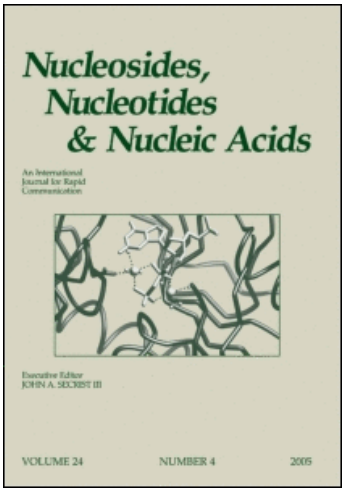

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Conformational Flexibility in a Triazole Nucleoside Derivative: 4-Cyano-5-cyanomethyl-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-1,2,3-triazole†

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ABSTRACT

The crystal-structure determination of the molecular structure of the hydrophobic compound, 4-cyano-5-cyanomethyl-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-1,2,3-triazole, $C_{16}H_{17}N_5O_7$, provides us with two different conformations of ribofuranosyl moieties [(C2′-exo, C3′-endo) and C2′-exo] with two markedly different N-glycosidic angles . There are two molecules in the asymmetric unit of the crystal and the overall stereochemistry of the molecules are influenced predominantly by weak intramolecular bifurcated and trifurcated hydrogen bonds of the type C–H. . .O and C–H. . .N, where endo-H atoms attached to C2′ and C3′ are involved. The molecules in the crystal are interconnected with longer intermolecular bonds of the same type. There are empty channels (occupying 14.0 % of the whole volume of the unit cell), which are extended along b-axis of the entire crystal.

Key Words: β-D-ribofuranosyl nucleoside; Glycosidic bond; Conformational analysis.

†In honor and celebration of the 70th birthday of Professor Leroy B. Townsend.

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INTRODUCTION

3-Deazaguanosine[1] and its analogues are considered as interesting synthetic objectives regarding their versatile biological activity and recently as non-natural building blocks in oligonucleotide synthesis aimed versus the introduction of the absence of N_3-nitrogen that might disrupt the minor groove spine of hydration.

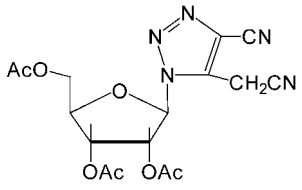
Our specific involvement deals with the introduction of another feature; e.g. by positioning an additional nitrogen atom on position 8 of the aglycon which requires a different synthetic approach.[2] This effect was attributed to the increased electron-withdrawing ability of the triazole ring thus increasing the reactivity of the aromatic carboxylic acid derivative relative to the aliphatic one.

4-Cyano-5-cyanomethyl-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-1,2,3-triazole (Scheme 1) was considered as a suitable intermediate to furnish the targeted 8-aza-3-deazaguanosine by analogous ring closure to the imidazole series.[3]

The synthetic route was attempted either by acid or base-catalysed cyclizations. Again the v-triazole ring fitted out with appropriate substituents affected the course and the direction of the ring closure, namely due to electronic and steric reasons. To the best of our knowledge the comparison to the structural parameters of such dinitrile features has never been attempted, and we now report the crystal and the molecular structure of this interesting and useful intermediate, crucial for further work on 8-aza-3-deazaguanosines and isoguanosines and their derivatives.[4] A thorough search of the Cambridge Structural Database (Version 5.2.4 Nov 2002,[5]) gave only six X-ray structural determinations with v-triazole five membered ring as the aglycon moiety attached at position 1 to a ribose group (Refcodes: AZADEN20[6] DESSOJ,[7] MATKEX,[8] QIMMOO,[9] SAHCYB10,[10] VASVAM[11]). The intention of this research was to find how our data could be fitted in the already available structural data, especially regarding the conformation of the ribose derivative and the N-glycosidic bond. Moreover, with the two independent molecules in the crystal unit cell we had a unique opportunity to compare the conformations of the two. It was surprising to find out that there exists considerable flexibility of the molecule also in the crystalline state.

EXPERIMENTAL

Suitable crystals for the X-ray structure analysis were obtained by the procedure already described elsewhere[4] and the compound crystallized as yellow needles from diethyl ether/methanol or ethyl acetate (melting point: 98–99.5°C). Accurate cell



Scheme 1. 4-Cyano-5-cyanomethyl-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-1,2,3-triazole.

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Table 1. Summary of crystallographic data for $C_{16}H_{17}N_5O_7$.

Molecular formula	$C_{16}H_{17}N_5O_7$
Formula weight	391.35
Colour and shape	Yellow needles
Temperature (K)	293(2)
Crystal system	Monoclinic
Space group	P 2_1 (No. 4)
Unit cell parameters	
a(Å)	13.8427(10)
b(Å)	10.3728(8)
c(Å)	15.4376(11)
β(°)	106.392(1)
Volume (Å^3)	2126.5(3)
Z	4
D_{calc} (g.cm^{-3})	1.222
Diffraction data and results	
Reflections collected	9582
Independent reflections	3974 [R_{int} = 0.0161]
Completeness to 2θ = 26.2° (%)	88.2
Final R indices [I > 2σ(I)]	R_1 = 0.0524, wR_2 = 0.1541
R indices (all data)	R_1 = 0.0620, wR_2 = 0.1648
Largest diff. peak and hole (e.Å^{-3})	+ 0.365 and − 0.165

dimensions were calculated from least-squares refinement of θ values 25 high-order reflections. Diffraction data were carefully collected at room temperature on an Enraf–Nonius CAD-4 diffractometer with monochromatized MoKα radiation. The crystal was stable during data collection and no decomposition was observed, however it had bad scattering properties for X-rays. The usual procedure was used with the data reduction. The procedures for solving and refining the structure, and the production of figures and interpretation of the results were the same as that reported in earlier structural determinations.[12–18] With the absence of anomalous scatterers for MoKα radiation, the determination of the absolute configuration was not possible. The absolute configuration was assigned to agree with the known chirality of the sugar moiety (i.e. β-D-ribofuranose) and the Friedel diffraction data were merged.

The summary of crystallographic data is given in Table 1, full crystallographic details, excluding structure factors, have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 225520. This data may be obtained on request, from The Director, CCDC, 12 Union Road, Cambridge, CBZ 1EZ, U.K. (Tel.: + 44-1223-336-408; Fax: + 44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or website: http://www.ccdc.cam.ac.uk).

RESULTS AND DISCUSSION

The structural analysis revealed two independent molecules A and B, $C_{16}H_{17}N_5O_7$, of the title compound in the asymmetric unit of the crystal. The molecules with the

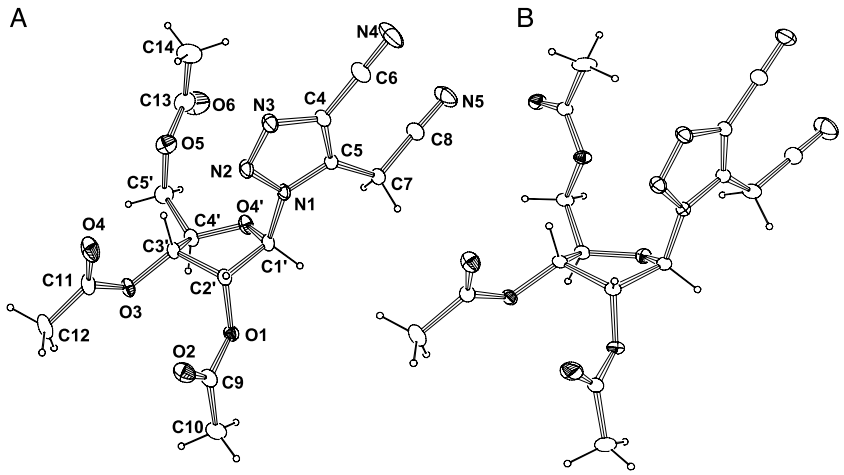

Figure 1. ORTEP (From Ref. [18]) view of the molecules A and B with atomic numbering for A. Anisotropic thermal displacement ellipsoids are drawn at the 10 % probability level. H atoms are displayed as small circles at arbitrary scale.

appropriate atomic numbering scheme are depicted in Figure 1. The number 1 was added to the atom label of the non-hydrogen atoms of molecule A to obtain the numbering of the molecule B. Selected geometric parameters are given in Table 2. The overall geometries (bond lengths and valence angles) are normal and in the agreement with the values given in literature for related compounds[19] The bond distances and valence angles in both molecules were checked in both molecules, however they were not significantly different. The bond lengths of the 1,2,3-triazole ring N1–C5 1.351(5) and , N1–N2 1.359(5), N2–N3 1.293(6), N3–C4 1.359(6) and C4–C5 1.373(7) Å in the molecule A and the corresponding ones 1.338(5), 1.353(5), 1.301(5), 1.359(6) and 1.374(6) Å in the molecule B, suggest considerable delocalisation of electrons and the prevalent double bond character of N2–N3 bond.

The arrangement of the heterocyclic base relative to the sugar moiety in nucleosides, which is defined as *anti* or *syn*, is represented by the torsion angle about the N-glycosidic bond. In the cases of modified nucleosides with a e.g. five-membered base or fused ring systems, the sequence of atoms is chosen as far as possible to correspond closely to the normal substrates.[20,21] The appropriate torsion angles O4′–C1′–N1–C5 and O4′–C1′–N1–N2 in this study are −87.9(5) and 91.5(5)° for molecule A, and −57.5(5) and 118.9(4)° for molecule B, respectively, with the lengths of C1′–N1 bonds of 1.486(5) Å in the molecule A and of 1.488(5) Å in B, suggesting high-*anti* conformation of the aglycon with respect to the sugar moiety.[22] The ribofuranosyl moieties exhibit a β-D configuration with the twisted C2′-exo,C3′-endo pucker in the molecule A, whereas an envelope conformation with a C2′-exo arrangement was found in the molecule B. The conformations about the bond C4′–C5′ [torsion angle O4′–C4′–C5′–O5 of −63.1(6) in A and −65.3(4)° in B molecule, respectively] is in the *gauche* range. The Cremer–Pople puckering parameters[23] q_2 and φ_2 are 0.363(5) Å and 277.1(7)° for the molecule A and 0.318(4) Å and 249.0(8)° for B, respectively. The corresponding puckering amplitude, τ_m, and pseudorotation

Table 2. Selected geometric parameters (Å, °) and hydrogen bonding geometry.

	Molecule A	Molecule B
Bond lengths (Å)		
C1′–O4′	1.415(6)	1.403(5)
C1′–N1	1.486(5)	1.488(5)
C1′–C2′	1.515(6)	1.524(6)
C2′–C3′	1.532(6)	1.539(6)
C3′–C4′	1.510(7)	1.527(6)
C4′–C5′	1.478(8)	1.508(6)
C4′–O4′	1.437(5)	1.444(5)
N1–N2	1.359(5)	1.353(5)
N2–N3	1.293(6)	1.301(5)
N3–C4	1.359(6)	1.359(6)
C4–C5	1.373(7)	1.374(6)
N1–C5	1.351(5)	1.338(5)
Torsion angles (°)		
C5–N1–C1′–O4′	−87.9(5)	−57.5(5)
N2–N1–C1′–O4′	91.5(5)	118.9(4)
O4′–C1′–C2′–C3′	−27.1(4)	−32.1(4)
C1′–C2′–C3′–C4′	36.2(4)	29.5(4)
C2′–C3′–C4′–O4′	−32.9(4)	−17.5(4)
C3′–C4′–O4′–C1′	16.4(5)	−3.0(4)
C4′–O4′–C1′–C2′	7.3(5)	22.6(4)
C4′–C5′–O5–C13	126.6(6)	−172.3(4)
C3′–C4′–C5′–O5	55.4(6)	53.5(5)
O4′–C4′–C5′–O5	−63.1(6)	−65.3(4)

Hydrogen bonding (Å, °)

D–H...A	D–H	H...A	D...A	D–H...A
C3′–H3...O4	0.98	2.31	2.652(7)	99.4
C3′–H3...O5	0.98	2.54	2.936(6)	104.1
C3–H3...N2	0.98	2.54	3.046(7)	112.4
C2′–H2...O2	0.98	2.43	2.667(7)	93.2
C2′–H2...N2	0.98	2.50	2.748(6)	93.8
C31′–H20...O41	0.98	2.37	2.668(6)	96.6
C31′–H20...O51	0.98	2.41	2.847(5)	106.0
C31′–H20...N21	0.98	2.85	3.254(6)	105.3
C21′–H19...O21	0.98	2.35	2.646(6)	96.5
C21′–H19...N21	0.98	2.43	2.777(7)	100.0

phase angle, P,[24] for the molecule A is 37.2(3) and 7.6(4)°, whereas 33.0(3) and 336.3(4)° were found for the molecule B.

The most interesting features of the structures are the different conformations of the ribofuranosyl moieties as well as the different orientation of the acetyl group attached to C5′ atom (Figure 2) in the molecule A and B.

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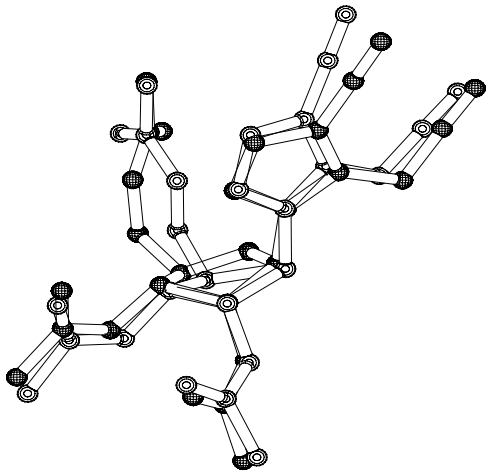

Figure 2. Superposition of the two molecules A and B (From Ref. [17]). H atoms are omitted for clarity.

The appropriate torsion angles C4′–C5′–O5–C13 are completely different: 126.6(6)° in the molecule A compared to −172.3(4)° in the molecule B. A possible explanation for this effect is the weak intermolecular hydrogen bonds of the type C–H...O and C–H...N. Because of the fact that the –OH groups of the ribofuranosyl group are protected with acetyl groups, the molecule is hydrophobic on the whole, and only weak intramolecular and intermolecular interactions were expected. These interactions are relatively weak[25,26] but are important and govern the packing and the individual shape of the hydrophobic molecules. In recognizing these interactions, the significance of the distances H...A rather than that of the traditional D...A

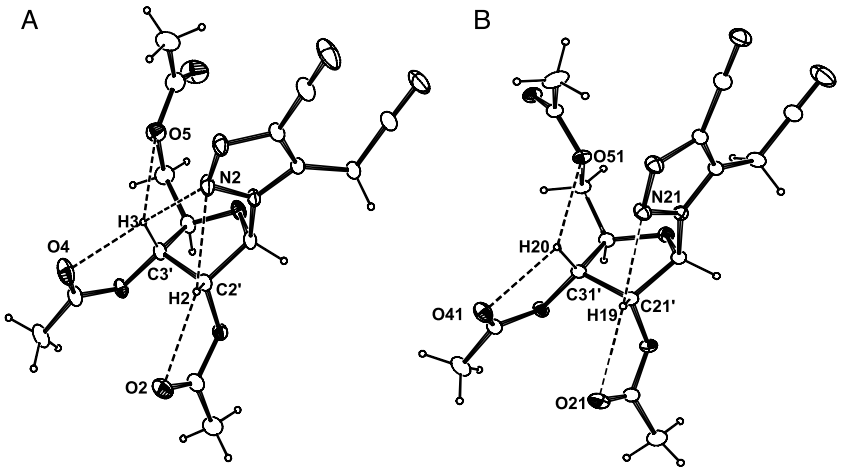

Figure 3. Intramolecular hydrogen bonds C–H...O and C–H...N for molecules A and B.

distances (for hydrogen bond type D–H...A; D = donor; A = acceptor) was firstly stressed in the study of N–H...O–C hydrogen bonds by Taylor & Kennard.[27] It has been also believed for a long time that the van der Waals sum cut-off definition of the H-bond requires that the H...A and D...A distances must be smaller than than the sum of van der Waals radii. For the case of C–H...O, the separation H...O was then taken as 2.6–2.7 Å. At this distance, the interaction was thought to be switched off from ''hydrogen bond'' to ''van der Waals'' type interaction. However, this definition was recently declared as dubious with the argument that the electrostatic field of dipoles does not terminate sharply at any cut-off distance. Longer H...O distances up to 3.2 Å and an angular cut-off at angles greater than 90° were therefore suggested.[28,29] Taking into account the additional discussions of C–H...O hydrogen bonding[30–32] and having considered all these facts, the difference in the conformations of the molecule A and B could be explained.[33] There are two endo hydrogen atoms involved in the intramolecular hydrogen bond formation on each molecule, H2 and H3 of the molecule A, and the corresponding H19 and H20 of the molecule B (Figure 3 and Table 2). The hydrogen H3 is involved in the trifurcated hydrogen bond to O4, O5 and N2, whereas H2 is participating in bifurcated hydrogen bond with O2 and N2 in the molecule A.

The corresponding H20 of the molecule B is linked only to O41 and O51 (bifurcated bond) , but the N2 is at the considerably longer distance H20...N21 of 2.85 Å and the corresponding distance C31′...N21 is 3.254(6) Å accordingly. H19 atom attached to C21′ is also linked to the O21 and N21 with the bifurcated H bond. There are also significant differences between the angles O4–H3–O5 = 131.6°, O5–H3–N2 = 91.6° in the molecule A, and O41–H20–O51 = 149.2°, O51–H20–N21 = 76.8° in the molecule B. All the molecules are loosely packed in the crystal with the weak C–H...O and C–H...N interactions. Altogether 14.0 % of the unit-cell volume is void and the channels are running along the b-axis of the entire crystal forming nanotubular array (Figure 4).

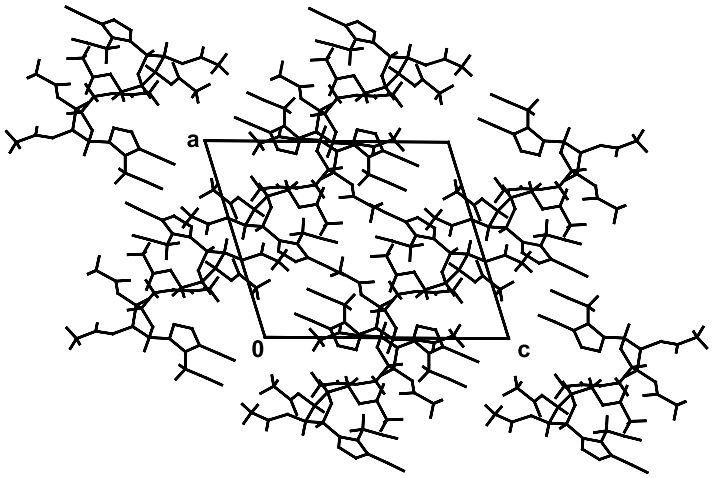

Figure 4. The packing of the molecules in the crystal structure as viewed along b-axis. Channels are running along the [010] edges of the unit cell.

The SQUEEZE option of the PLATON programme[34] did not reveal any substantial electron density in the region of the voids.

SUMMARY OF THE RESULTS

Once again it can be concluded also from this investigation that the interpretation of the structural data on the basis of ''standard''or ''average'' conformations may lead to inaccurate results and that the combination of the structural X-ray analysis and other methods, which also provide structural information, is necessary to obtain reliable and satisfactory results.[7] It was also proved that in the absence of the strong, oriented hydrogen bonds the presence of the weak C–H...O and C–H...N hydrogen bonds contribute to the greater flexibility of the molecule even in the crystalline state.

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