organic compounds

(1S*,2S*,4S*,5S*)-Cyclohexane-1,2,4,5-tetrol monohydrate

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In the title compound, $C_6H_{12}O_4 \cdot H_2O$, 1,4/2,5-cyclohexane-tetrol and water molecules are seen to possess twofold symmetry. All four hydroxyl groups of the tetrol participate in extensive intermolecular $O-H \cdots O$ hydrogen bonding to form molecular tapes propagating along the a axis. Translationally related tapes along the c axis are held together by four coordinated water molecules.

Comment

The title compound, (I), belongs to the class of only three cyclohexanetetrol isomers which have been isolated from nature to date (Maras *et al.*, 1998). These are betitol (von Lippmann *et al.*, 1901), *D*-(+)-1,4/2,5-cyclohexanetetrol (Ramanathan *et al.*, 1966; Craigie *et al.*, 1968) and toxocarol (Zeying & Mingzhe, 1987). Betitol was reported to be present in very small amounts in sugarbeet molasses. However, the occurrence of betitol has never been confirmed and the structure remains uncertain (Anderson, 1972). Toxocarol, isolated from a plant source (*Toxocarpus himalensis* Falc. Ex. Hook. f.) was found to be 1,4/2,3-cyclohexanetetrol and its structure, as determined by single-crystal X-ray crystallography, has been reported (Zeying & Mingzhe, 1987).
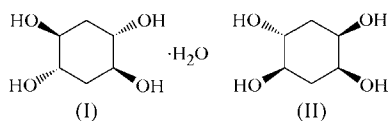

Tetrol (I) was first isolated from the marine alga *Monochrysis lutheri* and later from an alga of the genus *Porphydium* (Ramanathan *et al.*, 1966; Craigie *et al.*, 1968). The molecular structure of (I) was deduced on the basis of its physical and spectroscopic data, and its absolute configuration was assigned by comparison of the calculated and experimental circular dichroism (CD) spectrum.

From a purely synthetic perspective, tetrol (I) is intriguing, as it is obtained as the sole product in the acid-catalysed hydrolysis of *syn*- or *anti*-cyclohexane diepoxide (Zelinsky & Titowa, 1931; Craig *et al.*, 1967). Direct hydroxylation of 1,4-cyclohexadiene with SeO_2/H_2O_2 (Maras *et al.*, 1998) or with

silver benzoate/iodine (Prevost reaction; McCasland *et al.*, 1954, 1963) gave only (I) or predominantly (I). The expected formation of the isomeric *meso* tetrol, *i.e.* (1S*,2S*,4R*,5R*)-cyclohexane-1,2,4,5-tetrol, either failed to occur or formed an extremely minor alternative during the course of the reaction. Although a number of synthetic routes towards (I) have appeared in the literature, the single-crystal X-ray diffraction analysis of (I), unlike toxocarol, has not been reported so far. Against this background, we report here the crystal structure of (I).

Although the synthetic route adopted in this study yields (I) in the racemic form, spontaneous resolution during crystallization causes tetrol (I) to pack in the chiral space group $C2$ ($Z = 2$). Hence, the crystal structure reported in this communication corresponds to any one of the enantiomers of the title compound. Such a spontaneous resolution for a different cyclohexanetetrol, (II) (also obtained as a racemic modification through synthesis), has been recently reported by us (Mehta *et al.*, 2005). It is well known that 90% of the compounds that are capable of crystallizing in racemic or chiral space groups prefer the former (Gavezzotti, 2002; Brock *et al.*, 1991). Therefore, the preference of the two racemic cyclohexanetetrols, (I) and (II), to crystallize as a conglomerate of two enantiomeric forms is interesting and probably the consequence of a kinetically favoured pathway.

The D_2-symmetric tetrol crystallizes as a monohydrate (Fig. 1). The tetrol and water molecules exhibit twofold symmetry, coincident with the crystal symmetry. The puckering parameters (Cremer & Pople, 1975) for the cyclohexane ring [$q_2 = 0.031$ (2) Å, $q_3 = 0.556$ (2) Å, $\varphi_2 = 150$ (4)°, $Q_T = 0.557$ (2) Å and $\theta_2 = 3.4$ (2)°] describe a slightly distorted chair conformation. The total puckering amplitude Q_T is smaller than that for an ideal chair (0.63 Å). The φ_2 value of 150° corresponds to a twisted-boat conformation. Therefore, the cyclohexane ring is distorted from an ideal chair conformation and is flattened at atom C2, allowing the C1—C2—C3 bond angle to increase to 113.04 (14)°, while the other internal ring angles remain close to the tetrahedral values. The flattening of the cyclohexane ring at C2 can be attributed to the non-bonded 1,3-diaxial interaction between atom O1 and the H atoms bonded to atoms C2(2 − x, y, 1 − z) and C3.
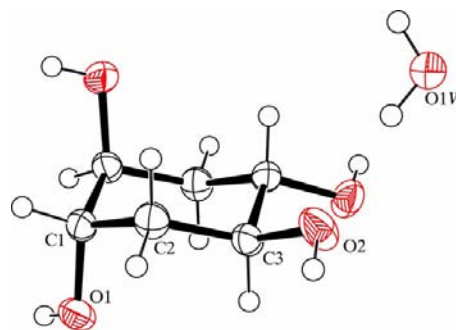
Figure 1
A view of tetrol (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. Unlabelled atoms are related to labelled atoms by the symmetry code (2 − x, y, 1 − z).

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Each water molecule is linked to four tetrol molecules *via* O—H···O hydrogen bonds in a pseudo-tetrahedral coordination (Fig. 2). This supramolecular assembly involves the equatorial hydroxyl groups (O2) acting as acceptors and the axial hydroxyl groups (O1) acting as donors. The –OH groups in (I) maximize their hydrogen-bonding potential (O2—H2O···O1; Table 2) by connecting the tetrol molecules further along the direction of the 2_1 axis. Therefore, a closer analysis of the O—H···O hydrogen-bond connectivity among the tetrol molecules reveals a helical O—H···O hydrogen-bond motif, with the helix axis coinciding with the 2_1 axis at $(\frac{1}{4}, y, \frac{1}{2})$ and $(\frac{3}{4}, y, \frac{1}{2})$ (Figs. 2 and 3).

To summarize, the supramolecular assembly of the title compound can be described as molecular tapes along the
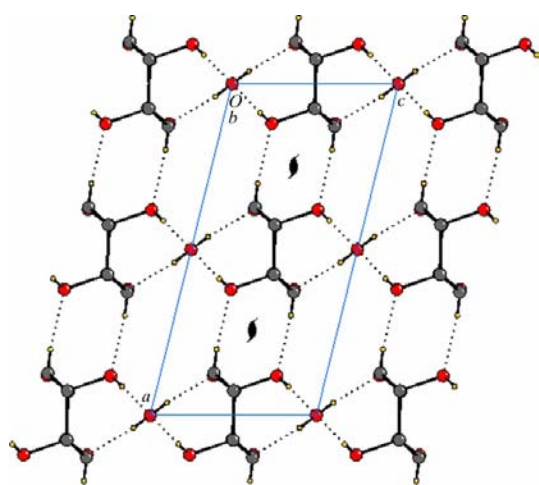
Figure 2
The molecular packing of (I), viewed along the *b* axis. H atoms bonded to C atoms have been omitted for clarity. Dotted lines indicate hydrogen bonds. Symbols of the 2_1 axis are shown for one unit cell, around which the helical O—H···O hydrogen-bonding motif is formed.
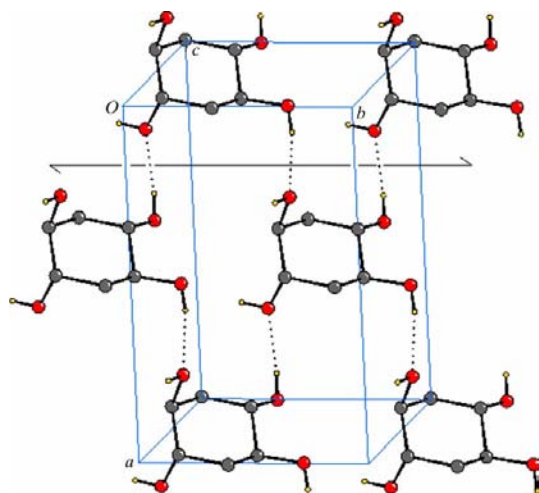
Figure 3
The molecular tapes, formed by the tetrol molecules of (I), propagating along the *a* axis. H atoms bonded to C atoms, and the water molecules, have been omitted for clarity. Dotted lines indicate hydrogen bonds. The symbol of the 2_1 axis parallel to the *b* axis at $(\frac{1}{4}, y, \frac{1}{2})$ is shown.

longest crystallographic axis, *i.e.* $a = 10.675$ Å (Fig. 3). The tapes are translated along the *c* axis and are held in space by water molecules which are sandwiched between them.

Experimental

Although a number of synthetic routes towards (I) have been reported in the literature, we found the following procedure particularly convenient as it avoids the use of any hazardous or expensive chemicals. To a solution of *m*-chloroperbenzoic acid (70% purity, 3.173 g, 12.87 mmol) in dichloromethane (10 ml), cooled to 273 K, was added 1,4-cyclohexadiene (0.500 g, 0.6 ml, 6.24 mmol). The reaction was stirred at the above temperature for 8 h and then at room temperature for 14 h. The excess peracid was decomposed with 20% Na_2SO_3 solution, followed by extraction of the mixture of epoxides with dichloromethane. The combined extracts were washed with saturated $NaHCO_3$ solution and then dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded a crude mixture (0.800 g) of *syn*- and *anti*-diepoxides, which was used directly for the next step. The mixture of diepoxides was stirred with 10% aqueous acetic acid (1 ml) at 325 K for 24 h. Complete evaporation of the volatiles under reduced pressure and repeated washing of the residue with dichloromethane gave (I) as a colourless solid (yield 0.740 g, 80%, over two steps). Suitable crystals of (I) were obtained by slow evaporation of an ethanol solution.

Crystal data

$C_6H_{12}O_4 \cdot H_2O$	$D_x = 1.394$ Mg m^{-3}
$M_r = 166.17$	Mo $K\alpha$ radiation
Monoclinic, $C2$	Cell parameters from 500
$a = 10.675$ (2) Å	reflections
$b = 7.3502$ (15) Å	$\theta = 3.4$–27.2°
$c = 5.1968$ (11) Å	$\mu = 0.12$ mm^{-1}
$\beta = 103.877$ (3)°	$T = 296$ (2) K
$V = 395.86$ (14) Å^3	Block, colourless
$Z = 2$	$0.50 \times 0.45 \times 0.43$ mm

Data collection

Bruker SMART CCD area-detector diffractometer	465 independent reflections
	461 reflections with $I > 2\sigma(I)$
φ and ω scans	$R_{int} = 0.022$
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)	$\theta_{max} = 27.0°$
	$h = -13 \rightarrow 13$
$T_{min} = 0.922$, $T_{max} = 0.950$	$k = -8 \rightarrow 9$
1567 measured reflections	$l = -6 \rightarrow 6$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0529P)^2 + 0.07P]$
$R[F^2 > 2\sigma(F^2)] = 0.033$	
$wR(F^2) = 0.082$	where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.17$	$(\Delta/\sigma)_{max} < 0.001$
465 reflections	$\Delta\rho_{max} = 0.21$ e Å^{-3}
58 parameters	$\Delta\rho_{min} = -0.30$ e Å^{-3}
H atoms treated by a mixture of independent and constrained refinement	Extinction correction: *SHELXL97* (Sheldrick, 1997)
	Extinction coefficient: 0.52 (4)

Table 1
Selected geometric parameters (°).

C1—C2—C3	113.04 (14)	C3^i—C3—C2	110.20 (10)
C2—C1—C1^i	111.24 (11)		
C1—C2—C3—O2	176.33 (14)	C3—C2—C1—O1	66.39 (16)
C1—C2—C3—C3^i	56.40 (19)	C3—C2—C1—C1^i	−53.7 (2)

Symmetry code: (i) $2 - x, y, 1 - z$.

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Table 2
Hydrogen-bond geometry (Å, °).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
O1—H1O$\cdots$O1W^{ii}	0.82	1.96	2.777 (2)	176
O2—H2O$\cdots$O1^{iii}	0.82	1.95	2.756 (2)	169
O1W—H1$W\cdots$O2	0.81 (3)	1.92 (3)	2.724 (2)	172 (3)

Symmetry codes: (ii) $x, y - 1, z + 1$; (iii) $-x + \frac{3}{2}, +y + \frac{1}{2}, -z + 1$.

Due to the absence of any significant anomalous scatterers ($Z >$ Si), attempts to confirm the absolute structure by refinement of the Flack (1983) parameter led to an inconclusive value of -0.5 (1) (Flack & Bernardinelli, 2000). Therefore, the intensities of the Friedel pairs (289) were averaged prior to merging of data in $C2$ and the absolute configuration was assigned arbitrarily. The reported value of R_{int} corresponds to subsequent merging of equivalent reflections in this space group. All CH$_2$, CH and OH H atoms of the tetrol were placed in geometrically idealized positions and constrained to ride on their parent atoms, with C—H distances in the range 0.97–0.98 Å and $U_{iso}(H) = 1.2U_{eq}(C)$, and O—H distances fixed at 0.82 Å and $U_{iso}(H) = 1.5U_{eq}(O)$. The H atom of the water molecule was located in a difference Fourier map and its position was refined freely, along with an isotropic displacement parameter.

Data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT* (Bruker, 1998); data reduction: *SAINT*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997) and *CAMERON* (Watkin *et al.*, 1993); software used to prepare material for publication: *PLATON* (Spek, 2003).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: OB1226). Services for accessing these data are described at the back of the journal.

References

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.

Anderson, L. (1972). *The Cyclitols*, Vol. I, *The Carbohydrates, Chemistry and Biochemistry*, Part A, edited by W. Pigman & D. Horton, pp. 519–579. New York: Academic Press.

Brock, C. P., Schweizer, B. & Dunitz, J. D. (1991). *J. Am. Chem. Soc.* **113**, 9811–9820.

Bruker (1998). *SMART* (Version 6.028) and *SAINT* (Version 6.02). Bruker AXS Inc., Madison, Wisconsin, USA.

Craig, T. W., Harvey, G. R. & Berchtold, G. A. (1967). *J. Org. Chem.* **32**, 3743–3749.

Craigie, J. S., McLachlan, J. & Tocher, R. D. (1968). *Can. J. Bot.* **46**, 605–611.

Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.

Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.

Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.

Flack, H. D. & Bernardinelli, G. (2000). *J. Appl. Cryst.* **33**, 1143–1148.

Gavezzotti, A. (2002). *Synlett*, pp. 201–214.

Lippmann, E. O. von (1901). *Berichte*, **34**, 1159–1162.

McCasland, G. E., Furuta, S., Johnson, L. F. & Shoolery, J. N. (1963). *J. Org. Chem.* **28**, 894–900.

McCasland, G. E. & Horsewill, E. C. (1954). *J. Am. Chem. Soc.* **76**, 1654–1658.

Maras, A., Erden, M., Seçen, H. & Sütbeyaz, Y. (1998). *Carbohydr. Res.* **308**, 435–437.

Mehta, G., Sen, S. & Dey, S. (2005). *Acta Cryst.* E**61**, o920–o922.

Ramanathan, J. D., Craigie, J. S., McLachlan, J., Smith, D. G. & McInnes, A. G. (1966). *Tetrahedron Lett.* **14**, 1527–1531.

Sheldrick, G. M. (1996). *SADABS*. University of Göttingen, Germany.

Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.

Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.

Watkin, D. M., Pearce, L. & Prout, C. K. (1993). *CAMERON*. Chemical Crystallography Laboratory, University of Oxford, England.

Zelinsky, N. D. & Titowa, A. N. (1931). *Berichte*, **64**, 1399–1406.

Zeying, Z. & Mingzhe, Z. (1987). *Jiegou Huaxue*, **6**, 128–131.