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The Crystal Structure of 4,6-Dideoxy-4-(N,N-dimethylamino)-α-D-talopyranoside Methiodide

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The crystal structure of 4,6-dideoxy-4-(N,N-dimethylamino)-α-D-talopyranoside methiodide has been determined by X-ray diffraction. The crystals belong to the orthorhombic space group $P2_12_12_1$ with unit-cell dimensions $a=13\cdot179$ (9), $b=10\cdot604$ (8) and $c=9\cdot770$ (7) Å. The structure was solved by Patterson–Fourier techniques; least-squares refinement yielded a final discrepancy index of $R=0\cdot031$. The structure was found to occur in the $1C$ trans chair conformation owing to the presence of a trimethylammonium group in the 4 position.

Introduction

A series of antibiotics, isolated between 1953 and 1958, (Flynn, Hinman, Carol & Woolf, 1953; Haskell, Ryder, Frohardt, Fusari, Jakubawski & Bartz, 1958) has been shown to contain a new class of carbohydrates, the 4-amino-4,6-dideoxyaldohexoses. The antibiotics, amicetin (Stevens, Blumbergs & Daniher, 1963) and bamicetin (Haskell, 1958; Stevens, Blumbergs, Daniher, Otterbach & Taylor, 1966) contained respectively the N,N-dimethyl and N-monomethyl sugar derivative in the D-gluco configuration. The isolation of the parent 4,6-dideoxy-4-amino-D-glucose from the cell wall of the bacteria Chromobacterium violaceum (Stevens, Blumbergs, Daniher, Wheat, Kiyomoto & Rollins, 1963) and from E. coli strain B (Stevens, Blumbergs, Daniher, Strominger, Matsuhashi, Dietzer, Suzuki, Okazaki, Sugimoto & Okazaki, 1964) increased the biological interest in these compounds. Further, the isolation of the D-galacto derivative from the cell wall of E. coli strain Y10 (Stevens, Blumbergs, Otterbach, Strominger, Matsuhashi & Dietzler, 1964) and the D-manno derivative from an antifungal antibiotic (Lee & Schaffner, 1966; Stevens, Gupta, Glinski, Taylor, Blumbergs, Schaffner & Lee, 1968) indicated the wide occurrence of these sugars.

Chemical synthesis of all eight possible configurations has been accomplished by Stevens and co-workers. The relationship of basicity to configuration and

conformation is under investigation because of the possible importance in biological activity. The most interesting case to date involves the isolation of the crystalline α and β forms of the 4,6-dideoxy-4-dimethylaminotalose (Stevens, Glinski & Taylor, 1968). It was found that on initial dissolution of these sugars, which mutarotate in aqueous solution, the β-form (pKa 8·22) is four times more basic than the α-form (7·60).

The three-dimensional X-ray analysis of 4,6-dideoxy-4 (N,N-dimethylamino)-α-D-talopyranoside methiodide, reported herein, confirms the general formulation of this class of sugars and suggests a possible explanation for the difference in basicity mentioned previously. In the crystalline state we find this salt exists in the $1C$ geometry; if the α-form of the 4,6-dideoxy-4-dimethylamino talose retains this geometry and the β-form exists in the more usual $C1$ geometry, the difference in basicity may be a result of the different environment (i.e. equatorial vs. axial) of the dimethylamino group.

Experimental

Transparent, colorless, needle-shaped crystals of 4,6-dideoxy-4-(N,N-dimethylamino)-D-talopyranoside methiodide were crystallized from a methanol–ethyl ether mixture. Lattice parameters were obtained with Mo Kα radiation on a previously aligned Picker four-circle automatic X-ray diffractometer. Fifteen reflections

were used in a least-squares analysis of the cell lengths, orientation angles, and the 'zeros' of χ and ω.* The unit-cell was determined to be orthorhombic with lattice constants $a = 13.179$ (9), $b = 10.604$ (8) and $c = 9.770$ (7) Å. The systematic absences of reflections $h = 2n + 1$ for $h00$, $k = 2n + 1$ for $0k0$, and $l = 2n + 1$ for

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* The following programs were used in the solving of this structure: *PICK*2 – a local version of J. A. Ibers' least-squares program for lattice constants and orientation angles based on W. C. Hamilton's *MODE*1; *DACOR* – a local program for Lp corrections and calculation of intensity standard deviations; *FORDAP* – A. Zalkin's Fourier program; *ORFLS* and *ORFEE* – W. R. Busing, K. O. Martin and H. A. Levy's full-matrix least-squares program and function and error program; *ORTEP* – C. K. Johnson's program for drawing thermal ellipsoids of crystal structures.

$00l$ are uniquely consistent with the space group $P2_12_12_1 - D_2^4$. The calculated density of 1.690 g.cm^{-3} for 4 chemical species per unit cell is in good agreement with the experimental density of 1.69(3) g.cm^{-3} measured by flotation.

For collection of intensity data, a crystal of length 0.18 mm and diameter 0.08 mm was mounted on the end of a glass fiber, with Duco glue, such that the needle axis (c axis) was approximately collinear with the fiber axis. The arcs were deliberately offset so that no crystallographic axis coincided with the φ axis of the diffractometer.

The diffraction data were collected automatically using Mo $K\alpha$ radiation filtered through 2.8 mils of Zr foil with the pulse height analyser set to accept 90%

Table 1. *Final atomic parameters*

(a) Final coordinates ($\times 10^4$) and thermal parameters ($\times 10^4$) for non-hydrogen atoms

The form of the anisotropic thermal ellipsoid is

$$\exp\left[-(h^2\beta_{11} + k^2\beta_{22} + l^2\beta_{33} + 2hk\beta_{12} + 2hl\beta_{13} + 2kl\beta_{23})\right].$$

Standard deviations estimated by least-squares for the least significant digit are given in parentheses.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C(1)	-2211 (9)	-3832 (16)	-6446 (13)	53 (9)	67 (14)	119 (17)	-2 (13)	-5 (10)	-10 (18)
C(2)	-2662 (12)	-2698 (14)	-7158 (17)	47 (11)	75 (16)	162 (28)	-16 (11)	5 (15)	22 (18)
C(3)	-2370 (11)	-1515 (12)	-6375 (14)	75 (11)	21 (16)	96 (18)	32 (9)	10 (12)	21 (13)
C(4)	-1207 (9)	-1488 (13)	-6235 (12)	41 (8)	71 (17)	73 (14)	8 (10)	2 (9)	-23 (13)
C(5)	-779 (12)	-2702 (11)	-5587 (12)	61 (10)	52 (11)	74 (20)	18 (11)	3 (14)	-1 (11)
C(6)	-986 (19)	-2977 (17)	-4073 (22)	132 (23)	67 (17)	104 (22)	7 (20)	-19 (20)	0 (19)
C(7)	-2226 (16)	-6048 (27)	-6506 (20)	58 (14)	184 (34)	245 (29)	5 (23)	-41 (19)	39 (30)
C(8)	-1116 (16)	76 (18)	-4254 (18)	100 (18)	123 (22)	129 (31)	-22 (16)	-4 (14)	-71 (19)
C(9)	-1039 (14)	802 (16)	-6631 (24)	86 (18)	67 (16)	191 (28)	-24 (14)	-33 (19)	8 (16)
C(10)	349 (11)	287 (15)	-5707 (18)	48 (12)	129 (19)	180 (29)	-30 (11)	-2 (14)	-29 (18)
O(1)	-2434 (10)	-4883 (11)	-7214 (11)	75 (8)	71 (10)	160 (15)	-9 (7)	-39 (10)	6 (11)
O(2)	-3709 (7)	-2722 (9)	-7184 (10)	59 (8)	114 (12)	171 (14)	11 (8)	-16 (8)	-16 (11)
O(3)	-2868 (6)	-1482 (9)	-5075 (9)	61 (6)	111 (11)	106 (14)	17 (7)	5 (7)	-5 (11)
O(4)	-1142 (5)	-3714 (12)	-6439 (8)	40 (6)	74 (8)	131 (11)	-5 (9)	2 (6)	-20 (14)
N	-755 (11)	-263 (9)	-5676 (10)	61 (9)	79 (11)	103 (18)	-4 (10)	-2 (12)	-2 (10)
I	-683 (1)	-1278 (1)	-302 (1)	66 (1)	82 (1)	102 (1)	3 (1)	-1 (1)	-3 (1)

(b) Final coordinates ($\times 10^3$) and bond distances for hydrogen atoms

Estimated standard deviations for hydrogen positions are about 0.15 Å.

	x	y	z	D
H(C1)	-250 (7)	-366 (12)	-545 (12)	1.06 Å
H(C2)	-215 (12)	-262 (14)	-805 (13)	1.11
H(C3)	-247 (11)	-79 (12)	-687 (14)	0.92
H(C4)	-90 (9)	-153 (12)	-727 (12)	1.09
H(C5)	14 (10)	-259 (11)	-560 (14)	1.21
H(C6)	-83 (12)	-370 (18)	-397 (13)	0.80
H(C6')	-155 (10)	-270 (16)	-394 (19)	0.81
H(C6'')	-84 (12)	-222 (13)	-345 (13)	1.02
H(C7)	-233 (9)	-572 (11)	-525 (14)	1.28
H(C7')	-155 (10)	-615 (19)	-638 (13)	0.90
H(C7'')	-284 (10)	-631 (14)	-622 (13)	0.89
H(C8)	-102 (11)	91 (14)	-407 (13)	0.91
H(C8')	-56 (14)	-24 (16)	-370 (16)	0.97
H(C8'')	-180 (10)	54 (12)	-422 (13)	1.03
H(C9)	-57 (9)	140 (14)	-624 (13)	0.96
H(C9')	-49 (9)	56 (12)	-755 (12)	1.18
H(C9'')	-163 (10)	86 (21)	-656 (16)	0.78
H(C10)	66 (10)	56 (12)	-548 (12)	1.01
H(C10')	42 (11)	-63 (12)	-658 (13)	0.93
H(C10'')	53 (11)	-58 (10)	-475 (14)	1.01
H(O2)	-360 (9)	-324 (11)	-788 (13)	0.89
H(O3)	-335 (9)	-81 (12)	-507 (14)	0.95

Table 2. *Comparison of the observed and calculated structure factors for 4,6-dideoxy-4-(N, N-dimethylamino)-α-D-talopyranoside methiodide*

of the incoming radiation. The moving-counter moving crystal scan technique was used with a drive speed of 1° per minute and a take off angle of 2·0°. The intensity for each reflection was recorded on punch cards after a 2° continuous scan (0·9° before the peak maximum and 1·1° after) through the peak and backgrounds of 30 sec at both ends of the scan. The reflection data were collected in the octant $+h,+k,+l$, out to a 2θ of 45°. Additional data were not collected due to the decomposition of the crystal as manifested by the final opacity and yellowness.

A total of 948 reflections were collected, of which 798 had net intensities above 2 standard deviations. The intensities of five standard reflections (040, 006, 600, 120, 004) were checked after every one hundred data in order to follow the rate of decomposition or other systematic changes in intensity.

The raw data were corrected for Lorentz and polarization factors, background, and loss of intensity due to decomposition. The rate of apparent decomposition was taken to be the average of the rates of decrease in intensity of the five standard reflections which were approximately linear, equivalent, and equal to 1% per 100 reflections. Standard deviations for the intensities were calculated using the formula $[\text{DATA}+2\ \text{BK}1+2\ \text{BK}2-0\cdot03^2\ (\text{DATA}-2\ \text{BK}1-2\ \text{BK}2)^2]^{1/2}$ (Corfield, Doedens & Ibers, 1967). The absorption of the crystal was not taken into account since μ equals 23·7 cm^{-1} for Mo $K\alpha$ radiation.

Structure analysis

Solution of a three-dimensional Patterson map gave the coordinates of the iodides in the unit cell. A Fourier synthesis phased on the iodide positions yielded the locations of the 10 carbon, 4 oxygen and one nitrogen atom of the sugar. After several cycles of full-matrix least-squares refinement the anomalous scattering of the iodide was taken into account.[*] It was found that the set of coordinates corresponding to the D-isomer yielded a discrepancy index $R(=\sum||F_o|-|F_c||/\sum|F_o|)$ of 0·055 vs. that of 0·057 for the L-isomer, consistent with the chemical evidence. Anisotropic refinement of this isomer resulted in an R of 0·041.

A difference electron density map was calculated and the largest residual peak of 0·50 e.A^{-3} corresponded to a likely hydrogen atom position. Of the 20 largest peaks on the map, 16 corresponded to hydrogen atom positions with the remaining 6 hydrogen atoms among the 50 largest peaks. Least-squares refinement of the hydrogen atom positions with the thermal parameters set at 3·0 yielded a final R of 0·031. The final weighted $R=(\sum w(|F_o|-|F_c|)^2/\sum wF_o^2)^{1/2}$ was 0·029 and the error of fit was 0·7228. The final difference map contained a maximum peak of 0·44 e.A^{-3}.

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[*] The f_i values were obtained from *International Tables for X-ray Crystallography* (1968).

The final positional coordinates and thermal parameters, along with their standard deviations calculated from the variance–covariance matrix, are given in Table 1. Table 2 contains the comparison of the observed and calculated structure factors.*

Description of structure

The configuration and atomic numbering scheme of 4,6-dideoxy-4-(N, N-dimethylamino)-α-D-talopyrano-

* The FO values of reflections whose observed intensities were below 2 standard deviations have been left blank in this Table. The 332 reflection was not recorded due to machine failure.

side methiodide can be seen in Fig. 1. This compound is the first three-dimensionally characterized talopyranoside and is one of the few 1C trans chair conformations which have been studied by X-ray diffraction. A partial structure of methyl-2-chloromercuri-2-deoxy-α-D-talopyranoside, however, has been determined by two-dimensional projections and contains the ring in the C1 conformation (Bain & Harding, 1965).

A comparison of the 'instability factors' (Reeves, 1950) between the two talopyranosides is significant in explaining the distortion of the angles in the amino substituted sugar. The C1 structure placed the HgCl group in the axial position on the same side of the ring as the axial oxygen atom bonded to the 4 position.

Table 3. *Bond distances and angles for* 4,6-*dideoxy*-4-(N,N-*dimethylamino*)-D-*talopyranoside methiodide*

Standard deviations given in parentheses are for least significant figures.

| i	j	D_{ij}	i	j	k	$\angle ijk$
C(1)	C(2)	1·51 (2) Å	C(1)	C(2)	C(3)	109·1 (1·3)°
C(2)	C(3)	1·52 (2)	C(2)	C(3)	C(4)	108·2 (1·1)
C(3)	C(4)	1·54 (2)	C(3)	C(4)	C(5)	112·7 (1·2)
C(4)	C(5)	1·54 (2)	C(4)	C(5)	O(4)	105·3 (1·1)
C(5)	C(6)	1·53 (2)	C(5)	O(4)	C(1)	113·5 (1·1)
C(1)	O(1)	1·38 (2)	O(4)	C(1)	C(2)	108·9 (1·3)
C(2)	O(2)	1·38 (2)				
C(3)	O(3)	1·43 (2)	O(4)	C(1)	O(1)	106·7 (1·2)
C(1)	O(4)	1·41 (1)	O(1)	C(1)	C(2)	108·1 (1·0)
C(5)	O(4)	1·44 (2)	C(1)	C(2)	O(2)	112·8 (1·2)
C(7)	O(1)	1·44 (2)	O(2)	C(2)	C(3)	106·3 (1·3)
C(4)	N	1·53 (2)	C(2)	C(3)	O(3)	110·5 (1·2)
C(8)	N	1·51 (2)	O(3)	C(3)	C(4)	112·2 (1·1)
C(9)	N	1·51 (2)	C(3)	C(4)	N	115·8 (1·1)
C(10)	N	1·46 (2)	N	C(4)	C(5)	114·8 (0·9)
			C(4)	C(5)	C(6)	119·4 (1·2)
			C(6)	C(5)	O(4)	110·9 (1·3)
			C(7)	O(1)	C(1)	113·1 (1·3)
			C(4)	N	C(8)	114·0 (1·2)
			C(4)	N	C(9)	108·5 (1·0)
			C(4)	N	C(10)	111·6 (1·1)
			C(8)	N	C(9)	108·1 (1·4)
			C(8)	N	C(10)	109·8 (1·4)
			C(9)	N	C(10)	104·4 (1·3)
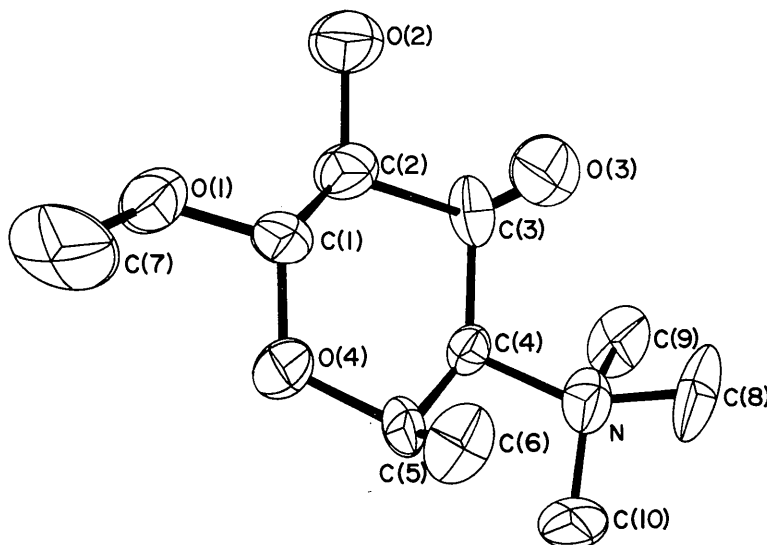
Fig. 1. The molecular structure, numbering scheme, and thermal ellipsoids for 4,6-dideoxy-4-(N,N-dimethylamino)-α-D-talopyranoside methiodide.

The instability caused by the steric interaction of these two groups is evidently of less magnitude than the instability caused by the ring going into the $1C$ conformation and producing the Hassel–Ottar effect, *i.e.* the sixth carbon atom and the third oxygen atom being axial on the same side of the ring. In the amino substituted sugar the very strong energetic preference of the relatively bulky trimethylammonium group for the equatorial position dictates the conformation $1C$ and results in a molecule which has the Hassell–Ottar effect frozen in.

The strain in the sugar framework from the above effects is manifested in the non-ideal angles associated with the ring. The conformation angles, which have been calculated to be between 55·8 and 61·7° (Berman & Kim, 1968) for an idealized pyranose ring, range from 55·2 to 67·2° with the larger angles occurring between the ammonium group and its neighbors. The interior ring angles vary from 105·3 to 113·5° while the exterior angles run between 106·3 and 119·4°. Both of these ranges are broader than most other pyranose systems. All N-methyl hydrogen atoms are staggered with respect to the other carbon atoms attached to the nitrogen atoms.

The bond distances are comparable with previously determined sugars with carbon–carbon distances varying between 1·51 and 1·54 Å, carbon–oxygen 1·38 to 1·44 Å, and carbon–nitrogen 1·46 to 1·53 Å. The C(1)–O(1) bond is shorter than the average as has been noted in similar systems (Berman, Chu & Jeffrey, 1967). Table 3 contains all the bond distances and angles for this sugar.
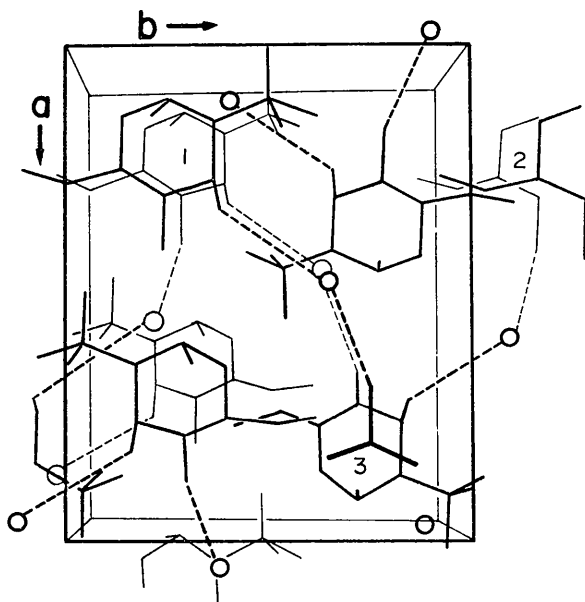
The packing scheme can be seen in Fig. 2. A network of rings, comprising a ribbon two sugar units wide, is formed by the weak hydrogen bonding between the hydroxy groups and the iodides. The bonding is traced by the dashed line from O(2) of ring 1 to the iodide to O(3) of ring 3, and then from O(2) of ring 3 to the iodide to O(3) of ring 2 which is a unit cell translation from ring 1. The two hydrogen bond distances of O(3)···H···I of 3·52 Å, and O(2)···H···I of 3·73 are relatively weak as indicated by the sum of the ionic radii of oxygen and iodine of 3·55 Å (Pauling, 1960).

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Fig. 2. The packing scheme as seen down the *c* axis. The circles represent the iodides and the dashed lines represent the hydrogen bonding.