C4—C5	1.545 (9)	C15—C16	1.542 (9)
C4—C23	1.536 (6)	C16—C17	1.526 (10)
C4—C24	1.520 (10)	C17—C18	1.559 (7)
C5—C6	1.499 (7)	C17—C22	1.540 (9)
C5—C10	1.535 (9)	C17—C28	1.517 (8)
C6—C7	1.548 (9)	C18—C19	1.548 (9)
C7—C8	1.550 (9)	C19—C20	1.492 (7)
C8—C9	1.570 (7)	C19—C21	1.553 (11)
C8—C14	1.590 (7)	C20—C29	1.379 (16)
C8—C26	1.546 (8)	C20—C30	1.427 (14)
C9—C10	1.559 (8)	C21—C22	1.531 (10)
C9—C11	1.529 (9)	C28—O33	1.324 (7)
C10—C25	1.553 (8)	C28—O34	1.205 (8)
C2—C1—O32	126.5 (5)	C7—C8—C9	109.8 (5)
C1—C2—C10	118.2 (5)	C14—C8—C26	110.6 (4)
C1—C2—C3	109.2 (4)	C9—C8—C26	111.7 (4)
C3—C2—C10	103.4 (4)	C9—C8—C14	107.8 (3)
C2—C3—O31	110.0 (4)	C8—C9—C11	111.4 (5)
C2—C3—C4	106.1 (4)	C8—C9—C10	114.0 (4)
C4—C3—O31	114.8 (5)	C10—C9—C11	114.9 (4)
C3—C4—C24	111.8 (5)	C5—C10—C9	107.1 (4)
C3—C4—C23	111.4 (5)	C2—C10—C9	114.2 (4)
C3—C4—C5	102.4 (4)	C2—C10—C5	97.8 (5)
C23—C4—C24	107.8 (5)	C9—C10—C25	113.2 (5)
C5—C4—C24	110.2 (5)	C5—C10—C25	114.6 (4)
C5—C4—C23	113.3 (5)	C2—C10—C25	109.1 (5)
C9—C11—C12	113.3 (5)	C16—C17—C28	108.7 (4)
C11—C12—C13	111.5 (4)	C16—C17—C22	116.3 (5)
C12—C13—C18	114.2 (4)	C16—C17—C18	108.3 (6)
C12—C13—C14	110.0 (5)	C22—C17—C28	108.3 (5)
C14—C13—C18	111.3 (5)	C18—C17—C28	114.3 (5)
C8—C14—C13	106.3 (3)	C18—C17—C22	101.0 (4)
C13—C14—C27	111.8 (4)	C13—C18—C17	112.7 (4)
C13—C14—C15	109.8 (5)	C17—C18—C19	103.9 (5)
C8—C14—C27	112.7 (4)	C13—C18—C19	119.6 (5)
C8—C14—C15	110.3 (3)	C18—C19—C21	103.2 (5)
C15—C14—C27	106.1 (4)	C18—C19—C20	116.7 (6)
C14—C15—C16	114.9 (4)	C20—C19—C21	112.8 (5)
C15—C16—C17	109.2 (4)	C19—C20—C30	119.6 (7)
C4—C5—C10	107.0 (4)	C19—C20—C29	115.9 (7)
C4—C5—C6	120.7 (4)	C29—C20—C30	124.5 (8)
C6—C5—C10	114.4 (5)	C19—C21—C22	108.4 (6)
C5—C6—C7	107.5 (4)	C17—C22—C21	102.9 (5)
C6—C7—C8	113.7 (4)	C17—C28—O34	127.0 (5)
C7—C8—C26	107.3 (4)	C17—C28—O33	112.4 (5)
C7—C8—C14	109.7 (4)	O33—C28—O34	120.7 (5)
C2—C3—C4—C5	4.3 (6)	C12—C13—C14—C8	−63.9 (5)
C3—C4—C5—C10	25.8 (6)	C13—C14—C8—C9	63.3 (5)
C4—C5—C10—C2	−44.8 (5)	C14—C8—C9—C11	−58.3 (6)
C5—C10—C2—C3	46.1 (5)	C13—C14—C15—C16	−50.6 (6)
C10—C2—C3—C4	−32.6 (6)	C14—C15—C16—C17	56.6 (6)
C5—C6—C7—C8	56.7 (6)	C15—C16—C17—C18	−59.0 (6)
C6—C7—C8—C9	−51.7 (6)	C16—C17—C18—C13	61.8 (6)
C7—C8—C9—C10	50.3 (6)	C17—C18—C13—C14	−57.0 (6)
C8—C9—C10—C5	−53.0 (6)	C18—C13—C14—C15	49.2 (6)
C9—C10—C5—C6	60.3 (6)	C17—C18—C19—C21	29.2 (6)
C10—C5—C6—C7	−62.0 (6)	C18—C19—C21—C22	−3.0 (7)
C8—C9—C11—C12	52.8 (6)	C19—C21—C22—C17	−24.6 (7)
C9—C11—C12—C13	−52.1 (7)	C21—C22—C17—C18	41.8 (6)
C11—C12—C13—C14	58.4 (6)	C22—C17—C18—C19	−44.6 (6)

Data collection: Enraf–Nonius CAD-4 diffractometer. Program used to determine space group: STATCW (Sekar, 1991). Program used to solve structure: SHELX90 (Sheldrick, 1990). Program used to refine structure: SHELX76 (Sheldrick, 1976). Program used to calculate molecular parameters: PARST (Nardelli, 1983). Program used to draw stereodiagram: PLUTO (Motherwell & Clegg, 1978). Refinement was by full-matrix least-squares methods. All calculations were performed on a MicroVAX II computer.

Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and complete geometry have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55618 (18 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: LI1025]

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Structure and Absolute Configuration of a Monohydrate of Calcipotriol, (1α,3β,5Z,7E,22E,24S)-24-Cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1,3,24-triol

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Abstract

The absolute configuration of calcipotriol was established to be 1S,3R,8R,14S,17R,20S,24R. The molecular geometry of calcipotriol is similar to the stereochemistry observed in the structures of the related D vitamins.

Comment

Calcipotriol (I) (MC903, calcipotriene) is a structural analog of 1α,25-dihydroxy-vitamin D_3 (Calverly, 1987). Calcipotriol inhibits cell proliferation and stimulates cell differentiation (Binderup & Bramm, 1988). Kragballe and co-workers (Kragballe, Beck & Søgaard, 1988; Kragballe, 1989; Kragballe et al., 1991) have lately proved its efficiency in the treatment of psoriasis.

(I)
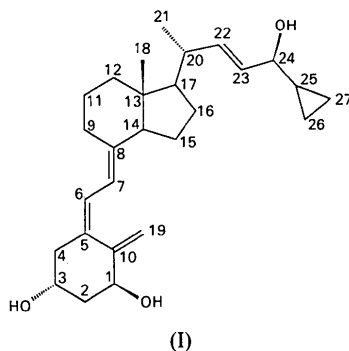
The absolute configuration of the skeleton of (I) is known from the synthetic route starting from vitamin D_2, whereas the absolute configuration of the side chain has only been determined indirectly through a Sharpless-type synthesis (Martin, Woodard, Yamada, Ikeda & Sharpless, 1981; Calverly, 1987).

The main purpose of this investigation was to confirm the absolute configuration of the side chain of (I) using single-crystal X-ray diffraction methods.

The commercial preparation of calcipotriol (I) gives a well defined reproducible crystal modification (Binderup, 1990), which unfortunately is not ideal for X-ray crystallographic investigations. Suitable crystals could, however, be isolated by successive recrystallization from water-saturated ethyl acetate giving (I) as a monohydrate.

Calcipotriol is structurally related to vitamin D, calciferol, and it is of obvious interest to examine how the stereochemistry of calcipotriol compares to the related calciferol structures. The three-dimensional structure of vitamin D_2 has been described (Hodgkin, Rimmer, Dunitz & Trueblood, 1963). Other structural studies of the biologically important fat-soluble D vitamins include the structures of vitamin D_2, ergocalciferol (Hull, Leban, Main, White & Woolfson, 1976); vitamin D_3, cholecalciferol (Trinh-Toan, DeLuca & Dahl, 1976); and its 25-OH substituted monohydrate (Trinh-Toan, Ryan, Simon, Calabrese, Dahl & DeLuca, 1977). The bond lengths, bond and torsion angles that are listed in Tables 2 and 3 agree well with those observed in the other structures. The stereochemistry of calcipotriol is illustrated by the ORTEP (Johnson,

1976) drawing in Fig. 1. It shows that its absolute configuration is $1S,3R,8R,14S,17R,20S,24R$. In the vitamin D structures the cyclohexane fragment is often referred to as ring A, and it has been observed in two different conformations. In calcipotriol the A ring is the so-called α conformer.
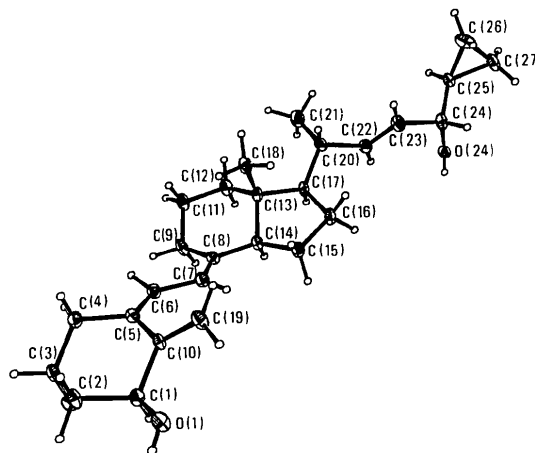

Fig. 1. ORTEP drawing of calcipotriol illustrating the stereochemistry and the atomic labelling. The thermal ellipsoids are scaled to enclose 50% probability. The H atoms are drawn as spheres with a fixed radii.

The conformation of the two fused rings appears to be virtually invariant in all the vitamin D structures, and calcipotriol fits well into this pattern. The only structural difference observed is in the conformation of the side chain. In the crystal structures of vitamin D_2 and D_3 molecules are found with this side chain in two different orientations. In calcipotriol the side chain C(20)—C(27) is found in an almost planar zigzag arrangement as in the case of 25-hydroxy-vitamin D_3 monohydrate (Trinh-Toan et al., 1977). This similarity may be related to the similarity between their hydrogen-bonding systems. The crystal packing in calcipotriol monohydrate is influenced by hydrogen bonds. These are described in Table 4 and illustrated on the stereopair in Fig. 2. The water molecule donates its two protons to two O(24)—H groups from molecules related by the symmetry of the twofold screw axis. In the 25-OH vitamin D_3 monohydrate the water plays an equivalent role connecting 25-OH groups. One of the hydroxy groups [O(3)—H] of the cyclohexane ring is hydrogen bonded to the O(1)—H of a molecule related by translational symmetry along the b axis. The O(1)—H group donates a proton to the water molecule. These strong interactions in the directions of the crystallographic b and c axes explain why the crystals grow as plates. The program used to solve the structure was SHELXS86 (Sheldrick, 1990). The remaining programs used were from the Enraf–

Nonius *SDP* system (Enraf–Nonius, 1985). The known absolute configuration of the vitamin D related fragment (Hodgkin, Rimmer, Dunitz and Trueblood, 1963) was used to assign the chirality of calcipotriol. Refinement was by full-matrix least-squares methods.
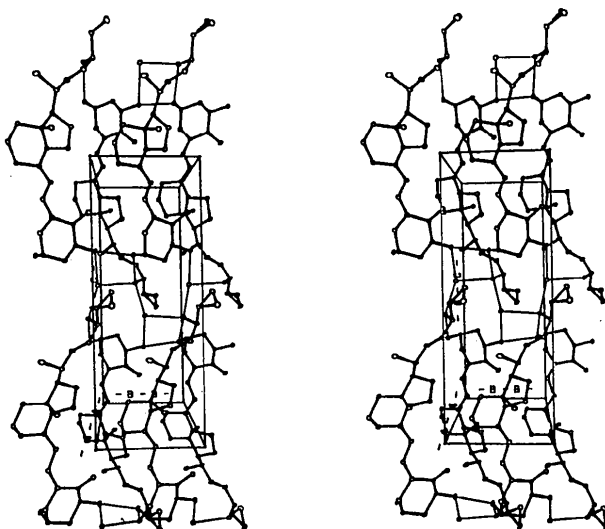

Fig. 2. Stereopair illustrating the crystal packing in calcipotriol viewed along the *a* axis. The hydrogen bonds in the structure are drawn as thin lines.

Experimental

Crystal data

$C_{27}H_{40}O_3 . H_2O$
$M_r = 430.63$
Monoclinic
$P2_1$
$a = 9.4377 (10)$ Å
$b = 6.9780 (11)$ Å
$c = 18.559 (3)$ Å
$\beta = 93.240 (13)°$
$V = 1220.2 (5)$ Å^3
$Z = 2$
$D_x = 1.172$ Mg m^{-3}

Cu $K\alpha$ radiation
$\lambda = 1.54184$ Å
Cell parameters from 22
    reflections
$\theta = 37–42°$
$\mu = 0.569$ mm^{-1}
$T = 122 (0.5)$ K
Plates
$0.40 \times 0.25 \times 0.03$ mm
White

Data collection

Enraf–Nonius CAD-4
    diffractometer
$\omega–2\theta$ scans
4850 measured reflections
3913 observed reflections
    $[F^2 > 3\sigma(|F|^2)]$
$R_{int} = 0.038$
$\theta_{max} = 75°$

$h = 0 \rightarrow 11$
$k = -8 \rightarrow 8$
$l = -20 \rightarrow 20$
3 standard reflections
    frequency: 167 min
    intensity variation: <4%
Linear correction for decay

Refinement

Refinement on F
Final $R = 0.050$
$wR = 0.064$

$w = [\sigma^2(F) + 9.0 \times 10^{-4}|F|^2]^{-1}$
$(\Delta/\sigma)_{max} = 0.29$
$\Delta\rho_{max} = 0.3$ e Å^{-3}

$S = 1.56$
3913 reflections
405 parameters
H-atom coordinates refined,
    fixed $B = 2.0$ Å^2

$\Delta\rho_{min} = -0.4$ e Å^{-3}
Atomic scattering factors
    from *International Tables*
    for X-ray Crystallography
    (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic thermal parameters* (Å^2)

$$U_{eq} = \tfrac{1}{3}\Sigma_i \Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j.$$

	x	y	z	U_{eq}
C(1)	0.6211 (3)	0.7952 (3)	0.7160 (1)	0.0150 (5)
C(2)	0.7072 (3)	0.7017 (4)	0.6581 (1)	0.0170 (5)
C(3)	0.7506 (3)	0.4972 (4)	0.6781 (1)	0.0168 (5)
C(4)	0.8343 (3)	0.4952 (4)	0.7503 (1)	0.0168 (5)
C(5)	0.7596 (3)	0.5962 (4)	0.8098 (1)	0.0127 (5)
C(6)	0.7573 (3)	0.5081 (4)	0.8745 (1)	0.0171 (5)
C(7)	0.7031 (3)	0.5729 (4)	0.9423 (2)	0.0174 (5)
C(8)	0.7086 (3)	0.4648 (4)	1.0029 (1)	0.0151 (5)
C(9)	0.7570 (3)	0.2576 (4)	1.0080 (1)	0.0201 (6)
C(10)	0.6991 (3)	0.7876 (4)	0.7899 (1)	0.0142 (5)
C(11)	0.8763 (3)	0.2262 (4)	1.0657 (2)	0.0222 (6)
C(12)	0.8400 (3)	0.3084 (4)	1.1392 (2)	0.0203 (6)
C(13)	0.7970 (3)	0.5201 (3)	1.1325 (1)	0.0138 (5)
C(14)	0.6700 (3)	0.5363 (4)	1.0758 (1)	0.0156 (5)
C(15)	0.6166 (3)	0.7409 (4)	1.0854 (2)	0.0200 (6)
C(16)	0.6409 (3)	0.7779 (4)	1.1670 (1)	0.0193 (6)
C(17)	0.7297 (3)	0.6095 (4)	1.1990 (1)	0.0156 (5)
C(18)	0.9233 (3)	0.6411 (4)	1.1107 (1)	0.0185 (6)
C(19)	0.7139 (3)	0.9417 (4)	0.8323 (2)	0.0198 (6)
C(20)	0.8298 (3)	0.6733 (4)	1.2628 (1)	0.0182 (5)
C(21)	0.9201 (4)	0.5114 (5)	1.2976 (2)	0.0313 (8)
C(22)	0.7446 (3)	0.7640 (4)	1.3202 (1)	0.0174 (5)
C(23)	0.7747 (3)	0.9294 (4)	1.3519 (2)	0.0199 (6)
C(24)	0.7011 (3)	1.0154 (4)	1.4140 (1)	0.0179 (5)
C(25)	0.7973 (3)	1.0142 (4)	1.4811 (1)	0.0176 (5)
C(26)	0.9073 (4)	1.1680 (5)	1.4928 (2)	0.0301 (8)
C(27)	0.7817 (4)	1.1624 (4)	1.5389 (2)	0.0256 (6)
O(1)	0.5900 (2)	0.9896 (3)	0.6966 (1)	0.0205 (4)
O(3)	0.6213 (2)	0.3888 (3)	0.6805 (1)	0.0179 (4)
O(24)	0.5762 (2)	0.9096 (3)	1.4305 (1)	0.0170 (4)
O(W1)	0.5538 (2)	0.50000	0.4395 (1)	0.0219 (4)

Table 2. *Geometric parameters* (Å, °)

C(1)—C(2)	1.530 (3)	C(13)—C(17)	1.551 (3)
C(1)—O(1)	1.430 (3)	C(13)—C(18)	1.534 (3)
C(1)—C(10)	1.520 (3)	C(13)—C(14)	1.554 (3)
C(2)—C(3)	1.524 (3)	C(14)—C(15)	1.528 (3)
C(3)—O(3)	1.439 (3)	C(15)—C(16)	1.541 (3)
C(3)—C(4)	1.516 (4)	C(16)—C(17)	1.542 (3)
C(4)—C(5)	1.517 (3)	C(17)—C(20)	1.538 (3)
C(5)—C(6)	1.351 (3)	C(20)—C(21)	1.535 (4)
C(5)—C(10)	1.491 (3)	C(20)—C(22)	1.508 (3)
C(6)—C(7)	1.458 (3)	C(22)—C(23)	1.320 (3)
C(7)—C(8)	1.353 (3)	C(23)—C(24)	1.504 (3)
C(8)—C(9)	1.517 (3)	C(24)—O(24)	1.438 (3)
C(8)—C(14)	1.505 (3)	C(24)—C(25)	1.499 (4)
C(9)—C(11)	1.525 (4)	C(25)—C(26)	1.501 (3)
C(10)—C(19)	1.335 (3)	C(26)—C(27)	1.501 (4)
C(11)—C(12)	1.536 (3)	C(27)—C(25)	1.503 (3)
C(12)—C(13)	1.535 (3)		
C(2)—C(1)—C(10)	111.7 (2)	C(14)—C(13)—C(17)	100.1 (2)
C(2)—C(1)—O(1)	109.7 (2)	C(14)—C(13)—C(18)	111.3 (2)
O(1)—C(1)—C(10)	110.0 (2)	C(17)—C(13)—C(18)	110.4 (2)
C(1)—C(2)—C(3)	112.0 (2)	C(8)—C(14)—C(15)	120.9 (2)
C(2)—C(3)—C(4)	110.1 (2)	C(8)—C(14)—C(13)	111.5 (2)
C(2)—C(3)—O(3)	106.5 (2)	C(13)—C(14)—C(15)	103.6 (2)
O(3)—C(3)—C(4)	111.6 (2)	C(14)—C(15)—C(16)	103.9 (2)
C(3)—C(4)—C(5)	113.5 (2)	C(15)—C(16)—C(17)	107.4 (2)
C(4)—C(5)—C(10)	115.1 (2)	C(13)—C(17)—C(16)	103.8 (2)
C(4)—C(5)—C(6)	117.9 (2)	C(13)—C(17)—C(20)	117.9 (2)
C(6)—C(5)—C(10)	127.0 (2)	C(16)—C(17)—C(20)	111.9 (2)
C(1)—C(10)—C(5)	114.4 (2)	C(17)—C(20)—C(22)	109.6 (2)
C(1)—C(10)—C(19)	122.2 (2)	C(17)—C(20)—C(21)	114.4 (2)

C(5)—C(10)—C(19)	123.4 (2)	C(21)—C(20)—C(22)	108.5 (2)
C(5)—C(6)—C(7)	130.6 (2)	C(20)—C(22)—C(23)	124.9 (2)
C(6)—C(7)—C(8)	123.1 (2)	C(22)—C(23)—C(24)	126.5 (2)
C(7)—C(8)—C(9)	125.5 (2)	C(23)—C(24)—C(25)	110.5 (2)
C(7)—C(8)—C(14)	124.2 (2)	C(23)—C(24)—O(24)	112.2 (2)
C(9)—C(8)—C(14)	110.4 (2)	O(24)—C(24)—C(25)	106.6 (2)
C(8)—C(9)—C(11)	112.8 (2)	C(24)—C(25)—C(26)	119.8 (2)
C(9)—C(11)—C(12)	112.2 (2)	C(24)—C(25)—C(27)	120.7 (2)
C(11)—C(12)—C(13)	111.0 (2)	C(26)—C(25)—C(27)	60.0 (2)
C(12)—C(13)—C(14)	108.3 (2)	C(25)—C(26)—C(27)	60.1 (2)
C(12)—C(13)—C(18)	110.2 (2)	C(25)—C(27)—C(26)	60.0 (2)
C(12)—C(13)—C(17)	116.2 (2)		

Table 3. Torsion angles (°)

C(10)—C(12)—C(2)—C(3)	54.5 (3)
C(1)—C(2)—C(3)—C(4)	−57.0 (3)
C(2)—C(3)—C(4)—C(5)	52.5 (3)
C(3)—C(4)—C(5)—C(10)	−46.8 (3)
C(4)—C(5)—C(10)—C(1)	43.9 (3)
C(10)—C(5)—C(6)—C(7)	−2.8 (5)
C(5)—C(6)—C(7)—C(8)	179.7 (3)
C(6)—C(7)—C(8)—C(9)	−6.4 (4)
C(7)—C(8)—C(9)—C(11)	−53.8 (3)
C(8)—C(9)—C(11)—C(12)	51.8 (3)
C(9)—C(11)—C(12)—C(13)	−53.8 (3)
C(11)—C(12)—C(13)—C(14)	56.8 (3)
C(12)—C(13)—C(14)—C(8)	−60.2 (3)
C(15)—C(14)—C(13)—C(17)	46.2 (2)
C(13)—C(14)—C(15)—C(16)	−34.6 (3)
C(14)—C(15)—C(16)—C(17)	9.5 (3)
C(15)—C(16)—C(17)—C(13)	19.2 (3)
C(16)—C(17)—C(13)—C(14)	−39.4 (3)
C(16)—C(17)—C(20)—C(22)	57.3 (3)
C(17)—C(20)—C(22)—C(23)	−131.5 (3)
C(20)—C(22)—C(23)—C(24)	−173.7 (3)
C(22)—C(23)—C(24)—C(25)	110.5 (3)
C(23)—C(24)—C(25)—C(26)	81.2 (3)
C(23)—C(24)—C(25)—C(27)	151.9 (3)
C(24)—C(25)—C(26)—C(27)	110.4 (3)
C(24)—C(25)—C(27)—C(26)	−109.0 (3)

Table 4. Hydrogen-bond geometry (Å, °)

D—H···A	D—A	D—H—A	H—A
O(1)—H(10)—O(W1)ⁱ	2.801 (3)	172 (3)	2.10 (4)
O(3)—H(30)—O(1)ⁱⁱ	2.818 (4)	148 (4)	2.23 (4)
O(24)—H(240)—O(3)ⁱⁱⁱ	2.703 (3)	169 (4)	2.01 (4)
O(W1)—H(W1)—O(24)ⁱᵛ	2.871 (3)	153 (3)	2.15 (4)
O(W1)—H(W2)—O(24)ᵛ	2.838 (2)	170 (3)	1.95 (3)

Symmetry code: (i) $1 - x, \frac{1}{2} + y, 1 - z$; (ii) $x, y - 1, z$; (iii) $1 - x, \frac{1}{2} + y, 2 - z$; (iv) $x, y, z - 1$; (v) $1 - x, y - \frac{1}{2}, 2 - z$.

Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and complete geometry have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55648 (35 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: LI1021]

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Structure of β,β-Trehalose

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Abstract

The structure of β,β-trehalose (β-D-glucopyranosyl β-D-glucopyranoside) tetrahydrate, $C_{12}H_{22}O_{11}.4H_2O$, is described. The molecule, unlike its α,α-isomer, has exact twofold symmetry through the O(1) atom. The two glucopyranosyl residues adopt a slightly distorted chair $^4C_1$ conformation, as defined by the Cremer & Pople puckering parameters, $Q = 0.567$, $q_2 = 0.067$, $q_3 = 0.563$ Å, $\theta = 6.8°$ and $\varphi_2 = 159.4°$. The packing of the crystal is determined by a complex system of hydrogen bonds, each hydroxyl group of the sugar forming two hydrogen bonds and each water molecule forming four hydrogen bonds. The ring and the glycosidic O atoms are, however, not involved in any hydrogen bonding.

Comment

The structure, chemistry and biochemistry of the naturally occurring non-reducing disaccharide, α,α-trehalose (α-D-glucopyranosyl α-D-glucopyranoside), also known as mycose or mushroom sugar, has been widely studied (Birch, 1963; Lee, 1980). Little is known, however, of the synthetic isomeric β,β-trehalose and α,β-trehalose (Fischer & Delbrück, 1909; Schlubach & Maurer, 1925; Haworth & Hickinbottom, 1931; Helferich & Weis, 1956). Interest has recently been shown (Colaco, 1992) in the use of these synthetic analogues in biochemical and medical studies, hence our interest