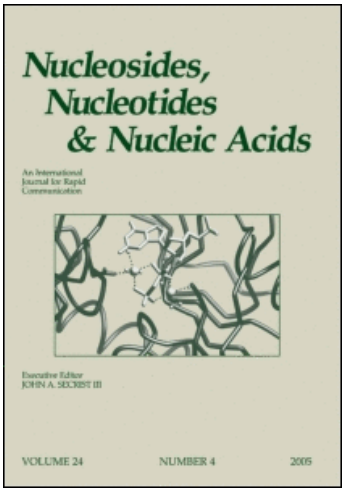

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Kálmán, Alajos , Yoritsánszky, Tibor , Béres, József and Sági, Gyula(1990) 'Crystal and Molecular Structure of ( )-Carba-Thymidine, C_{11} H_{10} N_2 O_6', Nucleosides, Nucleotides and Nucleic Acids, 9: 2, 235 — 243
To link to this Article: DOI: 10.1080/07328319008045135
URL: http://dx.doi.org/10.1080/07328319008045135

NUCLEOSIDES & NUCLEOTIDES, 9(2), 235-243 (1990)

CRYSTAL AND MOLECULAR STRUCTURE OF (+)-CARBA-THYMIDINE, $C_{11}H_{16}N_2O_6$

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Abstract. The molecular structure of (+)-carba-thymidine possessing notable anti-HSV activity has been determined by single crystal X-ray diffraction. It crystallizes in the monoclinic space group $P2_1$ with unit cell dimensions a = 4.810(2), b = 11.560(1), c = 10.014(1) Å, β = 92.34(2)°, Z = 2. The structure was solved by direct methods and refined by least squares to a final R = 0.038 for 1027 reflections ($I > 3\sigma(I)$). The torsion angle χ around the glycosidic N1-C1′ bond agrees with that of thymidine (37.5° vs 39.1°) whereas the C3′-*exo* pucker of the five-membered ring is shifted to an even less common C1′-*exo* form.

INTRODUCTION

A part of our ongoing research programs in the field of the synthesis of modified DNA's required enantiomerically pure carbocyclic 2′-deoxyribonucleoside analogues in which the furanose oxygen atom of the natural compounds is replaced with a methylene group. Substances of this kind were earlier available only as racemates. Recently we described the first stereospecific synthesis of (+)- and (-)-carba-thymidines and also published antiviral data for both enantiomers.[1,2] The marked activity obtained with (+)-carba-thymidine against herpes simplex virus type 1 (0.2 μg/mL) and type 2 (2 μg/mL) are in agreement with those reported previously by Shealy et al. for the racemic carba-thymidine.[3,4] In contrast, the (-)-enantiomer turned out to be totally inactive. Our results show that the whole

antiviral activity of (±)-carba-thymidine resides in its (+)-enantiomer. Our original idea was to synthesize oligo- and poly-2'-deoxyribonucleotides via enzyme-catalyzed reactions. Unfortunately, (+)-carba-thymidine 5'-triphosphate proved not to be a suitable substrate for Klenow DNA polymerase since its low terminal incorporation was only observed into DNA's of different structures.[5] Surprisingly, compared to natural thymidine, (+)-carba-thymidine reacted sluggishly also in the chemical synthesis of the modified DNA's. This anomalous behaviour of (+)-carba-thymidine prompted us to substantiate its relative stereochemistry by X-ray crystallography. The absolute configuration derives, of course, from the stereostructure of the starting compound.[1] Since, to our best knowledge, only a few X-ray structures were published for carba-nucleosides e.g. (-)-aristeromycin[6], (-)-neplanocin A[7], and carba-6'β-fluoro-2'-deoxyuridine[8], furthermore (+)-carba-thymidine per se exhibits remarkable anti-HSV activity, we feel worth reporting its X-ray structure.

EXPERIMENTAL

A white prismatic crystal having approximate dimensions of 0.10x0.15x0.20 mm was mounted on a glass fiber in a random orientation.

Crystal data. $C_{11}H_{16}N_2O_4$, MW = 240.26, monoclinic, a = 4.810(2), b = 11.560(1), c = 10.014(1) Å, β = 92.34(2)°, U = 556.3(3) Å^3, Z = 2, D_c = 1.43 g·cm^{-3}, space group $P2_1$ (from systematic absences) F(000) = 256.

Intensities of 1134 unique, symmetry independent and non zero reflections were collected in the range $2\theta \leq 150.0°$ by an ω-2θ scan on an Enraf-Nonius CAD-4 diffractometer with graphite monochromated CuK_α (λ = 1.5418 Å) radiation. Cell constants were determined by least squares refinement from the setting angles of 25 reflections. After data reduction 1027 reflections with $I > 3\sigma(I)$ were taken as observed. The phase problems were solved by the MULTAN[9] program using 277 E > 1.20 normalized structure factors. At the end of the isotropic refinement an empirical absorption correction was

applied by the use of program DIFABS[10]. Relative transmission coefficients ranged from 0.805 to 1.805 with an average value of 1.017. The H positions, except those which are bound to N or O atoms were generated from assumed geometries and were only included in structure factor calculations with individual isotropic temperature factors ($B_{iH}=(B_{iX}$ + 1 Å^2, X=C,N and O). H3, HO3′ and HO5′ were located in $\Delta\rho$ synthesis. Full-matrix refinement of the positional and anisotropic vibrational parameters of non-hydrogen atoms resulted in a final R = 0.038 (R_w = 0.043). Maximum peak height in the final difference-density map was $\Delta\rho$ 0.26(5) e. Å^{-3} while max. Δ/σ in the last cycle of refinement was 0.26. All calculations were performed by the use of the Enraf-Nonius SDP Plus Programme Package which includes atomic scattering factors[11]. Anomalous dispersion effects were included in F_c values as suggested in the literature.[12] For $\Delta f'$ and $\Delta f''$ values see ref. 13.

RESULTS AND DISCUSSION

The X-ray analysis substantiated the expected relative stereostructure of the title compound. A perspective view of the structure computed from the final relative atomic coordinates given with their e.s.d.'s in Table 1 is depicted in Figure 1.

The majority of the bond lengths and angles listed in Tables 2 and 3 agrees within experimental error with the corresponding values observed for thymidine,[14] 5-isopropyl-2′-deoxyuridine,[15] etc. Of course, the carbocyclic ring exhibits visible differences from the furanose moiety of thymidine. The amount of rotation about the glycosidic C1′-N1 bond χ = 37.5(6)° also falls in the anti range like in thymidine (39.1°) whereas the rare C3′-exo pucker of the five-membered ring is shifted to the even less common C1′-exo form, the corresponding lowest asymmetry parameter[16] ΔC_s = 6.3°, while the pseudorotation phase angle[17] P = 118.6° (for $_1$E P = 126°). In contrast with the trans-gauche(+) oriented 5′-CH_2OH moiety of thymidine,

TABLE 1. Atomic coordinates ($x10^4$) for non-hydrogen atoms and ($x10^3$) for hydrogen atoms with their e.s.d.'s.

	x	y	z	B^*_{eq}/B_{iso}
O4	-3656(6)	-3953(0)	-3685(2)	3.4(1)
O2	2814(6)	-2539(2)	- 691(3)	3.0(1)
O3'	2936(6)	-3025(2)	4218(2)	2.8(1)
O5'	- 607(5)	-6437(2)	4025(2)	2.7(1)
N1	326(6)	-4127(3)	- 71(3)	2.1(1)
N3	- 397(7)	-3299(3)	-2175(3)	2.3(1)
C1'	1681(7)	-4115(3)	1295(3)	1.9(1)
C2	1065(8)	-3270(3)	- 951(3)	2.2(1)
C2'	- 78(8)	-3507(3)	2318(4)	2.7(1)
C3'	1140(7)	-3917(3)	3676(3)	2.1(1)
C4'	2779(8)	-5041(3)	3404(3)	2.2(1)
C4	-2498(7)	-4054(3)	-2570(3)	2.2(1)
C5'	2130(8)	-6028(4)	4314(4)	2.7(1)
C5	-3138(7)	-4940(3)	-1609(3)	2.0(1)
C6'	2217(9)	-5303(3)	1907(4)	2.5(1)
C6	-1701(7)	-4930(3)	- 421(3)	2.1(1)
C7	-5269(8)	-5838(4)	-1962(4)	2.6(1)
H3	9	-273	-281	3.3
H6	-212	-551	21	3.1
H7a	-544	-636	-123	3.6
H7b	-471	-626	-272	3.6
H7c	-700	-548	-216	3.6
H1'	339	-373	114	2.8
H2'a	8	-269	223	3.6
H2'b	-197	-373	220	3.6
H3'	- 24	-407	430	3.0
H4'	471	-494	360	3.1
H6'a	379	-566	153	3.5
H6'b	64	-579	177	3.5
H5'a	343	-664	418	3.7
H5'b	230	-577	521	3.7
HO5'	-166	-693	445	4.0
HO3'	459	-332	473	4.0

*The equivalent isotropic thermal parameters ($Å^2$) are defined as:

$$B_{eq} = \frac{4}{3}\text{trace}(B\underline{G}) \text{ where } \underline{G} \text{ is the direct metric tensor}$$

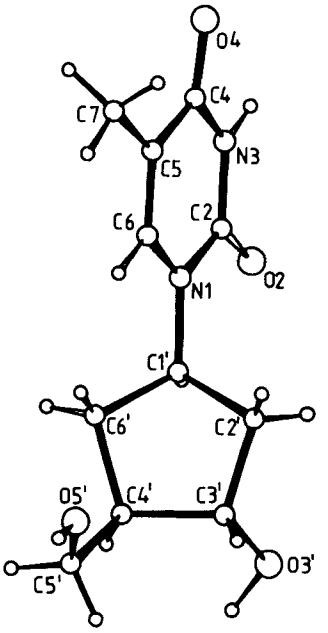

FIGURE 1. Perspective view of (+)-carba-thymidine as found in the crystal structure.

in the title compound this group assumes gauche(+)-gauche(-) conformation. All relevant torsion angles are given in Table 4.

Similarly to thymidine the crystal structure of the title compound is stabilized by three hydrogen bonds. As shown by Figure 2 the molecules related by the screw axes at $0,Y,\pm\frac{1}{2}$ are bound together by infinite helical chains of the hydrogen bonds: O5'-HO5'···O3' (O···O = 2.81, H··O = 1.95 Å, ∢ HHO = 161.7°). Each O5' donor and O3' acceptor unit pertaining to two bonded molecules respectively acts simultaneously as acceptor and donor in the other two hydrogen bonds developed with the N3-HN3 moiety and O4 atom of a third molecule. The NH···O bond (N···O = 2.89, H··O = 1.95 Å, ∢ NHO = 171.4°) donor (N3) and acceptor (O5') are related by a relative symmetry operation $-x,y+\frac{1}{2},-z$. In the crystal of thymidine the NH···O bond is donated to O3' separated by a symmetry operation $\frac{1}{2}-x,1-y,\frac{1}{2}+z$ and there is

TABLE 2. Bond lengths (A) with e.s.d.'s

O4 -C4	1.233(5)	N1 -C6	1.382(5)	C3'-C4'	1.550(6)
O2 -C2	1.213(5)	N3 -C2	1.389(5)	C4'-C5'	1.500(6)
O3'-C3'	1.437(5)	N3 -C4	1.381(5)	C4'-C6'	1.541(6)
O5'-C5'	1.418(5)	C1'-C2'	1.526(6)	C4 -C5	1.448(6)
N1 -C1'	1.491(5)	C1'-C6'	1.521(6)	C5 -C6	1.351(5)
N1 -C2	1.381(5)	C2'-C3'	1.533(6)	C5 -C7	1.491(6)

TABLE 3. Bond angles (°) with e.s.d.'s

C1'-N1 -C2	117.7(5)	C2'-C3'-C4'	106.3(5)
C1'-N1 -C6	121.1(5)	C3'-C4'-C5'	114.3(6)
C2 -N1 -C6	121.2(6)	C3'-C4'-C6'	105.4(5)
C2 -N3 -C4	127.3(6)	C5'-C4'-C6'	114.1(6)
N1 -C1'-C2'	112.7(5)	O4 -C4 -N3	119.8(6)
N1 -C1'-C6'	115.0(5)	O4 -C4 -C5	124.7(6)
C2'-C1'-C6'	103.6(6)	N3 -C4 -C5	115.5(6)
O2 -C2 -N1	123.9(6)	O5'-C5'-C4'	110.1(6)
O2 -C2 -N3	121.8(6)	C4 -C5 -C6	117.7(6)
N1 -C2 -N3	114.3(6)	C4 -C5 -C7	119.8(6)
C1'-C2'-C3'	104.5(6)	C6 -C5 -C7	122.5(6)
O3'-C3'-C2'	108.4(5)	C1'-C6'-C4'	103.6(6)
O3'-C3'-C4'	111.5(5)	N1 -C6 -C5	124.0(6)

TABLE 4. Relevant torsion angles (°) with e.s.d.'s

τ_0	C4'-C6'-C1'-C2'	-40.6(5)	
τ_1	C6'-C1'-C2'-C3'	37.4(5)	
τ_2	C1'-C2'-C3'-C4'	-19.7(5)	
τ_3	C2'-C3'-C4'-C6'	- 5.1(5)	
τ_4	C3'-C4'-C6'-C1'	28.0(5)	
χ	C6'-C1'-N1 -C2	-145.8(7)	(new)
	C6'-C1'-N1 -C6	37.5(6)	(old)[19]
	C3'-C2'-C1'-N1	162.3(6)	
ψ	O5'-C5'-C4'-C3'	69.5(6)	
	O5'-C5'-C4'-C6'	-51.9(6)	
ψ'	C5'-C4'-C3'-O3'	110.9(6)	

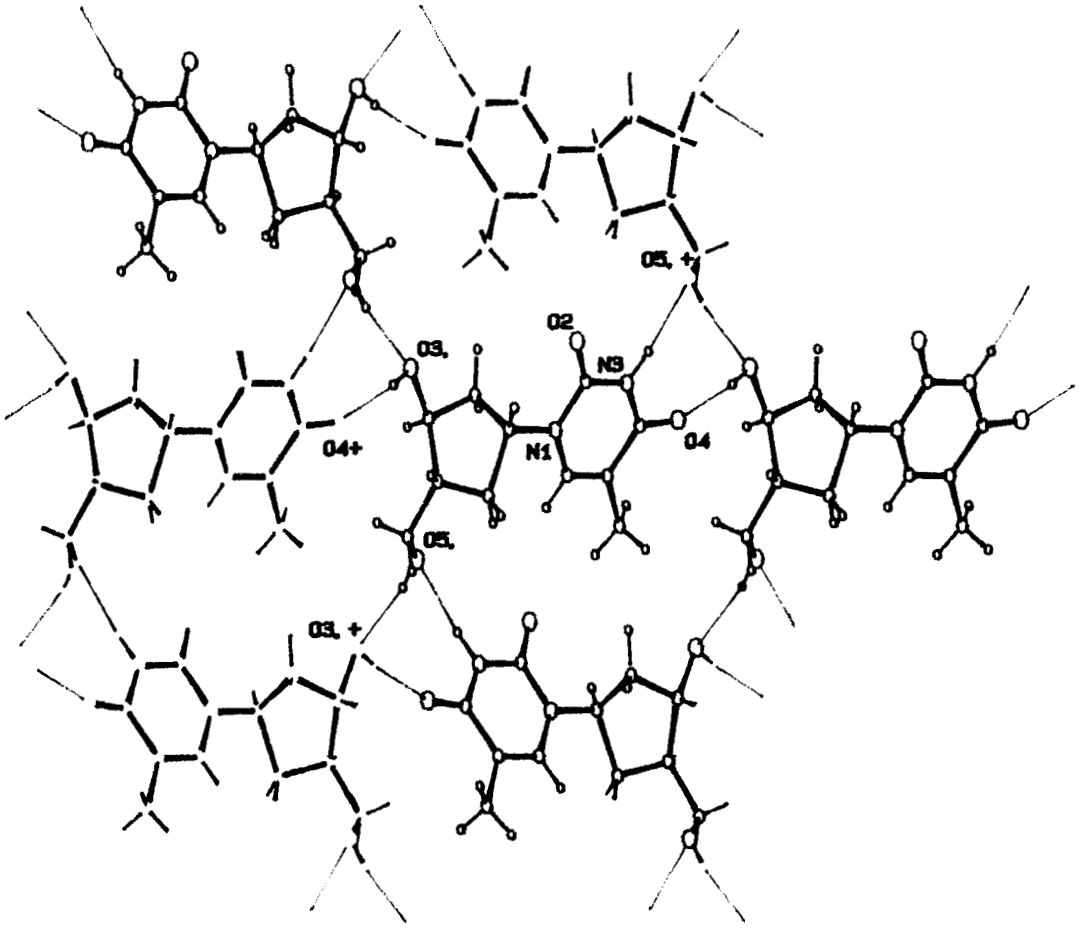

FIGURE 2. The hydrogen bond network of the molecules showing the infinite helical chains along the b axis.

an O5'···O5' bridge related by a screw axis at $X,\frac{1}{4},\frac{1}{2}$. Remarkably, in both structures the third hydrogen bond is of the similar type: O3'-HO3'···O4. In the title compound (O···O = 2.82, H···O = 1.92 Å, ∢ OHO = 151.5°) the molecules are related by unit cell translations along a and c axes, whereas in thymidine the symmetry operator is $2_1(0,Y,\frac{1}{4})$. Nevertheless, the quasi identical χ values (*vide supra*) developed in these structures suggest that the effect of these hydrogen bonds upon the rotation around the C1'-N1

bond is limited by intrinsic molecular properties. This conclusion is supported by the comparison of the conformation of several 5-substituted 2'-deoxyuridines with those of their 3',5'-diacetyl derivatives (see Figure 3 in ref. 18). Even the different pucker of the five membered ring in these compounds may primarily be attributed to the replacement of the ring oxygen by a bulky CH_2 moiety rather than by any hydrogen bond effect. The secondary effect of the hydrogen bonds maintained by the substituents on the cyclopentane ring may possibly be checked by the structure determination of its 3',5'-diacetyl derivative. Preparation of appropriate crystals is in progress.

ACKNOWLEDGEMENTS

The authors thank Professor L. Ötvös for his kind interest. Thanks are also due to Mr. Cs. Kertész and Mrs. Gy. Cs.-Tóth for their technical assistance.

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Received May 23, 1989.