Concomitant dimorphism and helical self-assembly in a C_{2h}-symmetric 'locked' cyclitol†

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Communication

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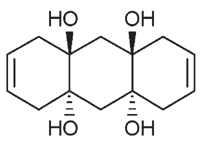
A conformationally locked C_{2h} symmetric tetrol concomitantly crystallized in two polymorphic modifications, differing principally in the mode of molecular association by C–H···O hydrogen bonds; the non-centrosymmetric tetragonal polymorph exhibits two complementary helical molecular arrangements mediated by O–H···O and C–H···O hydrogen bonds.

Polyhydroxylated compounds, which include many biologically important molecules such as sugars and inositols, have long been used as model systems for the systematic study of O–H···O hydrogen bonds.[1] Since the mode of molecular association in such compounds alters with varying spatial disposition of hydroxyl groups in the molecule, it appeared intuitively interesting to study the self-assembly in the solid state of a novel class of cyclitols, conformationally locked, with the hydroxyl groups constrained in an unnatural and high energy all axial disposition.[2] The tetrols **1** and **2** are among the simplest cyclitols, which embody such a structural feature. They essentially consist of a 1,2,4,5-cyclohexanetetrol constrained in an *all-trans* conformation in the central ring of a linearly fused tricyclic carbon framework. Owing to their 1,3-*syn*-diaxial relationship, the hydroxyl groups in **1** and **2** now become congenially placed for the formation of intramolecular O–H···O hydrogen bonds.[1] This in turn can be expected to restrict the number of possible modes in which the self-assembly of the tetrol molecules can take place in the solid state *via* the optimization of directional intermolecular O–H···O hydrogen bonds. Against this background we report herein the occurrence of the tetrol **1** in two concomitant polymorphic modifications[3] differing primarily in the mode of molecular association by C–H···O hydrogen bonds[4] in the presence of the relatively unchanged O–H···O hydrogen bonding pattern. The role of the C–H···O interactions in the crystal structures of the two polymorphs of **1** has been analysed further by a direct comparison with the molecular packing of the saturated variant **2**.



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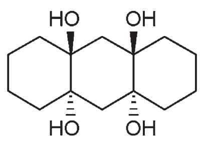
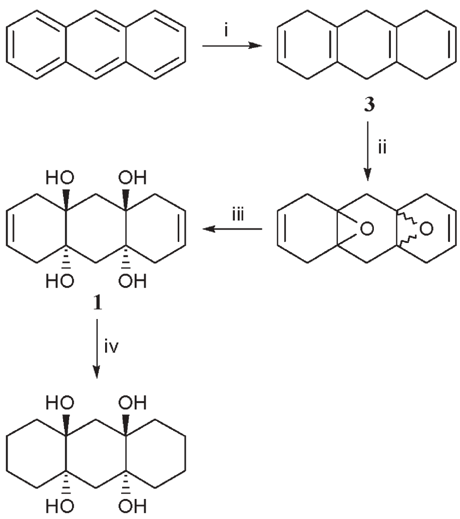


2

The C_{2h}-symmetric tetrol **1** was synthesized from the Birch reduction product of anthracene **3**, following a regioselective electrophilic epoxidation and mild acid catalysed stereoselective epoxide ring opening strategy (Scheme 1).[5] Upon slow evaporation of a saturated solution in methanol at ambient temperature (25 °C), **1** concomitantly crystallized in two distinct polymorphic modifications—a predominant square pyramidal (α) and a less prevalent rectangular block-type (β) (Fig. 1). With more volatile solvents and their combinations, such as acetone, 1 : 1 ethyl acetate–acetone and 4 : 1 acetone–benzene, only the α-form was obtained. The β-form predominated when **1** was crystallized from less volatile solvents such as acetonitrile or 1 : 1 ethyl acetate–acetonitrile. That the proportion of the β-polymorph increased with increase in the time of the crystallization process, appeared to point at the possibility of the β-form corresponding to the thermodynamically more stable polymorph. This was confirmed through subsequent DSC analyses of the two polymorphs.† While the crystals of the major α-form showed a lower mp 253–256 °C and a broad endotherm with multiple phase transitions, those of the minor β-form showed a significantly higher and sharper mp of 292 °C.

X-Ray data collected on the single crystals of the two poymorphs showed that while the α-form belonged to the polar space group $P4_1$ (or $P4_3$, $Z = 4$),[6] the minor β-form packed in the centrosymmetric $P\bar{1}$ ($Z = 4$). It is well known that achiral organic molecules tend to pack largely into centrosymmetric crystal structures.[7a] In such a case, the preponderance of the non-centrosymmetric α-form over the higher melting β-form further supports a kinetically favored chiral molecular association during nucleation.[7b]



Scheme 1 *Reagents and conditions* i, Na, liq. NH_3, EtOH, THF, −78 °C, 12 h, 80%; ii, *m*CPBA, CH_2Cl_2, −20 °C, 5 min, 89% overall yield (*syn* : *anti* diepoxide = 10 : 3); iii, 10% AcOH (aq.), 50–60 °C, 6 h, 95%; iv, H_2, 5% Pd–C, MeOH, RT, 1 h, 95%.

† Electronic supplementary information (ESI) available: ORTEP diagrams with atom numbering schemes, tables providing details of the hydrogen bonding schemes, DSC characteristics and the detailed packing diagrams of all revalent compounds. See http://dx.doi.org/10.1039/b506591g

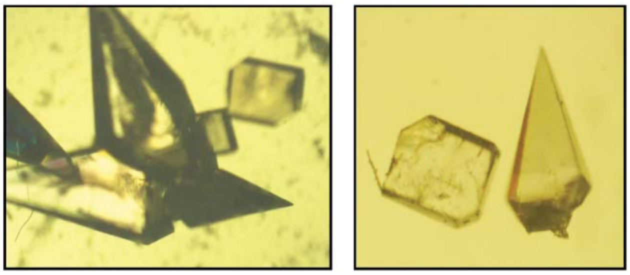


Fig. 1 Photographs of the representative crystals of the α- and β-dimorphs of **1**, shown separately (right) and as obtained concomitantly (left).

The crystal structure of the α-form displays molecules of **1** interlinked by two O–H···O hydrogen bonds [$d_{O\cdots H}$ = 1.82 Å, $\theta_{O–H\cdots O}$ = 167°] to form right-handed helical chains around the crystallographic 4_1 screw axis located at (0,0,0) [Fig. 2(a),(b)].[8] The lateral O–H···O hydrogen bonds [$d_{O\cdots H}$ = 1.84 Å, $\theta_{O–H\cdots O}$ = 167°] connect the neighboring helices, thus creating an intricate three-dimensional network of interconnected parallel helical molecular strands. As expected *a priori*, the *syn*-diaxial hydroxyl groups in each tetrol molecule further participate in intramolecular hydrogen bonding, thus effecting the formation of infinite O–H···O hydrogen bonding chains.

A closer analysis of the molecular packing in the α-form revealed that the molecules are interconnected by weaker C–H···O hydrogen bonds [$d_{O\cdots H}$ = 2.71 Å, $\theta_{C–H\cdots O}$ = 149°] in addition to the O–H···O hydrogen bonds.[9] These interactions, involving one of the olefinic C–H hydrogen atoms, link the molecules in the translationally related O–H···O helices to generate an independent helical arrangement of molecules, following the symmetry of the 4_1 axis located at (0.5, 0.5, 0) [Fig. 2(c), (d)]. The parallel C–H···O hydrogen bonded helices are interconnected by additional C–H···O soft contacts [$d_{O\cdots H}$, $\theta_{C–H\cdots O}$: 2.79 Å, 123°; 2.78 Å, 119°] involving two allylic C–H of the neighboring molecules.

The C–H···O interaction pattern, described above for the α-form, changes completely in the centrosymmetric β-dimorph. In contrast to the α-form, none of the olefinic C–H participates in the formation of a C–H···O hydrogen bond, rather the C–H···O motif observed in this case is generated by the participation of only the allylic hydrogens. The molecules are packed in the crystal structure in two discrete groups (A and B), organized in layers parallel to the *ab* plane in an A–B–A–B... kind of arrangement.† While molecules of the B-type are interconnected by four C–H···O hydrogen bonds [$d_{O\cdots H}$, $\theta_{C–H\cdots O}$: 2.49 Å, 126°; 2.57 Å, 129°] to form ladder-type chains along the (110) direction, those of the A-type do not involve C–H···O hydrogen bonding among themselves but link with the B-type molecular chains by two weaker C–H···O interactions [$d_{O\cdots H}$, $\theta_{C–H\cdots O}$: 2.70 Å, 126°; 2.65 Å, 131°] (Fig. 3, top).

Unlike the C–H···O hydrogen bonds, the cooperative O–H···O hydrogen bonding pattern, as seen in the α-form, remain essentially similar in the β-form (see ESI†). The four axially disposed hydroxyl groups in each molecule of tetrol **1** participate in two intra- and four intermolecular O–H···O hydrogen bonds [$d_{O\cdots H}$, $\theta_{C–H\cdots O}$: 2.09 Å, 167° (A to A); 1.77 Å, 169° (B to B); 1.87 Å, 169° (A to B); 1.90 Å, 168° (B to A)], stabilizing the C–H···O bonded molecular ladders and linking the molecules of the A-type as chains along the (−110) direction (Fig. 3, bottom).

We now focussed our attention on tetrol **2**, which was obtained from **1** through exhaustive hydrogenation (Scheme 1) and was found to crystallize in the triclinic space group $P\bar{1}$ (Z = 1), with the molecular inversion centers coinciding with the crystallographic centers of symmetry at (½, 0, ½). Though structurally related to **1**, this perhydro variant gave a completely different packing mode supported exclusively by O–H···O hydrogen bonds, as against the dimorphs of **1** in which both O–H···O and C–H···O hydrogen bonds are present (Fig. 4). The striking points of difference between the packing patterns of tetrols **1** and **2** were, (a) the truncation of the infinite O–H···O hydrogen bonding chains to a closed centrosymmetric $R^4_4(8)$ hydrogen bonding pattern,[10] and (b) a distinct separation of the hydrophilic and hydrophobic functional groups in the packing of the molecules of **2**, as opposed to those in **1**.

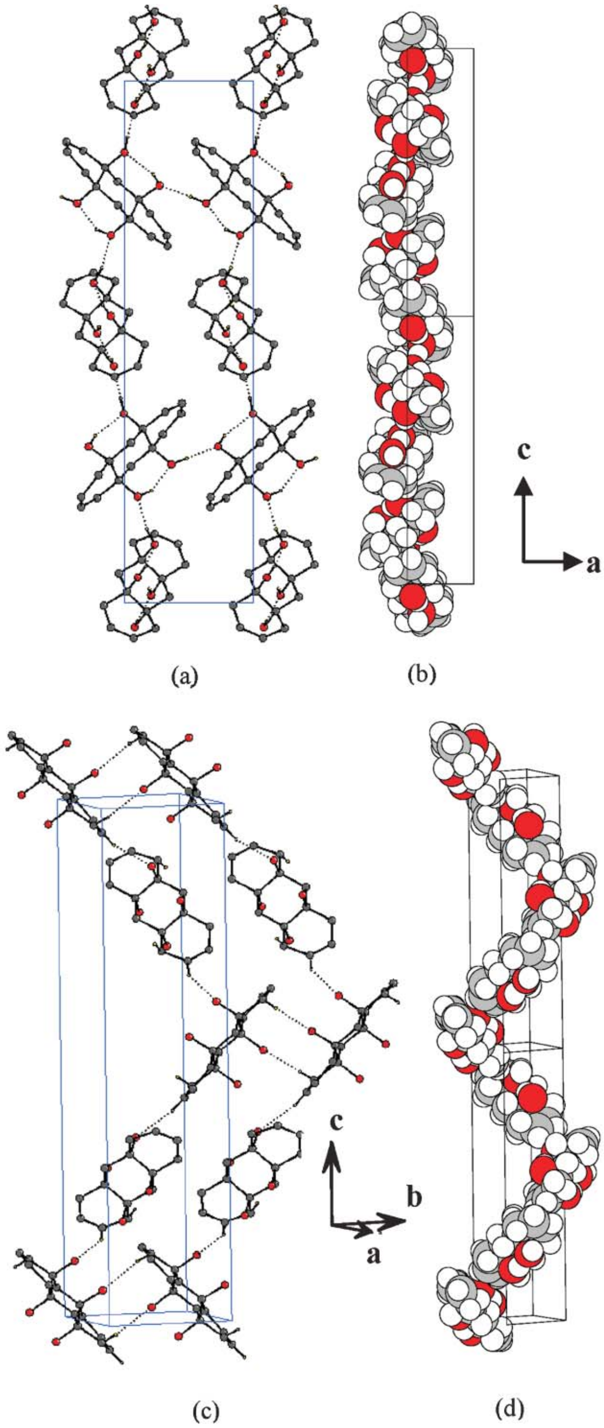
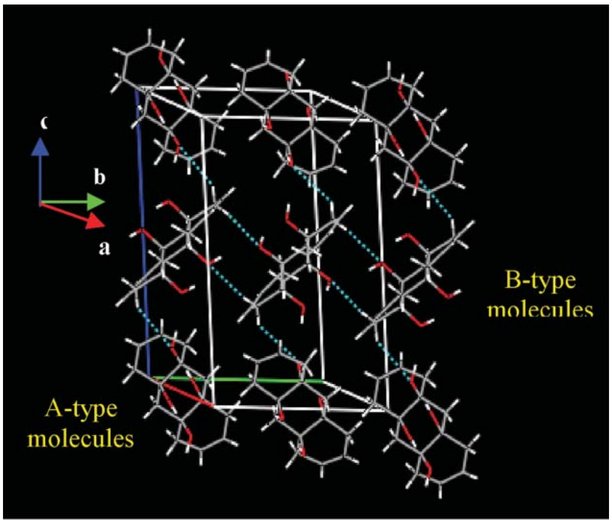


Fig. 2 The two independent helical molecular organizations in the α-form of **1** mediated by (a) O–H···O hydrogen bonding (click here to access a 3D image of Fig. 2a) and (c) the intermolecular C–H···O hydrogen bonds and soft contacts (click here to access a 3D image of Fig. 2c). The non-interacting hydrogen atoms in each case have been omitted for clarity. The space filling models of the O–H···O and the C–H···O hydrogen bonded helices have been shown in (b) and (d) respectively.



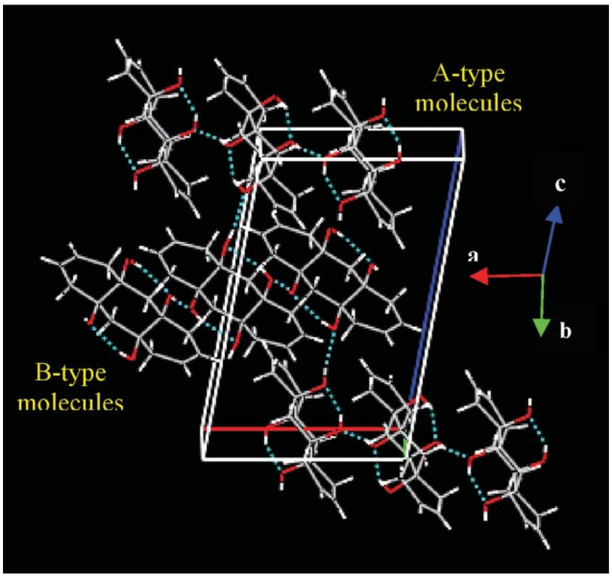


Fig. 3 The packing diagram of the β-form, showing the molecular assemblage mediated by C–H···O (top, click here to access a 3D image of Fig. 3 top) and O–H···O (bottom, click here to access a 3D image of Fig. 3 bottom) hydrogen bonding.

Though strikingly dissimilar, the packing patterns of the tetrols **1** and **2** appeared to highlight on a common and essential principle of molecular self-assembly, *i.e.* it strives to maximize all possible interactions at its disposal.[11] A hydroxyl group is capable of being the donor of one hydrogen bond, but an acceptor of two. However, in all the tetrols described in the study, the OH groups can involve themselves as acceptors of only one O–H···O hydrogen bond. Therefore in the dimorphs of **1**, the presence of C–H···O hydrogen bonds is a manifestation of a molecular self-assembling process to maximize the non-covalent interactions possible in the crystal lattice. Unlike **1**, the tetrol **2** is typically devoid of any acidic C–H donor. Hence, in **2**, as evident from the parallel stacking of the molecules, the only non-covalent available interaction, apart from the O–H···O hydrogen bonds, *i.e.* the isotropic van der Waals interactions, was maximized by optimizing the intermolecular contact area between the cyclohexane rings.

It is also interesting to note the subtle interplay of both O–H···O and C–H···O interactions in governing the crystal packing of the dimorphs of the tetrol **1**. The intramolecular O–H···O hydrogen bonds between the spatially constrained 1,3-diaxial hydroxyl groups and the rigid carbon frame work in **1** renders the O–H···O hydrogen bonding motif too robust to undergo much change from one dimorph to the other. It is the weaker and more flexible C–H···O hydrogen bonds that differ significantly in both strength and the position of the C–H donor functionality, among the two crystalline forms of **1**. The results obtained in this study are significant and are being currently utilized for a systematic investigation into the cooperativity among the various non-covalent interactions in determining the modes of self-assembly in conformationally locked cyclitols and sugars, possessing higher levels of oxyfunctionalization.‡

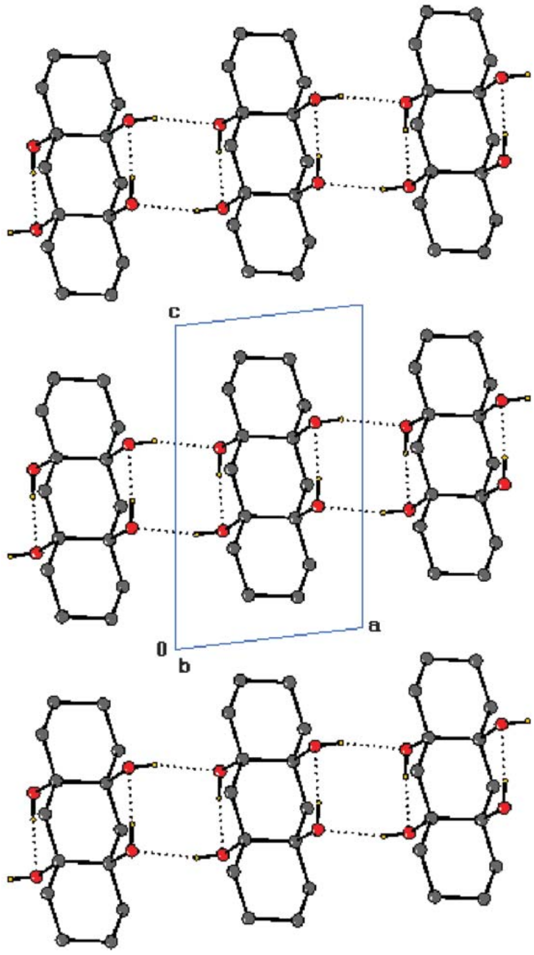


Fig. 4 The packing diagram of the tetrol **2**, showing the parallel stacking of the molecules to form molecular chains, running along the *a* axis. The non-interacting hydrogen atoms have been omitted for clarity. Click here to access a 3D image of Fig. 4.

Acknowledgements

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Notes and references

‡ Photographs of the representative crystals of the α- and β- dimorphs as observed under an OLYMPUS SZX12 optical microscope equipped with an optical polarizer and an OLYMPUS DP11 digital camera are given in the text. The DSC data on the dimorphs were recorded on a Mettler Toledo STARe System. The single crystal X-ray diffraction data were collected on a Bruker AXS SMART APEX CCD diffractometer at 292 K for **2** and at 100.0(2) K, using the OXFORD Cryosystem with N_2 flow, for the two polymorphs of **1** (this ensured accuracy in the determination of hydrogen atom positions from the difference Fourier map so that variations in the intermolecular interactions in the two forms can be judged with a reasonable amount of reliabity). The X-ray generator was operated at 50 KV and 35 mA using MoK_α radiation. The data were collected with a ω scan width of 0.3°. A total of 606 frames per set were collected using

SMART[13] in four different settings of φ (0°, 90°, 180° and 270°) keeping the sample to detector distance of 6.062 cm and the 2θ value fixed at −25°. The data were reduced by SAINTPLUS;[13] an empirical absorption correction was applied using the package SADABS[14] and XPREP[13] was used to determine the space group. The structures were solved using SIR92[15] and refined using SHELXL97.[16] The geometric calculations were done by PARST[17] and PLATON.[18] Crystal data of the α-form of **1**: $C_{14}H_{20}O_4$, $M = 252.31$, tetragonal, space group $P4_1$, $a = 6.7802(9)$ Å, $c = 27.425(7)$ Å, $V = 1260.74(4)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.33$ g cm^{-3}, $T = 100$ K, crystal size 0.24 × 0.12 × 0.20 mm, $R = 0.042$, $R_w = 0.099$, GOF = 1.224 for 1415 reflections with $I > 2\sigma(I)$, CCDC 250223. Crystal data of the β-form of **1**: $C_{14}H_{20}O_4$, $M = 252.31$, triclinic, space group $P\bar{1}$, $a = 9.281(2)$ Å, $b = 9.926(2)$ Å, $c = 13.927(3)$ Å, $\alpha = 92.912(3)°$, $\beta = 101.065(3)°$, $\gamma = 91.848(4)°$, $V = 1256.40(9)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.33$ g cm^{-3}, $T = 100$ K, crystal size 0.10 × 0.14 × 0.09 mm, $R = 0.052$, $R_w = 0.132$, GOF = 1.021 for 3422 reflections with $I > 2\sigma(I)$, CCDC 250224. Crystal data of **2**: $C_{14}H_{24}O_4$, $M = 256.31$, triclinic, space group $P\bar{1}$, $a = 5.958(5)$ Å, $b = 5.994(5)$ Å, $c = 9.867(8)$ Å, $\alpha = 86.17(1)°$, $\beta = 82.55(1)°$, $\gamma = 73.20(1)°$, $V = 334.3(1)$ Å^3, $Z = 1$, $\rho_{calcd} = 1.27$ g cm^{-3}, $T = 292$ K, crystal size 0.10 × 0.14 × 0.09 mm, $R = 0.050$, $R_w = 0.140$, GOF = 1.058 for 1038 reflections with $I > 2\sigma(I)$, CCDC 250461. CCDC reference numbers 250223, 250224 and 250461. See http://dx.doi.org/10.1039/b506591g for crystallographic data in CIF or other electronic format.

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5 The synthetic procedure adopted for the preparation of the tetrol **1** is a tactical modification of an earlier report, see: P. J. Garatt and F. Sondheimer, *J. Chem. Soc. C*, 1967, 565. The authors reported a tetrol of undetermined stereochemistry, melting in the range 253–256 °C. The present study therefore not only provides an unambiguous formulation of **1**, but also enables one to identify the previously reported tetrol as corresponding to the major α-polymorph of **1**.

6 Due to the absence of any significant anomalous scatterers (Z > Si), attempts to confirm the absolute structure by refinement of the Flack parameter led to an inconclusive value of −0.4 (10) (see ref. 12). Therefore the intensities of the Friedel pairs (1243) were averaged prior to merging of data in $P4_1$ and the absolute configuration was assigned arbitrarily. The reported value of R_{int} corresponds to subsequent merging of equivalent reflections in this space group.

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