Using Hydrogen-Bonds and Herringbone Packing to Design Interfaces of 4,4′-Disubstituted *meso*-Hydrobenzoin Crystals. The Importance of Recognizing Unfavorable Packing Motifs

Jennifer A. Swift,* Rajib Pal, and J. Michael McBride*

Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06520-8107

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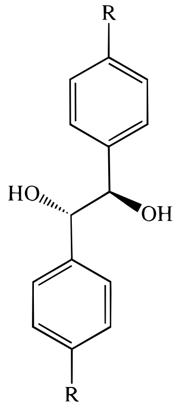
Abstract: Five pure 4,4′-disubstituted *meso*-hydrobenzoins and one solid solution have been investigated crystallographically. The aim was to establish whether a favorable hydrogen-bonding network and aromatic herringbone packing motif might make the lamellar structure shared by *meso*-hydrobenzoin (mHB) and *meso*-hydroanisoin sufficiently robust to serve as a reliable template on which to construct isomorphous surfaces containing various functional groups. Complete structures of the 4,4′-difluoro-, 4,4′-dichloro-, and 4,4′-dibromo-*meso*-hydrobenzoins and an average structure of the disordered 4,4′-dimethyl derivative were determined by X-ray diffration. Partial structures of twinned or disordered crystals of the 4,4′-diethyl derivative and of the 1:1 mixed crystal of the 4,4′-dimethyl and 4,4′-dibromo derivatives were determined by morphological and optical studies supplemented by diffraction. While the fluoro and ethyl compounds preserve the complete layer structure of mHB, and the bromo and chloro compounds preserve most of its features, the methyl compound packs in a completely different structure. Unlike either of its pure components, the methyl/bromo solid solution packs in the mHB layer structure. Hydrogen bonding and herringbone packing do not overwhelmingly favor a constant layer motif. Competing influences due to size, charge, and O−H···X hydrogen bonding (X = Cl, Br) of substituents are discussed. For crystal design purposes it is important to identify unfavorable packing motifs, such as the side-by-side arrangement of parallel C−Cl or C−Br groups.

Introduction

Monolayers of long-chain adsorbates have been used to tailor surface properties and to study the macroscopic and microscopic characteristics of a variety of terminal functional groups in organic molecules.[1] For detailed comparison of well ordered functional groups on a more perfect surface, it would be advantageous to replace the adsorbed monolayer with the plane face of a single crystal. However, the regularity that makes crystals preferable to monolayers also makes it much more difficult to vary functionality without varying structure. Comparative studies of the surface properties of a range of groups requires designing a series of otherwise isostructural crystals that display the groups of interest in high density on a conveniently prepared crystal facet.

Designing the packing of molecular crystals *de novo* is a daunting task.[2] It might be easier to identify in an existing crystal a particularly resilient packing motif that could survive modest changes in molecular substituents. For example, terminally substituted long-chain diacyl peroxides have allowed the study of various groups densely packed on otherwise isostructural single-crystals layers.[3] The scope of application for the peroxides is limited, because they are rather low-melting and reactive. The present work tests the possibility of designing a more robust series of isostructural crystal surfaces based on *meso*-hydrobenzoin (mHB).



R = H, F, Cl, Br, Me, Et, OMe

The morphology and cleavage of the monoclinic mHB crystal demonstrates that it is lamellar and has much stronger cohesion within the *bc* plane than along the *a* axis. Thus, mHB grows slowly along *a* to give a thin plate in the form of a rhombus with large {100} faces and small {011} sides, and the plate is easily cleaved to expose a fresh (100) face by pressing a razor blade against (011).

The molecular packing of mHB[4] explains the macroscopic anisotropy of the crystal. Figure 1 is an edge-on view showing

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[1] Numerous examples exist in the literature. For an overview, see: (a) Ulman, A. *Ultrathin Organic Films from Langmuir Blodgett to Self-Assembly*; Academic Press: San Diego, CA, 1991.

[2] Gavezzotti, A. *Acc. Chem. Res.* **1994**, *27*, 309−314.

[3] (a) McBride, J. M.; Bertman, S. B.; Semple, T. C. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 4743−4746. (b) McBride, J. M.; Bertman, S. B.; Cioffi, D. Z.; Segmuller, B. E.; Weber, B. A. *Mol. Cryst. Liq. Cryst. Nonlin. Opt.* **1988**, *161*, 1−24. (c) Bertman, S. B. Ph.D. Thesis, Yale University, 1990.

[4] Pennington, W. T.; Chakraborty, S.; Paul, I. C.; Curtin, D. Y. *J. Am. Chem. Soc.* **1988**, *110*, 6498−6504.

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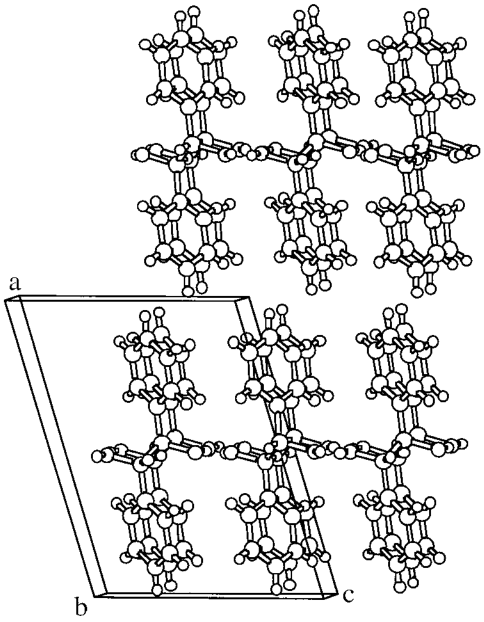

Figure 1. Layered packing of *meso*-hydrobenzoin (mHB).

two successive (100) or *bc* layers. In the middle of a layer, the two hydroxyl groups of each molecule participate in four H-bonds incorporating the molecule into two antiparallel H-bonded chains along the *b* axis to give a two-dimensional network (Figure 2a).[5] Above and below the H-bond network, phenyl groups pack in the commonly observed herringbone motif[6] that combines the virtues of offset stacking[7] and edge-to-face contacts (Figure 2b).[8] The layer surface consists of the edges of phenyl groups with projecting *p*-hydrogen atoms. The crystal morphology and cleavage confirm that layer-to-layer attraction between edges of phenyl groups is much weaker than the H-bonding and herringbone phenyl attractions within a layer.

If the H-bonding network and herringbone packing are sufficiently dominant, one might be able to introduce a variety of *p*-substituents while preserving the layer structure of mHB and thus achieve the goal of preparing surfaces that differ only in the nature of the exposed functional group.

The structure of *meso*-hydroanisoin (MeO-mHB, the 4,4′-methoxy analogue of mHB) demonstrates this possibility (see Table 1).[9] It has the same $P2_1/c$ packing as mHB, and its *b* and *c* cell parameters, which determine the layer structure, differ from those of mHB by only 0.04 and 0.10 Å (0.8% and 1.1%), respectively. Of course the methoxyl groups make the layer thicker and impose a different layer-to-layer offset along *c*.

As expected, MeO-mHB shows the same (100) plate morphology as mHB.[10] Since the layers of MeO-mHB and mHB are otherwise so similar, it is natural to attribute the higher melting point of the former (171 °C vs 135 °C for mHB) to favorable interactions involving methoxyl groups at the layer−layer interface.[11] In mHB, the closest interlayer contacts are 2.56 Å between *p*- and *m*-hydrogens (Figure 3a). In MeO-mHB, the closest interlayer contacts are 2.76 Å C−H···O interactions (Figure 3b).

Since groups as different in size as H and methoxyl give identical layers, the present work was undertaken to test the general utility of mHB as a robust frame for constructing isomorphous functionalized crystal layers.[12] Although isomorphism with mHB was achieved in three new cases, the H-bonding and herringbone motifs seem to be less dominant than had been anticipated from their prevalence in discussions of nonbonded interactions. Some *p*-substituents with sizes between H and methoxyl alter the layer motif. The nature of these alterations is instructive.

Experimental Section

General Methods. All ^{1}H NMR spectra were recorded on a Bruker 300-mHz instrument. Melting points were obtained on a Fisher-Johns instrument. Crystals were grown by slow evaporation of supersaturated solutions at room temperature. Except as noted crystal sizes were typically >1 mm in all dimensions.

Materials. ***meso*-Hydrobenzoin (mHB)** was purchased commercially (Aldrich, 99%) and used without further purification. Rhombic single crystals grown from diethyl ether or methanol solutions show large {100} plate faces and smaller {011} side faces.

4,4′-Difluoro-*meso*-hydrobenzoin (F-mHB) was prepared by the reduction of 4,4-difluorobenzil (Aldrich, 99%) following the method of Fieser (mp 150−151 °C).[13] ^{1}H NMR ($CDCl_3$) δ: 7.0−7.4 (8H, m), 4.8 (2H, s), 2.4 (2H, s). Single crystals from diethyl ether show morphology identical with that of mHB. Crystals from methanol, ethanol, and 2-propanol showed the same morphology.

4,4′-Diethyl-*meso*-hydrobenzoin (Et-mHB). 4,4′-Diethylbenzoin was prepared from 4-ethylbenzaldehyde (Aldrich, 98%) and subsequently reduced to the hydrobenzoin (mp 161−162 °C).[13] ^{1}H NMR($CDCl_3$) δ: 7.2 (8H, m), 4.7 (2H, s), 2.6 (4H, q), 2.1 (2H, s), 1.2 (6H, t). Single crystals from diethyl ether show a morphology identical with that of mHB.

4,4′-Dichloro-***meso*-hydrobenzoin (Cl-mHB).** 4,4′-Dichlorobenzoin (mp 109−110 °C (lit.[14] mp 109−110 °C) was prepared from 4-chlorobenzaldehyde (Aldrich, 97%) and subsequently reduced to the hydrobenzoin as above, allowing an increase in the reaction time (24 h) of the first step. ^{1}H NMR($CDCl_3$) δ: 7.0−7.4 (8H, m), 4.8 (2H, s), 2.6 (2H, s). Attempts at single-crystal growth from diethyl ether were unsuccessful. Rod-shaped single crystals from 1:1 $EtOH:H_2O$ show elongation along the *b* axis, with {100} and {001} side faces.

4,4′-Dibromo-*meso*-hydrobenzoin (Br-mHB) was prepared by the reduction of 4,4′-dibromobenzil (Aldrich, 97%) as above (mp 134−135 °C (lit.[14] mp 137−138 °C)). ^{1}H NMR($CDCl_3$) δ: 7.0−7.4 (8H, m), 4.8 (2H, s), 2.4 (2H, s). Attempts at single-crystal growth from diethyl ether were unsuccessful. Rod-shaped single crystals from 1:1 $EtOH:H_2O$ show elongation along the *a* axis, with {010} and {001} side faces.

4,4′-Dimethyl-*meso*-hydrobenzoin (Me-mHB). 4,4′-Dimethylbenzoin was prepared from tolualdehyde (Aldrich, 97%) and subsequently reduced to the hydrobenzoin as above (mp 140−142 °C (lit.[15] 145−146 °C)). ^{1}H NMR($CDCl_3$) δ: 7.2 (8H, m), 4.7 (2H, s), 2.4 (6H, s), 2.1 (2H, s). Prismatic single crystals of Me-mHB grown from diethyl ether show slight elongation along *b* with {001}, {100}, and {110} faces.

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[5] The H···O bond distance is 1.94 Å (O···O distance, 2.80 Å); the O−H···O bond angle is 172°.

[6] (a) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525−5534. (b) Desiraju, G. R.; Gavezzotti, A. *J. Chem. Soc., Chem. Commun.* **1989**, 621−623. (c) Gavezzotti, A. *Chem. Phys. Lett.* **1989**, *161*, 67−72.

[7] Center−center distance = 5.08 Å.

[8] Dihedral angle = 91.1°; center−center distance = 5.15 Å.

[9] Karlsson, O.; Lundquist, K.; Stomberg, R. *Acta Chem. Scand.* **1990**, *44*, 617−624. The paper reports a completely different packing for *meso*-hydroveratroin, where additional methoxyl groups in the 3 and 3′ positions would disrupt the herringbone packing.

[10] Personal communication from R. Stomberg.

[11] Note that any extra entropy of melting for MeO-mHB, due to the freeing of torsional degrees of freedom of the methoxyl group, must tend to lower its melting point. Of course, analyzing melting points in terms of group interactions has only qualitative significance, since melting points compare solids with the corresponding liquids, not with gas-phase molecules. Although liquids should be less able to optimize intermolecular attractions than solids, they do not eliminate them.

[12] Several of these crystals were also used in an AFM study of crystal dissolution. Results to be published.

[13] Fieser, L. F.; Williamson, K. L. *Organic Experiments*, 3rd ed.; D. C. Heath: Lexington, MA, 1975.

[14] Trahanovsky, W. S.; Gilmore, J. R.; Heaton, P. C. *J. Org. Chem.* **1973**, *38*, 760−763.

[15] Grimshaw, J.; Ramsey, J. S. *J. Chem. Soc. C.* **1966**, 653−655.

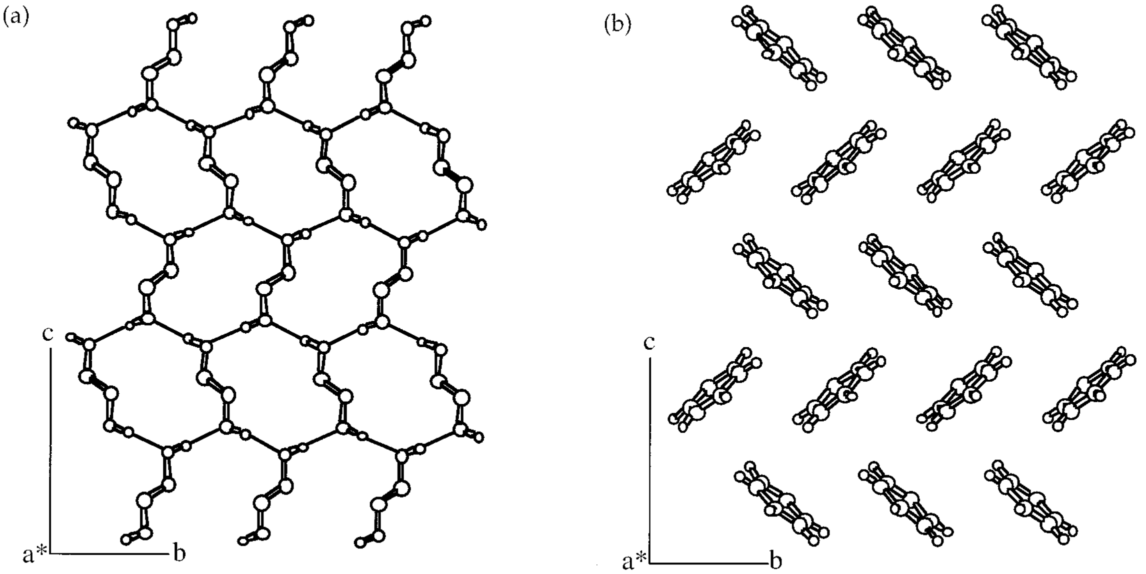

Figure 2. (a) Intermolecular hydrogen bonding in mHB. For clarity, only the alkyl C, and O and hydrogen bonded H atoms are shown. (b) Aromatic herringbone packing in mHB. In each, the view is along *a**.

Table 1. Corresponding Layer Cell Parameters,[a,b] Layer Thicknesses[c] and Offsets[d] (Å), Substituent Volumes (cm^3/mol)[e] and Radii (Å),[f] and Melting Points (°C)

X-mHB, (X=)	*a*	*b*	*c*	b°	thickness[c]	offset[d]	volume[e]	radius[f]	mp
H	12.54	5.08	9.31	106.67	12.02	3.60		1.20	135
MeO	15.27	5.04	9.20	98.95	15.08	2.38	17.37	3.52	171
F	13.02	5.07	9.36	107.05	12.45	3.82	5.80	1.35	150
Et	16.63	5.10	9.29	95.57	16.55	1.61	23.90	4.00	161
Cl[a]	15.62	4.99	9.28	100.47	15.36	2.84	12.00	1.80	110
Br[a]	16.07	5.02	9.22	100.55	15.80	2.94	15.12	1.95	134
Me[b]	11.19	5.00	11.86	90.57	11.19	2.50	13.67	2.00	142
1:1 Br/Me	15.62	4.98	9.37	101.25	15.32	3.05			150

[a] For the $P2_1/c$ structures (all but Cl, Br, Me), these are the unit cell parameters. For X = Cl and X = Br they are dimensions of the analogous partial layers (see Table 2 for the standard unit cells). [b] For X = Me, the packing remains lamellar, but the layer motif is too different from the others to consider *b* and *c* as corresponding. [c] $a \sin(\beta)$. [d] Layer-to-layer offset in the *c* direction = $|a \cos(\beta)|$, except for Me-mHB, where C-centering gives an offset of $b/2$ in the *b* direction. [e] Bondi, A. *Physical Properties of Molecular Crystals, Liquids & Glasses*; Wiley: New York, 1968. [f] Pauling, L. *The Nature of the Chemical Bond*; Oxford: London, 1940.

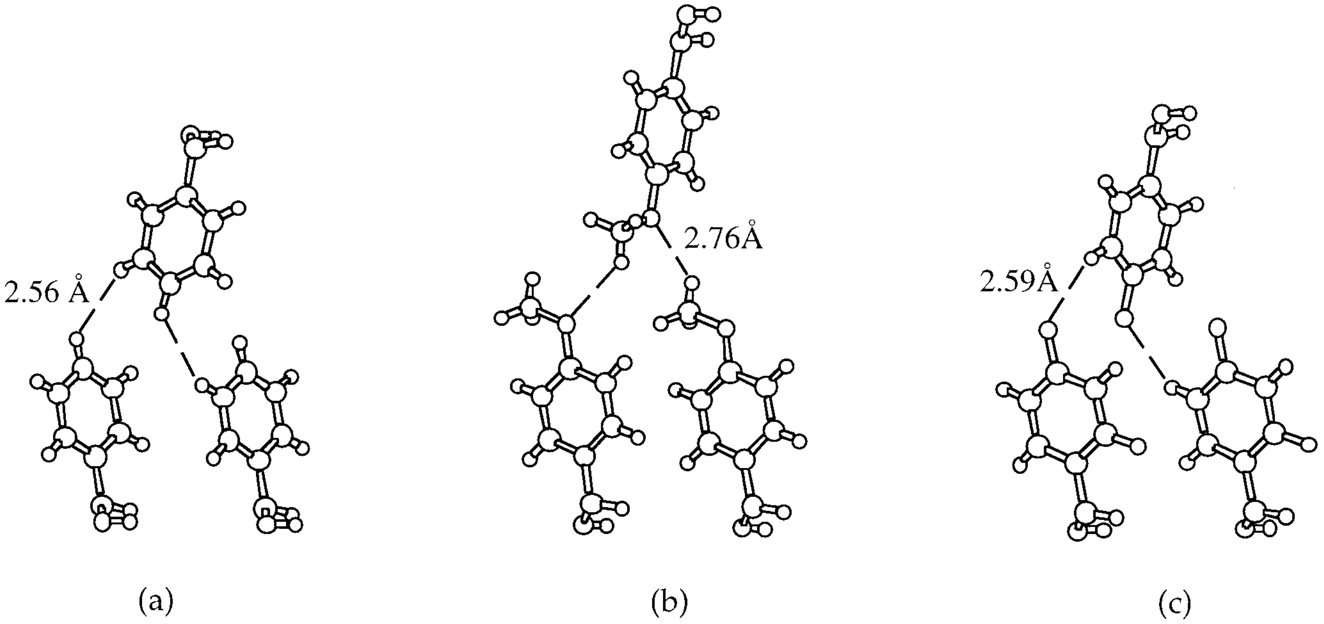

Figure 3. Comparison of closest interlayer contacts in (a) mHB (H···H), (b) MeO-mHB (O···H), and (c) F-mHB (F···H).

Mixed Me-mHB/Br-mHB crystals. Slow evaporation of diethyl ether containing equimolar concentrations of Me-mHB and Br-mHB resulted in very thin (0.05 mm) rhomboid single crystals with large {001} and smaller {011} faces, similar in morphology to mHB.

X-ray Crystallography. Experimental details of the X-ray analysis are provided in Table 2. Single-crystal X-ray structural data were collected on either a Rigaku AFC5S or Enraf-Nonius CAD4 diffractometer with graphite-monochromated Mo Kα radiation ($\lambda = 0.710\ 69$).

Table 2. Crystallographic Data for 4,4′-Disubstituted *meso*-Hydrobenzoins

	F-mHB	Cl-mHB	Br-mHB	Me-mHB
formula	$C_{14}H_{12}O_2F_2$	$C_{28}H_{24}O_4Cl_4$	$C_{28}H_{24}O_4Br_4$	$C_{16}H_{18}O_2$
FW	250.54	566.31	744.11	242.32
dimensions (mm^3)	0.30 × 0.30 × 0.30	0.40 × 0.20 × 0.20	0.20 × 0.20 × 0.40	0.30 × 0.15 × 0.40
color, shape	clear, prism	clear, needle	clear, needle	clear, prism
space group	$P2_1/c$ (No. 14)	$P2_1/n$ (No. 14)	$P\bar{1}$ (No. 2)	$C2/c$ (No. 15)
cryst syst	monoclinic	monoclinic	triclinic	monoclinic
a (Å)	13.021 (2)	11.149(2)	10.472(3)	22.375 (3)
b (Å)	5.067 (2)	9.281(2)	11.521(2)	5.010 (2)
c (Å)	9.357 (3)	26.643(9)	13.006(1)	11.858 (3)
α (deg)	90	90°	89.17(1)	90°
β (deg)	107.05(5)	100.65(2)	73.92(1)	90.59(1)
γ (deg)	90	90	70.07(2)	90
vol. (Å^3)	590.3(5)	2709(1)	1411.8(5)	1329(1)
Z	2	8	4	4
D_{calcd} (g/cm^3)	1.408	1.388	1.750	1.211
F(000)	260.00	1168.00	728.00	520.00
μ (Mo Kα) (cm^{-1})	1.08	4.69	56.76	0.73
diffractometer	AFC5S	CAD4	CAD4	AFC5S
temp (°C)	23.0	−10.0	23.0	23.0
scan type	$\omega - 2\theta$	ω	ω	$\omega - 2\theta$
$2\theta_{max}$ (deg)	60.0	52.6	52.6	60.0
scan rate	8.0	1.0−16.5	1.5−16	4.0
reflns collected	2008	5971	6048	2189
unique reflections	1905	5848	5722	2137
no . of obsd ($I > 3\sigma$)	895	1814	2291	679
no . of variables	82	337	325	91
R^a	0.048	0.056	0.047	0.066
$R_w{}^b$	0.054	0.065	0.044	0.060
GOF	1.66	2.13	2.03	2.87

^{a} $R = \sum||F_o| - |F_c||/\sum|F_o|$. ^{b} $R_w = [(\sum w(|F_o| - |F_c|)^2/\sum w F_o{}^2)]^{1/2}$, $w = 4F_o{}^2/\sigma^2(F_o{}^2)$.

Three standard reflections were measured every 150 reflections. All structures were corrected for Lorentz and polarization effects, and absorption corrections were additionally applied to F-mHB and Br-mHB. Structures were solved by direct methods and expanded using Fourier techniques.[16]

All non-hydrogen atoms were refined anisotropically. Aromatic hydrogen atoms were introduced in idealized positions and then refined isotropically. The oxygen atom of Me-mHB was found to be disordered between two sites whose occupancies were held at 50% during refinement. When occupancies were refined separately, they changed by less than 1%. Alkyl hydrogens of Me-mHB and Br-mHB were located in difference maps, while those in F-mHB and Cl-mHB were included in idealized positions and refined isotropically. Alcoholic hydrogens in Cl-mHB and Me-mHB were located in difference maps and refined isotropically. The alcoholic hydrogens of F-mHB and Br-mHB were calculated using the O−H distance (0.87 Å), C−O−H angle (108.04°), and C−C−O−H torsion (−91.42°) of the analogous hydrogen atom in mHB and were not refined.

Neutral atom scattering factors were taken from Cromer and Waber.[17] The values for the mass attenuation coefficients are those of Creagh and Hubbel.[18] All calculations were performed using the teXsan[19] crystallographic software package of Molecular Structure Corporation.

Differential Scanning Calorimetry (DSC). Melting point ranges for the mixed crystals were obtained on a Perkin-Elmer DSC-4 differential scanning calorimeter. Samples were finely ground with an agate mortar and pestle and sealed in aluminum pans. DSC sample weights were 1−2 mg. Samples were scanned from 70 to 180 °C at 2°/min.

Cambridge Structural Database (CSD) Search.[20] Data were retrieved from the CSD (Version 5.11) for all organic molecules containing both halogen (X = Cl or Br) and OH groups. The search was limited to intermolecular interactions in crystal structure determinations with R factors <10%. To eliminate X···H_2O and/or O−H···X^- interactions, additional constraints were imposed, namely the oxygen was bound to a carbon and X was required to have a formal charge of zero (i.e., C−O−H···X^0). Geometrical calculations were performed on the retrieved data using an automatic nonbonded search program of the CSD. For statistics, unique intermolecular interactions were considered up to the sum of the van der Waals radii, taken as 3.0 Å for H···Cl and 3.2 Å for H···Br.

Results and Discussion

Conformations of the X-mHB molecules are very similar. The conformation is determined by the torsional angle about the central C−C bond and by those about the carbon-phenyl bonds. In four cases (X = H, F, Me, OMe), the central C−C−C−C is 180° by centrosymmetry; in the others, it deviates from 180° by less than 2° (X = Cl 0.4°, 0.5°; X = Br 1.3°, 1.8°). The carbon−carbon−phenyl torsions are 74 ± 10°.[21]

In packing, two p,p'-disubstituted mHB derivatives (F-mHB and Et-mHB) preserve the layer structure of mHB and MeO-mHB. Two others (Cl-mHB and Br-mHB) show variant packings each retaining many features of the mHB layer. Me-mHB gives a completely different layer motif. A 1:1 solid solution of Br-mHB in Me-mHB apparently gives the same layer structure as mHB, although the pure components give two different structures. Table 1 summarizes layer dimensions, substituent sizes, and melting points for the compounds.

The existence of four different packing structures among these closely related compounds suggests that any one of them might

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(16) Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; de Gelder, R.; Israel, R.; Smits, J. M. M. *DIRDIF94*: The DIRDIF-94 program system; Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands, 1994.

(17) Cromer, D. T.; Waber, J. T. *International Tables for X-ray Crystallography, Vol. IV*; The Kynoch Press: Birmingham, England, 1961; Table 2.2A.

(18) Creagh, D. C.; Hubbell, J. H. *International Tables for Crystallography, Vol C;* Wilson, A. J. C., Ed.; Kluwer: Boston, MA, 1992; Table 4.2.4.3, pages 200−206.

(19) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation, 1985 and 1992.

(20) Allen, F. H.; Kennard, O. *Chem. Des. Automat. News.* **1993**, *8* (1), 31−37.

(21) The torsions, measured by the two C−C−C_{ipso}−C_{ortho} angles are the following: H, 76.7°; F, 78.8°; Me, 83.2°; MeO, 78.1°; Cl, 74.8°, 70.8°, 74.0°, 72.1°; Br, 64.1°, 76.5°, 68.8°, 70.7°.

occur in several structures, but we have not observed any evidence for polymorphism. No X-ray powder diffraction data were collected, but the well-formed crystals of each compound had similar morphology.

4,4′-Difluoro-*meso*-hydrobenzoin (F-mHB). The structure of F-mHB is closely similar to that of mHB. The *b* and *c* translations that establish the layer structures differ by only 0.01 and 0.05 Å (0.2% and 0.5%), respectively. Positions of corresponding non-hydrogen atoms in mHB and F-mHB differ by only 0.04−0.12 Å with an RMS deviation of 0.075 Å. Layers in F-mHB are 0.4 Å thicker than those in mHB, largely because the two C−F bonds are each 0.28 Å longer than C−H. The lateral offset along *c* from one layer to the next differs by 0.2 Å.

That F-mHB melts 17 °C higher than mHB must indicate stabilization due to the F atoms, since the two crystals are otherwise isostructural. Not surprisingly the shortest atom−atom distances between adjacent layers involve F···H contacts (2.59 Å) (see Figure 3c). If such C−F···H−C contacts are not strongly attractive,[22] increased stability of crystalline F-mHB may be due to attraction between antiparallel C−F dipoles.

4,4′-Diethyl-*meso*-hydrobenzoin (Et-mHB). Plates of Et-mHB grown from various ethers and alcohols also showed the same rhomboid morphology and (100) cleavage as mHB. Although polarized microscopy revealed intimate, multiple twinning that prevented complete X-ray structure determination, 19 low-angle reflections from one component of a twin showed a monoclinic unit cell with *b* and *c* axes that differ from those of mHB by only 0.4% and 0.2%, respectively.

The similarity to mHB in morphology and lattice dimensions suggests a common layer structure. The size of the ethyl groups makes layers of Et-mHB 4.5 Å thicker than those of mHB and 1.5 Å thicker than those of MeO-mHB. The 10 °C reduction in melting point from that of MeO-mHB is consistent with loss of C−H···O attraction[23] between layers of otherwise similar structure. The 26 °C increase in melting point from that of mHB suggests better attraction between ethyl groups than between the edges of phenyl rings.[24]

Studies of morphology by optical microscopy and atomic force microscopy (AFM) suggested two common types of twinning across the (100) layer interface.[25] In one type, the layers are mutually rotated by 180° about *a**, or possibly about *c*, and retain two-dimensional lattice registry. In the other, they are rotated by 180° about [011], or by 122.5° about *a**, and retain registry only in one dimension. Twinning has also been reported for MeO-mHB, though the crystals examined in the present work were not twinned.[9]

4,4′-Dichloro-*meso*-hydrobenzoin (Cl-mHB). Superficially the $P2_1/n$ cell of Cl-mHB bears no similarity to the $P2_1/c$ cell of mHB, since it contains twice as many molecules and the orientation of molecules with respect to the symmetry elements is entirely different. However, in length, the *b* axis of Cl-mHB is within 0.3% of the *c* axis of mHB, and comparison of atomic positions shows that this is no accident. Cl-mHB includes ribbons of molecules along [010] that are 10.2 Å wide (Figure 4),[26] and these ribbons fit well in the [001] direction on the (100) layers of mHB (compare Figures 5a and 2a).

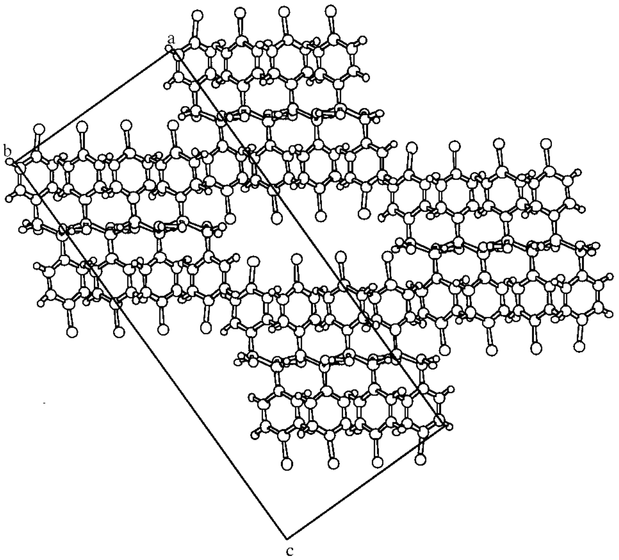

Figure 4. Crystal packing of Cl-mHB viewed along the ribbon axis [010]. Each block of four molecules is the asymmetric unit of a different ribbon.

The mHB structure may be converted to that of Cl-mHB by slicing each layer into strips parallel to the *b* axis and shifting every other strip out of the plane by about half of the layer thickness. The offset from ribbon to ribbon still allows herringbone packing of phenyl rings in infinite sheets, but it interrupts the O−H···O chains.

In place of the infinite chains of H-bonded OH groups in mHB, Cl-mHB has chains four OH groups long that run across the ribbon.[27] The final OH in the chain forms an O−H···Cl hydrogen bond to a chlorine atom in an adjacent parallel ribbon that is offset by half of a layer thickness. The H-atom was placed 1.095 Å from the O atom in the direction indicated by a peak in the difference density map to give H···Cl 2.37 Å, significantly smaller than the 3.0 Å sum of their van der Waals radii, O−H···Cl 157°, O···Cl = 3.41 Å. The generality of the O−H···Cl interaction was investigated by searching the Cambridge Structural Database (CSD). The search resulted in 712 structures with OH and Cl functional groups, of which 84 showed H···Cl distances less than the 3.0 Å. Only eight of these showed H···Cl distances <2.40 Å,[28] suggesting that the 2.37 Å O−H···Cl interaction in Cl-mHB is uncommonly short.

In cleaving and offsetting an mHB layer, each interrupted chain loses two O−H···O bonds and the cooperativity of a continuous chain, and gains a single O−H···Cl bond. This exchange of H-bonds is almost certainly energetically unfavorable, an assertion supported by the morphology of Cl-mHB. Instead of plates, crystals grown by slow evaporation of 1:1 EtOH/H_2O solutions were rods. The rods were long in the [010] direction in which molecules are linked continuously by O−H···O hydrogen bonding, and narrow in directions where O−H···Cl bonding is involved.

Cl-mHB melts 25 °C lower than mHB, but this difference is not due solely to the difference in H-bonding. A hypothetical polymorph of Cl-mHB with the same layer structure as mHB is presumably even less stable, despite possessing continuous H-bonded chains. By what mechanism does chlorine substitution destabilize the mHB crystal lattice?

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[22] Dunitz, J.; Taylor, R. *Chem. Eur. J.* **1997**, *3*, 89.

[23] (a) Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* **1982**, *104*, 5063−5070. (b) Desiraju, G. R. *Acc. Chem. Res* **1996**, *29*, 441−449.

[24] Of course the increase in melting point is also due in some measure to increased intralayer cohesion.

[25] Indirect AFM evidence suggests that twin domains can be as thin as a single molecular layer. Manuscript in preparation.

[26] To measure ribbon width the nonhydrogen atoms are projected on the plane analogous to (100) of mHB. The most remote atom, which defines the edge of the ribbon, is C(10). In Br-mHB, it is O(2).

[27] In mHB, the hydrogen-bonded O··O distance is 2.80 Å, in Cl-mHB the three O···O distances range from 2.79 to 2.80 Å.

[28] CSD Refcodes: HQNLSE, JICRAO, SEZLIS, SORYIH, THAMCU, VEWRIY, WECBOV, YILTUI.

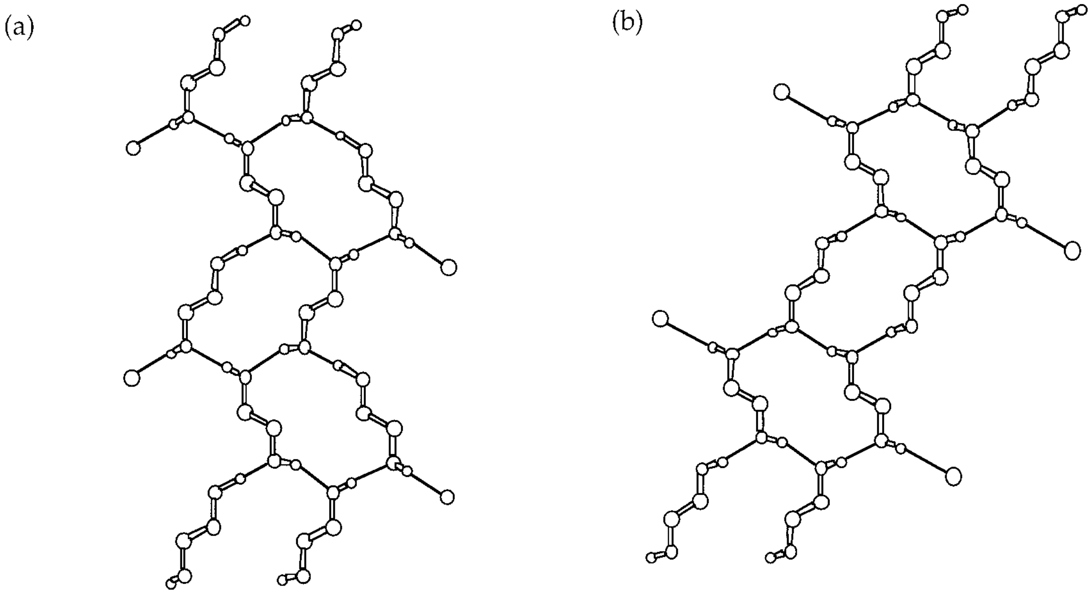

Figure 5. Comparison of 1D hydrogen-bonded ribbons in (a) Cl-mHB and (b)Br-mHB. For clarity, only the alkyl C and O and hydrogen-bonded H, Cl, or Br are shown. Note the similarity to the 2D hydrogen-bonding network of mHB seen in Figure 2a.

Previous discussions have tended to focus on the weakly attractive Cl···Cl interactions that stabilize chloroaromatic crystals through the "chloro effect".[29] Desiraju concluded from an examination of 600 chloroaromatic structures, that C−Cl···Cl−C contacts have the following two preferred orientations: C−Cl bonds antiparallel with C−Cl···Cl angles 160 ± 10° and L-shaped with one C−Cl···Cl angle near 80° and the other near 175°.[30]

The most obvious mechanism for electrostatic destabilization from chlorine−chlorine interaction would be accumulation of parallel side-by-side C−Cl dipoles within layers and of antiparallel nearly coaxial C−Cl···Cl−C arrangements between adjacent layers.

In Cl-mHB there are no L-shaped C−Cl···Cl−C contacts. There are three distinct, short (3.4−3.8 Å),[31] antiparallel C−Cl···Cl−C contacts between adjacent ribbons (which correspond to adjacent layers in the mHB structure), but they are far from coaxial, and the C−Cl···Cl angles are favorable (127−147°) by Desiraju's criterion. Two of these three favorable contacts are unaffected by slicing along [010]. There are five distinct, short (4.2−5.0 Å) side-by-side contacts between nearly parallel C−Cl dipoles within each ribbon surface.[32] Three of these five unfavorable contacts are lost by slicing along [010].

It seems plausible that upon chlorination the layer of mHB cleaves into shifted ribbons in order to relieve the most unfavorable C−Cl dipole−dipole interactions, while retaining the most favorable ones and replacing the lost O−H···O hydrogen bonds by O−H···Cl bonds.

4,4′-Dibromo-*meso*-hydrobenzoin (Br-mHB). Substitution of Br in the para positions of mHB, yields a new crystal packing with space group $P\bar{1}$ and two independent molecules in the asymmetric unit (Figure 6).

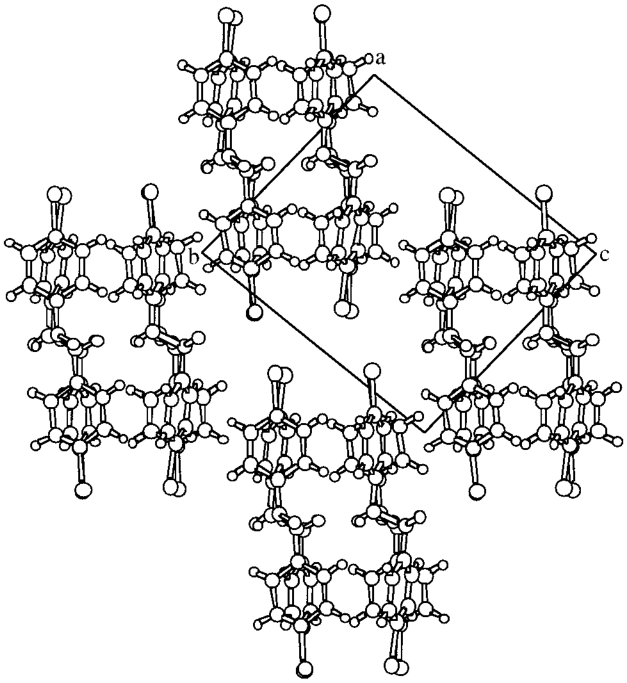

Figure 6. Crystal packing of Br-mHB viewed along the ribbon axis [100].

Like Cl-mHB, Br-mHB contains offset ribbons cut from (100) layers of mHB, but they are different ribbons (Figure 5b). Hydrogen-bonded ribbons in Br-mHB are 7.2 Å wide and extend in the [01$\bar{1}$] direction of mHB, while those in Cl-mHB are 10.2 Å wide and extend in the [001] direction of mHB. Like Cl-mHB, Br-mHB crystallizes as rods elongated in the direction of the ribbons.

Across the ribbons in Br-mHB run chains involving three O−H···O hydrogen bonds[33] and a terminal O−H···Br hydrogen bond (H···Br, 2.99 Å; O−H···Br, 144°; O···Br, 3.73 Å). The H···Br distance is only slightly smaller than the sum of their van der Waals radii (3.15 Å), but it is based on an assumed O−H distance of 0.87 Å (chosen to match the literature value of mHB). A more realistic 1.08 Å O−H distance gives an H···Br distance of 2.78 Å.

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[29] Schmidt, G. M. J. *Pure Appl. Ch*em. **1971**, *27*, 647.

[30] Desiraju, G. R. *Organic Solid State Chemistry, Studies in Organic Chemistry, vol 32*; Elsevier: New York, 1987.

[31] Distances (Cl···Cl) and angles: 3.40 Å, C−Cl(2)···Cl(1) 146.89°, Cl(2)···Cl(1)−C, 137.66°; 3.49 Å, C−Cl(4)···Cl(4), 144.93°; 3.76 Å, C−Cl(4)···Cl(3), 126.84°; Cl(4)···Cl(3)−C, 134.71°.

[32] C−Cl···Cl angles range from 90 to 107°; C−Cl···Cl−C torsional angles, from 0 to 13°.

[33] H···O 1.92−1.96 Å; O···O 2.77−2.80 Å; O−H···O 163−167°.

A CSD search for molecules containing both O−H and Br functional groups resulted in 282 hits with 40 H···Br contacts <3.2 Å, 11 of which are <2.8 Å.[34] Thus, the O−H···Br hydrogen bond observed in Br-mHB is uncommonly short. As in Cl-mHB, the cleavage of the mHB-type layer into ribbons preserves short layer-to-layer contacts between antiparallel C−Br groups[35] while reducing the number of side-to-side contacts between parallel C−Br groups within layers.[36]

Although one might discover polymorphs in which Cl-mHB and Br-mHB exchange packing patterns, it is easy to rationalize their differing preferences for the observed structures. The different ribbon shapes for Br-mHB and Cl-mHB result in different offsets between adjacent ribbons, both of which provide herringbone packing of phenyl groups between adjacent ribbons. In Br-mHB, the offset gives an O···Br distance of 3.73 Å where the O−H···Br bond is to form. In Cl-mHB, the corresponding O···Cl distance is 3.41 Å. Br-mHB would be inhibited from packing in the Cl-mHB motif by the short O···Br contact (0.14 Å less that the sum of van der Waals radii), and the O−H···Cl bond of Cl-mHB would be weakened if the O···Cl distance were stretched by 0.32 Å in order to pack in the Br-mHB motif.

4,4′-Dimethyl-*meso*-hydrobenzoin (Me-mHB). Among the eight mHB derivatives discussed here, Me-mHB stands alone in showing no trace of the parent crystal motif in its layer packing.[37] In the other mHBs, the long axis of the phenyl group is nearly perpendicular to the layer plane (tilted by 11° in mHB), exposing a layer surface composed of phenyl edges and *p*-substituents. In Me-mHB, the phenyl axis is tilted by 35°, partially exposing the phenyl face on the layer surface (see Figure 7). This presumably allows stronger van der Waals adhesion between layers than would be possible with projecting methyl groups, but it disrupts the hydrogen-bonding network in the middle of the layer to the extent that the X-ray results show oxygen disorder.

Since it seems surprising that weak van der Waals forces should disrupt the favorable H-bonding network of mHB, it is particularly relevant to see what type of H-bonding exists in Me-mHB.

The oxygens of Me-mHB are within 1 Å of the median plane of the (100) molecular layer, which is 11 Å thick (in mHB they are within 0.3 Å). There is no occupancy pattern for the disordered oxygens that would provide the long, straight chains of hydrogen-bonded OH groups observed in the other mHB structures.[38] The number and cooperativity of hydrogen bonds is optimized by the occupancy pattern indicated by filled circles at the left and bottom of Figure 8. This pattern allows C-shaped OH···OH···OH···OH chains with reasonable geometry for hydrogen bonding, although the O···O distance in the second bond is 0.2 Å longer than that in mHB chains.[39]

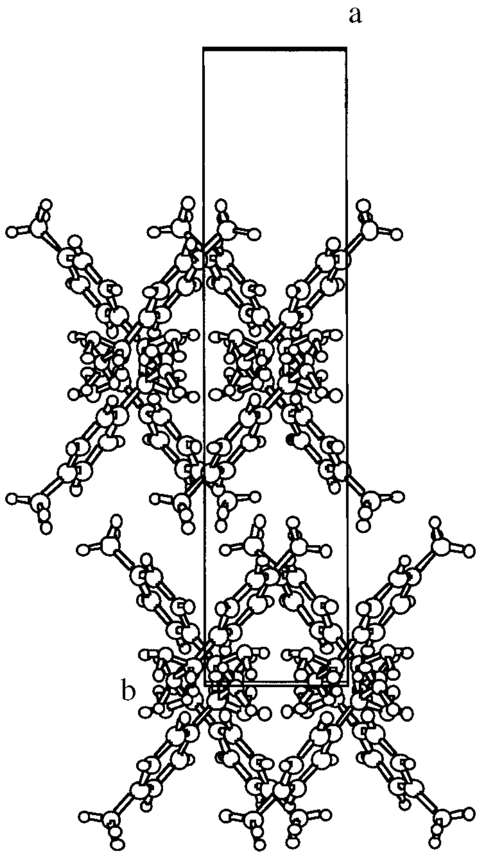

Figure 7. Crystal packing of Me-mHB viewed along [001].

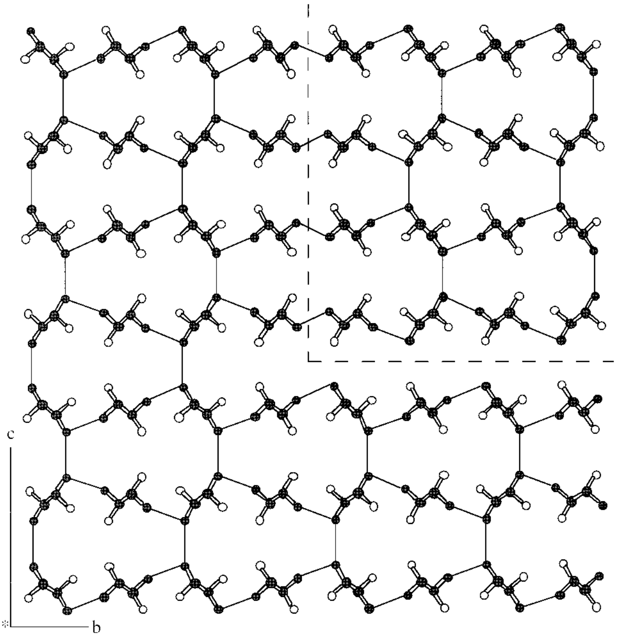

Figure 8. Hydrogen bonding in Me-mHB. Only the central alkyl C and attached O (each with 50% occupancy) are shown. Shaded atoms represent the proposed superstructure network. The dashed superstructure domain boundary illustrates the observed oxygen disorder involving a shift by one molecular distance along *b*.

Dominance of this pattern would require 50:50 occupancy of the oxygen sites, in agreement with the refined occupancy ratio of 49.3:50.7. If coherent domains of this ordered structure were large, the unit cell *b* axis would double, generating new reflections with half-integral *k* indices. Careful scans at (0, $k+1/2$, 0) for $k = 0, 1, 2, 3$ showed no net scattering intensity, suggesting that coherent superstructure domains are small.

It is easy to understand why the domains might be small.

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[34] CSD Refcodes: BAJVOX, BOCHOO, BOTDET, DEFSUC, FATJUF, JEWXUE, KONVEO, LINMIE, PACFOL, SAXITB, YISZUV.

[35] Slicing to form the ribbon preserves three of four short antiparallel C−Br···Br−C contacts with Br···Br distances 3.76−4.34 Å and C−Br···Br angles 122−134°.

[36] Slicing to form the ribbon removes the shortest three parallel C−Br···Br−C contacts with Br···Br distances 4.52−4.87 Å, C−Br···Br angles 91−100°; C−Br···Br−C torsional angles 0−8°.

[37] Similarity of the *b* cell parameters (Table 1) is purely accidental.

[38] The choice of occupancy is not completely arbitrary, since individual molecules must remain meso.

[39] O···O distances: 2.86, 3.02, 2.86 Å. C−O···O angles: 136°, 144°, 107°. C−C−O···O torsional angles: −76°, 103°, −87°. Note that a symmetry dyad of the *C*2/*c* space group passes through the middle of the C-shaped chain, meaning that the chain could change its polarity by rotation of the four OH groups. The H-atoms are almost certainly disordered, perhaps dynamically.

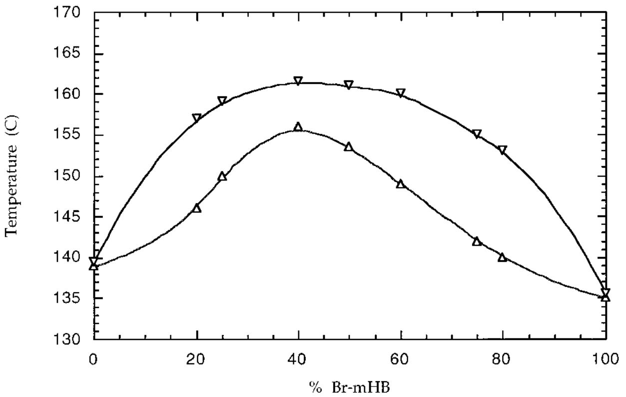

Figure 9. Phase diagram constructed from DSC melting point ranges of mixed ratios (mol %) of Br-mHB and Me-mHB.

Only the oxygens are disordered, and they are buried in the middle of the layer, so there is no obvious mechanism to enforce coherence between layers. Even within a single layer a growing crystal could easily make the kind of mistake illustrated at the top right of Figure 8. Consider a crystal growing toward the right. In adding to the growth surface, successive columns of *meso* molecules alternate in approaching with their *R*- and *S*-configured carbons. Molecules that add in the odd columns (counting from the left) form more hydrogen bonds than those in the even columns.

In the fifth column, the top four molecules have approached with the wrong carbon.[40] Although addition in this orientation forms only one H-bond, it is not much less favorable than adding a molecule in the preceding, even-numbered column. Such a mistake would be difficult to correct once the molecule is built into the growing column, since it is unlikely that molecules could rotate end for end. This defect introduces an extra column of molecules and thus lowers the coherence length of the superstructure without affecting the disordered substructure.

Br-mHB/Me-mHB Mixed Crystals. Similar radii of methyl and bromo groups make the Me-mHB and Br-mHB molecules nearly isosteric. However, their crystal packings differ from that of mHB in different ways and for different reasons. The discussion above attributes the packing difference for Me-mHB to poor van der Waals contact between adjacent mHB-like layers that have projecting methyl groups. It attributes the difference for Br-mHB to unfavorable contact between parallel C−Br groups within a mHB-like layer, despite favorable C−Br···Br−C contact between layers. A mixed crystal of Me-mHB and Br-mHB might distribute molecules in such a way as to avoid the Br···Br contacts that disfavor the mHB packing pattern.

Evaporation of diethyl ether solutions containing equimolar Me-mHB and Br-mHB deposited diamond-shaped plates that were too thin and imperfect for conventional X-ray structure determination. Five reflections from an unusually thick crystal (0.15 mm) were indexed to give a monoclinic unit cell closely similar to the $P2_1/c$ cell of mHB (Table 1). As in mHB, the large face was (100), the lateral faces were {011}, and the plate showed extinction along [010] and [001] on the polarizing microscope. The similarity in lattice dimensions, morphology, and symmetry confirms the isomorphism with mHB.

The melting phase diagram for Me-mHB/Br-mHB mixtures (Figure 9) is remarkable in three ways:

First, pure Me-mHB is higher melting than pure Br-mHB (142 °C vs 134 °C), whereas substutition of bromine for methyl commonly raises the melting point because of increased van der Waals and dipolar attraction.[41] This confirms that, in addition to these attractions, certain Br···Br interactions are unfavorable relative to $CH_3\cdots CH_3$ analogues. Repulsion is assigned in the discussion above to the side-by-side arrangements of parallel C−Br bonds that are minimized in Br-mHB (at the expense of reduced hydrogen bonding). It is not possible to measure the effect quantitatively with these substances, because the observed crystals are not isomorphous.

Second, the eutectic mixture near 1:1 composition is high melting (150 °C). This suggests that it is indeed possible in mixed crystals to replace some of the unfavorable Br···Br interactions with $Br\cdots CH_3$ interactions. It is conceivable that there could be a special attractive interactions for $Br\cdots CH_3$, but removing unfavorable Br···Br interactions and preserving favorable ones seems a more conservative explanation for the increase in melting temperature. We hope at some time to determine the arrangement of molecules in the mixed crystals, but disorder is likely, and our efforts thus far have been fruitless.

Third, there are no obvious discontinuities in the phase diagram, suggesting formation of solid solutions for all compositions, even though nonisomorphous crystal packings are involved ($C2/c$, $P2_1/c$, $P\bar{1}$). Perhaps even small admixtures of one component in the other suffice to induce the $P2_1/c$ packing analogous to mHB, and the observed crystals of the pure compounds are not dramatically more stable than their hypothetical $P2_1/c$ polymorphs.

Conclusion

This work demonstrates again the current superiority of molecules over chemists in discovering stable crystal packing patterns. The obvious virtues of herringbone packing and of continuous hydrogen-bond chains in the layer packing pattern of mHB allowed extending the list of substituents that it accommodates. But faced with even modest challenges from unfavorable interactions between parallel, side-by-side C−Br or C−Cl groups, or from inefficient methyl group packing, *meso* hydrobenzoins have no difficulty in locating superior structures with similar or different virtues.

Structural correlation studies that use the Cambridge Structural Database to identify attractive intermolecular interactions have been quite successful. Their success may have diverted attention from another consideration that is also important for crystal design, namely the necessity of avoiding unfavorable motifs. It is not obvious how one would use the CSD to identify patterns that are avoided. The type of study described above, where one attempts to understand why a crystal fails to adopt what appears to be a favorable packing, is one way to identify repulsive motifs.

Acknowledgment. This work was supported by grant no. N00014-90-J-4015 from the Mechanics Division of the Office of Naval Research and by a summer studentship to R.P. through a grant to Yale from the Howard Hughes Medical Foundation. We thank Nir Goldman for synthesis and crystal growth of Cl-mHB, Divakar Gupta and Hye Kwan for work on the phase diagram of mixed crystals, Susan de Gala for X-ray assistance, Professor Rolf Stomberg, University of Gothenburg, for un-

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[40] The new hydrogen bond has O···O distance 3.14 Å, C−O···O angle 95°, C−C−O···O torsion 92°.

[41] For example, 11-bromoundecanoyl peroxide melts 20 °C higher than isomorphous 11-bromoundecanoyl dodecanoyl peroxide (72.3−75.7 °C vs 53.0−53.8 °C); even-numbered α,*ω*-dibromoalkanes melt 20−50 °C higher than their dimethyl analogues. There are many counter examples, such as the odd-numbered α,*ω*-dibromoalkanes, where the melting points differ by only a few degrees. See: Breusch, F. L. *Fort. Chem. Forsch.* **1969**, *12*, 119 and ref 3c.

published information on MeO-mHB morphology, and Professor Angelo Gavezzotti for helpful comments on the original manuscript.

Supporting Information Available: Tables of X-ray data collection/refinement parameters, atomic position parameters, anisotropic displacement parameters and thermal ellipsoid plots for F-mHB, Cl-mHB, Br-mHB, and Me-mHB (25 pages). See any current masthead page for ordering and Internet access instructions.

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