### Which, if any, hydrates will crystallise?

# Predicting hydrate formation of two dihydroxybenzoic acids

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## 1 Evidence for the existence/non-existence of hydrates: solid form screen for polymorphs, hydrates and solvates

#### **1.1 Solvent Screen**

2,4–Dihydroxybenzoic acid (2,4–DHB, purity  $\geq$  98.0%) was purchased from Fluka and 2,5–dihydroxybenzoic acid (2,5–DHB, purity  $\geq$  99.0%) from Merck. The two isomers were recrystallised for purification from a hot saturated ethanol solution at 8 °C. For the solvent screens a set of 30 solvents was chosen, which were all of analytical quality and all organic solvents were purchased from Aldrich or Fluka. The set of solvents was methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 1-pentanol, toluene, xylene, heptane, cyclohexane, dichloromethane, dichloroethane, chloroform, ethyl methyl ketone, acetone, diethyl ether, diisopropyl ether, cyclohexanone, 1,4-dioxane, tetrahydrofurane, ethyl acetate, acetic acid, formic acid, acetonitrile, nitromethane, pyridine, dimethyl formamide, dimethyl sulfoxide and water. Crystallisation experiments included solvent evaporation, fast and slow crystallisation, precipitation with a miscible anti-solvent, vapour diffusion and solvent-mediated transformation. In total more than 300 manual crystallisation experiments were performed for the two acids at ambient pressure and mainly at room temperature (RT). The crystallisation products were identified with hot-stage microscopy, IR spectroscopy and powder X-ray diffractometry.

#### 2,5-Dihydroxybenzoic Acid (2,5-DHB):

The polymorph screen (Table S1 – S5) resulted in the two previously structurally characterised anhydrates (form I – disordered polymorph and form  $II^{\circ}$  – ordered polymorph)<sup>1</sup> and four new solvates (acetic acid monosolvate, dioxane monosolvate, dioxane hemisolvate and dimethyl formamide monosolvate).

Solvent	Description	Form
1-Butanol	Needles, plates	I, II°
2-Butanol	Needles, mp 205.5 °C	Ι
1-Propanol	Needles, plates	I, II°
2-Propanol	Needles, plates	I, II°
Ethanol	Needles, plates	I, II°
Methanol	Needles, plates	I, II°
Acetic acid	Plates, desolvate on heating	$S_{AA}$
Acetone	Needles, plates	I, II°
Acetonitrile	Needles, plates	I, II°
Diethyl ether	Needles, plates	I, II°
Diisopropyl ether	Needles, plates	I, II°
1,4-Dioxane	Pseudomorphosis (desolvated Solvate)	I, II° (desolvated)
Dimethyl formamide	Pseudomorphosis (desolvated Solvate)	I, II <sup>o</sup> (desolvated)
Dimethyl sulfoxide	Long plates	II°
Ethyl methyl ketone	Plates (and few needles)	I, II°
Ethyl acetate	Needles, plates	I, II°
Nitromethane	Needles and few plates	I, II°
Pyridine	Big spherulithes (fiber twisting)	Salt
Tetrahydrofuran	Needles, plates	I, II°
Water	Plates	II°

**Table S1** Results of 2,5–DHB: evaporation experiments<sup>a</sup> ( $II^{\circ}$  – form  $II^{\circ}$ , I – form I, S<sub>AA</sub> – acetic acid monosolvate).

<sup>a</sup>A saturated solution (at RT) of 2,5–DHB was filtered and the solvent was evaporated from a watch glass at RT.

monosorrate, SDX-M	utonune mono	boltute, b <sub>DA-H</sub> alonalie hellisoltute).	
Solvent	Method	Description	Form
1-Butanol	F	Thin needles	Ι
	S	Prismatic plates	II°
2-Butanol	F	Needles	Ι
	S	Plates	II°
1-Propanol	F	Plated and needles	II°, I
	S	Prismatic plates	II°
2-Propanol	F/S	Needles	Ι
Ethanol	F/S	Plates	II°
Methanol	F/S	Plates	II°
Acetic acid	F/S	Rhombic plates	$S_{AA}$
Acetone	F	Prisms	II° (+I ?)
	S	Prisms and needles	I, II°
Acetonitrile	F/S	Plates	II°
Diethyl ether	F/S	Big plates and smaller needles	I, II°
Diisopropyl ether	F	Needles, plates	I, II°
	S	Needles, plates	$I > II_{\circ}$
1,4-Dioxane	F	Platy crystals	$S_{DX-M}$
	S	Platy crystals	$S_{DX-H}$
Ethyl methyl ketone	F	Plates	II°
	S	Plates and needles	I, II°
Ethyl acetate	F/S	Prismatic plates	II°, I
Formic acid	F/S	Mixture of I and II°	I, II°
Nitromethane	F/S	Prismatic plates	II°
Pyridine	F/S	Plates	Salt
Tetrahydrofuran	F/S	Plates	II°
Water	F/S	Plates	II°

**Table S2** Results of 2,5–DHB: crystallisation experiments<sup>a</sup> (II° – form II°, I – form I,  $S_{AA}$  – acetic acidmonosolvate,  $S_{DX-M}$  – dioxane monosolvate,  $S_{DX-H}$  – dioxane hemisolvate).

<sup>a</sup>A hot saturated solution (close to the boiling point of each solvent used) was either cooled fast (F, in ice) or slow (S, test tube wrapped in aluminum foil) to  $0^{\circ}$  C or RT, respectively.

1 <sup>st</sup> Solvent	2 <sup>nd</sup> solvent	Description	Form
1-Butanol	DCM	Needles	Ι
	CH	Needles, few plates	I, (II°)
	Tol	Prismatic plates	II°
2-Butanol	DCM	Mixture of needles and plates	I, II°
	CH	Mixture of needles and plates	I, II°
	Tol	Needle like plates	II°
1-Propanol	DCM	Needle like plates	II°
	CH	Long needles	Ι
	Tol	Plates	II°
2-Propanol	DCM	Mixture of needles and plates	II°, I
-	CH	Needles	Ι
	Tol	Plates	II°
Ethanol	DCM	Mixture of needles and plates	I, II°
	СН	Plates and needles	I, II°
	Tol	Prisms	II°
Methanol	DCM	Plates and fine crystals (needles)	I, II°
Acetic acid	DCM	Rhombic plates	S <sub>AA</sub>
	СН	Rhombic plates	$S_{AA}$
Acetone	DCM	Mixture of needles and plates	I, II°
	СН	Mainly plates, few needles	$II_{\circ} > I$
	Tol	Plates	II°
Acetonitrile	DCM	Needles, plates	I, II°
	Tol	Prisms	II°
Diethyl ether	DCM	Prismatic plates	II°
-	СН	Plates, few needles	I <<<< II
	Tol	Plates	II°
Diisopropyl ether	DCM	Needles	Ι
	СН	Needles and few plates	I, (II°)
	Tol	Platty crystals	II°
1,4-Dioxane	DCM	Crystals desolvate upon heating	S <sub>DX-H</sub>
•	СН	Crystals desolvate upon heating (small) + forms I + II°	S <sub>DX-H</sub> , I, II°
	Tol	Prismatic plates	II°

Table S3 Results of 2,5–DHB: Precipitation experiments <sup>a</sup> (DCM – dichloromethane, CH – cyclohexane, Tol -
toluene, II° - form II°, I – form I, $S_{DX-H}$ – dioxane hemisolvate and $S_{AA}$ – acetic acid monosolvate).

Ethyl methyl ketone	DCM	Needles and plates	I, II°
	СН	Prismatic plates	II°
	Tol	Plates	II°
Ethyl acetate	DCM	Needles	Ι
	СН	Prismatic plates	II°
	Tol	Prismatic plates	II°
Nitromethane	DCM	Plates	II°
	CH	Needles and prismatic plates	I, II°
Pyridine	DCM	Plates	Salt
Tetrahydrofuran	DCM	Plates	II°
	CH	Needles	Ι
	Tol	Needles	Ι
Water	Tol	Plates	II°

<sup>a</sup>A saturated solution (at RT) of 2,5–DHB was prepared in solvent 1 and after filtration approx. three times the amount of solvent 2 was added.

 $\label{eq:solvent} \begin{array}{l} \textbf{Table S4} \ Results \ of 2,5-DHB: \ solvent \ mediated \ transformation \ experiments^a \ (II^\circ - \ form \ II, \ S_{AA} - \ acetic \ acid \ monosolvate, \ S_{DX-M} - \ dioxane \ monosolvate, \ S_{DMF} - \ dimethyl \ formamide \ monosolvate). \end{array}$ 

Solvent	Form	Solvent	Form
1-Butanol	II°	1,4-Dioxane	$S_{DX-M}$
2-Butanol	II°	Dimethyl formamide	$S_{DMF}$
1-Propanol	II°	Dimethyl sulfoxide	II°
2-Propanol	II°	Ethyl methyl ketone	II°
Ethanol	II°	Ethyl acetate	II°
Methanol	II°	Formic acid	II°
Acetic Acid	$S_{AA}$	Nitromethane	II°
Acetone	II°	Pyridine	Salt
Acetonitrile	II°	Tetrahydrofurane	II°
1-Propanol	II°	Water	II°
Chloroform	II°	Toluene	II°
Dichloromethane	II°	Xylene	II°
Dichloroethane	II°	Cyclohexane	II°
Diethyl ether	II°	Cyclohexanone	II°
Diisopropyl ether	II°	Heptane	II°

<sup>a</sup>2,5-DHB and few drops of solvent were ground in a Retsch MM301 grinding mill for 7.5 minutes.

Table S5 Results of 2,5–DHB: Vapor diffusion	experiments <sup>a</sup>	$(II^{\circ} - form II^{\circ}, I -$	form I, S <sub>AA</sub> –	acetic acid
monosolvate).				

Solvent	Description	Form
1-Butanol	Needles	Ι
2-Butanol	Prismatic plates	II°
1-Propanol	Prismatic plates	II°
2-Propanol	Prismatic plates	II°
Ethanol	Prismatic plates	II°
Methanol	Plates and needles	$II^{\circ} + I$
Acetic acid	Rhombic plates	S <sub>AA</sub>
Acetone	Prismatic plates	II°
Acetonitrile	Prismatic plates	II°
Diethyl ether	Prismatic plates	II°
Diisopropyl ether	Prismatic plates	II°
Dioxane	? desolvated	II°, I
Dimethyl formamide	Plated and needles	I, II <sup>o</sup>
Dimethyl sulfoxide	Plates	II°
Ethyl methyl ketone	Mixture of needles and prismatic crystals	$I + II^{\circ}$
Ethylacetate	Prismatic crystals	II°
Nitromethane	Prismatic crystals	IIº
Pyridine	Yellow crystals (plates)	Salt
Tetrahydrofuran	Plated and needles	$II_{o} + I$
Water	Needles and plates	$I + II^{\circ}$

<sup>a</sup>A saturated solution of 2,5–DHB was prepared at RT and placed in a small open vial, which was placed upright in a larger closed vial in which a quantity of toluene had been added.

#### 2,4-Dihydroxybenzoic acid (2,4-DHB):

Our corresponding solid state screen of 2,4–DHB produced two anhydrates, two hydrates (hemi– and monohydrate) and five solvates (acetic acid monosolvate, dimethyl formamide 0.75–solvate, dimethyl formamide hemisolvate, dimethyl sulfoxide hemisolvate and dioxane hemisolvate).<sup>2</sup>

#### **1.2 Moisture sorption experiments**

Isothermal ( $25 \pm 0.1$  °C) moisture sorption isotherms were acquired using a SPS-11 moisture sorption analyzer (Project Messtechnik, D). The samples were gently ground prior to measurement to exclude the influence of particle size and surface area. The measurement cycles were started at 40% relative humidity (RH). Sorption and desorption cycles covered the 10% to 90% RH range in 10% steps and the 0% to 10% range in 5% steps for 2,4–DHB. The equilibrium condition for each step was set to a mass constancy of  $\pm$  0.001% over 35 minutes.

2,4–DHB forms I and II° transformed only to the hemihydrate at the highest RH values (90%) at different rates,<sup>2</sup> whereas no hydrate formation was observed for the 2,5–DHB isomer (Fig. S1).



**Fig. S1** Moisture sorption isotherms of 2,4– and 2,5–DHB performed at 25 °C. Figure for 2,4–DHB taken from ref. 2.

#### 2 Stability determination of the 2,4–DHB and 2,5–DHB anhydrates

The thermodynamic forms at room temperature were determined with solvent-mediated transformation and slurry experiments, as well as Differential Scanning Calorimetry (DSC) measurements. Based on thermochemical data (melting point, heat of fusion, heat of transition) semi-schematic energy temperature diagrams could be constructed, which allowed us to obtain the stability order at 0 K. (Application of the Burger-Ramberger heat of fusion and heat of transition rules.<sup>3,4</sup>)

DSC measurements were performed with a DSC 7 (Perkin-Elmer, Norwalk, Ct., USA) using the Pyris 2.0 software. Approximately  $1-3 \pm 0.0005$  mg sample (UM3 ultramicrobalance, Mettler, CH) was weighed into Al-pans (25 µl). Dry nitrogen was used as the purge gas (purge: 20 mL min<sup>-1</sup>). A heating rate of 10 K min<sup>-1</sup> was used. The instrument was calibrated for temperature with pure benzophenone (m.p. 48.0 °C) and caffeine (m.p. 236.2 °C) and the energy calibration was performed with pure indium (purity 99.999%, m.p. 156.6 °C, heat of fusion 28.45 J g<sup>-1</sup>).

#### 2,5-Dihydroxybenzoic Acid:

DSC curves of the phase pure polymorphs are given in Fig. S2(a). Form I shows an onset of melting temperature at 205.8 °C ± 0.5 °C and a heat of fusion  $(\Delta_{fus}H_I)$  of  $31.0 \pm 0.1$  kJ mol<sup>-1</sup>. The lower melting polymorph (form II°, onset: 203.0 ± 0.1 °C) shows a higher  $\Delta_{fus}H_{II°}$  (33.9 ± 0.1 kJ mol<sup>-1</sup>). According to the Burger-Ramberger heat of fusion rule<sup>3,4</sup> the two polymorphs are enantiotropically related (Fig. S2(b)). From the melting temperatures and heats of fusion of the two polymorphs it was possible to calculate<sup>5</sup> the thermodynamic transition point of the two polymorphs, which was found to be 178 °C.



**Fig. S2** (a) DSC traces for 2,5–DHB anhydrates I and II° (heating rate: 10 K min<sup>-1</sup>, closed pan). (b) Semi-schematic energy/temperature diagram of 2,5–DHB polymorphs. I, II°: melting point of the polymorphs, *G*: Gibbs free energy, *H*: enthalpy,  $\Delta_{fus}H$ : enthalpy of fusion,  $T_{trs}$ : transition point, *liq*: liquid phase (melt).

#### 2,4–Dihydroxybenzoic Acid:<sup>2</sup>

The weak endotherm in the DSC curve (Fig. S3) at an experimental transition temperature ( $T_{trs,exp}$ ) of 159.8 ± 0.5 °C corresponds to the solid-solid transformation II°  $\rightarrow$  I with a transition enthalpy of  $\Delta_{trs}H = 2.1 \pm 0.1 \text{ kJ mol}^{-1}$ . From the fact that the transition is endothermic it can be concluded that the two polymorphs are enantiotropically related (heat of transition rule<sup>3,4</sup>).



**Fig. S3** (a) Hot-stage microscopy photographs of 2,4–DHB form II° to form I transformation, along with the DSC curve that shows the transformation (II°  $\rightarrow$  I), melting (mp) and decomposition (dec.) of form I (heating rate: 10 K min<sup>-1</sup>). (b) Semi-schematic energy/temperature diagram of 2,4–DHB polymorphs.  $T_{\text{fus}}$ : melting point, G: Gibbs free energy, H: enthalpy,  $\Delta_{\text{fus}}H$ : enthalpy of fusion,  $T_{\text{trs}}$ : transition point,  $\Delta_{\text{trs}}H$ : transition enthalpy, liq: liquid phase (melt). Figures taken from ref. 2.

Each of the two polymorphic systems forms a pair of enantiotropically related anhydrates, with a phase transformation occurring above room temperature. Therefore, form II° is the most stable polymorph of both molecules, both at room temperature and 0 K.

#### **3** Computer model for lattice energies

#### 3.1 Modeling of observed 2,4- and 2,5-DHB structures

To be able to calculate  $E_{\text{stab}}$  (Fig. 1) for the different hydrates of the two isomers we optimised the structures of the thermodynamically most stable experimental 2,4–DHB (form II°) and 2,5–DHB (form II°) anhydrates<sup>6</sup> with the program CrystalOptimizer,<sup>7</sup> followed by a polarisable continuum model (PCM) calculation<sup>8,9</sup> to provide the lattice energy  $E_{\text{latt}}$ . The four torsion angles involving oxygen atoms (Fig. S4), the cell parameters, positions and orientation of each independent molecule were varied to minimise  $E_{\text{latt}}$  as the sum of the intermolecular lattice energy,  $U_{\text{inter}}$ , and the conformational intramolecular energy penalty,  $\Delta E_{\text{intra}}$ , i.e.  $E_{\text{latt}} = U_{\text{inter}} + \Delta E_{\text{intra}}$ . GAUSSIANO3<sup>10</sup> was used to perform PBE0 6-31G(d,p) *ab initio* calculations on the isolated molecules to determine  $\Delta E_{\text{intra}}$  and the torsional forces and to calculate the PBE0 aug-cc-pVTZ charge density. All atomic multipole models<sup>11</sup> included moments up to hexadecapole and were generated from the isolated-molecule wavefunction using GDMA2.<sup>12</sup> DMACRYS<sup>13</sup> was used for intermolecular lattice energy calculations. The model for the intermolecular forces used the FIT<sup>14-16</sup> potential parameters. Polarisation of the molecular charge distribution in the crystal was accounted for by including a polarisable continuum around the molecule during an additional final PBE0 aug-cc-pVTZ electron density calculation, using  $\varepsilon$ =3, a value typical for organic crystals.<sup>8,9</sup> The intramolecular energy was taken from the same PCM calculation, and does not include the interaction energy between the molecule and the polarisable continuum.



**Fig. S4** Global and second lowest conformational minima of (left) 2,4– and (right) 2,5–DHB. The dihedral angles that were optimised within the crystal energy minimisation are indicated with arrows.

The same method was used for the hemihydrate, with the water molecule held rigid at the isolated molecule optimised conformation.

The computational model was successful in reproducing the proton-ordered experimental anhydrates and the 2,4–DHB hemihydrate structure (Table S6).

	Ι	attice para	cell	rmsd <sup>a</sup>				
	A	b	С	α	β	γ	g cm <sup>-3</sup>	(Å)
2,4-DHB_HH(exp.)	7.027	9.545	11.176	96.68	104.32	98.90	1.530	
calc.	6.905	9.756	11.032	94.49	105.99	101.38	1.563	0.218
2,4-DHB_II° (exp.)	3.674	22.341	8.236	90	106.5	90	1.580	
calc.	3.766	22.313	8.134	90	10593	90	1.553	0.130
$2,4$ -DHB_I (exp.) <sup>b</sup>	23.198	5.547	5.198	90	92.22	90	1.532	
calc.	20.948	4.982	6.022	90	92.615	90	1.634	1.03
2,5-DHB_II° (exp.)	5.561	4.869	23.688	90	100.19	90	1.622	
calc.	5.444	4.969	23.799	90	99.66	90	1.613	0.133
$2,5$ -DHB_I (exp.) <sup>c</sup>	4.911	11.828	11.058	90	91.06	90	1.594	
calc.	5.175	11.760	10.496	90	91.21	90	1.603	0.306

Table S6 Quality of representation of the experimental 2,4- and 2,5-DHB crystal structures (exp.).

<sup>a</sup>Reproduction of the crystal structures was evaluated by the optimal root-mean square overlay of all non-hydrogen atoms in a 15 molecule coordination cluster (rmsd<sub>15</sub>).<sup>17</sup> <sup>b</sup>Proton ordered analogue. <sup>c</sup>Proton disorderd Z'=1 structure found as ordered Z'=2 structure.

The most stable 2,5–DHB structure is more stable ( $E_{latt}$ ) than the corresponding structure of the 2,4–DHB isomer (Table S7), which packs less densely and has a less stable conformation ( $\Delta E_{intra}$ ). The conformational distortion improves the geometry of the hydrogen bond.

**Table S7** Stability comparison of the thermodynamic 2,4– and 2,5–DHBs.

	2,4-DHB	2,5-DHB
E <sub>latt</sub> (kJ mol <sup>-1</sup> )	-121.44	-126.97
$U_{\text{inter}}$ (kJ mol <sup>-1</sup> )	-127.57	-128.15
$\Delta E_{intra}$ (kJ mol <sup>-1</sup> )	+5.88	+1.18
Density (g cm <sup>-3</sup> )	1.553	1.613

#### 3.2 Modeling of ordered ice polymorphs

To predict hydrate formation we compared  $E_{\text{stab}}$  with the lattice energy of ice calculated with the same lattice energy model as the DHBs (3.1). Although the value of  $\varepsilon=3$  was used for consistency, it is close to the value found<sup>18</sup> for the ice polymorphs II (approx. 3.7) and VIII (approx. 4). At 0 K, the nominal temperature of lattice energies, the stable ice phases, namely ice II<sup>19</sup> (pressure < 0.8 GPa), ice XV<sup>20</sup> (0.8 to 1.5 GPa) and ice VIII<sup>21</sup> (> 1.5 GPa), are proton–ordered. These structures are satisfactorily reproduced (Table S8), albeit all calculated ice polymorphs were reproduced as too dense. The ambient pressure ice II was wrongly calculated to be the least stable of the three 0 K thermodynamic ice polymorphs in lattice energy (calculated at p=0 GPa, T=0 K). The ice polymorph XI used as reference for ice in an earlier crystal structure prediction work on hydrates,<sup>22</sup> was found within the lattice energy range of the thermodynamic 0 K ice polymorphs. The choice of the ice polymorph alters the limit for hydrate formation over a 3.5 kJ mol<sup>-1</sup> range and consequently the number of putative thermodynamic hydrate structures, but not the fact that 2,4-DHB hemi- and monohydrate structures are calculated to be thermodynamically stabilised by the inclusion of water over the anhydrates. The top of this range (ambient pressure ice II) may be the most appropriate comparison, as it is the stable 0 K and 0 GaP form of ice, but the problems in modeling ice structures and the effect of plausible variations in  $\varepsilon$ , leads us to make the comparison with the range of ice lattice energies in Fig. 2.

	Lattice parameters (cell vectors/Å, angles/°)						F	coll donaity	rmad <sup>a</sup>
	а	В	С	α	β	γ	kJ mol <sup>-1</sup>	g cm <sup>-3</sup>	(Å)
Ice II <sup>19</sup>	7.780	7.780	7.780	113.10	113.10	113.10		1.180	
calc.	7.461	7.440	7.435	112.81	112.73	112.77	-66.61	1.319	0.182
Ice VIII <sup>21</sup>	6.585	6.585	4.724	90	134.18	90		1.629	
calc.	6.402	6.402	4.612	90	133.95	90	-70.11	1.756	0.164
Ice XI <sup>23</sup>	4.502	7.974	7.328	90	90	90		0.930	
calc.	4.415	7.722	7.150	90	90	90	-67.96	0.982	0.075
Ice XV <sup>20</sup>	6.232	6.244	5.790	90.06	89.99	89.92		1.328	
calc.	5.904	5.990	5.782	91.32	87.82	98.87	-67.00	1.482	0.210

**Table S8** Quality of representation of the experimental (thermodynamically most stable at 0 K) ice polymorphs using the methodology described above.

<sup>a</sup>reproduction of the crystal structures was evaluated by the optimal root-mean square overlay of all non-hydrogen atoms in a 15 molecule coordination cluster ( $rmsd_{15}$ ).<sup>17</sup>

#### 4 The crystal energy landscapes: generation and low energy crystal structures

#### 4.1 Conformational analysis of the two acids

Potential energy surface scans revealed that the two acids each exhibit eight planar conformational minima arising from the rotation of the two hydroxyl (C–C–O–H) and the carboxylic acid group (C–C–C–O). The *meta* proton of 2,5–DHB and the *para* proton of 2,4–DHB can rotate significantly for minimal energy cost. This is consistent with all conformations observed being close to the two conformers for each molecule shown in Fig. S4. The PCM model reverses the stability order of the lowest 2,4–DHB conformational minima (Fig. S4). There are significant energy barriers for swapping the carboxylic acid proton and breaking the intramolecular hydrogen bond (*approx.* 50 kJ mol<sup>-1</sup> at HF 6-31G(d,p) and PBE0 6-31G(d,p) level of theory).

#### 4.2 Generation of crystal energy landscapes of hydrate structures

Hypothetical crystal structures of each isomer and hydrate stoichiometry were generated using the program CrystalPredictor, which uses a low-discrepancy sequence to search the crystal packing space with quasi-random values for unit cell dimensions, molecular orientations and positions, followed by rigid molecule lattice energy minimisation.<sup>24</sup> Due to the high cost of crystal structure prediction studies with multiple crystallographically independent molecules  $(Z_{-})$  in the asymmetric unit as required for hydrates, we considered only the global and second lowest conformational minima for each of the acids (HF 6-31G(d,p) optimised geometries of structures in Fig S4) and only considered three low hydrate stoichiometries. Figure 1 defines the conformers used in the searches: for the hemihydrate searches (Z =3) only the combination of conformers observed in the experimental 2,4–DHB hemihydrate structure was used; monohydrate searches were performed using either one of the two conformers (Z = 2) or a combination of the two low-energy conformers (Z = 4); for the dihydrates (Z = 3) each of the two lowest energy conformers was used. For each of these 12 searches, crystal structures were C2/c, Cc, C2, Pc, Cm, P2<sub>1</sub>/m, C2/m, P2/c, C222<sub>1</sub>, Pmn2<sub>1</sub>, Pnna, Pccn, Pbcm, Pmmn, and Pnma), with the molecule in a general position and held rigid. Searches were continued until 230 000 structures had been energy minimised for each search. The model for the intermolecular forces was an isotropic atom-atom potential (FIT<sup>14-16</sup> with modified A<sub>ii</sub> for the carboxylic acid proton, 3018 kJ mol<sup>-1</sup>) using atomic charges fitted to the MP2(fc)/6-31G(d,p) electrostatic potential using the CHELPG scheme.<sup>25</sup>

Following each CrystalPredictor search, the 7500 lowest energy crystal structures were used as starting points for local lattice energy minimisations (DMACRYS<sup>13</sup>) using distributed multipoles<sup>11</sup> derived from the PBE0 aug-cc-pVTZ charge densities and the original FIT<sup>14-16</sup> parameters. Conformations were kept rigid at the search conformations.

The most stable structures were refined allowing for conformational flexibility using CrystalOptimizer,<sup>7</sup> using the method of evaluating the lattice energies already described for the experimental structures (ESI, section 3.1). 130 structures were miminised with the polarisable continuum model: 15 hemihydrate, 30 monohydrate, and 20 dihydrate structures for each isomer. It has to be noted that the search method did not allow conformational transitions. Thus, for instance, a possible hemihydrate with two identical HBA conformations would not have been found. All Z =2 structures were run through the ADDSYM function of PLATON<sup>26</sup> in order to determine whether they corresponded to a Z = 1 structure. Z = 1 structures derived from Z = 2 searches, showing proton disorder, are marked with an asterisk (\*) in Tables S9 and S10. Shading denotes possible experimental structures (see 6.3 ESI). All calculated hydrate structures are available in .res format from the authors on request.

Structure	Space	Cell parameters			E1-4/	Density/	E-+-1/				
Siructure	group	a/Å	h/Å	c/Å	allieters	ß/°	$\gamma/^{\circ}$	$k I mol^{-1}$	g cm <sup>-3</sup>	$k I mol^{-1}$	
	(7)	u/ 1 1	0/11	<b>U</b> /1 <b>I</b>	0.7	Ρ′	17	no mor	5 0111	no mor	
Hemihvdrates											
C12 595	$P_{-1}(1)$	8 3 1 4	8 314	10 443	89.87	75.84	77 20	-317.67	1 577	-63 74	
$C12_{3333}$	$P2_{1/c}(1)$	7 3 50	6.870	27 441	90	99.50	90	-317.07	1.5%	-63.35	
$C12_{3333}$	$\frac{121}{2}$ (1)	27 599	4.676	10.835	90	90	90	-316.37	1.550	-62.44	
$C12_{000}$	$P2_1/c(1)$	0.260	12.063	15 124	90	126.06	90	315.02	1.530	61.00	
$C12_595$	$\frac{121}{C(1)}$	6.806	7 /30	13.124	95.46	03.66	00 30	315.92	1.565	-01.33 61.53	
$C12_0329$	$P_{1}(1)$	2 726	7.439	13.956	78.02	95.00	99.39	214 21	1.500	-01.33	
$C12_049$	$P_{1}(1)$	7.061	7.460	12 012	100.92	101.02	01.10	212.48	1.545	-00.27	
$C12_{1300}$	$\frac{1-1(1)}{2}$	/.001	12 221	12.915	111 70	101.05	91.22	-312.48	1.535	-38.33	
$C12_{2320}$	$\frac{1-1}{1}$	4.920	8 226	12.903	102.85	04.64	71.51	-312.42	1.555	-38.49	
$C12_1313$	$\frac{F-1(1)}{D2/a(1)}$	7.217	0.550	12.327	102.83	94.04	/1.31	-312.10	1.555	-36.17	
$C12_{3940}$	$P_{21/C}(1)$	23.401	3./1/	13.193	90	90.12	90	-310.39	1.307	-30.43	
$C12_184$	$P_{21/C}(1)$	12.780	3.072	30.218	90	108.30	90	-310.10	1.010	-30.23	
$C12_133$	$PZ_1Z_1Z_1(1)$	2.725	12.103	29.184	90	90	90	-309.14	1.589	-33.20	
<u>C12_928</u>	P-1(1)	3.735	15.270	24.809	100.50	90	90	-308.00	1.598	-54.72	
<u>C12_5221</u>	P-1(1)	4.862	10.267	14.211	90.93	98.65	98.31	-307.12	1.562	-53.19	
C12_2286	P-1(1)	7.510	13.342	14.385	90	90	102.40	-307.11	1.540	-53.17	
C1 001	$\mathbf{D}$	4 501	15 450	10.400	Monohy	drates	00	100.77	1 500	(5.01	
<u>CI_891</u>	$P2_{1}/c(1)$	4.501	15.452	10.429	90	99.55	90	-192.77	1.598	-65.81	
<u>CI_6230</u>	$P2_{1}/c(1)$	4.499	15.458	10.431	90	99.57	90	-192.74	1.598	-65.77	
<u>C1_1</u>	$P2_{1}/c(1)$	4.820	15.714	9.568	90	99.56	90	-192.16	1.600	-65.19	
<u>C12_30</u>	Pbca(2)	13.920	13.797	14.928	90	90	90	-191.75	1.595	-64.78	
60	$P2_1/c$ (1*)	3.572	13.880	14.849	90	101.26	90	-191.66	1.583	-64.69	
C124	$P2_{1}/c(2)$	7.148	13.808	14.838	90	101.44	90	-191.22	1.593	-64.25	
83	$P2_{1}/c(1)$	9.696	7.574	10.136	90	106.59	90	-190.88	1.603	-63.92	
C12_982	$P2_1/c$ (1*)	9.623	7.561	10.291	90	107.66	90	-190.18	1.603	-63.21	
C12_1100	$P2_1/c$ (1*)	18.871	7.560	10.296	90	103.73	90	-190.15	1.603	-63.19	
C123	$P2_1/c$ (1*)	7.137	13.860	14.865	90	102.16	90	-190.08	1.591	-63.12	
C1_3609	<i>P</i> -1 (1)	4.786	7.149	10.663	96.38	92.74	107.40	-190.07	1.658	-63.10	
C12_1	$P2_{1}/c$ (2)	7.221	14.198	14.242	90	102.13	90	-189.98	1.602	-63.01	
C1_16	C2/c(1)	10.486	15.792	8.646	90	97.80	90	-189.73	1.612	-62.76	
C1_76	$P2_{1}/c(1)$	9.575	7.554	10.390	90	108.09	90	-189.53	1.601	-62.56	
C2_441	$P2_{1}/c(1)$	8.078	12.912	7.491	90	115.18	90	-188.67	1.617	-61.70	
C1_88	$P2_{1}/c(1)$	7.181	21.865	4.692	90	110.13	90	-188.42	1.653	-61.45	
					Dihydı	rates					
C1_720	$P2_12_1\overline{2_1(1)}$	3.765	13.985	15.097	90	90	90	-259.35	1.591	-66.19	
C2_90	$P2_{1}/c(1)$	8.920	3.809	22.988	90	90.80	90	-258.09	1.617	-65.56	
C2_428	$P2_{1}/c(1)$	10.792	10.481	7.534	90	108.02	90	-257.27	1.617	-65.15	
C2_138	$P2_{1}/c(1)$	10.016	4.498	18.594	90	93.82	90	-256.75	1.512	-64.89	
C1_135	Pbca(1)	11.334	7.112	20.049	90	90	90	-256.02	1.563	-64.53	
C1_1676	P2 (1)	11.322	19.735	3.635	90	90	90	-255.97	1.555	-64.50	
C1 1898	$P2_{1}/c(1)$	3.653	19.631	11.427	90	90.40	90	-255.26	1.541	-64.15	
C1 3307	$P2_12_12_1(1)$	3.780	14.240	15.073	90	90	90	-255.11	1.557	-64.07	
C1 1200	$P2_1/c(1)$	3.672	15.493	14.380	90	96.69	90	-254.00	1.554	-63.52	
C2 7352	Pbcn(1)	10.572	7.222	21.412	90	90	90	-253.18	1.545	-63.10	
C2 5573	$P2_1/n(1)$	4.583	12,753	14.408	90	90.43	90	-253.08	1.500	-63.06	
C2 1981	C2/c(1)	12.338	4.548	29,000	90	94.08	90	-252.00	1.556	-62.52	
C2 3061	I2/c(1)	17.382	3.949	23.032	90	93,69	90	-252.01	1.601	-62.52	
C1 907	$P2_1/c(1)$	3 576	21.075	10 79	90	94 59	90	-249.85	1 557	-61 44	
C1 4309	$P2_1/c(1)$	6.503	16.962	7.080	90	93.04	90	-249 63	1.620	-61 33	

 Table S9 Hypothetical low-energy crystal structures of 2,5–dihydroxybenzoic acid hydrates.

Structure	Space	Cell parameters					Elatt/	Density/	E <sub>stab</sub> /		
	group	a/Å	b/Å	c/Å	α/°	ß/°	γ/°	kJ mol <sup>-1</sup>	g cm <sup>-3</sup>	kJ mol <sup>-1</sup>	
	(Z)					P,	17		U		
Hemihvdrates											
exp	<i>P</i> -1	7.027	9.545	11.176	96.68	104.32	98.90				
C12 3324	$P2_{1}/c(1)$	3.803	45.089	8.326	90	105.03	90	-314.44	1.572	-71.55	
C12 4	<b>P-1</b> (1)	6.905	9.756	11.032	94.49	105.99	101.38	-313.01	1.563	-70.12	
C12 605	P-1 (1)	6.803	9.161	11.484	101.71	96.02	99.18	-312.26	1.576	-69.37	
C12 29	$P2_{1}/n(1)$	6.783	12.057	16.773	90.04	90	90	-311.08	1.580	-68.20	
C12 299	<i>P</i> -1 (1)	6.748	9.038	12.188	103.55	100.14	102.30	-310.36	1.580	-67.48	
C12 718	C2/c(1)	29.503	3.791	25.471	90	109.42	90	-310.08	1.613	-67.19	
C12 203	$P2_{1}/c(1)$	12.526	6.777	16.769	90	104.69	90	-309.93	1.574	-67.04	
C12 171	$P2_{1}/c(1)$	14.738	7.814	12.728	90	115.52	90	-309.47	1.640	-66.58	
C12_6561	<i>P</i> -1 (1)	6.748	7.311	14.773	91.85	97.00	107.68	-309.34	1.576	-66.45	
C12_480	$P2_{1}/c(1)$	3.790	25.194	14.467	90	101.50	90	-308.86	1.601	-65.97	
C12_2076	$P2_{1}/c(1)$	6.971	3.684	52.826	90	92.43	90	-308.78	1.599	-65.89	
C12_990	$P2_{1}/c(1)$	13.874	6.803	14.875	90	94.73	90	-308.51	1.549	-65.62	
C12_2449	$P2_{1}/c(1)$	3.709	7.121	52.165	90	93.55	90	-308.48	1.576	-65.59	
C12_321	$P2_{1}/c(1)$	3.701	14.208	27.505	90	96.22	90	-307.49	1.613	-64.60	
				Mo	onohydra	tes					
exp	<i>P</i> -1	3.804	8.926	11.587	75.18	89.02	81.60				
C2_4815	<b>P-1</b> (1)	3.828	8.267	11.848	76.80	89.73	78.51	-193.24	1.599	-71.80	
C12_429	<i>P</i> -1 (2)	5.510	8.969	14.851	86.91	81.84	79.38	-192.62	1.602	-71.18	
C2476	<i>P</i> -1 (1)	3.759	6.625	14.980	79.17	89.09	83.43	-191.21	1.571	-69.77	
C2_1725	$P2_{1}/c(1)$	6.818	3.694	29.932	90	102.67	90	-191.11	1.555	-69.66	
C12_241	<i>P</i> -1 (2)	7.811	8.339	12.058	97.79	106.78	102.10	-189.38	1.590	-67.94	
<u>C12_464</u>	<i>P</i> -1 (1*)	3.887	8.375	11.572	77.71	88.16	78.12	-189.16	1.587	-67.72	
C12_3160	<i>P</i> -1 (1*)	3.880	8.376	11.577	77.62	88.13	78.12	-189.11	1.590	-67.66	
<u>C2_2514</u>	$P2_{1}/c(1)$	5.277	4.522	32.062	90	96.79	90	-189.09	1.529	-67.64	
<u>C12_256</u>	<i>P</i> -1 (1*)	3.877	8.377	11.589	77.55	88.17	78.20	-189.03	1.589	-67.58	
C12_6018	<i>P</i> -1 (1*)	3.908	8.375	11.528	77.81	87.59	78.18	-188.80	1.584	-67.36	
C12_2367	$P2_1(2)$	5.107	7.555	23.964	90	128.64	90	-188.61	1.584	-67.16	
<u>C2_75</u>	P-1(1)	5.300	7.172	9.859	104.10	102.00	91.51	-188.11	1.613	-66.66	
<u>C2_755</u>	$P2_{1}/c(1)$	13.022	12.007	4.632	90	95.65	90	-187.7	1.587	-66.31	
<u>C2</u> 269	$P2_{1}/c(1)$	9.660	4.800	17.331	90	116.43	90	-187.36	1.589	-65.97	
C125	<b>P-I</b> (1)	3.983	8.457	11.265	78.62	86.33	77 <b>.18</b>	-185.06	1.577	-63.61	
$C2_{3160}$	P-1(1)	3.133	0.138	15.110	95.03	94.44	91./1	-254.52	1.535	-00.54	
$C1_{2100}$	$PZ_{1}/C(1)$	10.939	4.154	20.19/	90	113.34	90	-252.94	1.501	-03./3	
$C1_{3190}$	$\Gamma - 1 (1)$ C 2/m (1)	2.935	19.214	4.234	00	/9.03	110.70	-232.39	1.581	-03.37	
$C2_{4104}$	$D_{1}(1)$	4 006	4.394	10.23/	90	93.30	90 70.57	-231.00	1.322	-03.08	
$C_{1}^{-}$	$F^{-1}(1)$	4.900	1 2 2 2	13.103	02.42	02.00	10.37	-231.09	1.555	-04.82	
$C1_{5/7}$	$\frac{12}{C}(1)$	1 650	4.332	12.800	90	92.00	90	-230.97	1.597	-04.70	
$C1_{007}$	$\frac{\Gamma \Delta_1 / \mathcal{C}(1)}{D2 / c(1)}$	4.030	6 254	21.113	90	95.85	90	-230.08	1.530	-04.02	
$C1_{2033}$	$F \angle_1 / C(1)$ P2, 2, 2, (1)	4.304	11 056	20.403	90	95.08	90	-230.39	1.534	-04.47	
$C_{2}^{-133}$	$\frac{1}{2}\frac{1}{2}\frac{1}{2}\frac{1}{1}\frac{1}{1}$	10 165	10 567	8 085	90	90 111.06	90	-247.37	1.579	-04.00	
$C_{2}^{3434}$	$\frac{1}{21/c}(1)$ $\frac{1}{21/c}(1)$	12/13/	3 720	0.005	90	03.62	90	-240.01	1.500	-62.30	
$C1_{3040}$	$\frac{12_1/u(1)}{P_{2_1/c}(1)}$	13 188	3 890	15 380	90	100.63	90	-240.30	1.504	-62.43	
$C_{1}^{+2/1}$	$P_{1/c}(1)$	9 752	10 702	7 670	90	94 46	90	-245.75	1.529	-62.15	
C2 4075	$P2_{1}/c(1)$	4.550	28.109	7.948	90	124.68	90	-245.62	1.505	-61.65	

Table S10 Hypothetical and known (see 6.3) low-energy crystal structures of 2,4–dihydroxybenzoic acid hydrates.

#### 4.3 Generation of crystal energy landscapes of anhydrates

For completeness, and to further test the models we have also performed searches on the anhydrates, applying the methodology described in 4.2. For each isomer we considered all eight conformational minima (Z = 1) and the combination of the two lowest energy conformers (Z = 2) in the CrystalPredictor searches (Fig. S5).



Fig. S5. Definition of the molecules and starting conformations used in the searches for possible anhydrate structures. Intramolecular energy penalties ( $\Delta E_{intra}$ ) were calculated at the PBE0/6-31G(d,p) level of theory.

The most stable Z = 1 anhydrate structures generated with each conformer (Fig. S5) show that the conformations without an intramolecular hydrogen bond can pack with an additional intermolecular hydrogen bond, but the improvement in the intermolecular lattice energy does not compensate for the loss of the intramolecular hydrogen bond. Only the two most stable conformations, differing in the *p*-OH and *m*-OH proton, generate crystal structures within the likely energy range of polymorphism.

#### 2,4-Dihydroxybenzoic Acid:

The 12 lowest energy structures (reported in ref. 2) were miminised with the polarisable continuum model. Form I is found as the global minimum structure and form  $II^{\circ} 0.46 \text{ kJ mol}^{-1}$  above form I (Fig. S6, left), i.e. the stability order of the two experimental polymorphs is wrong.

#### 2,5-Dihydroxybenzoic Acid:

The 40 lowest flexible refined energy structures were minimised with the polarisable continuum model. The two 2,5-DHB anhydrate polymorphs were found among the calculated low energy structures, albeit not as the lowest energy structures (Fig. S6, right). The proton disordered Z = 1 structure of form I was was found as the ordered equivalent in the Z = 2 search with the two conformations of the *m*-OH proton. It is incorrectly calculated to be more stable than form II°.

The finding of all four anhydrate structures among the lowest calculated energy structures further validates the search method. The incorrect stability orders of the experimental anhydrate polymorphs and 2,4–DHB hydrates shows the limitations of the method used to calculate the crystal energies. However, the results would have been improved if we had used the lattice energy of the other anhydrate polymorph



(form I) or even the most stable calculated anhydrate structure for  $E_{\text{stab}}$ , as this would have destabilised the 2,5–DHB hydrates even further.

**Fig. S6.** Crystal energy landscapes of 2,4–DHB (left) and 2,5–DHB anhydrates (right) plotted by lattice energy ( $E_{latt}$ ) vs density. Each symbol denotes a crystal structure.

#### 5 Comparison of 2,4–DHB hemihydrate and anhydrate structures

The finding of the experimental 2,4–DHB hemihydrate structure as the second most stable in lattice energy validates the search method. However, a comparison between the most stable 2,4–DHB hemihydrate structures generated in the search and the experimental anhydrate structures<sup>6,27</sup> shows (Fig. 7) that the most stable structures and form II° (anhydrate) are composed of the same 2D supramolecular construct,<sup>28</sup> which involves all O(2,4–DHB)–H··O(2,4–DHB) hydrogen bonds. The two structures differ in the way in which the 2D units are linked to its adjacent units along the respective *b*-axis. In form II° (Z'=1) a *n* glide plane relates the constructs, whereas in the calculated global minimum hemihydrate structure the molecules adopting the alternative conformation (ca. 180° rotation of *p*-OH proton) are centrosymmetrically related and interlinked by water bridges. This similarity to a known form suggests that the global minimum hemi-hydrate structure might be produced in crystallisations at higher pressure or lower temperature, although the experimental screen shows that it is not formed at ambient pressure and temperature.

The hemihydrate and form II° show less structural resemblance.<sup>2</sup>



**Fig. S7** Packing diagram of 2,4–DHB hemihydrate search minimum, 2,4–DHB form II<sup>o</sup>, and experimental 2,4–DHB hemihydrate. Acid conformations are distinguished by colour.

#### 6 Experimental characterisation of the 2,4–DHB monohydrate

#### 6.1 Powder X-ray diffractometry (Le Bail fitting)

The powder X-ray diffraction pattern of the 2,4–DHB monohydrate was obtained using an X'Pert PRO diffractometer (PANalytical, Almelo, The Netherlands) equipped with a theta/theta coupled goniometer in transmission geometry, programmable XYZ stage with well plate holder, Cu-K $\alpha_{1,2}$  radiation source with a focussing mirror, a 0.5° divergence slit and a 0.02° Soller slit collimator on the incident beam side, a 2 mm antiscattering slit and a 0.02° Soller slit collimator on the diffracted beam side and a solid state PIXcel detector. The patterns were recorded at a tube voltage of 40 kV, tube current of 40 mA, applying a step size of  $2\theta = 0.013^{\circ}$  with 40 s per step in the  $2\theta$  range between 2° and 40°.

The fact that the monohydrate is unstable at room temperature (i.e. transforms in minutes to form II° (anhydrate) if removed from the mother liquor or to the hemihydrate if kept in water) limited measurement time. The transformation to the hemihydrate was found to be slightly slower (approx. after 8 to 10 minutes). We therefore measured the sample wet, which is why the PXRD pattern (Fig. S8) shows a broad hump. Since the monohydrate phase is mechanically unstable (grinding the needle-shaped crystals induces a transformation) it is not possible to avoid preferred orientation in the PXRD pattern. Hence the PXRD data quality did not allow a structure determination or refinement of atomic positions from the proposed structures.



**Fig. S8** 2,4–DHB monohydrate. Refined unit cell parameters *a*, *b*, *c* (Å) = 3.8037, 8.9263, 11.5873;  $\alpha$ ,  $\beta$ ,  $\gamma$  (°) = 75.177, 89.016, 81.601; Pawley  $\chi^2$  = 1.954. (Black – observed, red – calculated, green – difference plot, blue – reflection positions).

#### 6.2 Raman and Infrared spectroscopy

Fourier Transform Raman (FT-Raman) Spectra were recorded with a Bruker RFS 100 Ramanspectrometer (Bruker Analytische Messtechnik GmbH, D), equipped with a Nd:YAG Laser (1064 nm) as the excitation source and a liquid-nitrogen-cooled, high sensitivity Ge-detector. The spectra (128 scans per spectrum) were recorded in aluminum sample holders with a laser power of 200 mW and a resolution of 2 cm<sup>-1</sup>.

Fourier Transform Infrared (FT-IR) Spectra were recorded with a Bruker (Bruker Optic GmbH, D) IFS 25 spectrometer connected to a Bruker IR microscope I (15x-Cassegrain-objective, spectral range 4000 to 600 cm<sup>-1</sup>, resolution 4 cm<sup>-1</sup>, 64 scans per spectrum). The samples were rolled on a ZnSe disc and measured in transmission mode.

Raman (Fig. S9) and IR spectroscopy (Fig. S10) were used to get some insight into the structural features of the two experimental hydrates. The absence of bands in the spectral range of 1760 to 1735  $\text{cm}^{-1}$  and 1730 to 1705  $\text{cm}^{-1}$  indicates that the carboxylic acid is dimerised in the two hydrate structures.<sup>29</sup>

The most characteristic region for discriminating the two hydrates is the region of the v(O-H) vibrations. The two hydrates each exhibit two sharp v(O-H) vibrations arising from water…acid hydrogen bonds, i.e. O-H…O, in the IR spectrum. The hemihydrate exhibits a third distinct v(O-H) vibration arising from the O-H…O hydrogen bond involving the *p*-OH group of the acid.



**Fig. S9** FT-Raman spectra of 2,4–DHB hydrates.



Fig. S10 FT-IR spectra of 2,4–DHB hydrates.

#### 6.3 Proposed 2,4–DHB monohydrate structure

There are seven structures which are isostructural<sup>28</sup> (Fig. S11, Table S11) in that they differ only significantly in the *p*-OH and adjacent water proton positions (marked in Table S10), and are consistent with the PXRD (6.1, Fig. S6) and vibrational spectra (6.2 Figs S7, S8). In all these structures, the 2,4–DHB acid molecules form carboxylic acid dimers which then form cascaded layers linked by water molecules (layer shown in Fig. 4). The structures all provide a reasonable match to the experimental cell parameters, except C12\_241, for which *a* is doubled. The simulated powder diffraction patterns for the global monohydrate minimum (C2\_4815, Fig S9 top)), the least stable of this set (C1\_25, with the alternative *p*-OH proton position, Fig S11 middle), and one of the structures with molecules in both proton positions (C12\_464, Fig S11 bottom) are shown in Fig 5. The simulated PXRD patterns of C12\_464, C12\_3160, C12\_256 and C12\_6018 are very similar as would be expected from the cell parameters (Table S10) and the overlays of 25 molecule clusters (Table S11).



**Fig. S11** Packing diagram of three of the seven calculated, isostructural 2,4–DHB monohydrate structures matching the experimental information (ESI, 6.1 and 6.2) showing the different *p*-OH and adjacent water proton positions.

mereury.							
	C2_4815	C12_241	C12_464	C12_3160	C12_256	C12_6018	C1_25
C2_4815							
C12_241	0.208 Å						
C12_464	0.183 Å	0.073 Å					
C12_3160	0.177 Å	0.076 Å	0.015 Å				
C12_256	0.173 Å	0.079 Å	0.019 Å	0.009 Å			
C12_6018	0.223 Å	0.073 Å	0.045 Å	0.054 Å	0.058 Å		
C1_25	0.389 Å	0.201 Å	0.205 Å	0.213 Å	0.218 Å	0.175 Å	

**Table S11** Comparison of the seven structures matching the experimental 2,4–DHB monohydrate powder pattern: Given are the  $rmsd_{25}$  values for a cluster of 25 2,4-DHB acid molecules using COMPACK<sup>17</sup> as implemented in Mercury.<sup>30</sup>

The .res file for the most stable of the seven isostructural structures (C2\_4815, global minimum structure) is given below. Because this is calculated to be the most stable, it is the most probable fully proton ordered structure. However, we cannot eliminate the other structures or proton disorder from the experimental evidence we have been able to obtain.

TITL 24DHB MH C2 4815.res CELL 1.0 8.2669 12.8054 3.8284 97.1388 101.4896 64.2593 ZERR 2 0.0 0.0 0.0 0.0 0.0 0.0 LATT 1 SFAC C O H C1 1 0.10841759 0.17869039 0.32137417 C2 1 0.08213079 0.29436118 0.42914160 C3 1 -0.07480506 0.36929438 0.56668618 C4 1 -0.20443862 0.33068062 0.59556475 C5 1 -0.17943508 0.21603939 0.49233851 C6 1 -0.02397000 0.14179729 0.35821363 C7  $1 \quad 0.27399042 \quad 0.10175694 \quad 0.18329590$ 01 2 0.29576313 -0.00833905 0.11399952 02 2 0.39006999 0.13168093 0.13328874 O3 2 0.20300771 0.33461039 0.40390036 04 2 -0.35437243 0.40740720 0.72772691 05 2 0.42477897 0.36347208 0.01213377 3 0.40979709 -0.04840503 H1 0.02361113 H2 3 0.30021689 0.27156575 0.29067602 H3 3 -0.41478873 0.36599266 0.79945101 H4 3 -0.09474871 0.45746409 0.65029988 H5 3 -0.28230576 0.18708723 0.51565485 H6 3 -0.00223028 0.05308478 0.27688505 H7 3 0.40112857 0.43814589 0.13063171 H8 3 0.32300102 0.37866653 -0.17773987 END

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