Polymorphs of 1,1-bis(4-hydroxyphenyl)cyclohexane and multiple Z' crystal structures by melt and sublimation crystallization†

Bipul Sarma, Saikat Roy and Ashwini Nangia*

Received (in Cambridge, UK) 19th July 2006, Accepted 21st September 2006
First published as an Advance Article on the web 12th October 2006
DOI: 10.1039/b610323e

Close packing conflict in a metastable polymorph of the pure title host (Z' = 2, melt crystal 1m) is resolved in the stable form (Z' = 1, sublimed crystal 1s) as O–H···O hydrogen bond changes to O–H···π interaction. Melt crystallization and sublimation show a greater percentage of high Z' structures in CSD statistics.

The synthesis and characterization of guest-free crystalline forms of host molecules is generally difficult because they do not crystallize in the absence of a second component, usually a solvent and/or water molecule, which acts as a crystallization aid and/or filler in the voids.[1] Some recent methods to obtain guest-free crystalline forms of lattice inclusion host compounds are the use of (1) solvents having size/shape misfit[2a–c] with the host or (2) unfavorable electrostatic contacts,[2d] (3) removal of the guest by leaching,[2e] (4) desolvation of the guest–host compound by heating,[2f–i] (5) sublimation,[2j] and (6) melt crystallization.[2k] There are 31 solvates/cocrystals of 1,1-bis(4-hydroxyphenyl) cyclohexane **1** in the Cambridge Structural Database.[3,4] Host **1** is hydrogen bonded to solvent or partner molecules either as donor (O_{phenol}–H···O/$N_{solvent}$), or acceptor (O/$N_{solvent}$–H···O_{phenol}), or both, as is common in phenolic host molecules.[5] The crystal structure of pure **1** has not been reported. We attempted crystallization of **1** from several common solvents (including trifluorotoluene)[2d] to obtain a guest-free form; only solvent inclusion crystals or ill-defined powders were obtained. The thermodynamics of phase relationships between solvated and desolvated forms[2f] and subtle structural differences among pure host polymorphs[2g] is an important topic in microporous solids because of its application in gas storage technology.[1] We report polymorphs of pure host **1** from melt crystallization and sublimation. These solvent-free crystallization methods are shown to have a much greater probability of multiple Z' structures compared to overall Z' frequencies.[6]

Compound **1** was synthesized[4] and purified to afford the pure host molecule as a white solid. Sublimation at 150–175 °C for 6 h (or 140–150 °C, 0.2 Torr, 2 h) afforded thin plate and fine needle shaped crystals on the cold finger. When the pure host **1** was heated to 180–190 °C and the resulting neat liquid phase cooled rapidly (by bathing the outer wall of the test tube with volatile solvent), crystals of plate and block morphology were obtained.

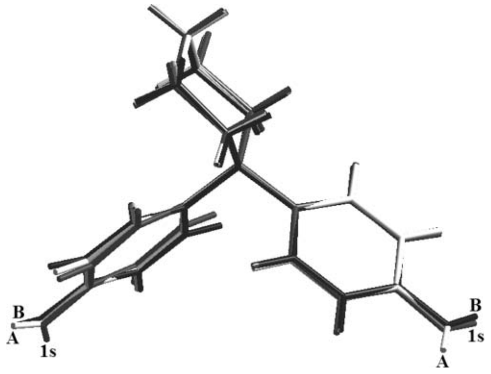


Fig. 1 Overlay of molecular conformers to show superposition of the tricyclic skeleton except the OH group orientation labelled as **1**s, A (**1**m), and B (**1**m). The OH groups are *syn* in conformer **1**s and A (**1**m) and *anti* in B (**1**m). See Fig. S1 of the ESI for the overlay diagram in color.†

There is good consistency in obtaining the respective crystals under optimized crystallization conditions (see ESI).† Single crystal X-ray diffraction confirmed that the sublimed and melt phases, **1**s and **1**m, are indeed polymorphs.‡ **1**s crystallizes in the triclinic space group $P\,\bar{1}$ (Z' = 1) and the structure of **1**m is in the orthorhombic space group *Pbca* (Z' = 2). The three conformers of **1** overlay nicely except for the different orientation of OH groups (Fig. 1); the OH groups are oriented *syn* in the triclinic rotamer and one of the orthorhombic rotamers (A) of **1**m whereas they are *anti* in the second molecule (B). One of the OH groups in **1**s is connected *via* a chain of O–H···O hydrogen bonds along [010] (Fig. 2) and the second hydroxyl group engages in an O–H···π interaction[7] (O1–H···O2 1.84 Å, 172.5°; O2–H···π 2.42 Å, 134.7°, π = Ph ring centroid). In the orthorhombic polymorph **1**m, molecule A has O–H···O chain along [010] and an O–H···π interaction with a B molecule (O1A–H···O2A 1.95 Å, 172.9°; O2A–H···πB 2.99 Å, 152.5°). Molecule B uses both its hydroxyl

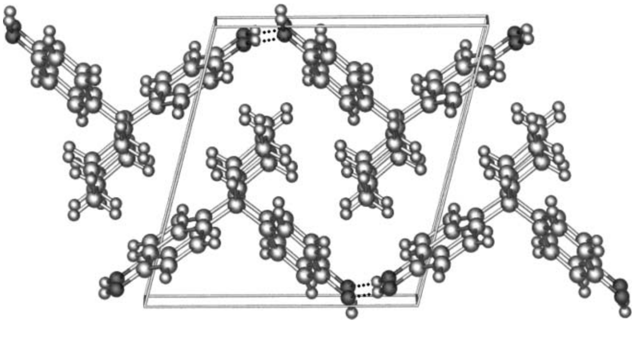


Fig. 2 O–H···O chain along [010] in the triclinic polymorph **1**s.

School of Chemistry, University of Hyderabad, Hyderabad, 500 046, India. E-mail: ashwini_nangia@rediffmail.com; Fax: +91 40 2310 1338

† Electronic supplementary information (ESI) available: Crystallization of 1s and 1m, packing diagrams of polymorphs, HSM frames at different temperatures, TG–IR of 1s, 1m crystals, and list of CSD refcodes. See DOI: 10.1039/b610323e

groups in a cooperative chain of H bonds along [100] (Fig. S2 of the ESI†) (O1B–H···O2B 1.91 Å, 172.8°; O2B–H···O1B 1.88 Å, 176.5°) to produce microporous molecular ladders (Fig. 3). The diol orientation and H bonding motifs are related: the *syn* conformer participates in O–H···O chain and O–H···π interaction whereas the *anti* conformer makes O–H···O chains on both sides.§ The infinite O–H···O chain motif in **1**m is rationalized by the presence of such H-bonded oligomers in the neat liquid, which solidify to polymorph **1**m upon rapid cooling. The occurrence of the symmetry-independent B molecule is consistent with recent results relating strong O–H···O H bonding with multiple Z' in crystal structures.[8]

Molecular conformer and crystal lattice energies were computed.[9] The molecule conformer energies of **1**s, A, B (**1**m) = 0.00, 0.23, 0.29 kcal mol^{-1} (relative energies); crystal lattice energy for **1**s, **1**m = −37.11, −36.23 kcal mol^{-1} (per molecule); total crystal energy **1**s, **1**m = conformer + lattice = −37.11, −35.97 kcal mol^{-1} (per molecule).¶ The sublimed phase is more stable than the melt form by 1.14 kcal mol^{-1}. The metastable state of **1**m and its lower crystal density and packing fraction (**1**m: 1.261 g cm^{-3}, 69.9%; **1**s: 1.275 g cm^{-3}; 71.1%) may be due to the longer inter-aromatic separation of 3.8 × 2.4 Å (C13B–C9B, C15A–C15A) between B molecules (Fig. 3 and Fig. S3) compared to no voids in **1**s (C15–C15, after subtracting 3.4 Å = π-plane diameter). The isolation of pure **1** dimorphs will allow us to study desolvation pathways of its host–guest complexes, analogous to the versatile *p*-*tert*-butylcalix[4]arene host.[2a,g,h,j]

We sought answers with regard to kinetic and thermodynamic forms, monotropic or enantiotropic phases, and the mechanism of transformation. Hot stage microscopy (HSM) showed that the a block of the melt crystal begins to melt at 178–182 °C and is completely liquid-like at 183–185 °C. Cooling afforded sublimed crystals of fine needle shape (Fig. 4). On the other hand, sublimed crystals **1**s do not show any apparent crystal form change in a similar heat–cool cycle on the hot stage (Fig. S4 of the ESI†). Differential scanning calorimetry (DSC) thermogram of **1**s has a single broad endotherm at ∼184 °C (T_{peak}) but **1**m shows two sharp endotherms at 183 and 188 °C with an exotherm in-between. These peaks correspond to the melting of **1**m, then solidification (exotherm) to the **1**s phase, followed by fusion of the sublimed form. After a heat–cool–heat cycle in DSC both melt and sublimed phases exhibit a single endotherm (Fig. 5). Sublimation occurs in both **1**s and **1**m (after a phase transition at 183–185 °C in the latter), based on TG–IR (thermal gravimetry–infrared spectroscopy, Fig. S5 of the ESI†) of the evolved vapor. The single endotherm peak after reheating is ascribed to the stable sublimed phase. DSC, HSM and computation indicate that **1**m is the kinetic polymorph and **1**s is the thermodynamic phase (T_{m} (**1**m) = 183 ± 1 °C; T_{m} (**1**s) = 188 ± 1 °C). Conformational polymorphs **1**m and **1**s are monotropic up to 160 °C and enantiotropic[10] between 180–200 °C. A structural model for the phase transition of the microporous structure in **1**m to the close-packed structure of **1**s is proposed in Scheme 1.

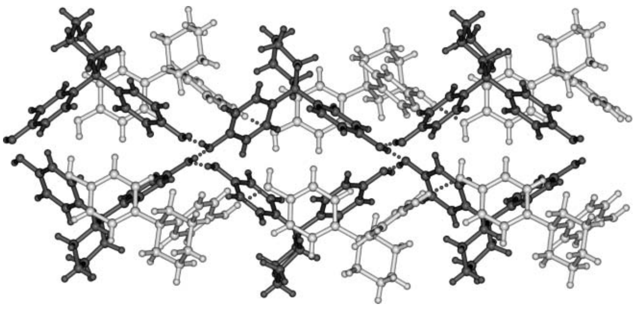


Fig. 3 Symmetry independent molecules in **1**m. The rectangular voids in the molecular ladders along [010] of B molecules (dark) have a cross-section of 3.6 × 2.2 Å. The O–H···O chain down [100] is not shown (see Fig. S2 of the ESI†). The A molecules (grey) have similar H bonding to **1**s.

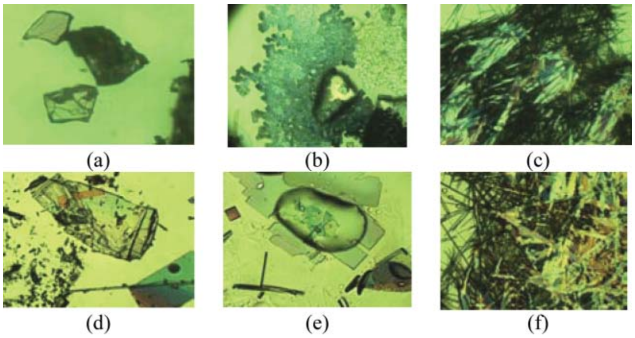


Fig. 4 HSM frames. **1**m: (a) at 25 °C, (b) 181–182 °C, (c) cool to rt. **1**s: (d) at 25 °C, (e) 183–184 °C, (f) cool to rt. Phase transition of a block crystal of **1**m to **1**s needle fibre (a–c). A plate-like crystal of **1**s shows change to needle morphology (d–f) but retains the same form. See the ESI† for more frames at different T values.

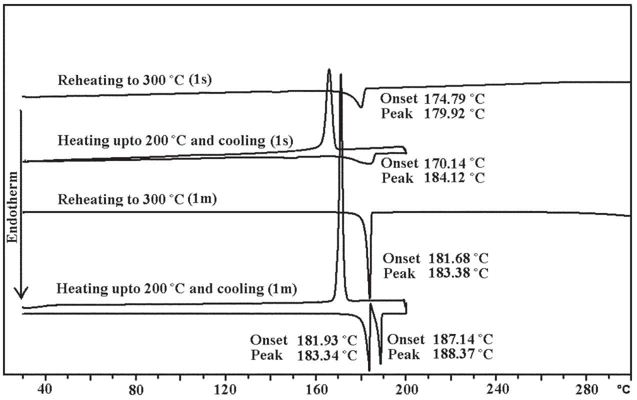
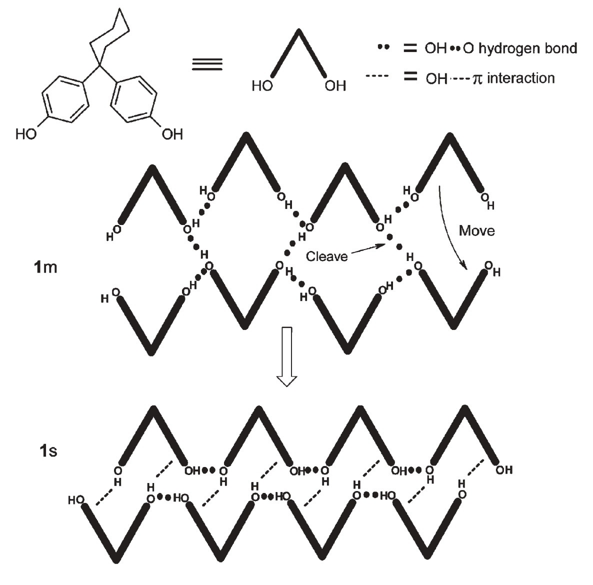


Fig. 5 DSC of **1**m and **1**s polymorphs. Metastable phase **1**m shows phase transition to the sublimation polymorph **1**s and transformation to the thermodynamic form upon heating up to 200 °C. Polymorph **1**s does not show phase changes under the same conditions except the sublimation endotherm. The reheating cycle endotherm is shifted to ∼5 °C lower temperature than the first heating cycle due to more efficient contact of the sample with the pan.

Crystal structures with multiple Z' (= number of molecules in the asymmetric unit) are more than just a crystallographic curiosity and they are now being increasingly studied.[8,9,11] In general, $Z' \leqslant 1$ is typical; <12% organic crystal structures have $Z' > 1$. We compare Z' distributions in organic crystals obtained under solvent-free conditions of sublimation and melt crystallization with the overall data for organic crystal structures[3] (Table 1). There is an increase in $Z' > 1$ frequency for solvent-free methods compared to solution crystallization, and the preference (last column ratio) is dramatic for $Z' \geqslant 3$. Interestingly, even as the ratio increases with increasing Z', the number of hits decreases and a more clear trend will emerge only after more crystal structures are available with



Scheme 1 Cleavage of O–H···O H bonds down [100] of B molecules in **1**m and movement of H bonded chains along [010] towards each other results in an O–H···π interaction and filling of the voids to give a close-packed structure similar to **1**s.

Table 1 Occurrence of Z' in organic crystals crystallized 'from the melt' (83 hits), 'by sublimation' (334 hits), and 'overall statistics' in the CSD. Overall percentages are values from 160 850 organic structures

Z'	Sublimation % (number of hits)	From melt % (number of hits)	Overall organic (%)	S + M ÷ 2 × O % age values
<1	29.04 (97)	22.89 (19)	17.64	1.47
1	53.89 (180)	59.04 (49)	71.88	0.78
>1	17.06 (57)	18.07 (15)	11.54	1.52
2	12.28 (41)	10.84 (9)	10.04	1.15
⩾3	3.89 (13)	7.23 (6)	1.24	4.48
>3	2.99 (10)	3.61 (3)	0.69	4.78
4	2.69 (9)	2.40 (2)	0.45	5.65

time. Carbamazepine is a notable example for which Z' is 1 from solution crystallization (3 polymorphs) whereas it is 4 upon crystallization from the melt.[12] The percentage of hits from the two solvent-free methods are comparable to each other and higher than the value from solution crystallization for all $Z' > 1$. The occurrence of high Z' from melt and sublimation crystallization is ascribed to rapid cooling of the hot liquid or vapor (100–300 °C) in the open flask or on the cold finger (kinetic phase), conditions under which hydrogen-bonded clusters are likely to condense in a pseudo-symmetric crystalline arrangement. On the other hand, Z' is generally $\leqslant 1$ in the slower nucleation process of solution crystallization. We note that the liquid phase crystallizes to **1**s during slow cooling in DSC (5 °C min^{-1}) but to **1**m upon rapid cooling of the hot vial.† High Z' structures have been variously referred to as fossil relic,[8a] kinetic form,[8d] and early snapshots of crystallization.[9] The present example is a remarkable illustration of how close packing conflicts[8b,c] in a metastable $Z' = 2$ structure are resolved in the thermodynamic $Z' = 1$ polymorph.[13]

We thank the DST (SR/S5/OC-02/2002, IRPHA), UGC (UPE, CMSD) for funding and CSIR (BS), UGC (SR) for a fellowship. S. Aitipamula and B. K. Saha (UH) are thanked for discussions.

Notes and references

‡ Crystal data were collected on Bruker SMART APEX CCD diffractometer with graphite-monochromator Mo Kα radiation (λ = 0.71073 Å) at 100 K. **1**s: $C_{18}H_{16}O_2$, Mr = 268.34, triclinic, $P\ \bar{1}$, a = 6.2275(6), b = 10.8480(10), c = 11.3359(11) Å, α = 101.611(2), β = 103.424(10), γ = 103.117(2), V = 698.90 (12) Å^3, Z = 2, ρ_{calcd} = 1.275 g cm^{-3}, R_1 = 0.0424, wR_2 = 0.1189, total reflections 2753, observed reflections 2255. **1**m: $C_{18}H_{16}O_2$, Mr = 268.34, orthorhombic, $Pbca$, a = 9.6278(5), b = 20.9561(11), c = 28.0324(14) Å, V = 5655.8(5) Å^3, Z = 16, ρ_{calcd} = 1.261 g cm^{-3}, R_1 = 0.0582, wR_2 = 0.1217, total reflections 4984, observed reflections 4167. Intensities were collected for absorption effects using the multi-scan technique SADABS. All non-hydrogen atoms were refined anisotropically and H atoms were located from difference electron density maps. Structure solution and refinement was carried out with Bruker SHELX-TL. The packing fraction was calculated in PLATON. CCDC 615422 and 620074. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b610323e

§ Among the 31 CSD structures, the *syn* rotamer generally connects host **1** *via* an O–H···O bond and has O–H···O$_{guest}$ H bonding (instead of O–H···π), whereas the *anti* rotamer (one structure, OFEQAN) forms a diamond-shaped motif through O–H···O bonds, as in pure **1**m.

¶ Gaussian 03 was used for molecule conformer (DFT, B3LYP/6-31G) and Cerius^2 for crystal lattice energy (Crystal Packer, COMPASS). See ref. 9*a*.

1 L. J. Barbour, *Chem. Commun.*, 2006, 1163.

2 (*a*) E. B. Brouwer, K. A. Udachin, G. D. Enright, J. A. Ripmeester, K. J. Ooms and P. A. Halchuk, *Chem. Commun.*, 2001, 565; (*b*) B. K. Saha and A. Nangia, *Chem. Commun.*, 2006, 1825; (*c*) P. O. Brown, G. D. Enright and J. A. Ripmeester, *CrystEngComm*, 2006, **8**, 381; (*d*) R. Bishop, A. N. M. M. Rahman, J. Ashmore, D. C. Craig and M. L. Scudder, *CrystEngComm*, 2002, **4**, 605; (*e*) P. S. Sidhu, G. D. Enright, K. A. Udachin and J. A. Ripmeester, *Chem. Commun.*, 2005, 2092; (*f*) E. B. Brouwer, G. D. Enright, K. A. Udachin, S. Lang, K. J. Ooms, P. A. Halchuk and J. A. Ripmeester, *Chem. Commun.*, 2003, 1416; (*g*) J. L. Atwood, L. J. Barbour, G. O. Lloyd and P. K. Thallapally, *Chem. Commun.*, 2004, 922; (*h*) G. D. Enright, K. A. Udachin, I. L. Moudrakovski and J. A. Ripmeester, *J. Am. Chem. Soc.*, 2003, **125**, 9896; (*i*) R. Banerjee, P. M. Bhatt and G. R. Desiraju, *Cryst. Growth Des.*, 2006, **6**, 1468; (*j*) J. L. Atwood, L. J. Barbour, A. Jerga and B. L. Schottel, *Science*, 2002, **298**, 1000; (*k*) B. K. Saha and A. Nangia, *CrystEngComm*, 2006, **8**, 440.

3 Cambridge Structural Database (CSD), version 5.27, ConQuest 1.8, May 2006 update, www.ccdc.cam.ac.uk.

4 F. Toda, K. Tanaka and T. Fujiwara, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 662; M. R. Caira, A. Horne, L. R. Nassimbeni and F. Toda, *J. Mater. Chem.*, 1998, **8**, 1481; Z. Urbanczyk-Lipkowska, K. Yoshizawa, S. Toyota and F. Toda, *CrystEngComm*, 2003, **5**, 114.

5 S. Aitipamula and A. Nangia, *Supramol. Chem.*, 2005, **17**, 17; S. Aitipamula and A. Nangia, *Chem.–Eur. J.*, 2005, **11**, 6727.

6 T. Steiner, *Acta Crystallogr., Sect. B: Struct. Sci.*, 2000, **56**, 673.

7 E. Weber, K. Skobridis, A. Wierig, L. R. Nassimbeni and L. Johnson, *J. Chem. Soc., Perkin Trans. 2*, 1992, 2123.

8 (*a*) J. W. Steed, *CrystEngComm*, 2003, **5**, 169; (*b*) H.-J. Lehmler, L. W. Robertson, S. Parkin and C. P. Brock, *Acta Crystallogr., Sect. B: Struct. Sci.*, 2002, **58**, 140; (*c*) C. P. Brock, *Acta Crystallogr., Sect. B: Struct. Sci.*, 2002, **58**, 1025; (*d*) D. Das, R. Banerjee, R. Mondal, J. A. K. Howard, R. Boese and G. R. Desiraju, *Chem. Commun.*, 2006, 555.

9 (*a*) S. Roy, R. Banerjee, A. Nangia and G. J. Kruger, *Chem.–Eur. J.*, 2006, **12**, 3777; (*b*) V. S. S. Kumar, A. Addlagatta, A. Nangia, W. T. Robinson, C. K. Broder, R. Mondal, I. R. Evans, J. A. K. Howard and F. H. Allen, *Angew. Chem., Int. Ed.*, 2002, **41**, 3848.

10 J. Bernstein, *Polymorphism in Molecular Crystals*, Clarendon, Oxford, 2002.

11 X. Hao, J. Chen, A. Cammers, S. Perkin and C. P. Brock, *Acta Crystallogr., Sect. B: Struct. Sci.*, 2005, **61**, 218; K. M. Anderson, A. E. Goeta, K. S. B. Hancock and J. W. Steed, *Chem. Commun.*, 2006, 2138.

12 A. L. Grzesiak, M. Lang, K. Kim and A. J. Matzger, *J. Pharm. Sci.*, 2003, **92**, 2260.

13 G. S. McGrady, M. Odlyha, P. D. Prince and J. W. Steed, *CrystEngComm*, 2002, **4**, 271.