# Polymorphism in Isomeric Dihydroxybenzoic Acids

**ARTICLE** *in* CRYSTAL GROWTH & DESIGN · APRIL 2010

Impact Factor: 4.89 · DOI: 10.1021/cg100220z



**3 AUTHORS:**

Bipul Sarma
Tezpur University
**33** PUBLICATIONS **442** CITATIONS
SEE PROFILE

Palash Sanphui
Indian Institute of Science
**26** PUBLICATIONS **510** CITATIONS
SEE PROFILE

Ashwini Nangia
University of Hyderabad
**273** PUBLICATIONS **7,110** CITATIONS
SEE PROFILE

DOI: 10.1021/cg100220z

CRYSTAL GROWTH & DESIGN Article
2010, Vol. 10
2388–2399

# Polymorphism in Isomeric Dihydroxybenzoic Acids

Bipul Sarma, Palash Sanphui, and Ashwini Nangia*

*School of Chemistry, University of Hyderabad, Prof. C. R. Rao Road, Gachibowli, Central University P.O., Hyderabad 500046, India*

*Received February 12, 2010; Revised Manuscript Received March 12, 2010*

**ABSTRACT:** Multifunctional molecules are capable of assembling via different supramolecular synthons, or hydrogen bond motifs, between the same or different functional groups, leading to the possibility of polymorphism. We have employed sublimation and melt crystallization to generate two new crystalline polymorphs of 3,5-dihydroxybenzoic acid (DHBA), and a second form for 2,3-dihydroxybenzoic acid and 3,4-dihydroxybenzoic acid each. Since hydroxybenzoic acids tend to give solvate/hydrate crystal structures by solution crystallization, solvent-free methods are necessary to obtain single crystals of unsolvated forms. In addition to guest-free polymorphs, a new hydrate polymorph of 3,4-dihydroxybenzoic acid was crystallized from cold water. Polymorphs of dihydroxybenzoic acids differ in the number of symmetry-independent molecules ($Z'$), the nature of the hydrogen bond synthon, the molecular packing, and the unit cell parameters. Structural and thermal characterization of polymorphic phases shows that the commercial material matches with the high $Z'$ phase for 2,3-DHBA, 3,5-DHBA, and 3,4-DHBA hydrate even though a low $Z'$ crystal structure is known in each case. Solventless crystallization conditions at high temperature are a practical method to generate new guest-free polymorphs and high $Z'$ crystal structures for high affinity functional group compounds.

## Introduction

Dihydroxybenzoic acids (DHBA for short; Scheme 1) possess interesting biological activity. For example, 2,3-dihydroxybenzoic acid is a salicylate metabolite while 2,5-dihydroxybenzoic acid (common name gentisic acid), 3,4-dihydroxybenzoic acid, and 3,4,5-trihydroxybenzoic acid (gallic acid) have antioxidant properties.[1] They are responsible for apoptosis characterized by DNA cleavage. Due to the presence of OH and COOH functional groups, these molecules are capable of exhibiting different hydrogen bond synthons, as shown in Scheme 2. DHBAs are prone to form solvate or hydrate structures when crystallized from various solvents.[2] Melt and sublimation techniques are known to afford guest-free structures and even new polymorphs under solvent-free conditions.[3] A recent survey of crystal structures suggested that the likelihood of obtaining high or multiple $Z'$ structures increases to 18% under solvent-free conditions at high temperature compared to the overall statistical frequency of 12% for $Z' > 1$.[3a] $Z'$ is defined as the number of symmetry-independent or crystallographic unique molecules/ions in the crystal lattice. Alternatively, $Z'$ is calculated by dividing the number of formula units ($Z$) by the number of independent general positions for that space group. Approximately 87% crystal structures have $Z'$ of 1 or 0.5.[4] A study of dihydroxybenzoic acids was undertaken with the following objectives: (1) to generate guest-free crystal structures of these compounds, (2) to discover new polymorphs using solvent-free conditions, (3) to find out if the presence of a phenol group[5] in DHB results in multiple $Z'$ structures, and (4) to study polymorphism based on differences in hydrogen bonding of OH and COOH functional groups (synthon polymorphism).[6] Among isomeric dihydroxybenzoic acids, 2,5-DHBA[7] and 2,6-DHBA[8] are known to be dimorphic, whereas one crystal structure is reported for 2,3-DHBA[9] and 2,4-DHBA,[10] each with 3D coordinates determined.[11] We report new polymorphs of dihydroxybenzoic acids and compare the relative stability of DHBA polymorphic crystal structures discovered in this study with those in the CCDC database.[12] The polymorphic identity of the commercial material is matched with the known forms and found to match with a high $Z'$ crystal structure.

## Results

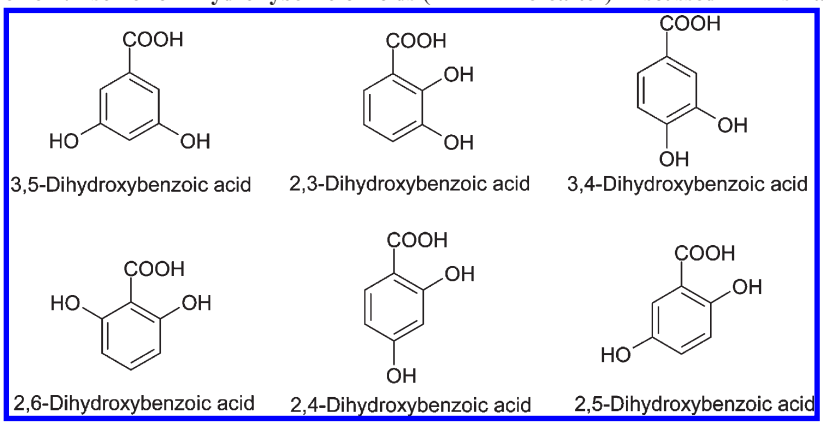
We recently obtained single crystals of guest-free polymorphs using solventless conditions for the host compound 1,1-bis(4-hydroxyphenyl)cyclohexane,[3a] which otherwise form solvates and cocrystals by solution crystallization. Melt and sublimation methods[13] of growing single crystals are now extended to dihydroxybenzoic acids, a class of bioactive molecules that are known to give solvates/hydrates,[2] cocrystals/molecular salts with bipyridine/aminopyridine,[14] and act as ligands in metal complexes.[15] Fortunately, all dihydroxybenzoic acids were found to be stable to heating up to their melt/sublimation temperature, except 2,6-DHBA and 2,4-DHBA, which decarboxylated to resorcinol above 130 and 160 °C, respectively.

**Polymorphs of 3,5-Dihydroxybenzoic Acid.** 3,5-DHBA is a tricky molecule to crystallize in guest-free form, since it readily includes a guest molecule in its crystal lattice from the crystallization medium. Of the six crystal structures archived in CSD version 5.30 (ConQuest 1.11, September 2009 update), three are cocrystals with bipyridyl derivatives (BEQWAV, VEFVEI, and VEFVIM) and the fourth is an amino acid complex (UCEMEV). The two remaining structures are Na (COLMUM) and Cu (TAYSAO) complexes. The OH groups adopt different orientations in these crystal structures (Scheme 3). Surprisingly, the carboxylic acid homo dimer[16] is absent in all reported structures of 3,5-DHBA. Attempts to grow single crystals of 3,5-DHBA from common solvents, such as water, ethyl acetate, ethanol,

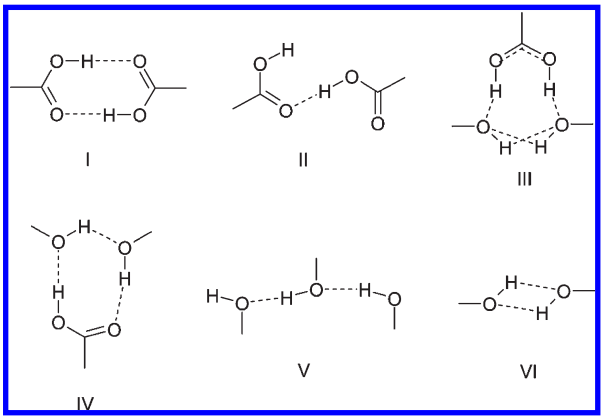
*E-mail: ashwini.nangia@gmail.com.

 Published on Web 04/05/2010 

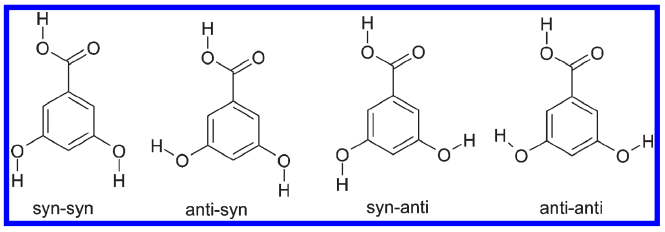
**Scheme 1. Isomeric Dihydroxybenzoic Acids (DHBA Hereafter) Discussed in This Paper**




**Scheme 2. Hydrogen Bond Motifs between OH and COOH Groups in DHBA Crystal Structures**




**Scheme 3. Conformation of the OH Group in 3,5-DHBA[a]**

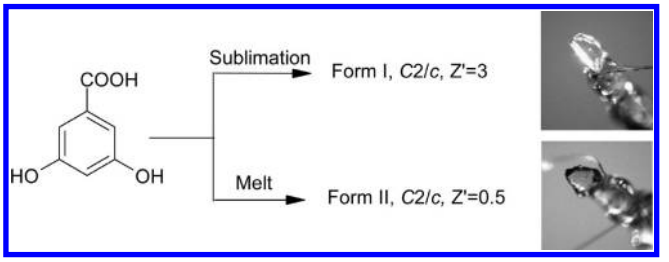



[a] The assignment of syn−anti OH is with respect to the *para*-H atom between the OH groups.

methanol, acetone, acetylacetone, dioxane, tetrahydrofuran, dimethyl sulfoxide, acetic acid, etc., resulted in the ready formation of solvated crystals. Three solvent inclusion hexagonal channel structures of 3,5-DHBA with acetylacetone, THF, and dioxane crystallized in our study are discussed next.

Sublimation and melt crystallization afforded two guest-free crystalline modifications of 3,5-DHBA of needle/plate and block morphology (Scheme 4). The sublimation phase crystallized in monoclinic space group $C2/c$ with three symmetry independent molecules in the unit cell ($Z' = 3$). The melt phase also crystallized in the same space group ($C2/c$) but now with half a molecule ($Z' = 0.5$) lying on the 2-fold axis (Figure S1). Crystal data are summarized in Table 1. The sublimed polymorph has two symmetry independent 3,5-DHBA molecules connected via O−H···O hydrogen bonds (O12−H12C···O3 1.71 Å, 2.689(6)Å, 175°; O4−H4A···O11 1.66 Å, 2.635(6)Å, 174°) in a 1D tape, and such tapes are interconnected through a carboxylic acid dimer (O1−H1A···O10 1.67 Å, 2.657(4) Å, 179°; O9−H9C···O2 1.68 Å, 2.637(5) Å, 164°) to make a 2D brick wall sheet (Figure 1a) parallel to the (110) plane. The third crystallographic molecule is arranged in a 1D tape which runs roughly perpendicular to the brick wall sheet and also acts as a filler in the rectangular voids (Figure 1b; O7−H7B···O8 1.74 Å, 2.719(5) Å, 172°). Hydrogen bond parameters are tabulated in Table 2.

**Scheme 4. Melt and Sublimation Afforded Two New Crystalline Monoclinic Modifications of 3,5-DHBA Having Plate and Block Morphology**




Melt crystallization afforded a new polymorphic modification with half a molecule in the asymmetric unit. The carboxylic acid dimer is absent in this layered structure. The hydroxyl groups participate in a tandem hydrogen bond motif (Scheme 2, synthon III). Strong hydrogen bonds between OH groups (O1−H1···O2 1.73 Å, 2.713(2) Å, 177°) assemble the 2D layer of the 3,5-DHBA polymorph (Figure 2). Adjacent layers are stabilized by $\pi\cdots\pi$ stacking at 3.0 Å separation. The COOH group is orientationally disordered because the molecule lies on a 2-fold axis. There are obvious differences in the calculated X-ray powder diffraction (XRPD) patterns of the two polymorphs (Figure S2).

To compare the relative stability of 3,5-DHBA polymorphs, density and packing fraction (Table 3) did not give a clear indication because their values are very close. DSC (Figure S3 in the Supporting Information) of the sublimed phase shows a 2 °C higher endotherm peak compared to the melt phase, with the polymorphs being monotropically related. The slightly higher melting point of the sublimed phase and its higher enthalpy of fusion are indicative that the sublimed phase is more stable, which is substantiated because the commercial material too matches with the sublimed phase by fingerprint matching of XRPD patterns (Figure 3). The greater stability of the sublimed crystalline

**Table 1. Crystal Data of DHBA Polymorphs**

| crystal data | 3,5-DHBA melt | 3,5-DHBA sublimed | 3,5-DHBA·acac | 3,5-DHBA·Diox | 3,5-DHBA·THF | 2,3-DHBA sublimed | 3,4-DHBA·$H_2O$ monoclinic | 3,4-DHBA melt |
|---|---|---|---|---|---|---|---|---|
| emp formula | $C_7H_6O_4$ | $C_7H_6O_4$ | $C_{33}H_{39}O_{22}$ | $C_9H_{10}O_5$ | $C_{32}H_{40}O_{21}$ | $C_7H_6O_4$ | $C_7H_8O_5$ | $C_7H_6O_4$ |
| formula wt | 154.12 | 154.12 | 787.64 | 198.17 | 760.64 | 154.12 | 172.13 | 154.12 |
| crystal system | monoclinic | monoclinic | monoclinic | monoclinic | monoclinic | monoclinic | monoclinic | triclinic |
| space group | $C2/c$ | $C2/c$ | $Cc$ | $P2_1/c$ | $Cc$ | $P2_1/n$ | $P2_1/c$ | $P\bar{1}$ |
| $T$/K | 298 | 298 | 298 | 100 | 298 | 298 | 298 | 298 |
| $a$/Å | 7.3447(15) | 14.101(2) | 9.3556(11) | 14.878(6) | 24.977(2) | 5.338(3) | 12.318(3) | 6.8800(8) |
| $b$/Å | 15.015(3) | 22.433(4) | 30.024(3) | 8.321(4) | 9.1454(9) | 5.486(3) | 3.6448(9) | 8.5444(10) |
| $c$/Å | 6.4840(13) | 14.161(2) | 13.4635(15) | 7.027(3) | 19.3903(19) | 22.496(11) | 18.182(3) | 17.549(2) |
| α/deg | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 77.982(3) |
| $\beta$/deg | 111.67(3) | 116.770(2) | 104.955(2) | 94.826(7) | 129.2530(10) | 103.043(8) | 112.516(12) | 85.210(2) |
| $\gamma$/deg | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 85.581(2) |
| $Z/Z'$ | 4/0.5 | 24/3 | 4/1 | 4/1 | 4/1 | 4/1 | 4/1 | 6/3 |
| volume/Å$^3$ | 664.5(2) | 3999.5(11) | 3653.7(7) | 866.9(6) | 3429.8(5) | 641.8(5) | 754.1(3) | 1003.6(2) |
| $D_{calc}$/g cm$^{-3}$ | 1.540 | 1.536 | 1.432 | 1.518 | 1.473 | 1.595 | 1.516 | 1.530 |
| $\mu$/mm$^{-1}$ | 0.129 | 0.129 | 0.122 | 0.126 | 0.125 | 0.134 | 0.132 | 0.128 |
| reflns collected | 3372 | 20096 | 11443 | 3494 | 11571 | 6248 | 6964 | 10622 |
| unique reflns | 653 | 3858 | 3745 | 1264 | 3142 | 1268 | 1468 | 3970 |
| $R_1$ ($I > 2\sigma(I)$) | 0.0484 | 0.0964 | 0.0472 | 0.0769 | 0.0456 | 0.0480 | 0.0893 | 0.0820 |
| $wR_2$ | 0.1582 | 0.1314 | 0.2170 | 0.1181 | 0.2044 | 0.1060 | 0.1155 | 0.1830 |
| GOF | 1.078 | 1.083 | 1.008 | 1.064 | 1.071 | 1.133 | 1.157 | 1.015 |

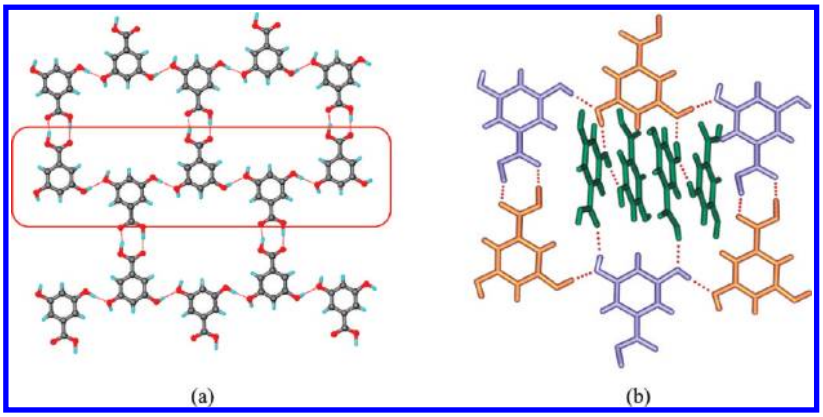



**Figure 1.** (a) 1D tape of O−H···O hydrogen bonds along the [100] direction in form I (sublimed polymorph) of 3,5-DHBA and COOH dimer connections leading to a 2D sheet parallel to the (110) plane. Symmetry-independent molecules are colored differently. (b) The third crystallographic molecule also forms a 1D tape of O−H···O hydrogen bonds perpendicular to the layer shown in part a. Symmetry independent molecules are colored in part b.

phase may be explained through the dense network of shorter (stronger) hydrogen bonds (Table 2) in the higher $Z'$ polymorph[17] and its higher melting temperature compared to that of the melt phase. Another factor for the stability of the sublimed form could be the syn−anti conformation (Scheme 3) of OH groups that is present in all its solvates and cocrystals, in contrast to the anti−anti orientation in the melt polymorph. There is no crystal structure of 3,5-DHBA in the CSD having the anti−anti OH orientation that is present in the melt polymorph. In contrast, energy computations in Gaussian 03[18] (Table 4) suggest that anti−anti is the most stable conformation, followed by syn−anti, anti−syn, and syn−syn. Despite its higher energy, the syn−syn conformation is present in four organic crystal structures (CSD refcodes BEQWAV, TAYSAO, UCEMEV, VEFVEI), anti−syn in one structure (COLMUM), and syn−anti in one metal−ligand structure (VEFVIM). The sublimed phase of 3,5-DHBA contains one anti−syn and two syn−anti conformers in the unit cell.

**Solvates of 3,5-Dihydroxybenzoic Acid.** When 3,5-DHBA was crystallized from acetylacetone by adding a few drops of methanol at ambient conditions, the single crystal composition was four 3,5-DHBA molecules, one acetyl acetone, and four water molecules in the unit cell of the *Cc* space group. The host molecules are arranged in a layer structure of hexagonal channels sustained by carboxylic acid homo dimer and hydroxyl group O−H···O hydrogen bonds (O6−H9···O2 1.67 Å, 2.648(3) Å, 174°; O7−H11···O4 1.77 Å, 2.738(3) Å, 169°; O3−H3A···O8 1.73 Å, 2.687(3) Å, 162°). The hydrogen between O5 and O1 in the acid homo dimer could not be located from a difference electron density Fourier map. Acetylacetone and two water molecules reside in the hexagonal channel formed by the host layers (Figure 4a). Crystallization of 3,5-DHBA from tetrahydrofuran (3,5-DHBA·THF) afforded single crystals which were refined and solved with four host molecules, one THF molecule, and four water molecules. The THF solvate (Figure 4b) shows a similar structural pattern to the 3,5-DHBA·acac hydrate. The host molecules are arranged in a hexagonal layer through a carboxylic acid dimer and O−H···O hydrogen bonds. THF and water guest molecules occupy the channel voids, with a water molecule acting as a linker between adjacent host layers. The host molecules make an isostructural lattice (Figure 5).

Crystallization of 3,5-DHBA from dioxane afforded block crystals of 1:1 3,5-DHBA·dioxane. The structure shows a different molecular arrangement compared to that of 3,5-DHBA·THF and 3,5-DHBA·acac hydrates. Dioxane

**Table 2. Hydrogen Bond Parameters (D−H Distances Are Neutron Normalized)**

| compd | interaction | $d$(H···A) (Å) | $d$(D···A) (Å) | ∠D−H···A (deg) | symmetry code |
|---|---|---|---|---|---|
| 3,5-DHBA sublimed | O1−H1A···O10 | 1.67 | 2.657(4) | 179 | $^1/_2 - x, ^1/_2 + y, ^1/_2 - z$ |
| | O3−H3A···O7 | 1.81 | 2.766(5) | 162 | $x, -y, -^1/_2 + z$ |
| | O4−H4A···O11 | 1.66 | 2.636(6) | 174 | $-x, y, ^1/_2 - z$ |
| | O5−H5B···O12 | 1.70 | 2.648(5) | 161 | $-^1/_2 + x, ^1/_2 - y, ^1/_2 + z$ |
| | O7−H7B···O8 | 1.74 | 2.719(5) | 172 | $x, -y, ^1/_2 + z$ |
| | O8−H8B···O4 | 1.69 | 2.671(4) | 173 | $-x, -y, 1 - z$ |
| | O9−H9C···O2 | 1.68 | 2.637(5) | 164 | $^1/_2 - x, -^1/_2 + y, ^1/_2 - z$ |
| | O11−H11C···O6 | 1.74 | 2.681(5) | 159 | $^1/_2 - x, ^1/_2 - y, 1 - z$ |
| | O12−H12C···O3 | 1.71 | 2.689(6) | 175 | $1 - x, y, ^1/_2 - z$ |
| 3,5-DHBA melt | O1−H1···O2 | 1.73 | 2.713(18) | 177 | $^1/_2 - x, ^1/_2 + y, ^1/_2 - z$ |
| | O2−H2···O2 | 1.85 | 2.641(2) | 136 | $-x, y, ^1/_2 - z$ |
| 2,3-DHBA sublimed | O2−H2···O1 | 1.68 | 2.661(3) | 178 | $2 - x, 2 - y, -z$ |
| | O4−H4···O2 | 2.17 | 3.006(3) | 142 | $-1 + x, -1 + y, z$ |
| | C7−H7···O4 | 2.44 | 3.516(3) | 174 | $1 + x, 1 + y, z$ |
| 3,4-DHBA melt | O3−H3···O6 | 2.03 | 2.833(4) | 138 | $1 + x, 1 + y, z$ |
| | O4−H4···O12 | 1.80 | 2.769(5) | 167 | $2 - x, 1 - y, 1 - z$ |
| | O7A−H7A···O3 | 2.04 | 2.868(5) | 140 | $1 - x, 1 - y, -z$ |
| | O8−H8···O3 | 1.84 | 2.769(4) | 157 | $-1 + x, y, z$ |
| | O11A−H11A···O1 | 1.72 | 2.702(6) | 173 | $1 - x, 1 - y, 1 - z$ |
| | O12−H12···O11A | 1.99 | 2.730(6) | 130 | $1 - x, 1 - y, 1 - z$ |
| | O9−H30···O1 | 1.73 | 2.694(5) | 166 | $-x, -y, 1 - z$ |
| | O5−H31···O6 | 1.61 | 2.595(4) | 175 | $1 - x, -1 - y, -z$ |
| | O2−H32···O10 | 1.63 | 2.606(5) | 169 | $1 + x, 1 + y, z$ |
| 3,4-DHBA·$H_2O$ monoclinic | O1−H1···O2 | 1.66 | 2.642(5) | 173 | $1 - x, 1 - y, -z$ |
| | O3−H3A···O3 | 1.86 | 2.778(4) | 155 | $-x, 2 - y, -z$ |
| | O3−H3B···O4 | 1.91 | 2.844(5) | 157 | $-x, ^1/_2 + y, ^1/_2 - z$ |
| | O4−H4···O5 | 1.75 | 2.730(5) | 171 | $x, 1 + y, z$ |
| | O5−H5B···O2 | 2.22 | 3.014(6) | 137 | $x, ^1/_2 - y, ^1/_2 + z$ |
| | O5−H5C···O3 | 1.98 | 2.844(5) | 145 | $-x, ^1/_2 + y, ^1/_2 - z$ |
| | O5−H5C···O4 | 2.32 | 3.036(6) | 129 | $-x, ^1/_2 + y, ^3/_2 - z$ |
| 3,5-DHB·acac | O12−H1···O19 | 1.66 | 2.641(4) | 173 | $-1 + x, y, z$ |
| | O9−H2O···14 | 1.66 | 2.640(3) | 178 | $^1/_2 + x, ^3/_2 - y, ^1/_2 + z$ |
| | O3−H3A···O8 | 1.73 | 2.687(3) | 162 | $^1/_2 + x, ^1/_2 + y, z$ |
| | O11−H4···O15 | 1.73 | 2.695(4) | 168 | $1 + x, 1 - y, ^1/_2 + z$ |
| | O4−H4A···O20 | 1.70 | 2.661(4) | 165 | $1 + x, y, z$ |
| | O16−H6···O12 | 1.76 | 2.730(4) | 167 | $x, -y, -^1/_2 + z$ |
| | O13−H8···O10 | 1.65 | 2.624(3) | 173 | $-^1/_2 + x, ^3/_2 - y, -^1/_2 + z$ |
| | O8−H8A···O21 | 1.68 | 2.638(4) | 165 | $^1/_2 + x, ^3/_2 - y, -^1/_2 + z$ |
| | O6−H9···O2 | 1.67 | 2.648(3) | 174 | $-^1/_2 + x, ^1/_2 - y, ^1/_2 + z$ |
| | O7−H11···O4 | 1.77 | 2.738(3) | 169 | $-^1/_2 + x, -^1/_2 + y, z$ |
| | O15−H15A···O22 | 1.67 | 2.658(5) | 179 | $-1 + x, y, z$ |
| | O19−H19A···O20 | 1.95 | 2.918(5) | 170 | $-1 + x, y, z$ |
| | O19−H19B···O11 | 1.89 | 2.839(4) | 162 | $-1 + x, y, z$ |
| | O20−H20A···O3 | 1.84 | 2.773(4) | 158 | $1 + x, y, z$ |
| | O20−H20B···O18 | 1.73 | 2.710(4) | 175 | $x, y, z$ |
| | O21−H21B···O7 | 1.94 | 2.815(4) | 147 | $^1/_2 + x, ^3/_2 - y, ^1/_2 + z$ |
| | O22−H22A···O16 | 2.00 | 2.815(5) | 139 | $x, y, z$ |
| | O22−H22B···O17 | 2.07 | 2.849(5) | 135 | $x, y, z$ |
| 3,5-DHBA·dioxane | O2−H2···O3 | 1.86 | 2.697(4) | 171 | $x, 1 + y, z$ |
| | O3−H3···O1 | 1.90 | 2.738(4) | 172 | $-x, -^1/_2 + y, ^3/_2 - z$ |
| | O4−H4···O5 | 1.88 | 2.701(4) | 167 | $x, -1 + y, z$ |
| | C3−H3A···O1 | 2.43 | 3.151(5) | 132 | $-x, ^1/_2 + y, ^1/_2 - z$ |
| 3,5-DHBA·THF | O1−H1A···O14 | 1.70 | 2.653(4) | 163 | $x, 1 - y, ^1/_2 + z$ |
| | O3−H3A···O18 | 1.69 | 2.648(4) | 163 | $x, 1 + y, z$ |
| | O4−H4A···O15 | 1.77 | 2.749(4) | 172 | $-^1/_2 + x, ^1/_2 - y, -^1/_2 + z$ |
| | O5−H5A···O12 | 1.79 | 2.762(4) | 169 | $x, 1 - y, ^1/_2 + z$ |
| | O6−H6A···O17 | 1.66 | 2.627(4) | 165 | $x, -1 + y, z$ |
| | O7−H7A···O10 | 1.67 | 2.651(4) | 178 | $-^1/_2 + x, ^1/_2 - y, -^1/_2 + z$ |
| | O9−H9A···O8 | 1.63 | 2.598(4) | 166 | $^1/_2 + x, ^1/_2 - y, ^1/_2 + z$ |
| | O11−H11A···O6 | 1.73 | 2.704(4) | 171 | $x, -y, -^1/_2 + z$ |
| | O12−H12A···O19 | 1.72 | 2.691(4) | 171 | $x, 1 - y, -^1/_2 + z$ |
| | O13−H13A···O2 | 1.63 | 2.616(4) | 176 | $x, 1 - y, -^1/_2 + z$ |
| | O15−H15A···O21 | 1.70 | 2.658(4) | 163 | $x, -1 + y, z$ |
| | O16−H16A···O3 | 1.75 | 2.727(4) | 176 | $^1/_2 + x, ^3/_2 - y, ^1/_2 + z$ |
| | O17−H17A···O20 | 1.75 | 2.699(4) | 161 | $x, 1 - y, -^1/_2 + z$ |
| | O17−H17B···O5 | 1.90 | 2.875(4) | 171 | $x, y, z$ |
| | O18−H18A···O19 | 2.10 | 2.978(6) | 147 | $-^1/_2 + x, ^1/_2 - y, -^1/_2 + z$ |
| | O18−H18B···O4 | 1.89 | 2.846(4) | 165 | $x, y, z$ |
| | O19−H19A···O14 | 2.19 | 2.918(5) | 130 | $x, -y, ^1/_2 + z$ |
| | O19−H19B···O11 | 1.74 | 2.718(4) | 173 | $x, -y, ^1/_2 + z$ |
| | O21−H21A···O10 | 1.98 | 2.927(5) | 162 | $x, y, z$ |
| | O21−H21B···O17 | 2.00 | 2.926(6) | 155 | $x, y, z$ |
| | C13−H13···O21 | 2.45 | 3.217(5) | 127 | $x, -1 + y, z$ |

acts as a connector between linear tapes of host molecules and extends it into a layer structure (Figure 6). COOH···OH hydrogen bonding is the main synthon, but the carboxylic acid homodimer is absent.

Solvates were readily obtained from acetone, water, DMSO, AcOH, EtOH, and MeOH, but their crystal structures could not be satisfactorily solved because of opaque nature and solvent disorder problems. Desolvation of THF solvate by grinding the material and keeping it at 100 °C for 1 day gave the sublimed polymorph (XRPD comparison).

**Polymorphs of 2,3-Dihydroxybenzoic Acid.** A triclinic polymorph of 2,3-DHBA that was crystallized from water is reported in the literature.[9] Sublimation at 170−175 °C afforded two types of crystals: a few thin plates and mostly those of block shaped morphology on the coldfinger of the apparatus. The block shaped crystals correspond to the known triclinic $P\bar{1}$ structure ($Z' = 2$). The thin plate crystals are a new polymorph in the monoclinic space group $P2_1/n$ ($Z' = 1$). Melting did not afford good quality single crystals. Even though the two polymorphs appeared concomitantly during sublimation (Scheme 5), they are easily identified by their different morphology.

The monoclinic polymorph of 2,3-DHBA contains a carboxylic acid dimer (O2−H2···O1 1.68 Å, 2.661(3) Å, 178°) between inversion related molecules and an intramolecular O−H···O hydrogen bond making up the basic building unit, which extends as molecular tape via O−H···O and weak C−H···O hydrogen bonds (O4−H4···O2 2.17 Å, 3.006(3) Å, 142°; C7−H7···O4 2.44 Å, 3.516(3) Å, 174°; Figure 7). C−H···O hydrogen bonds (C5−H5···O4 2.69 Å, 135°) connect such molecular tapes, leading to 3D packing. The triclinic form, on the other hand, has a layered structure in which the same dimer tapes now extend via an O−H···O synthon (Figure 8). The basic difference between the two polymorphs relates to how the same COOH dimer units are connected, which is highlighted by a circle around the hydrogen bond synthon. XRPDs of

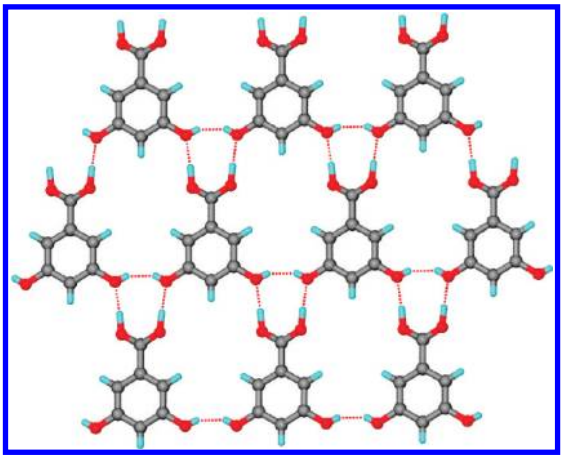


**Figure 2.** O−H···O hydrogen bonds connect to make a tape of 3,5-DHBA which extends into the 2D layer thorough hydrogen bonds with the COOH group form II (melt polymorph).

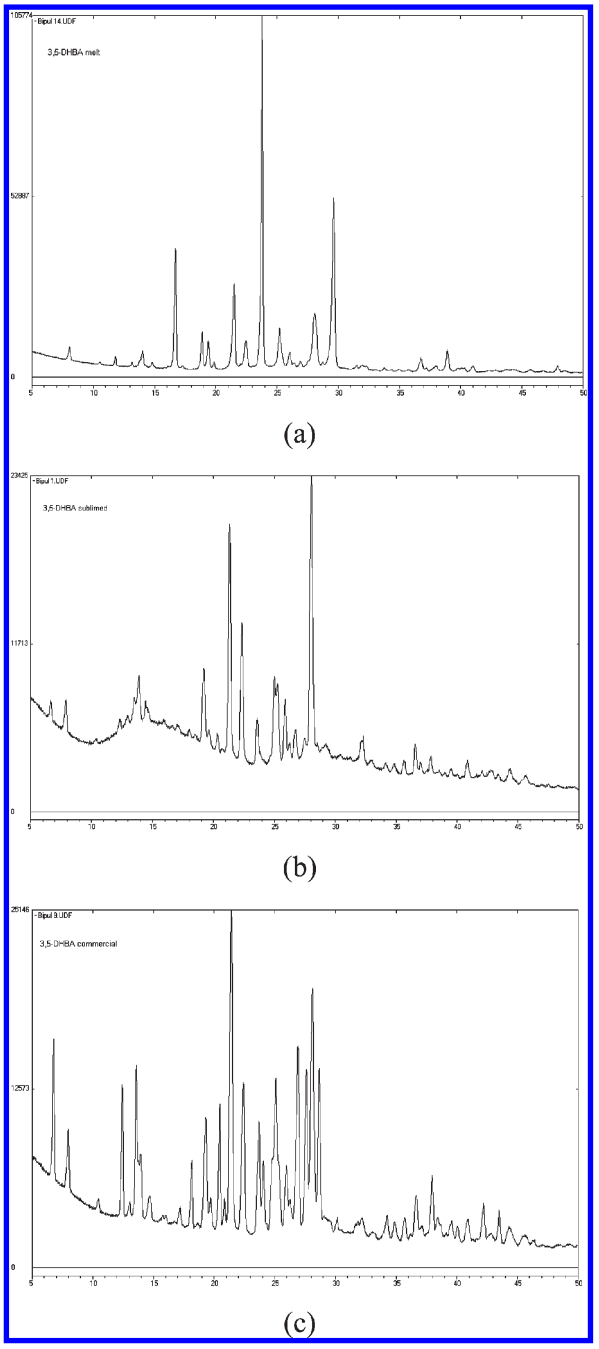
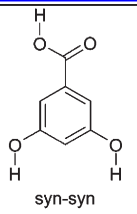
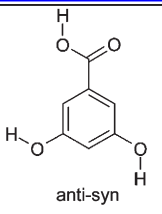
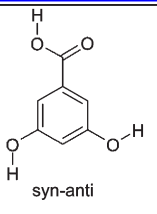
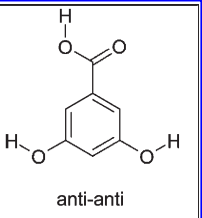



**Figure 3.** X-ray powder diffraction of the melt phase (a), the sublimed phase (b), and commercial material (c) of 3,5-DHBA. The sublimed phase is present in the commercial sample. Signature peaks for the melt phase (b) at $2\theta = 16.69$ and 29.82 are absent in the commercial material, but it could well be admixed with another polymorph (yet to be characterized) based on the complex line pattern in part c. See Figure S2 of the Supporting Information for the calculated XRPD lines.

**Table 3. Density, Packing Fraction, and Melting Point Comparison of Polymorphic Pairs**

| | 3,5-DHBA sublimed | 3,5-DHBA melt | 2,3-DHBA triclinic | 2,3-DHBA monoclinic | 3,4-DHBA triclinic | 3,4-DHBA·$H_2O$ triclinic | 3,4-DHBA·$H_2O$ monclinic |
|---|---|---|---|---|---|---|---|
| crystal density (g cm$^{-3}$) | 1.536 | 1.541 | 1.546 | 1.595 | 1.530 | 1.541 | 1.540 |
| packing fraction (%) | 71.0 | 71.6 | 71.8 | 74.6 | 70.7 | 73.6 | 73.1 |
| melting onset/peak (°C) | 238.2/238.5 | 232.9/236.7 | 206.4/208.1 | 207.6/208.5 | 201.0/201.5 | 203.34/204.09 | 194.41/196.89 |
| enthalpy of fusion (kJ mol$^{-1}$) | −39.40 | −29.23 | −29.69 | −21.63 | −30.91 | 34.10 | −22.27 |

**Table 4. Conformational Energy Using Gaussian03 (DFT, B3LYP/6-311G(d,p))**

| 3,5-DHBA Conformer |  syn-syn |  anti-syn |  syn-anti |  anti-anti |
|---|---|---|---|---|
| $E_{opt}$ (kcal mol$^{-1}$) | 1.62 | 0.57 | 0.17 | 0.00 |

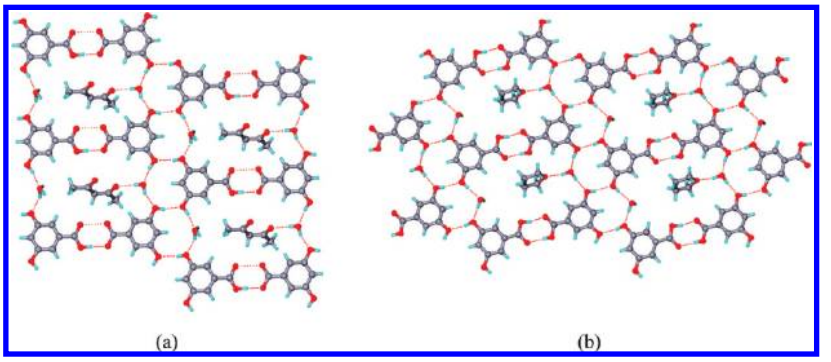



**Figure 4.** (a) Acetyl acetone solvent and water molecules in the hexagonal channel of 3,5-DHBA·acac hydrate. (b) The hexagonal channel of 3,5-DHBA is occupied by THF and water molecules.

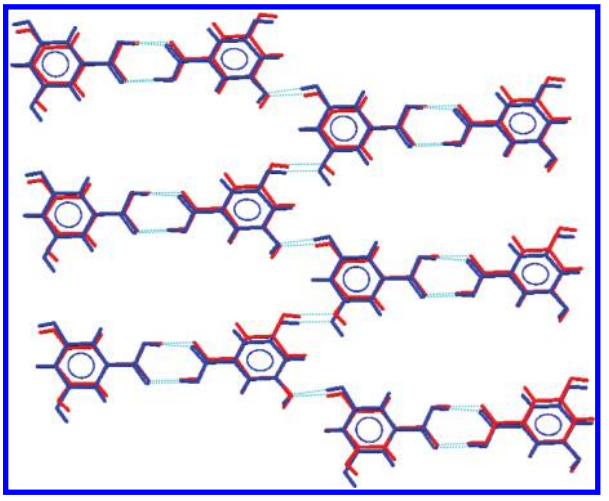


**Figure 5.** The hexagonal channel formed by the 3,5-DHBA host is identical in the two solvates displayed in Figure 4, i.e. 3,5-DHBA·acac·$H_2O$ (4:1:4, blue) and 3,5-DHBA·THF·$H_2O$ (4:1:4, red), despite having a different guest species and unit cell parameters. Guest species are excluded for clarity.

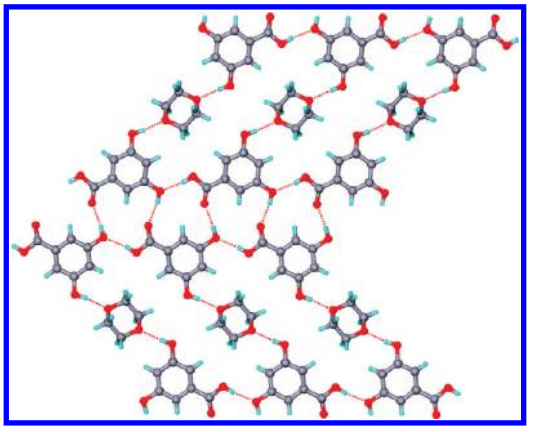
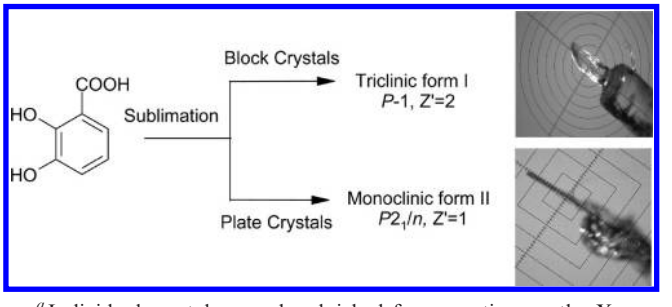


**Figure 6.** Dioxane connects 1D tapes of host molecules to form a 2D layer structure in 3,5-DHBA·dioxane.

**Scheme 5. Sublimation Afforded Two Crystalline Modifications of 2,3-DHBA: Triclinic (Known) and Monoclinic (New).**[a]




[a] Individual crystals were handpicked for mounting on the X-ray diffractometer.

the polymorphs are visibly different (Figure S4 of the Supporting Information), and the commercial material matches with a known triclinic form having $Z' = 2$ (Figure 9). Even though hydrogen bonding and molecular packing are different in these polymorphic structures, their melting point is the same (208 °C, DSC, Figure S5 of the Supporting Information). The concomitant appearance during sublimation means that their energies are very close.[19]

**3,4-Dihydroxybenzoic Acid.** Melting afforded a new guest free form of 3,4-DHBA ($P\bar{1}$, $Z' = 3$; Scheme 6). Of the three symmetry independent molecules (labeled **A**, **B**, and **C**; Figure S6 of the Supporting Information), the **A** molecule is fully ordered whereas **B** and **C** are orientationally disordered at the OH groups (the atom site occupancy factor,

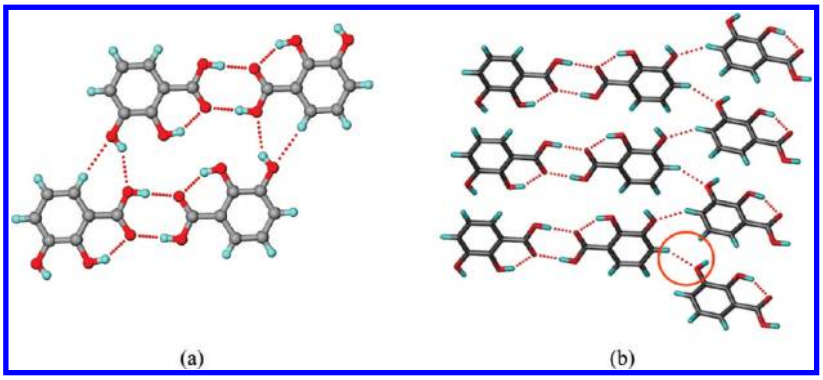



**Figure 7.** (a) Carboxylic acid dimer extends into molecular tapes in 2,3-DHBA monoclinic structure and C−H···O connection to screw axis related tapes along [010] (b).

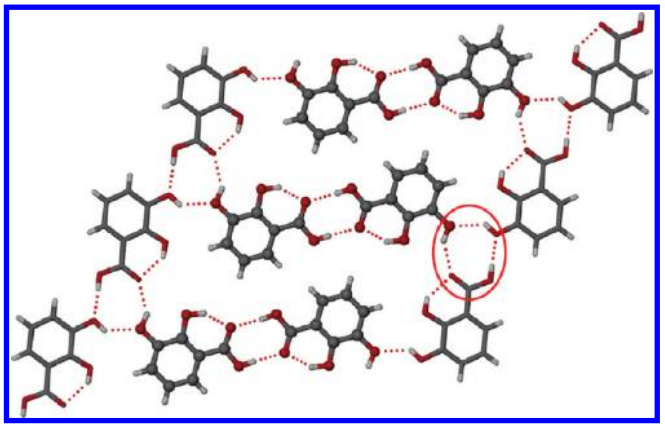


**Figure 8.** The triclinic form of 2,3-DHBA has a 2D layer structure sustained by extension of the dimers through O−H···O hydrogen bonds. Symmetry-independent molecules are shown differently. The main difference between this structure and the monoclinic polymorph is highlighted in the red circle (compare with Figure 7b).

s.o.f., of H11B, O11B, H20, H11, H7B, and O7B (**B**) is 0.3, and that of H11A, O11A, H18, O7A, O7B, and H13 (**C**) is 0.7). The carboxylic acid dimer of **A** and **B** molecules extends into the 1D tape, and **C** molecules are connected in an orthogonal direction (Figure 10). The DSC thermogram of the melt material (crystal density 1.53 g cm$^{-3}$) shows a single endotherm in DSC at 201 °C for melting (Figure S7 of the Supporting Information).

A new hydrate polymorph of 3,4-dihydroxybenzoic acid was isolated as needle-shaped, pale-brown crystals by slow evaporation of water at 5 °C in a refrigerator. The structure was solved and refined in space group $P2_1/c$ with one 3,4-DHBA and one water molecule in the unit cell (3,4-DHBA monohydrate, monoclinic). At ambient temperature, block morphology crystals of the reported triclinic monohydrate[2a] (CSD refcode BIJDON03)[20] were reproduced (Scheme 7). There are two more unit cells listed for 3,4-DHBA hydrate in the CSD (refcodes BIJDON and BIJDON02, no 3D coordinates reported), but our new hydrate is different from these structures. Carboxylic acid dimers of O−H···O hydrogen bonds are connected through water molecules in a helix along [010] (Figure 11). In contrast, the reported triclinic hydrate shows a 2D layer structure (Figure 12). Water hydrogens in the monoclinic hydrate form are disordered over three positions with s.o.f. of 0.67 each. Crystal density and packing fraction (triclinic 1.54 g cm$^{-3}$, 73.6%; monoclinic 1.54 g cm$^{-3}$, 73.1%) did not give a clear indication about the relative stability of these hydrates, but the higher water release and melting onset temperature of the triclinic hydrate confirm its greater stability (see DSC and TGA in Figures S7 and S8 of the Supporting Information, and the values listed in Table 3). XRPD recorded on commercial 3,4-DHBA matches better with the triclinic monohydrate ($Z' = 2$) than with anhydrate or other known forms such as monoclinic hydrate or the melt phase (Figure 13). The newly reported monoclinic hydrate is in fact a metastable form. It transforms to the triclinic hydrate polymorph after a few days under ambient conditions (Figure S9 of the Supporting Information). Even though hydrate polymorphs are not within the direct scope of this paper on guest-free polymorphs, these structures are included because they were crystallized during the same set of experiments and are relevant to the discussion on variable $Z'$ polymorphic structures and characterization of the commercial form of hydroxybenzoic acids with known polymorphs/hydrates.[21]

## Discussion

A study subdatabase was created of organic crystal structure polymorphs (Table 5) using the All Text phrase "polymorph", "phase", or "form" and having a COOH group in CSD version 5.30, November 2008 release, September 2009 update. The search criteria were "organic only", "3D coordinates available", "$R$ factor < 0.10", "no disorder", "no error", and "not polymeric". The lower $R$-factor structure was retained for duplicate refcodes. Out of 292 polymorphic hits, there are 61 sets of variable $Z'$ polymorphs, i.e. about 1 in 4.8 chance of variable $Z'$ in polymorphs of carboxylic acids. When both COOH and OH groups are considered, the probability of finding variable $Z'$ improves to 1 in 3 (7/21). These 21 crystal structures are listed in Table 6. This suggests that future studies on high $Z'$ crystal structures in polymorphs should focus on hydroxybenzoic acids and more specifically their crystallization by solvent-free methods at high temperature.

The carboxylic acid homodimer [graph set $R_2^2(8)$] is present in all polymorphic structures of DHBA except the 3,5-DHBA melt phase. Seventeen pairs of carboxylic acid group containing polymorph sets are reported wherein one polymorph contains COOH dimer, but this synthon is absent in the other form(s); that is, they are synthon polymorphs.[6] Oxalic acid (OXALAC04, OXALAC06)[22] and tetrolic acid (TETROL, TETROL01)[23] are examples of COOH dimer/catemer synthon polymorphs. A summary of isomeric dihydroxybenzoic acid polymorphs (reported previously and in this study) is given in Table 7 (hydrates are included for completeness).

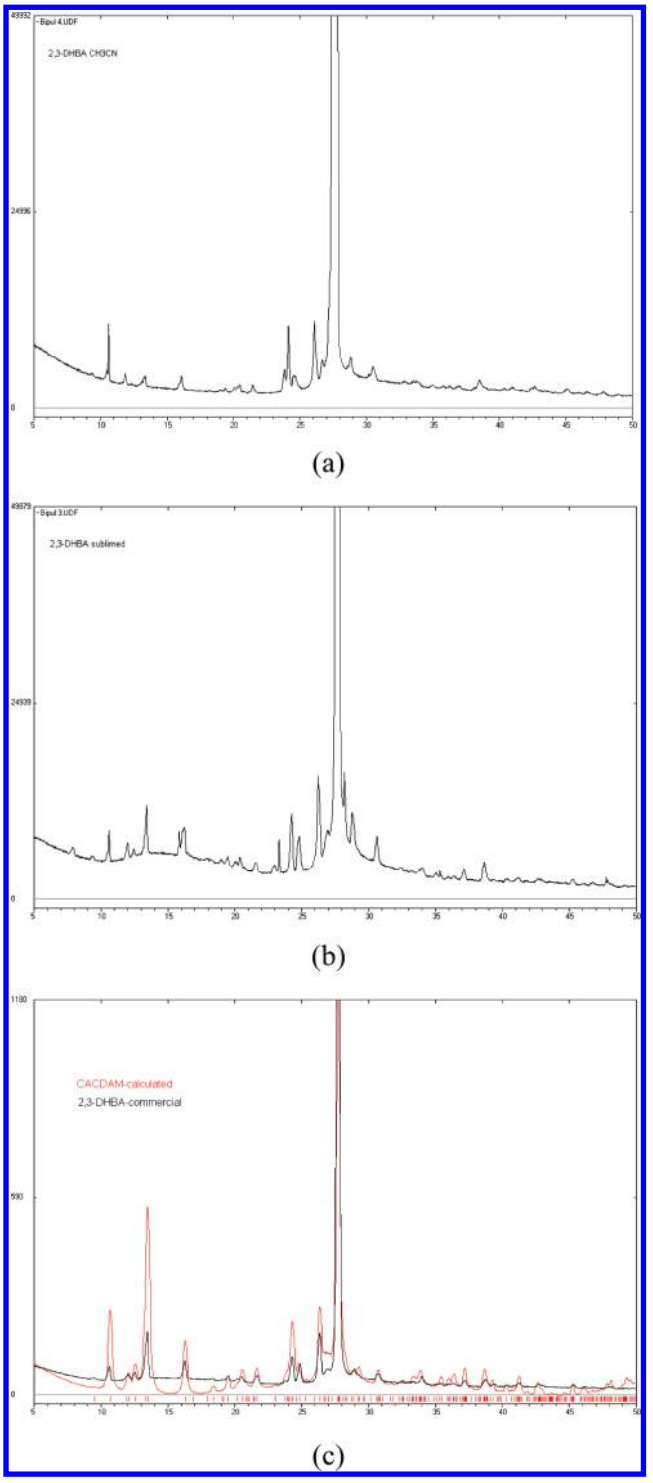



**Figure 9.** X-ray powder diffraction of 2,3-DHBA crystallized from $CH_3CN$ (a) reported as CACDAM, sublimed phase (b), and commercial material (c). The sublimed phase is a concomitant mixture of reported triclinic (CADCAM) and new monoclinic (sublimed) forms. The commercial sample in part c contains triclinic polymorph crystallized from $CH_3CN$ (major) along with sublimed monoclinic form (minor). See Figure S4 of the Supporting Information for calculated XRD of triclinic and monoclinic crystal structures.

2,3-DHBA, 3,5-DHBA, and 3,4-DHBA monohydrate constitute new variable $Z'$ polymorph sets generated through our work. Among melt and sublimation methods for crystal growth, sublimation quite often gives concomitant

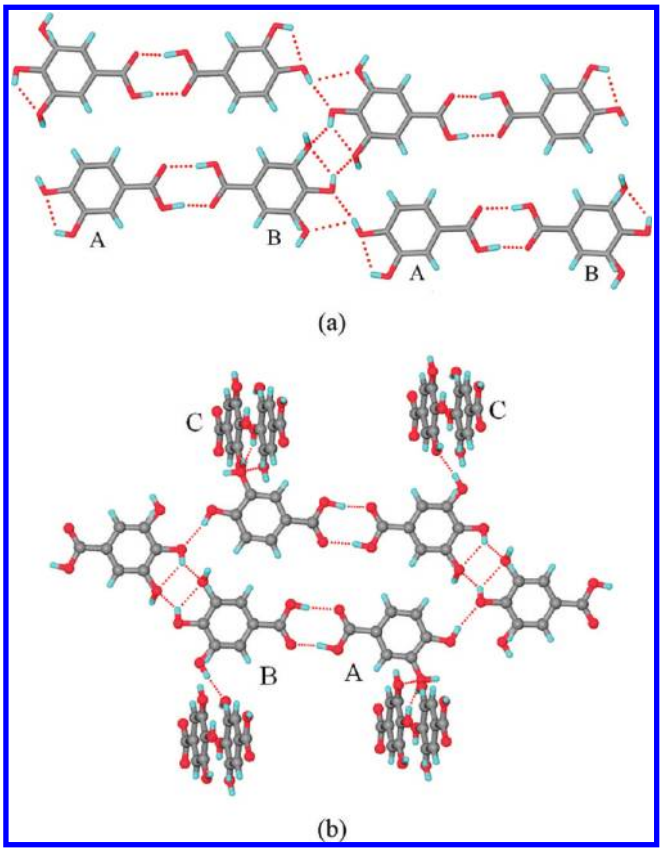
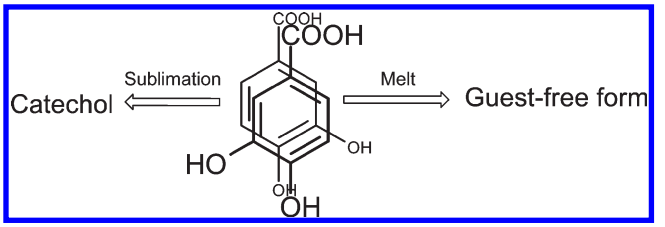


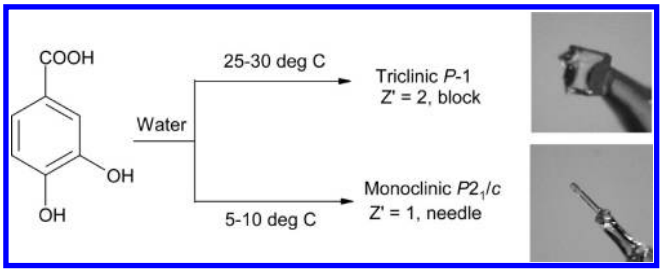

**Figure 10.** (a) Carboxylic acid dimer of 3,4-DHBA molecules **A** and **B** is connected by a *para* OH group. (b) A tape of C molecules runs orthogonal to the 2D sheet of **A** and **B**, making the 3D structure.

**Scheme 6. Melting Afforded a New Guest-Free Form of 3,4-DHBA[a]**




[a] Because of positional disorder of the OH group, the molecule mimics 3,4,5-trihydrohxybenzoic acid. 3,4-DHBA decomposes to catechol on attempted sublimation.

**Scheme 7. Crystallization under Cold Conditions Afforded Needle Shaped Crystals of a New Monoclinic Hydrate of 3,4-DHBA whereas the Known Triclinic Hydrate Was Obtained at Room Temperature**




polymorphs, as analyzed from the CSD survey (see Table S1 of the Supporting Information for refcodes). The commercial material is characterized as predominantly the triclinic

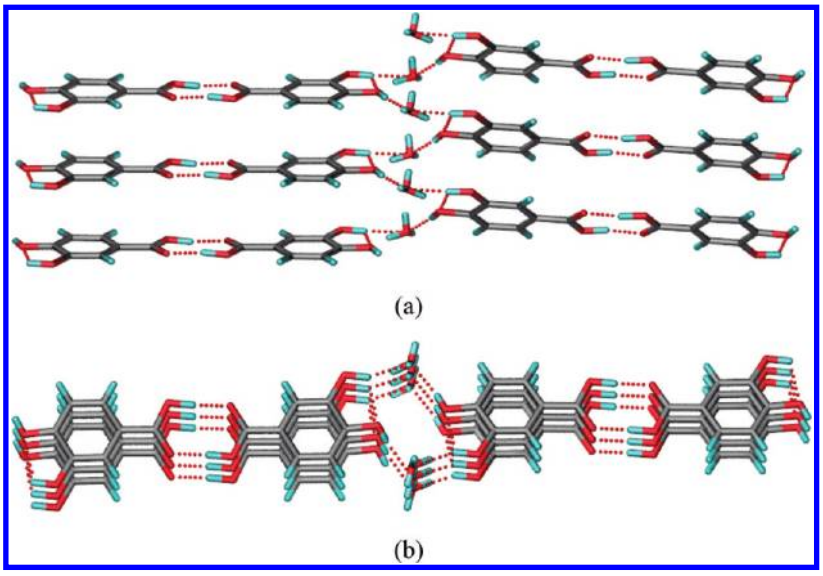



**Figure 11.** (a) Water molecules connect acid dimer units to extend the O−H···O helix along the *b*-axis (b) in the $P2_1/c$ polymorph of 3,4-DHBA monohydrate.

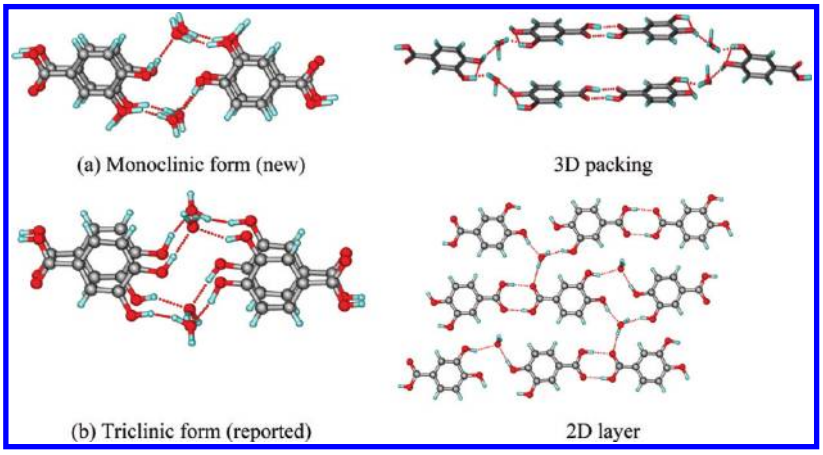



**Figure 12.** Differences in hydrogen bonding and molecular packing of 3,4-DHBA monohydrate polymorphs.

polymorph ($Z' = 2$) for 2,3-DHBA, the sublimed phase ($Z' = 3$) for 3,5-DHBA, and the triclinic monohydrate ($Z' = 2$) for 3,4-DHBA. A mixture of anhydrate and hemihydrate make up the 2,4-DHBA commercial material (see Figure S10 of the Supporting Information), 2,5-DHBA is monoclinic form 1 (Figure S11), and 2,6-DHBA is a mixture of polymorphs and monohydrate (Figure S12). Further studies are warranted to know the phase transitions during storage (between polymorphs and to the hydrate form) and the polymorphic composition depending on the commercial supplier. Interestingly, there is a high propensity of the commercial material to match with the high $Z'$ polymorph, suggesting that crystal structures with $Z' > 1$ can indeed be quite stable. This observation is counterintuitive, since most crystallographers and structural chemists tend to view higher $Z'$ polymorphs as metastable forms, crystal on the way, incipient crystallization, fossil relic, and so on.[3a,4,19b,24]

Despite our best efforts, we were not successful in crystallizing a new polymorph of 2,4-DHBA, 2,5-DHBA, or 2,6-DHBA. While analyzing the reported unit cell of 2,4-DHBA, we found that there is a large difference in the volume of the 2,4-DHBA crystal structure reported over 50 years ago,[11] and its actual cell volume determined accurately.[10] It appears that the crystal structure reported originally for 2,4-DHBA is actually its monohydrate (see Table S2 for the unit cell parameters), which was perhaps not quantified properly at that time. We were unable to reproduce the reported unit cell of ZZZEEU refcode in our experiments.

## Conclusions

New polymorphs of dihydroxybenzoic acids were crystallized and characterized by X-ray diffraction to add structural data to this family of bioactive compounds. Crystallization by melt and sublimation more often gives a high $Z'$ crystal structure. Interestingly, the commercial material corresponds to the high $Z'$ phase in at least three cases. The wider implications of this surprising observation are still to be fully understood by examining more polymorphic systems having a variable number of molecules in the asymmetric unit. In this respect, hydroxy acids are good candidate molecules because the chances of obtaining high $Z'$ crystalline forms are better than average.

## Experimental Section

All compounds were purchased from Sigma-Aldrich and used directly for experiments. All other chemicals were of analytical or chromatographic grade. Melting points were measured on a

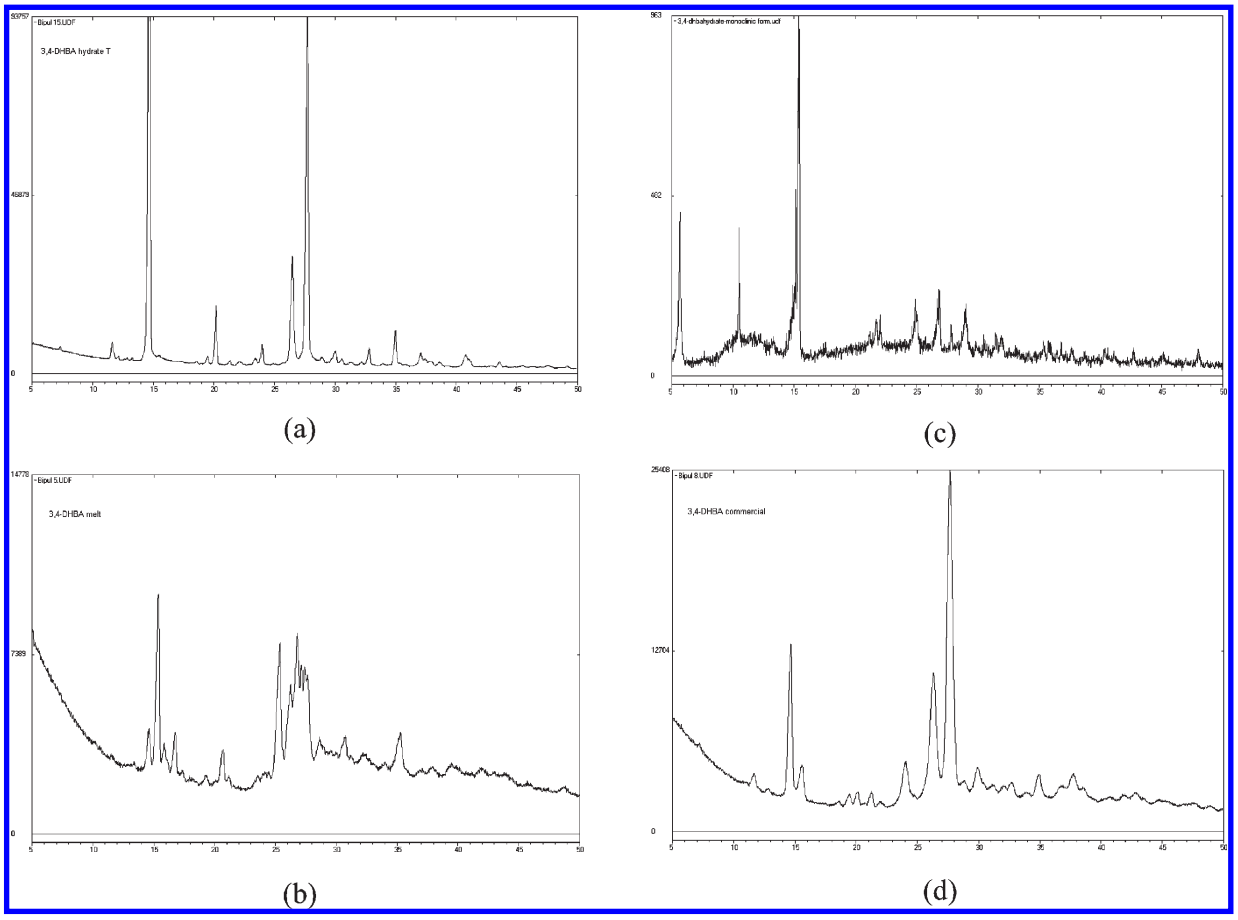



**Figure 13.** X-ray powder diffraction of commercial 3,4-DHBA (d) matches with the triclinic hydrate (major, a) along with the monoclinic hydrate (minor, c) but not the melt phase (b). The monoclinic hydrate ($2\theta$ = 15.29) transforms to the triclinic polymorph ($2\theta$ = 14.78°) after one week. See Figure S9 of the Supporting Information.

**Table 5. CSD Statistics of Carboxylic Acid Polymorphs**

| carboxylic acid group containing polymorph sets | 292 hits (135 molecules) |
|---|---|
| polymorph sets having different $Z'$ | 61 hits |
| polymorph sets containing COOH but no OH | 114 hits |
| polymorph sets containing COOH *and* OH | 21 hits |
| polymorph sets containing COOH group and having different $Z'$ structures | 53 hits |
| polymorph sets containing COOH *and* OH group having different $Z'$ | 7 hits |
| polymorph sets having COOH dimer in one polymorph and different hydrogen bonds in the other structure | 17 hits |
| polymorph sets containing COOH *and* OH groups having dimer in one polymorph and different hydrogen bonds in the other structure | 4 hits |

Fisher-Johns melting point apparatus. Water filtered through a double deionized purification system (Milli Q Plus Water System from Millipore, USA) was used in all experiments.

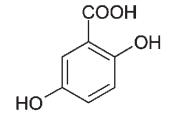
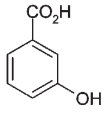
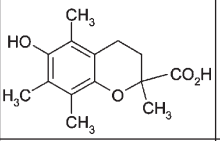
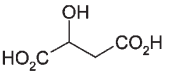
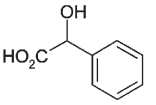
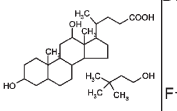
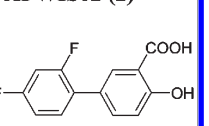
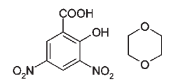
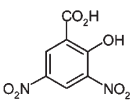
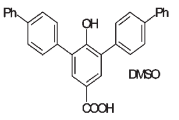
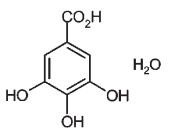
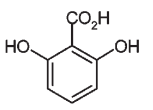
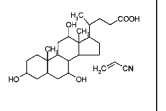
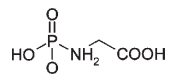
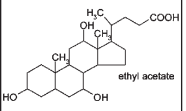
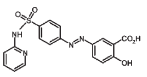
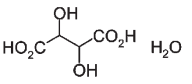
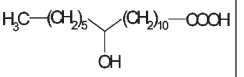
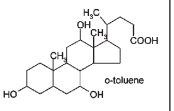
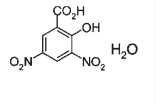
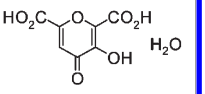
**X-ray Crystallography.** X-ray reflections were collected on a Bruker SMART CCD diffractometer using Mo Kα ($\lambda$ = 0.71073 Å) radiation. Data reduction was performed using Bruker SAINT software.[25] Intensities for absorption were corrected using SADABS.[26] Structures were solved and refined using SHELXL-97[27] with anisotropic displacement parameters for non-H atoms. Hydrogen atoms on O and N were experimentally located in all crystal structures. All C−H atoms were fixed geometrically using the HFIX command in SHELX-TL. X-Seed[28] was used to prepare figures and packing diagrams. A check of the final CIF file using PLATON[29] did not show any missed symmetry. The crystallographic parameters for all structures are summarized in Table 1. The hydrogen bond distances in the X-ray crystal structures (Table 2) are neutron-normalized by fixing the D−H distance to its accurate neutron value (O−H 0.983 Å, N−H 1.009 Å, C−H 1.083 Å). Crystallographic cif files (CCDC Nos. 764264−764271) are available at www.ccdc.cam.ac.uk/data_request/cif or available as part of the Supporting Information.

**X-ray Powder Diffraction.** Powder XRD of all samples was recorded on a PANlytical 1830 (Philips Analytical) diffractometer using Cu Kα X-radiation ($\lambda$ = 1.54056 Å) at 35 kV and 25 mA. Diffraction patterns were collected over a $2\theta$ range of 5−50° at a scan rate of 1° min$^{-1}$. The Powder Cell 2.3 program[30] was used for Rietveld refinement.

**Cambridge Structural Database Searches.** CSD version 5.30, ConQuest 1.11, November 2008 release, Sep 2009 update[12] was used in all searches, and crystal structures were visualized in Mercury 2.2. Only organic crystal structures with $R$ < 0.10, with no error, and that were not polymeric were retrieved from the database. The lower $R$-factor structure was retained for duplicate refcodes.

**Thermal Analysis.** DSC and TGA were performed on a Mettler Toledo DSC 822e module and a Mettler Toledo TGA/SDTA 851e module, respectively. Samples were placed in open alumina pans for TGA and in crimped but vented aluminum sample pans for DSC. A typical sample size is 4−6 mg for DSC and 9−12 mg for

**Table 6. CSD refcodes for 21 Pairs of Organic Polymorphs Having Both COOH and OH Groups[a]**

| | | | | | | |
|---|---|---|---|---|---|---|
| BESKAL (1)<br>BESKAL02 (1) | BIDLOP (1)<br>BIDLOP01 (1) | DEWVOQ (1)<br>DEWVOQ01 (1) | DLMALC (1)<br>DLMALC11 (1) | **DLMAND02 (2)**<br>**DLMAND03 (1)** | EWACAG (1)<br>EWACAG01 (1) | **FAFWIS (1)**<br>**FAFWIS01 (1)**<br>**FAFWIS02 (2)** |
|  |  |  |  |  |  |  |
| **GORXAM (2)**<br>**GORXAM01 (1)** | GORXEQ (1)<br>GORXEQ01 (1) | **HAKVAR (3)**<br>**HAKVAR01 (1)** | KONTIQ (1)<br>KONTIQ01 (1) | LEZJAB (1)<br>LEZJAB01 (1) | PEMZAI01 (1)<br>PEMZAI02 (1) | PHOGLY (1)<br>PHOGLY04 (1) |
|  |  |  |  |  |  |  |
| **PIWKOV01 (1)**<br>**PIWKOV02 (2)** | QIJZOY (1)<br>QIJZOY01 (1) | TARTMM (1)<br>TARTMM01 (1) | **TOZKOI (1)**<br>**TOZKOI01 (2)** | **YOYFIB (1)**<br>**YOYFIB02 (0.5)** | ZAJGUM (1)<br>ZAJGUM01 (1) | ZZZSSY01 (1)<br>ZZZSSY02 (1) |
|  |  |  |  |  |  |  |

[a] Seven pairs of variable Z′ are shown in bold. The Z′ value for each crystal structure is given in parentheses.

**Table 7. Summary of Dihydroxybenzoic Acid Polymorphs**

| | form 1 | | | | form 2 | | | | commercial |
|---|---|---|---|---|---|---|---|---|---|
| compound | refcode | space group | $Z'$ | crystallization solvent/method | CSD refcode | space group | $Z'$ | crystallization solvent/method | matches with polymorph |
| 2,3-DHBA | CACDAM | $P\bar{1}$ | 2 | water | this study | $P2_1/n$ | 1 | sublimation | triclinic |
| 2,4-DHBA | ZZZEEU | | | | ZZZEEU01 | $P2_1/n$ | 1 | acetone | mixture of anhydrate and hemihydrate |
| 2,5-DHBA | BESKAL02 | $P2_1/c$ | 1 | aq EtOH, water | BESKAL03 | $P2_1/c$ | 1 | aq EtOH, $CHCl_3$ + acetone | monoclinic form 1 |
| 2,6-DHBA | LEZJAB | $Pna2_1$ | 1 | common solvents | LEZJAB01 | $P2_1/c$ | 1 | toluene (hot) | mixture of forms and monohydrate |
| 3,4-DHBA | this study | $P\bar{1}$ | 3 | melt | | | | | |
| 3,5-DHBA | this study | $C2/c$ | 3 | sublimation | this study | $C2/c$ | 0.5 | melt | sublimed |
| 3,4-DHBA monohydrate | BIJDON03 | $P\bar{1}$ | 2 | water (ambient temperature) | this study | $P2_1/c$ | 1 | water (0−5 °C) | triclinic monohydrate |
| 2,4-DHBA hemihydrate | QIVTUK | $P\bar{1}$ | 2 | water + EtOH | | | | | triclinic hemihydrate |
| 2,6-DHBA monohydrate | LEZJEF | $Pnma$ | 0.5 | basic water | | | | | |

TGA. The temperature range was 30−250 °C at 2 K $min^{-1}$ for DSC and 10 K $min^{-1}$ for TGA. Samples were purged with a stream of dry $N_2$ flowing at 150 mL $min^{-1}$ for DSC and 50 mL $min^{-1}$ for TGA.

**Computations.** Conformer energies were calculated with Gaussian03 (B3LYP/6-31G(d,p)).[18] Since the observed conformation in the crystal structure is usually different from the gas phase minimized conformer and often higher in energy, constrained optimization of the crystal conformer was carried out by keeping bond distances and angles fixed. Lattice energies were computed in Cerius[2] using the COMPASS force field. Crystal structures were minimized ($U_{latt}$) by allowing small variations in cell parameters but not gross differences between the calculated and experimental crystal lattices.

**Acknowledgment.** B.S. and P.S. thank CSIR and UGC for fellowships. We thank the DST for research funding (SR/S1/RFOC-01/2007 and SR/S1/OC-67/2006) and DST (IRPHA) and UGC (PURSE Grant) for providing instrumentation and infrastructure facilities. We thank Prof. T. N. Guru Row for XRPDs recorded at the Indian Institute of Science, Bangalore.

**Supporting Information Available:** ORTEP drawings, XRPD patterns, DSC curves, CSD refcodes, and crystallographic files (cif) of dihydroxybenzoic acids. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) (a) Kawase, M.; Motohashi, N.; Kurihara, T.; Inagaki, M.; Satoh, K.; Sakagami, H. *Anticancer Res.* **1998**, *18*, 1069 and references therein. (b) Rice-Evans, C. A.; Miller, N. J.; Paganga, G. *Free Radical Biol. Med.* **1996**, *20*, 933. (c) Bian, S.; Doh, H. J.; Zheng, J.; Kim, J. S.; Lee, C. H.; Kim, D. D. *Euro. J. Pharm. Sci.* **2003**, *18*, 141.

(2) (a) Horneffer, V.; Dreisewerd, K.; Ludemann, H. C.; Hillenkamp, F.; Lage, M.; Strupat, K. *Int. J. Mass Spectrom. Ion Process* **1999**, *185*, 859. (b) Agmon, I.; Herbstein, F. H. *Eur. Cryst. Meet.* **1982**, *7*, 50. (c) Mazurek, J.; Dova, E.; Helmond, R. *Acta Crystallogr.* **2007**, *E63*, o3289. (d) Gdaniec, M.; Gilski, M.; Denisov, G. S. *Acta Crystallogr.* **1994**, *C50*, 1622. (e) Luo, T. J. M.; Palmore, G. T. R. *Cryst. Growth Des.* **2002**, *2*, 337.

(3) (a) Sarma, B.; Roy, S.; Nangia, A. *Chem. Commun.* **2006**, 4918. (b) Roy, S.; Bhatt, P. M.; Nangia, A.; Kruger, G. J. *Cryst. Growth Des.* **2007**, *7*, 476. (c) McGrady, G. S.; Odlyha, M.; Prince, P. D.; Steed, J. W.

*CrystEngComm* **2002**, *4*, 271. (d) Atwood, J. L.; Barbour, L. J.; Jerga, A.; Schottel, B. L. *Science* **2002**, *298*, 1000. (e) Saha, B. K.; Nangia, A. *CrystEngComm* **2006**, *8*, 440.

(4) Steed, J. W. *CrystEngComm* **2003**, *5*, 169.

(5) (a) Lehmler, H.-J.; Robertson, L. W.; Parkin, S.; Brock, C. P. *Acta Crystallogr*. **2002**, *B58*, 140. (b) Brock, C. P. *Acta Crystallogr*. **2002**, *B58*, 1025. (c) Brock, C. P.; Duncan, L. L. *Chem. Mater*. **1994**, *6*, 1307.

(6) (a) Jetti, R. K. R.; Boese, R.; Sarma, J. A. R. P.; Reddy, L. S.; Vishweshwar, P.; Desiraju, G. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1963. (b) Sreekanth, B. R.; Vishweshwar, P.; Vyas, K. *Chem. Commun*. **2007**, 2375. (c) Babu, N. J.; Reddy, L. S.; Aitipamula, S.; Nangia, A. *Chem.—Asian J*. **2008**, *3*, 1122.

(7) 2,5-DHBA: (a) Haisa, M.; Kashino, S.; Hanada, S.-I.; Tanaka, K.; Okazaki, S.; Shibagaki, M. *Acta Crystallogr*. **1982**, *B38*, 1480 (BESKAL). (b) Cohen, D. E.; Benedict, J. B.; Morlan, B.; Chiu, D. T.; Kahr, B. *Cryst. Growth Des*. **2007**, *7*, 492 (BESKAL02).

(8) 2,6-DHBA: (a) Gdaniec, M.; Gilski, M.; Denisov, G. S. *Acta Crystallogr*. **1994**, *C50*, 1622 (LEZJAB). (b) MacGillivray, L. R.; Zaworotko, M. J. *J. Chem. Cryst*. **1994**, *24*, 703 (LEZJAB01).

(9) 2,3-DHBA: Okabe, N.; Kyoyama, H. *Acta Crystallogr*. **2001**, *E57*, o1224 (CACDAM).

(10) 2,4-DHBA: (a) Parkin, A.; Adam, M.; Cooper, R. I.; Middlemiss, D. S.; Wilson, C. C. *Acta Crystallogr*. **2007**, *B63*, 303 (X-ray, ZZZEEU01). (b) Adam, M. S.; Gutmann, M. J.; Leech, C. K.; Middlesmiss, D. S.; Parkin, A.; Thomas, L. H.; Wilson, C. C. *New J. Chem*. **2010**, *34*, 85 (neutron).

(11) The unit cell of 2,4-DHBA was reported over 50 years ago but without solving the space group: Giacomello, A. *Nature* (*London*) **1956**, *177*, 944 (ZZZEEU). a = 9.670 Å, b = 11.560 Å, c = 7.050 Å, α = 105.63°, $\beta$ = 91.72°, $\gamma$ = 79.92°, V = 747.107 Å$^3$. A possible error in the composition of this structure is discussed at the end of this paper.

(12) Cambridge Structural Database, ver. 5.30, ConQuest 1.11, November 2008 release, www.ccdc.cam.ac.uk.

(13) (a) Brouwer, E. B.; Enright, G. D.; Udachin, K. A.; Lang, S.; Ooms, K. J.; Haulchuk, P. A.; Ripmeester, J. A. *Chem. Commun*. **2003**, 1416. (b) Mcgrady, G. S.; Odlyha, M.; Prince, P. D.; Steed, J. W. *CrystEngComm* **2002**, *4*, 271. (c) Nagel, N.; Bock, H.; Eller, P. *Acta Crystallogr*. **2002**, *B56*, 234.

(14) (a) Wheatley, P. S.; Lough, A. J.; Ferguson, G.; Glidewell, C. *Acta Crystallogr*. **1999**, *C55*, 1489. (b) Varughese, S; Pedireddi, V. R. *Chem.—Eur. J*. **2006**, *12*, 1597. (c) Liao, X.; Gautam, M.; Grill, A.; Zhu, H. J. *J. Pharm. Sci*. **2010**, *99*, 246. (d) Sarma, B.; Nath, N. K.; Bhogala, B. R.; Nangia, A. *Cryst. Growth Des*. **2009**, *9*, 1546.

(15) Metal−DHB complexes: (a) Kula, A.; Rzaczynska, Z.; Mazur, L. *J. Chem. Cryst*. **2008**, *38*, 723. (b) Bandoli, G.; Dolmella, A.; Gerber, T. I. A.; Perils, J.; du Preez, J. G. H. *Inorg. Chim. Acta* **1999**, *294*, 114–118. (c) Aletras, V.; Hadjiliadis, N.; Stabaki, D.; Karaliota, A.; Kamariotaki, M.; Butler, I.; Plakatouras, J. C.; Perlepes, S. *Polyhedron* **1997**, *16*, 1399. (d) He, H. Y.; Zhou, Y. L.; Chen, Y. N.; Zhu, L. G. *Z. Kristallogr., New Cryst. Struct*. **2005**, *220*, 448. (e) Yang, Q.; Nie, J. J.; Xu, D. J. *Acta Crystallogr*. **2008**, *E64*, m757.

(16) (a) The COOH dimer is a common synthon in carboxylic acids. Desiraju, G. R. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 2311. (b) Other motifs are also possible. Kolotuchin, S. V.; Fenlon, E. E.; Wilson, S. R.; Loweth, C. J.; Zimmerman, S. C. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 2654.

(17) In general, the high $Z'$ polymorph structure has shorter hydrogen bonds. Babu, N. J.; Nangia, A. *CrystEngComm* **2007**, *9*, 980.

(18) Gaussian 03 is the latest in the series of electronic structure and energy computation programs, www.gaussian.com.

(19) (a) Bernstein, J.; Davey, R. J.; Henck, J. *Angew. Chem., Int. Ed*. **1999**, *38*, 3440. (b) Roy, S.; Banerjee, R.; Nangia, A.; Kruger, G. J. *Chem.—Eur. J*. **2006**, *12*, 3777.

(20) Cell parameters of 3,4-DHBA monohydrate in CSD. BIJDON03, *a* = 8.045(2) Å, *b* = 8.134(2) Å, *c* = 12.692(4) Å, α = 71.58°, $\beta$ = 76.79°, $\gamma$ = 72.17°, *V* = 742.114 Å$^3$. BIJDON, *a* = 9.926(9) Å, *b* = 9.532(9) Å, *c* = 8.138(8) Å, α = 100.8(1)°, $\beta$ = 90.7(1)°, $\gamma$ = 102.40(1)°, *V* = 736.953 Å$^3$. BIJDON02, *a* = 12.32(1) Å, *b* = 3.64(1) Å, 17.6(2) Å, α = 90°, $\beta$ = 107.70(20)°, $\gamma$ = 90°, *V* = 751.906 Å$^3$.

(21) For example, 2,6-DHBA monohydrate, LEZJEF, *a* = 6.778(1) Å, *b* = 9.411(1) Å, *c* = 11.890(2) Å, α = $\beta$ = $\gamma$ = 90°, *V* = 758.436 Å$^3$; and 2,4-DHBA hemihydrate, QIVTUK, *a* = 7.026(2) Å, *b* = 9.547(3) Å, *c* = 11.199(4) Å, α = 96.78°, $\beta$ = 104.34°, $\gamma$ = 98.85°, *V* = 709.496 Å$^3$.

(22) (a) Derissen, J. L.; Smit, P. H. *Acta Crystallogr*. **1974**, *B30*, 2240. (b) Benghiat, V.; Leiserowitz, L. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1763.

(23) (a) Parveen, S.; Davey, R. J.; Dent, G.; Pritchard, R. G. *Chem. Commun*. **2005**, 1531. (b) Gavezzotti, A.; Filippini, G.; Kroon, J.; van Eijck, B. P.; Klewinghaus, P. *Chem.—Eur. J*. **1997**, *3*, 894.

(24) (a) Kumar, V. S. S.; Addlagatta, A.; Nangia, A.; Robinson, W. T.; Broder, C. K.; Mondal, R.; Evans, I. R.; Howard, J. A. K.; Allen, F. H. *Angew. Chem., Int. Ed*. **2002**, *41*, 3848. (b) Das, D.; Banerjee, R.; Mondal, R.; Howard, J. A. K.; Boese, R.; Desiraju, G. R. *Chem. Commun*. **2006**, 555. (c) Desiraju, G. R. *CrystEngComm* **2007**, *9*, 91. (d) Anderson, K. M.; Steed, J. W. *CrystEngComm* **2007**, *9*, 328. (e) Nichol, G. S.; Clegg, W. *CrystEngComm* **2007**, *9*, 959. (f) Bernstein, J.; Dunitz, J, D.; Gavezzoti, A. *Cryst. Growth Des*. **2008**, *8*, 2011.

(25) *SAINT-Plus*, version 6.45; Bruker AXS Inc.: Madison, WI, 2003.

(26) Sheldrick, G. M. *SADABS, Program for Empirical Absorption Correction of Area Detector Data*; University of Göttingen, Germany, 1997.

(27) (a) *SMART* (*Version 5.625*) *and SHELX-TL* (*Version 6.12*); Bruker AXS Inc.: Madison, WI, 2000. (b) Sheldrick, G. M. *SHELXS-97 and SHELXL-97*; University of Göttingen: Germany, 1997.

(28) Barbour, L. J. *X-Seed, Graphical Interface to SHELX-97 and POV-Ray*; University of Missouri—Columbia: 1999.

(29) Spek, A. L. *PLATON, A Multipurpose Crystallographic Tool*; Utrecht University: Utrecht, The Netherlands, 2002. Spek, A. L. *J. Appl. Crystallogr*. 2003, 36, 7.

(30) Powder Cell for structure visualization, powder pattern calculation and profile fitting, www.ccp14.ac.uk.