When is a polymorph not a polymorph? Helical trimeric O–H···O synthons in *trans*-1,4-diethynylcyclohexane-1,4-diol

Clair Bilton,[a] **Judith A. K. Howard,***[a] **N. N. Laxmi Madhavi,**[b] **Ashwini Nangia,**[b] **Gautam R. Desiraju,***[b] **Frank H. Allen**[c] **and Chick C. Wilson**[d]

[a] *Department of Chemistry, University of Durham, South Road, Durham, UK DH1 3LE.*
   E-mail: j.a.k.howard@durham.ac.uk
[b] *School of Chemistry, University of Hyderabad, Hyderabad 500 046, India. E-mail: grdch@uohyd.ernet.in*
[c] *Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK CB2 1EZ*
[d] *ISIS Department, CLRC Rutherford Appleton Laboratory, Chilton, Didcot, Oxon, UK OX11 0QX*

Two polymorphs (A and B) of *trans*-1,4-diethynylcyclohexane-1,4-diol represent a unique example of the simultaneous occurrence of both conformational polymorphism and conformational isomorphism, while a pseudopolymorphic monohydrate is closely related.

Definitions of *polymorphism*, the existence of two or more different crystal structures for the same compound,[1] and *pseudopolymorphism*, the existence of one or more solvated crystalline forms of the same compound,[2] are in common usage. Similarly, the existence of different conformations of the same molecule in crystals have been distinguished[3] by the terms *conformational polymorphism*, the occurrence of different conformers in different polymorphic structural modifications, and *conformational isomorphism*, the occurrence of different conformers in the same crystal structure. Here we describe two structural polymorphs and one pseudopolymorph of *trans*-
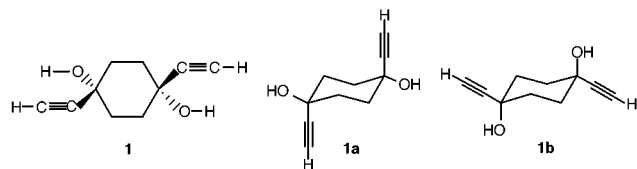
1,4-diethynylcyclohexane-1,4-diol **1**, in which the simultaneous occurrence of both conformational polymorphism and conformational isomorphism are the key distinguishing features of the crystal structures, and also provide a unique test of existing definitions.

Our studies of **1** were prompted by recent interest[4] in

structures containing the *gem*-hydroxyethynyl fragment **2**. As well as the expected O–H···O hydrogen bonds, arrays of C–H···O, O–H···π and C-H···π interactions (π = ethynyl, phenyl), sometimes stabilised by cooperativity, frequently dominate the crystal packing. This variety of interactions leads to considerable structural diversity amongst the > 90 structures containing **2** that are already available in the Cambridge Structural Database (CSD).[5] Simple mono-alcohols exhibit two types of O–H···O aggregates (chains and rings), but even here there is no predominant motif. Thus, the available evidence suggests that structures containing **2** are strongly influenced by the remaining portion of the molecule, prompting us to investigate the crystal structure of compound **1**, in which competitive effects are minimised so that the intrinsic hydrogen-bonding preferences of **2** may be more clearly discerned.

Diol **1** was synthesised by adding TMSC≡C-Li to cyclohexane-1,4-dione and hydrolysis of the TMS groups by KOH. The unwanted *cis*-isomer was separated by repeated recrystallisations from EtOAc. Further recrystallisation of pure *trans*-**1** yielded crystals of two modifications, **A** and **B**, in the same flask. We find that both forms crystallise in space group P1̄ with Z = 3,† both structures have three symmetry-independent half-molecules occupying distinct inversion centres, and both structures assemble around a spine of helical, cooperatively assisted, trimeric motifs formed *via* O–H···O bonds [**A**: Fig. 1(*a*), **B**: Fig. 1(*b*); d(O···H) = 1.70–1.76 Å, θ (O–H···O) = 163–177° over both structures, H-atom positions neutron-normalised). However, Fig. 1(*a*) shows that form **A** contains two molecules of conformer **1a** in which the hydroxy groups are diequatorial, while the third molecule has the diaxial OH conformation (**1b**). Fig. 1(*b*) shows that the reverse is true in form **B**: two molecules have diaxial OH groups (**1b**) and the third has the diequatorial OH conformation (**1a**). Interestingly, form **B** is 3% more efficiently packed than form **A** but this is compensated for by the better O–H···O hydrogen bonds in form A (mean d = 1.715 A *vs.* 1.745 in form **B**).

Amazingly, a third crystalline form was isolated from the same flask and characterised by both low-temperature X-ray and neutron diffraction.† Form **C** (P2₁/c, Z = 4) was shown to be a 1:1 hydrate of the diequatorial OH conformer **1a**, and the crystal structure maintains the helical O–H···O trimer *via* the assembly of two symmetry-independent half-molecules of **1a** and one O–H donor from a water molecule [Fig. 1(*c*), d = 1.64–1.80 Å, θ = 164–177°]. The second O–H donor of the water molecule interlinks inversion-related trimers (d = 1.91 Å, θ = 174°). In effect, the water molecule replaces the axial OH group in form **A** so that the trimeric O-H···O hydrogen-bonded helical spine is the dominant recurring pattern in all three crystalline forms of **1**.

It would appear that the presence of both conformers is required for the formation of the robust helical trimeric synthon in the unsolvated polymorphs, a supposition that is reinforced by the crystal structure of *trans*-cyclohexane-1,4-diol **3**.[6] The
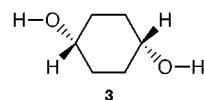
diol **3** also contains the helical O–H···O trimer and crystallises in space group P2₁/n with 1.5 molecules per asymmetric unit. The molecule in general positions has diequatorial OH groups, while the molecule on an inversion centre has diaxial OH groups. The O–H···O trimer is then formed by two diequatorial and one diaxial conformer, as in form **A** of **1**.

Why is it that both conformers are required for trimer formation in forms **A** and **B** of **1**, and in the diol **3**? It may be that the simultaneous presence of inversion centres (arising from the molecular structures of **1** and **3**), and the 3- or 3₁-axes that could arise if the trimer formed from three *identical* conformers of **1**

or **3**, would impose significant constraints on the packing efficiency. It appears that these constraints are alleviated by the presence of both conformers in forming the trimeric H-bonded synthon. There are no clear or simple ways of supporting or refuting this conjecture. Nevertheless, we note that the CSD contains no examples of single-conformation cyclohexane-1,4-diols that form O–H···O trimers, but that single-conformation alicyclic diols do form such trimers (around 3₁-axes), but only where the molecules do not have additional inversion symmetry. These arguments provide a rationale for the ready incorporation of water in form **C** as a replacement for the 'other' conformer of **1**.

In summary, the structures described above have a number of important implications. (i) This is the first example (to the best of our knowledge) in which the phenomena of conformational polymorphism and conformational isomorphism are observed simultaneously, revealing a new and unforeseen facet of polymorphism. Specifically, **A** or **B** when taken individually exhibit conformational isomorphism while the pair when taken together exhibit conformational polymorphism. (ii) The definition of forms **A** and **B** of **1** as polymorphs and form **C** as a pseudopolymorph can be viewed as somewhat subjective. If **1a** and **1b** are considered as rapidly equilibrating conformers of **1**, then the accepted definitions hold. However, if **1a** and **1b** are viewed as distinct molecular species, then forms **A** and **B** are simply binary crystals of 2:1 and 1:2 stoichiometry, and form **C** is a hydrate of **1a**. (iii) The isolation of three concomitant crystalline modifications of **1** suggest that the energy differences between them are small (1–2 kcal mol⁻¹) and that crystal forces influence the molecular conformation. The polymorph formation is not kinetically controlled and the three forms are stable over time. (iv) The recurrence of the O–H···O helical trimer in structures of **1** and **3** confirms that this is a robust supramolecular synthon which is insensitive to a change in substitution from ethynyl (in **1**) to the much smaller H-atom (in **3**). The extent to which a molecular structure can be perturbed without changing the structure-determining synthons in its crystal structure is a contemporary theme in crystal engineering. (v) The structures of the three forms of **1** resemble the structures of simple diols much more closely that they resemble structures of other *gem*-alkynols, in which there is considerable interference between the stronger O–H···O hydrogen bonds and weaker interactions (C–H···O, O–H···π, C–H···π) that involve the alkyne C–H and π-density. Further structural and computational studies of other *gem*-alkynols are in progress to shed more light on the role of this functional group in crystal packing.

Notes and references

1 T. L. Threlfall, *Analyst*, 1995, **120**, 2435.
2 A. Nangia and G. R. Desiraju, *Chem. Commun.*, 1999, 605; V. S. S. Kumar, S. S. Kuduva and G. R. Desiraju, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1069.
3 J. Bernstein, in *Organic Solid State Chemistry*, ed. G. R. Desiraju, Elsevier, London, 1987, pp. 471–518.
4 G. R. Desiraju and T. Steiner, *The Weak Hydrogen Bond in Structural Chemistry and Biology*, OUP, Oxford, 1999, pp. 175–185.
5 F. H. Allen, J. E. Davies, J. J. Galloy, O. Johnson, O. Kennard, C. F. Macrae, E. M. Mitchell, G. F. Mitchell, J. M. Smith and D. G. Watson, *J. Chem. Inf. Comput. Sci.*, 1991, **31**, 187.
6 T. Steiner and W. Saenger, *J. Chem. Soc., Perkin Trans. 2*, 1998, 371.
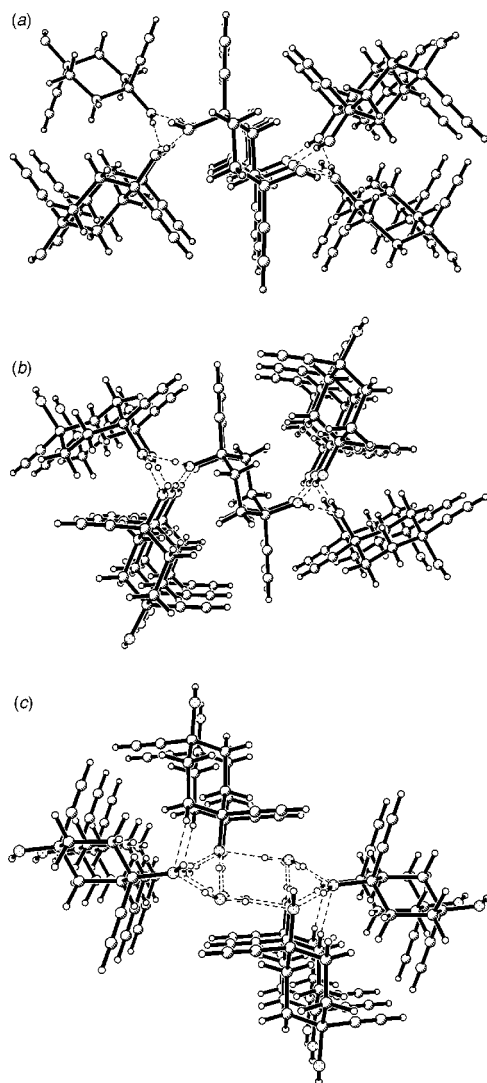

Fig. 1 Perspective views of the crystal structures of (*a*) form **A** of **1**, (*b*) form **B** of **1**, and (*c*) the monohydrated form **C** of **1**, showing the common helical O–H···O trimeric synthon and the conformations adopted by **1**.

Communication 9/05025F