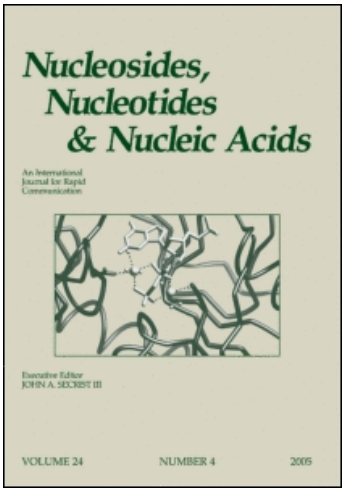

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O^2,1′-ANHYDRO-(β-D-PSICOFURANOSYL)THYMINE AND 1-(1′,4′-*O*-ANHYDRO-β-D-PSICOFURANOSYL)THYMINE: THE CRYSTAL STRUCTURES VERSUS THE ^{1}H NMR AND AB INITIO DATA

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□ *The crystal structures of the title compounds **1** and **2** have been determined. Relation between the stereochemistry of both nucleosides in the crystal state and the ^{1}H NMR data in solution as well as the ab initio calculations is discussed.*

Keywords Anhydro psicofuranosyl nucleosides; pyrimidine; x-ray analysis; conformation; ^{1}H NMR spectroscopy

INTRODUCTION

During the course of our studies on the synthesis of anhydro hexofuranosyl nucleosides,[1,2] we have synthesized O^2,1′-anhydro-(β-D-psicofuranosyl)thymine (**1**) and 1-(1′,4′-*O*-anhydro-β-D-psicofuranosyl)thymine (**2**) (Figure 1), spatial arrangement of which displayed some interesting features.

Originally, the structure of compounds **1** and **2** has been deduced from the careful analysis of the data of UV, CD and ^{1}H NMR spectroscopy.[1] The *spiro*-cyclic system of the former implies the fixed *anti*-conformation about the glycosidic bond and reduced conformational mobility of the pentofuranose ring in solution. Indeed, the CD spectrum of nucleoside **1**[1] displays some similarity in shape with that of natural pyrimidine nucleosides, e.g., thymidine,[3] in the region of B_{2u} and B_{1u} bands. However, molar ellipticity of these bands is essentially greater and, moreover, two CD peaks of opposite sign are appeared in the spectral region spanned by the 254 nm absorption

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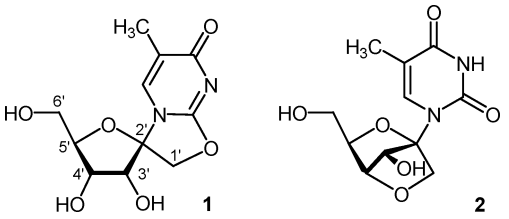

FIGURE 1 Structures of O^2,1′-anhydro-1-(β-D-psicofuranosyl) thymine (**1**) and 1-(1′,4′-*O*-anhydro-β-D-psicofuranosyl)thymine (**2**).

band. These peculiarities of the CD spectrum of nucleoside **1** versus thymidine clearly point to the higher conformational rigidity of the former (cf., e.g., the CD spectra of other rigid nucleosides[3,4]).

O^2,1′-Anhydro nucleoside **1** rearranged into thermodynamically more stable 1-(1′,4′-*O*-anhydro-β-D-psicofuranosyl)thymine (**2**) upon treatment with MeONa/MeOH at 50° (73% acc. to HPLC). Remarkably, an anhydro-ring closure of psicofuranosyl nucleosides depends strongly on the kind of the leaving group at C1′ atom and character of basic conditions as well.[1,5–7] The formation of compound **2** may be explained by the thermodynamically more favorable spatial arrangement of the O4′ versus O3′ for nucleophilic attack onto C1′ in a transition state. It is noteworthy that the reversed nucleophilic attack of the O1′ of 1-(3′,4′-*O*-anhydro-β-D-tagatofuranosyl)uracil is exclusively directed onto the C3′ atom of the 3′,4′-anhydro ring.[2]

The unusual conformational properties of compounds **1** and **2** in solution prompted us to study their solid-state structure. In the present communication, we report on the single crystal X-ray structures of the anhydro nucleosides **1** and **2**, and compare them with the ^{1}H NMR and ab initio data.

RESULTS AND DISCUSSION

O^2,1′-Anhydro nucleoside **1** is crystallizes in monoclinic space group $P2_1$ and the isomeric 1′,4′-*O*-anhydro nucleoside **2** is crystallizes in triclinic space group $P1$.[8] The glycosidic torsion angles, χ, are *anti*: −113.2 (2)° and −109.9 (2)° for **1** and **2**, respectively. The furanosyl rings adopt the *S*-type sugar pucker with following pseudorotational parameters: **1** − P_S = 178.1 (2)° (^2_3T) and ν_{max} = 40.3 (1)°, and **2** − P_S = 162.6 (1)° (^2E) and ν_{max} = 59.0 (1)°. The 1′,4′-anhydro bridge of the latter is forced the pentofuranose ring to adopt this conformation giving rise to an unusually high sugar pucker. The conformation around the C5′–C6′ bond is +*sc* (*gauche,gauche*; gg; +g) with a torsion angles γ of 49.4 (3)° and 66.09 (18)°, respectively. The thymine base as well as the oxazolidine anhydro ring of O^2,1′-anhydro nucleoside **1** are planar, deviations from least-squares plane are 0.0171 and 0.0154, respectively (Figure 2).

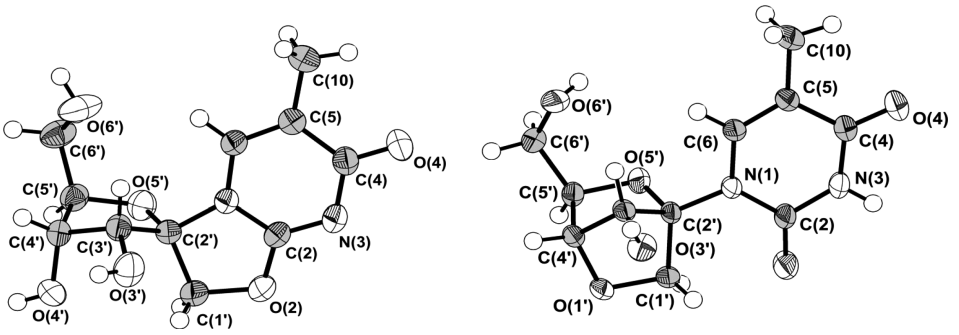

FIGURE 2 Perspective view of O^2,1′-anhydro-1-(β-D-psicofuranosyl) thymine (**1**) (left) and structurally isomeric 1-(1′,4′-*O*-anhydro-β-D-psicofuranosyl)thymine (**2**) (right). Displacement ellipsoids of non-hydrogen atoms are drawn at the 50% probability level and H atoms are shown as spheres of small arbitrary size.

Taking into account the structural peculiarities of nucleosides **1** and **2** in the solid state, it would be of interest to compare them with the ^{1}H NMR data and the ab initio calculations. Unfortunately, there is no possibility to perform conformational analysis of the pentofuranose ring of both anhydro nucleosides employing the PSEUROT program[9] based on the available two vicinal coupling constants, $^3J_{3',4'}$ and $^3J_{4',5'}$. Moreover, comparison of the mentioned couplings for the former nucleoside (4.73 and 2.08 Hz, respectively) with theoretically calculated for the full pseudorotational itinerary[10] does not allow to assume the most populated conformation of the pentofuranose ring. We attempted, therefore, to employ an approach by Chattopadhyaya and co-workers for conformational analysis of 1′,3′-*O*-anhydro *psico*-nucleosides[6,11] for compounds **1** and **2**.

A geometry optimization of O^2,1′-anhydro nucleoside **1** using the HyperChem program (Hypercube, Inc., 2002; release 7.1; ab initio calculation in the gas phase with the 3-21G* basis set) gave the following pseudorotation parameters: $P_S = 121.5^\circ$ [C(1)-*exo*; $_1E$] and $\nu_{max} = 36.8^\circ$. In contrast to 1′,3′-

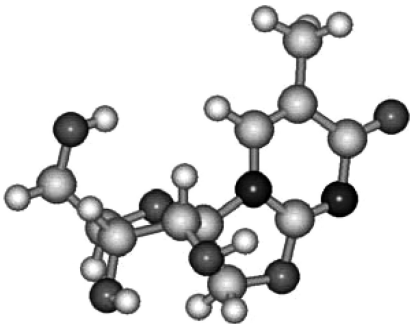

FIGURE 3 A geometry optimized (ab initio; 3-21G*) structure of O^2,1-anhydro-(β-D-psicoturanosyl)-thymine (1).

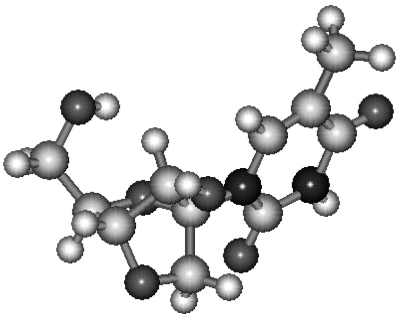

FIGURE 4 A geometry optimized (ab initio; 3-21G*) structure of 1-(1′-4′-*O*-anhydro-*β*-D-psicofuranosyl-thymine (2).

O-anhydro *psico*-nucleosides,[6,11] the phase angle of pseudorotation, $P_S = 121.5°$, differs remarkably from that found in the crystal state. Moreover, the order of values of $^3J_{3',4'} > ^3J_{4',5'}$ coupling constants is not corresponded to the calculated torsion angles for H3′/H4′ and H4′/H5′ protons of 23° and 124°, respectively (Figure 3). On the whole, these data show that the pentofuranose ring of O^2,1′-anhydro nucleoside **1** is not locked in solution in the *S*-type conformation observed in the crystal state.

Attempts to perform similar analysis of the pentofuranose ring of 1′,4′-*O*-anhydro nucleoside **2** gave, at first sight, puzzling results. Indeed, theoretically calculated coupling constants for D-ribofuranose[10] match no one region of the pseudorotational ring with both $^3J_{3',4'}$ and $^3J_{4',5'}$ less than 1.0 Hz as it is the case for compound **2**.[1] However, a geometry optimization of compound **2** as above furnished the $P_S = 155.8°$ and extremely high value for ν_{max} of 58.1°. These data are in fair agreement with the pseudorotational parameters in the solid state (vide supra). Moreover, in this rigid conformation of the pentofuranose ring torsion angles between H3′/H4′ and H4′/H5′ protons are accordingly 63.9° and 84.1° in the crystal and 65° and 82° resulted from the *ab initio* calculations (Figure 4). The low vicinal coupling constant $^3J_{3',4'} < 1.0$ Hz can be explained by the rigid *trans*-orientation of electronegative O4′ atom and proton H3′ (torsion angle of 173°) leading to reduction of $^3J_{3',4'}$ value.[13,14] Note that the CD spectrum of 1′,4′-*O*-anhydro nucleoside **2** (negative Cotton effect at 264 nm ($\Theta = -4{,}800$) and positive one at 293 nm ($\Theta = 2{,}750$)[1] has, to our knowledge, no analogy within the uracil and thymine nucleosides.

CONCLUSIONS

It is obvious that the structure of nucleosides **1** and **2** cannot be unequivocally established on the basis of the UV, CD and ^{1}H NMR spectroscopy. An interplay of stereochemical and electronic influences on the two observed

coupling constants dramatically changes the dependence of the $^3J_{3',4'}$ and $^3J_{4',5'}$ values on the relevant torsion angles versus the natural nucleosides. Single-crystal X-ray analysis of both compounds unequivocally proved their chemical structures, which previously have been deduced, to some extent intuitively, from the spectroscopic data. Noteworthy that in the case of the rigid 1′,4′-*O*-anhydro nucleoside **2**, the MM^+, PM3 (data not shown) and ab initio methods gave very similar results, which are in harmony with its structure in the solid state. On the contrary, the pentofuranose ring of isomeric O^2,1′-anhydro nucleoside **1** reveals more conformational freedom versus that of the former, and, as a consequence, the crystal structure and a spatial arrangement resulted from the ab initio calculations essentially differs.

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