but did not serve as template if dTTP was replaced by ds^{4}TTP. This different behaviour of poly d (A-s^{4}T) and poly d (A-T) towards DNA-polymerase iniated a thorough investigation of the physical properties of deoxy-4-thiothymidine derivatives. In this paper the crystal and molecular structure of 3′-*O*-acetyl-2′-deoxy-4-thiothymidine is reported.

2. Materials and methods

Yellow prismatic crystals were obtained by slow evaporation of an aqueous solution of 3′-acetyl-4-thiothymidine. Space group and cell dimensions of these crystals were $P2_12_12_1$ and a = 13.578 Å, b = 5.175 Å, c = 19.667 Å. The intensities of 1084 reflections were measured on a four circle diffractometer using Cu-radiation and corrected for geometrical factors but not for absorption. The structure was solved from a series of Patterson and Fourier syntheses and after several cycles of anisotropic least squares refinement a difference Fourier synthesis revealed the positions of all the hydrogen atoms. The final *R*-factor was 5.4%.

3. Results and discussion

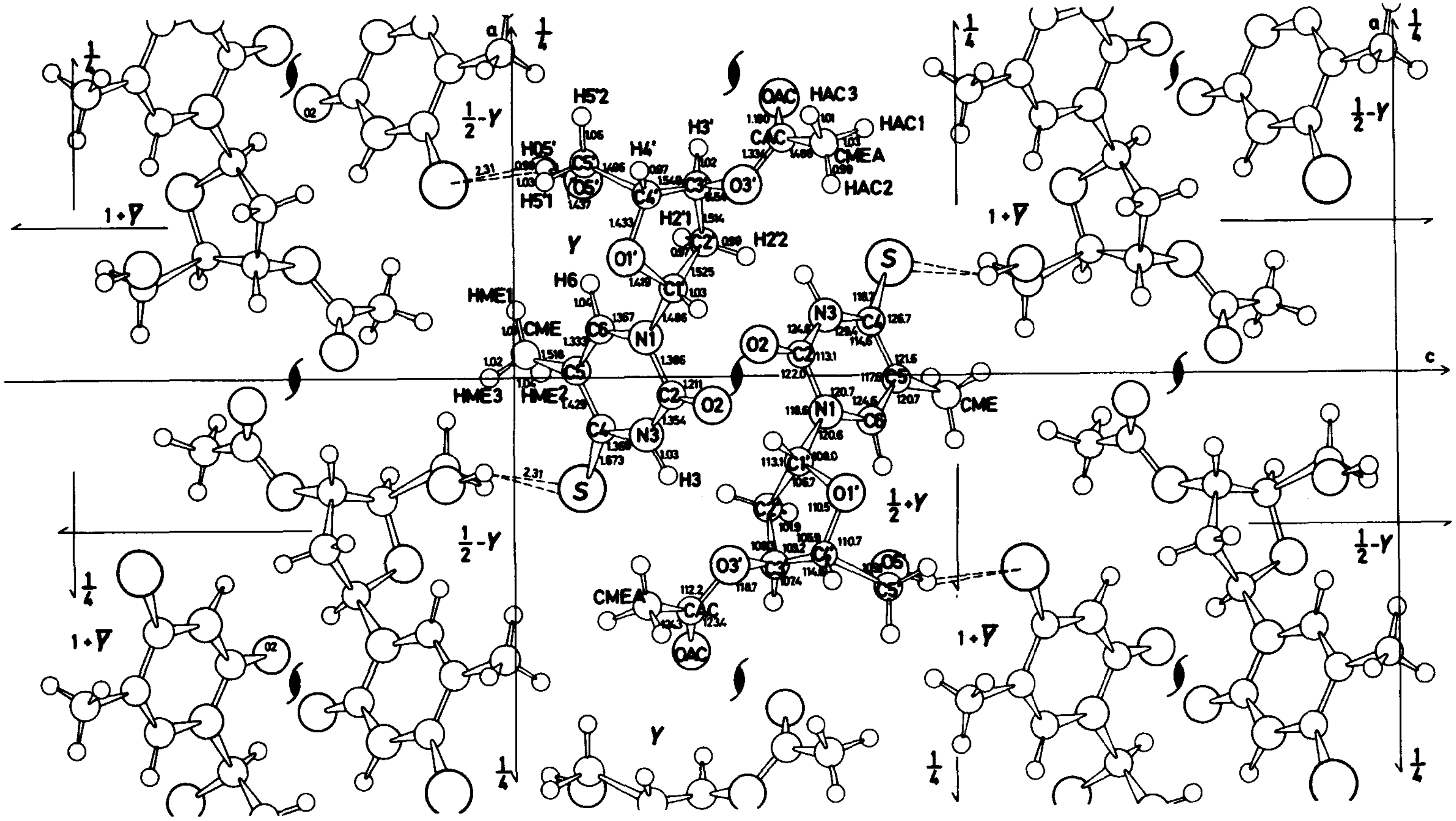
In the figure, bond distances and angles within the molecule are given.

The geometrical data of the heterocycles are in reasonable agreement with the values found for 1-methylthymine [2] and Ca thymdidilate [3]. The bonds C5-C6, C2-O2 and C-S of 1.333 Å, 1.211 Å and 1.673 Å length have double bond character. The arrangement of the atoms and substituents of the pyrimidine ring system is essentially planar except atom C1′, which is displaced by 0.124 Å from the plane.

The five membered deoxy-ribose ring is puckered with C2′ endo (envelope form): C2′ is 0.526 Å away from the best four atom plane. All the angles, dihedral angles and distances compare well with the corresponding values published for 5-fluoro-2′-deoxy-β-uridine [4] except the bond length C3′-C4′ which is increased by 0.05 Å. The conformation about the C4′-C5′ and the C3′-O3′ bond is gauche. The acetyl group is lying in a plane almost perpendicular to the deoxyribose ring.

The heterocycle of a nucleoside can take two preferred conformations with respect to the sugar moiety which are called *syn* and *anti* [5] depending upon the position of the oxygen atom O2 relative to the ribose, i.e. upon τ_{CN}, the dihedral angle C2′-C1′-N1-C6 [6]. In the *syn* conformation O2 is above or near the sugar residue and τ_{CN} is O to 180° whereas is the *anti* conformation O2 is away from the ribose and τ_{CN} is to -180°. In 3′-acetyl-4-thiothymidine CN is -63.7°, i.e. its conformation is *anti*.

This result is striking. 4-Thiouridine, an analogous molecule, crystallizes in *syn* conformation [7], τ_{CN} = 139°, but could be shown by NMR and ORD studies



Projection of the 3′-acetyl-4-thiothymidine molecule along 010. Bond distances and angles are indicated, their estimated standard deviations are 0.003 Å, 0.007 Å, 0.05 Å and 0.5° for the S-C bond, bonds between O, N and C, bonds from H to C and O and angles involving heavy atoms, respectively.

to exist in *anti* conformation [8] in aqueous solution. The reason for this conformational change of 4-thiouridine could be found in its peculiar crystal structure.

The 3′-acetyl-4-thiothymidine molecules are stacked along the crystallographic *b*-axis, the heterocycle being parallel to each other in a distance of 3.68 Å and tilted about 44.7° against the *b*-axis. The molecules are of hydrophobic character and there is only one hydrogen bond of 3.227 Å length from the sulfur to the O5′-oxygen atom.

The molecules of 4-thiouridine are also arranged in stacks but the heterocycles are perpendicular to a crystallographic axis and 3.4 Å apart. They constitute a linear hydrophobic channel whereas the ribose moieties together with 1.5 molecules of water of hydration per nucleoside unit build up a hydrophilic channel.

The differences in the structures of 3′-acetyl-4-thiothymidine and 4-thioridine are *anti* conformation and hydrophobic character of the molecules for the first and *syn* conformation and the arrangement of hydrophobic-hydrophilic channels for the second structure. One could suspect that the conformational change from *anti* to *syn* depends upon the development of a hydrophobic-hydrophilic structure but we feel that some more data are needed to support that idea.

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