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THE CRYSTAL STRUCTURES OF α AND β DIMORPHS OF 1,2:5,6-DIANHYDROGALACTITOL AND 3,4-DI-*O*-ACETYL-1,2:5,6-DIANHYDROGALACTITOL

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ABSTRACT

X-Ray crystal-structure analysis carried out on dimorphs (α and β) of the cytostatic drug 1,2:5,6-dianhydrogalactitol (DAG) and its 3,4-diacetate (DDAG) revealed conformational differences in the positioning of the oxirane termini with respect to the C-2–C-3 bond. As a consequence, the tail-to-head distances of the methylene groups at positions 1 and 6 are different in the two conformers denoted A and B (6.34 and 5.88 Å, respectively). The structures can be characterised as having conformations A in α-DAG, A,B in β-DAG, and B,B in DDAG.

INTRODUCTION

Some of the terminally disubstituted hexitols are known as dialkylating agents and as potent antitumor drugs. During an investigation of the chemical transformation and *in vivo* metabolism of 1,6-dibromo-1,6-dideoxygalactitol[1] (DBD, ELOBROMOL®), attention was focused on 1,2:5,6-dianhydrogalactitol (DAG). It was found that DAG possesses strong cytostatic activity, although somewhat different from that of DBD[1–5]. The 3,4-diacetate (DDAG) of DAG has even more favourable therapeutic activity: less side-effects and increased activity against tumor cells[5]. Recent investigations[6] indicate that DAG may act *via* interstrand cross-linking of cellular DNA. Geometrical considerations may play an important role in such a reaction and therefore X-ray analysis was undertaken. A further impetus was given when the preliminary studies revealed that DAG exists as dimorphs, the formation of which depends on solvent temperature and/or pressure.

EXPERIMENTAL AND RESULTS

The α-modification of DAG can be obtained from various solvents (*e.g.*, ethanol, 2-propanol, and dichloroethane), and its crystalline powder can be converted into the β-modification if relatively high pressure ~5 MPa) is applied. The β-dimorph can be transformed into α by raising the temperature of the sample. Crystals of the β-dimorph for X-ray work were obtained by slow evaporation of a methanol solution.

α-DAG. — (*a*) *Crystal data.* $C_6H_{10}O_4$, mol. wt. = 146.1; monoclinic, space group $P2_1/c$; a = 5.092(2), b = 5.433(2), c = 12.359(6) Å; β = 94.5°(2); Z = 2; D_c = 1.424 $Mg.m^{-3}$, *i.e.*, the crystallographic asymmetric unit contains half of the molecule. Cell data were obtained from the least-squares fitting of 25 reflexions having high values of sin θ.

(*b*) *Data collection.* In total, 583 independent reflexions ($2\vartheta_{max}$ = 116°) were measured from a crystal of poor quality at room temperature on a four-circle diffractometer, using monochromatised CuKα radiation; 528 data with $I - 2.0\sigma(I) \geqq 0$ were considered as observed and used for further work.

(*c*) *Structure analysis.* The structure was solved by direct methods (MULTAN program of the SAI XTL package[7]), using 104 values of E above E_{min} = 1.40. A phase combination with the best figure of merit revealed all of the non-hydrogen atoms. Block-diagonal, least-squares refinement of the initial model with anisotropic thermal parameters led to a relatively high R value of 0.115 for the 528 reflexions included in the refinement. Location of H atoms from difference synthesis was attempted, but failed. No further improvement of atomic parameters could be achieved by generated hydrogens.

β-DAG. — (*a*) *Crystal data.* $P\bar{1}$; a = 4.989(1), b = 7.957(1), c = 9.496(1) Å; α = 113.75(1), β = 98.90(1), γ = 78.90(1)°; Z = 2; D_c = 1.439 $Mg.m^{-3}$.

(*b*) *Data collection.* In total, 1155 independent reflexions were collected on a four-circle diffractometer, using monochromatised MoKα radiation.

(*c*) *Structure analysis.* The structure was solved by the automatic, direct-method routine of the SHELX program-system[8] for 210 values of E having E ≧ 1.25. The phase combination with the best consistency gave all non-hydrogen atoms of two crystallographically independent molecule-halves which are not related by the space-group symmetry. The refinement did not converge well due to some clumsiness in finding a good weighting scheme; therefore, arbitrary $\sigma(F_o)$ parameters $[\sigma(F_o) = \sqrt{F_o(min) + F_o}]$ were calculated. Thus, a weighting scheme of program SHELX[8] $[w = 1.0/[\sigma^2(F_o) + k.F_o]$ was used with $k = [1/F_o(max)]^2$, by analogy with that proposed by Cruickshank[9], with satisfactory results. Refinement of atomic parameters concluded at an R value of 0.061 (R_w = 0.065) for the 784 reflexions, including the contributions of constrained hydrogen atoms. The latter were taken from a difference electron-density synthesis computed near the completion of the refinement.

DDAG. — (*a*) *Crystal data.* Triclinic, $P\bar{1}$; a = 9.442(4), b = 7.997(3), c =

TABLE I

ATOMIC CO-ORDINATES ($\times 10^4$) OF α-DAG, β-DAG, AND DDAG (e.s.d. VALUES IN PARENTHESES); ATOMS OF Mol. II ARE DENOTED WITH AN ASTERISK

	α-DAG				*DDAG*		
	x/a	y/b	z/c		x/a	y/b	z/c
O-1	4402(11)	1014(9)	3645(3)	O-1	8130(3)	6812(4)	2206(3)
O-3	2534(9)	3034(8)	5586(3)	O-3	42(2)	622(3)	2958(3)
C-1	1611(16)	1512(16)	3362(6)	O-4	8095(3)	11761(4)	2436(4)
C-2	3445(13)	3494(14)	3682(5)	C-1	8155(5)	6245(5)	3800(6)
C-3	3606(12)	4645(12)	4819(4)	C-2	9388(4)	7728(5)	3649(4)
				C-3	9459(3)	9593(4)	4138(4)
	β-DAG			C-4	9255(4)	11638(5)	2180(4)
				C-5	10045(6)	12593(7)	1007(6)
	x/a	y/b	z/c	O-1*	4272(4)	2863(4)	2879(4)
				O-3*	5027(2)	8129(3)	3674(3)
O-1	14140(5)	2104(3)	4352(3)	O-4*	12479(3)	6764(4)	2797(4)
O-3	10165(5)	4101(3)	6521(3)	C-1*	5796(6)	8649(7)	8200(6)
C-1	12360(8)	776(5)	4161(5)	C-2*	3926(4)	1171(5)	3407(4)
C-2	11262(8)	2442(4)	3863(4)	C-3*	5115(4)	950(4)	4864(4)
C-3	9674(7)	4096(4)	4998(3)	C-4*	3716(4)	7029(4)	2584(4)
O-1*	17638(7)	8047(4)	9661(3)	C-5*	15970(5)	3723(6)	8902(3)
O-3*	15618(6)	4266(4)	8006(3)	H-11	8475(4)	5152(5)	4006(4)
C-1*	17082(9)	8606(5)	11239(4)	H-12	7477(4)	6441(5)	4278(5)
C-2*	15470(7)	7331(4)	9995(4)	H-3	11465(3)	10351(4)	5956(4)
C-3*	15989(6)	5293(4)	9635(3)	H-51	10720(4)	7832(5)	10107(5)
H-O3	12199(1)	4009(1)	6879(1)	H-52	8824(5)	7188(5)	8714(5)
H-11	12829(10)	−379(10)	3379(10)	H-53	10097(4)	6228(5)	9168(5)
H-12	11661(10)	675(10)	5212(10)	H-11*	6719(4)	8986(5)	9384(5)
H-2	11098(1)	2226(1)	2830(1)	H-12*	4881(5)	8923(5)	8392(5)
H-3	7707(1)	4067(1)	4584(1)	H-2*	7030(4)	9283(4)	6552(4)
H-O3	16467(10)	4070(10)	7380(10)	H-3*	3915(3)	8474(4)	5253(4)
H-11*	18918(10)	8043(10)	11891(10)	H-51*	3380(4)	6759(4)	−2(4)
H-12*	16721(1)	9977(1)	11619(1)	H-52*	4853(4)	6243(5)	1253(5)
H-2*	13573(1)	7826(1)	9712(1)	H-53*	3544(4)	5081(5)	732(4)
H-3*	17856(1)	4987(1)	10123(1)				

8.380(3) Å; $\alpha = 93.43(3)°$, $\beta = 105.22(3)°$, $\gamma = 106.52(3)°$; V = 579.1 Å^3; Z = 2; μ(CuKα) = 8.47 cm^{-1}.

(*b*) *Data collection.* In total, 2216 independent reflexions were collected on a four-circle diffractometer ($2\theta_{max} = 134°$), using monochromatised CuKα radiation. After data reduction, 1805 reflexions were considered as observed [$I \geqq 3\sigma(I)$] and used in the refinement.

(*c*) *Structure analysis.* The structure was solved by the SHELX[8] direct-method routine for 222 E values with $|E| \geqq 1.2$. As in the case of β-DAG, two symmetrically independent molecule-halves were revealed around non-equivalent centres of symmetry. Refinement of atomic parameters led to a final R of 0.062, using unit weights. Positions of all hydrogen atoms were deduced from difference electron-density synthesis and allowed to vary in the final step of the refinement.

TABLE II

BOND DISTANCES (Å) AND ANGLES (DEGREES) OF α-DAG, β-DAG, AND DDAG (e.s.d. VALUES IN PARENTHESIS); ATOMS OF Mol. II ARE DENOTED WITH AN ASTERISK

α-DAG					
O-1–C-1		1.462(10)	C-1–C-2		1.460(11)
O-1–C-2		1.435(9)	C-2–C-3		1.534(9)
O-3–C-3		1.430(8)	C-3–C-3′		1.504(9)
C-1–O-1–C-2	60.5(8)	O-1–C-2–C-3	114.7(9)	O-3–C-3–C-3′	111.1(9)
O-1–C-1–C-2	58.8(8)	C-1–C-2–C-3	122.4(10)	C-2–C-3–C-3′	110.9(9)
O-1–C-2–C-1	60.7(8)	O-3–C-3–C-2	111.2(9)		
β-DAG					
O-1–C-1		1.447(5)	O-1*–C-1*		1.437(2)
O-1–C-2		1.447(5)	O-1*–C-2*		1.444(4)
O-3–C-3		1.427(2)	O-3*–C-3*		1.45[illegible]
O-3–H-O3		1.018(2)	O-3*–H-O3*		0.731[illegible]
C-1–C-2		1.453(5)	C-1*–C-2*		1.458[illegible]
C-1–H-11		0.934(8)	C-1*–H-11*		1.146[illegible]
C-1–H-12		1.143(6)	C-1*–H-12*		0.990(4)
C-2–C-3		1.498(5)	C-2*–C-3*		1.494(5)
C-2–H-2		0.918(2)	C-2*–H-2*		0.993(3)
C-3–H-3		1.000(3)	C-3*–H-3*		1.006(3)
C-3–C-3′		1.533(3)	C-3*–C-3′*		1.519(2)
C-1–O-1–C-2		60.2(4)	C-1*–O-1*–C-2*		60.8(4)
C-3–O-3–H-O3		111.8(4)	C-3*–O-3*–H-O3*		131.9(10)
O-1–C-1–C-2		59.9(4)	O-1*–C-1*–C-2*		59.8(4)
O-1–C-1–H-11		113.0(9)	O-1*–C-1*–H-11*		109.5(7)
O-1–C-1–H-12		120.7(7)	O-1*–C-1*–H-12*		103.7(5)
C-2–C-1–H-11		123.1(9)	C-2*–C-1*–H-11*		120.1(8)
C-2–C-1–H-12		116.9(8)	C-2*–C-1*–H-12*		125.8(6)
H-11–C-1–H-12		113.3(10)	H-11–C-1*–H-12*		114.1(8)
O-1–C-2–C-1		59.9(4)	O-1*–C-2*–C-1*		59.4(4)
O-1–C-2–C-3		114.5(4)	O-1*–C-2*–C-3*		114.8(4)
O-1–C-2–H-2		108.4(5)	O-1*–C-2*–H-2*		115.9(5)
C-1–C-2–C-3		122.4(5)	C-1*–C-2*–C-3*		121.4(5)
C-1–C-2–H-2		112.5(5)	C-1*–C-2*–H-2*		117.7(5)
C-3–C-2–H-2		121.8(5)	C-3*–C-2*–H-2*		115.4(5)
O-3–C-3–C-2		111.9(4)	O-3*–C-3*–C-2*		110.6(4)
O-3–C-3–H-3		113.2(4)	O-3*–C-3*–H-3′*		114.3(4)
O-3–C-3–C-3′		110.1(3)	O-3*–C-3*–C-3′*		106.5(3)
C-2–C-3–H-3		106.0(4)	C-2*–C-3*–H-3*		108.4(4)
C-2–C-3–C-3′		111.0(4)	C-2*–C-3*–C-3′*		111.9(4)
H-3–C-3–C-3′		104.3(4)	H-3*–C-3*–C-3′*		105.1(3)
DDAG					
O-1–C-1		1.433(5)	C-1–O-1–C-2		60.5(3)
O-1–C-2		1.433(4)	O-1–C-1–C-2		59.7(3)
C-1–C-2		1.445(6)	O-1–C-2–C-1		59.7(3)
C-2–C-3		1.500(5)	O-1–C-2–C-3		114.0(3)
C-3–C-3′		1.513(6)	C-1–C-2–C-3		121.7(3)
O-3–C-3		1.443(4)	O-3–C-3–C-2		107.1(2)

TABLE II (*continued*)

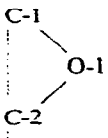
O-3–C-4	1.338(4)	O-3–C-3–C-3′	107.3(3)
O-4–C-4	1.199(5)	C-2–C-3–C-3′	113.6(3)
C-4–C-5	1.502(6)	C-3–O-3–C-4	118.9(2)
O-1*–C-1*	1.442(6)	O-3–C-4–O-4	123.1(3)
O-1*–C-2*	1.425(5)	C-3–C-4–C-5	110.7(3)
C-1*–C-2*	1.446(6)	O-4–C-4–C-5	126.2(4)
C-2*–C-3*	1.484(5)	C-1*–O-1*–C-2*	60.6(3)
C-3*–C-3′*	1.512(6)	O-1*–C-1*–C-2*	59.1(3)
O-3*–C-3*	1.448(4)	O-1*–C-2*–C-1*	60.3(3)
O-3*–C-4*	1.353(4)	O-1*–C-2*–C-3*	115.4(3)
C-4*–O-4*	1.189(4)	C-1*–C-2*–C-3*	121.5(3)
C-4*–C-5*	1.486(5)	O-3*–C-3*–C-2*	106.6(3)
		O-3*–C-3*–C-3′*	107.1(3)
C-1–H-11	1.01(4)	C-2*–C-3*–C-3′*	113.4(3)
C-1–H-12	0.88(4)	C-3*–O-3*–C-4*	117.5(2)
C-2–H-3	0.94(3)	O-3*–C-4*–O-4*	123.1(3)
C-3–H-3	0.87(3)	C-3*–C-4*–C-5*	111.3(3)
C-5–H-51	0.99(4)	O-4*–C-4*–C-5*	125.6(3)
C-5–H-52	0.99(4)		
C-5–H-53	1.00(4)		
C-1*–H-11*	1.09(4)		
C-1*–H-12*	1.00(4)		
C-2*–H-2*	0.88(3)		
C-3*–H-3*	0.93(3)		
C-5*–H-51*	1.12(3)		
C-5*–H-52*	0.76(4)		
C-5*–H-53*	0.93(4)		

RESULTS AND DISCUSSION

The fractional atomic co-ordinates for the compounds are listed in Table I. Table II shows the bond distances and angles. There are no significant differences in the dimensions of the five independent molecules. The observed molecular conformations (Table III and Figs. 1–3) can be assigned to two classes, A and B. Type A molecules build up the crystal lattice in α-DAG, whereas two distinct conformers, A and B, exist independently in the crystallographic asymmetric unit in β-DAG, which thus differs from DDAG where both independent molecules are of type B. Type B molecules can be derived from type A by applying a rotation of ~120° around the C-2–C-3 bond. As a consequence, C-1 and O-1 interchange their sites in the direction of the zigzag chain, and the tail-to-head C–C-termini distance also changes from 6.35 Å in A to 5.90 Å in B (means of 2 and 3 values, respectively). This finding may have some biological implications. The cross-linking of DNA segments by these alkylating agents[6] is generally believed to occur between N-7 of guanine residues of one-step-elevated DNA strands, which are ~9 Å apart. In establishing a cross-link of this type, the extended form of the DAG molecule might be favoured.

TABLE III

RELEVANT TORSION ANGLES (DEGREES) IN THE SYMMETRY-INDEPENDENT MOLECULES OF α-DAG, β-DAG, AND DDAG



	α-DAG	β-DAG		DDAG	
		Mol. I	*Mol. II*	*Mol. I*	*Mol. II*
O-1–C-1–C-2–C-3	−102	−102	−102	−101	−103
C-1–O-1–C-2–C-3	114	115	113	114	113
C-1–C-2–C-3–O-3	21	20	143	143	115
O-1–C-2–C-3–O-3	−48	−48	75	75	75
C-1–C-2–C-3–C-3′	145	143	−98	−99	−97
O-1–C-2–C-3–C-3′	76	75	−166	167	−167
C-1 · · · · C-1′ (Å)	6.38	6.34	5.88	5.94	5.89
Type of conformer	A	A	B	B	B

TABLE IV

HYDROGEN BONDS IN α-DAG AND β-DAG

α-DAG	β-DAG	
O-3 · · · · O-1[$-x,-y-1,-z$]	1.02 1.87	
2.82	O-3–H-O3 · · · · O-3*[$x,y,z-1$]	166°
	2.87	
	0.73 2.14	
	O-3*–H-O3* · · · · O-3[$1+x,y,z-1$]	153°
	2.81	

Consideration of intermolecular contacts may be of interest in the case of α-DAG and β-DAG, as these molecules possess active sites for hydrogen bonding. Relevant distances from this point are compiled in Table IV. The higher density of β-DAG accords with the more-extended hydrogen-bond network.

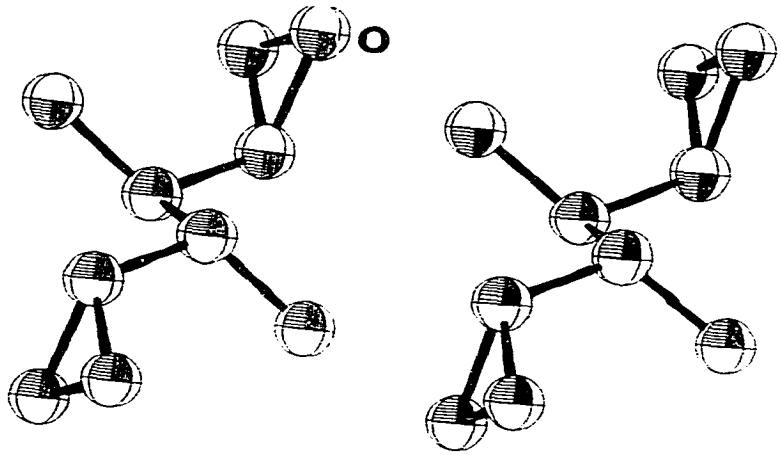


Fig. 1. Stereoscopic diagram of α-DAG.

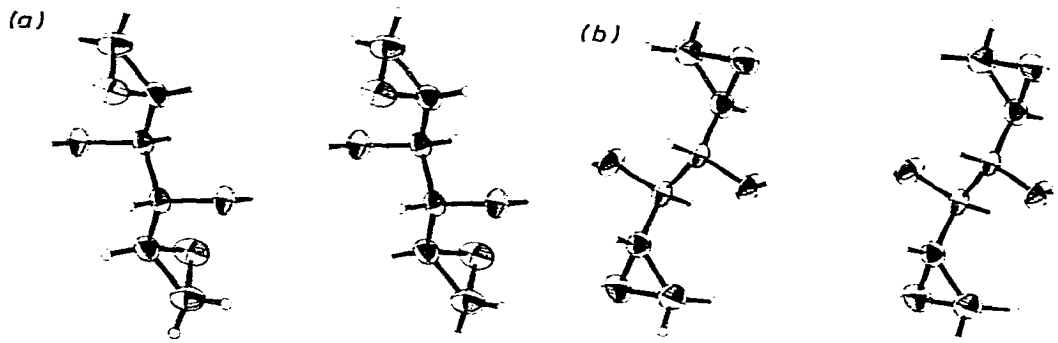


Fig. 2. Stereoscopic diagram of β-DAG, showing two crystallographically independent molecules (a and b) in conformations A and B, respectively.

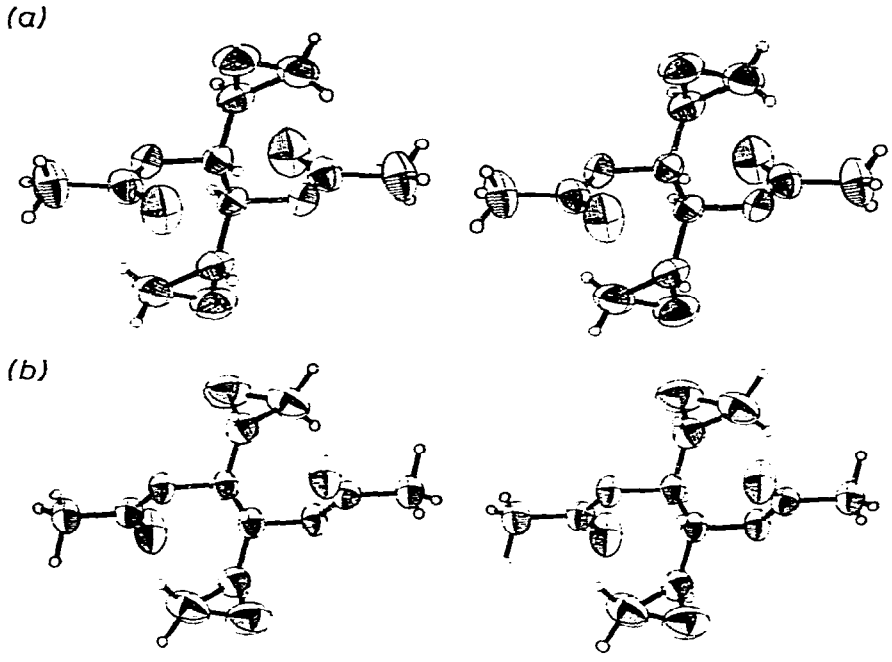


Fig. 3. Stereoscopic diagram of DDAG, showing two independent molecules of the crystallographic asymmetric unit with conformation B.

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