Solid-State Forms of β-Resorcylic Acid: How Exhaustive should a Polymorph Screen be?

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Electronic Supporting Information
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1 EXPERIMENTAL

1.1 Manual crystallization screen

Tables S1 – S5 list the results from the manual polymorphism screen.

**Table S1.** Results: evaporation experiments\(^a\) (II° – form II°, I - form II, HH – hemihydrate, S\(_{AA}\) – acetic acid monosolvate, S\(_{DX}\) – dioxane hemisolvate, S\(_{DMSO}\) – dimethyl sulphoxide hemisolvate).

| Solvent          | Description                                           | Form       |
|------------------|-------------------------------------------------------|------------|
| n-Butanol        | Needles and plates                                    | II°, I     |
| i-Butanol        | Needles and plates                                    | II°, I     |
| n-Propanol       | Needles and plates                                    | II°, I     |
| i-Propanol       | Needles and plates                                    | II°, I     |
| Ethanol          | Needles and plates                                    | II°, I     |
| Methanol         | Some of the crystals (needles) turn opaque on heating <100°C (hydrate), needles and plates | HH, II°, I |
| Acetic acid      | Needles, dehydrated/ desolvated crystals (pseudomorphosis) | II°, S\(_{AA}\) |
| Acetone          | Needles and plates                                    | II°, I     |
| Acetonitrile     | Mainly needles, few platy crystals                    | II°, I     |
| Chloroform       | Needles                                               | II°        |
| Diethyl ether    | Needles and few plates                                | II°, I     |
| Diisopropyl ether| Needles                                               | II°        |
| Dioxane          | Needles and few plates; some crystals showed pseudomorphosis, indicating the presence of a desolvated form. | II°, I, (S\(_{DX}\)) |
| Dimethyl formamide| Needles and plates                                   | I, II°     |
| Dimethyl sulphoxide| After 2 months crystallization of spherulithes (darken upon heating,) | S\(_{DMSO}\) |
| Ethyl methyl ketone | Hydrate (big, rectangular plates, desolvation ~90°C), needles and few plates | II°, HH, I |
| Ethyl acetate    | Needles and plates                                    | II°, I     |
| Nitromethane     | Needles and plates                                    | II°, I     |
| Pyridine         | Solution turned yellow, light yellow crystals melt between 150 and 158 °C | Salt       |
| Tetrahydrofurane | Needles                                               | II°        |
| Water            | Repeated several times: in some experiments HH was obtained, in others mixtures of HH and form II° | HH, II°    |

\(^a\)A saturated solution (at RT) of $\beta$RA was filtrated and the solvent was evaporated from a watch glass at RT.
### Table S2. Results: crystallization experiments

| Solvent       | Method | Description                               | Form          |
|---------------|--------|-------------------------------------------|---------------|
| n-Butanol     | F/S    | Needles                                   | II°           |
| i-Butanol     | F/S    | Mixture of forms II° and I                | II°, I        |
| n-Propanol    | F      | Plates and needles                        | II°, I        |
|               | S      | Needles                                   | II°           |
| i-Propanol    | F/S    | Needles                                   | II°           |
| Ethanol       | F/S    | Needles and plates                        | II°, I        |
| Methanol      | F/S    | Needles                                   | II°           |
| Acetic acid   | F      | Experiment repeated several times: unstable acetic acid solvate (dark crystals); however some of the clear crystals corresponded to form II°, SAC (SAC = solvate of acetamidochromate) | II°, SAC      |
|               | S      | Needles                                   | II°           |
| Acetone       | F      | Rectangular plates and needles            | HH, II°       |
|               | S      | Needles                                   | II°           |
| Acetonitrile  | F/S    | Needles                                   | II°           |
| Diethyl ether | F/S    | Needles and plates (part of the solvent evaporated) | II°, I        |
| Diisopropyl ether | F/S | Needles and plates (part of the solvent evaporated) | II°, I        |
| Dioxane       | F/S    | Needles                                   | II°           |
| Dimethyl formamide | F | Small crystals, which desolvated after removing form the mother liquor | SDMF-I and SDMF-II |
| Dimethyl sulphoxide | S | Needles and plates | II°, I        |
| Ethyl methyl ketone | F/S | Blocks | SDMSO |
| Ethyl acetate | F/S    | Needles                                   | II°           |
| Dimethyl formamide | F/S | Needles | II°    |
| Nitromethane  | F      | Needles                                   | II°, I        |
|               | S      | Needles                                   | II°           |
| Pyridine      | F/S    | Light yellow crystals                     | Salt          |
| Tetrahydrofuran | F    | Needles and plates                        | II°, I        |
|               | S      | Needles                                   | II°           |
| Water         | F      | Very thin needles, desolvation ~50°C      | MH            |
|               | S      | Desolvation ~90°C, at higher temperatures than MH | HH            |

a A hot saturated solution (close to the boiling point of each used solvent) was either cooled fast (F, in ice) or slow (S, test tube wrapped in aluminum foil) to 0° or RT, respectively.
**Table S3.** Results: Precipitation experiments\(^a\) (DCM – dichloromethane, CH – cyclohexane, Tol – toluene, II\(^\circ\) – form II, I – form I, HH – hemihydrate, SDX – dioxane hemisolvate and SAA – acetic acid monosolvate).

| 1\(^{st}\) Solvent | 2\(^{nd}\) solvent | Description (HTM) | Form |
|---------------------|-------------------|------------------|------|
| \(n\)-Butanol       | DCM               | Needles          | II\(^\circ\) |
|                     | CH                | Needles          | II\(^\circ\) |
|                     | Tol               | Needles          | II\(^\circ\) |
| \(i\)-Butanol       | DCM               | Needles          | II\(^\circ\) |
|                     | CH                | Form II\(^\circ\) and I | II\(^\circ\), I |
|                     | Tol               | Plates           | I, II\(^\circ\) |
| \(n\)-Propanol      | DCM               | Needles          | II\(^\circ\) |
|                     | CH                | Needles          | II\(^\circ\) |
|                     | Tol               | Small platy crystals | I, (II\(^\circ\)) |
| \(i\)-Propanol      | DCM               | Needles          | II\(^\circ\) |
|                     | CH                | Needles          | II\(^\circ\) |
|                     | Tol               | Needles and plates | II\(^\circ\), I |
| Ethanol             | DCM               | Needles          | II\(^\circ\) |
|                     | CH                | Needles, small plates and bigger rectangular plates | II\(^\circ\), I, HH |
|                     | Tol               | Needles and plates | II\(^\circ\), I |
| Methanol            | DCM               | Needles and plates | II\(^\circ\), I |
| Acetate             | DCM               | Needles and plates | II\(^\circ\), I |
| CH                  | Needles          | II\(^\circ\) |
| Tol                 | Part of the crystals desolvated (S\(_{AC}\)), needles dehydrate at ~90°C | S\(_{AA}\), HH |
| Acetone             | DCM               | Needles and plates | II\(^\circ\), I |
| CH                  | Needles          | II\(^\circ\) |
| Tol                 | Needles and plates | II\(^\circ\), I |
| Acetonitrile        | DCM               | Needles          | II\(^\circ\) |
|                     | Tol               | Needles and plates | II\(^\circ\), I |
| Chloroform          | DCM               | Needles          | II\(^\circ\) |
|                     | Tol               | Needles and plates | II\(^\circ\), I |
| Diethyl ether       | DCM               | Needles and plates | II\(^\circ\), I |
| CH                  | Needles          | II\(^\circ\) |
| Tol                 | Needles and plates | II\(^\circ\), I |
| Disopropyl ether    | DCM               | Needles          | II\(^\circ\) |
| CH                  | Needles          | II\(^\circ\) |
| Tol                 | Needles and plates | II\(^\circ\), I |
| Dioxane             | DCM               | Different crystal forms | II\(^\circ\), I, HH |
| CH                  | Desolvation (?) and dehydration | (S\(_{Dx}\)), HH |
| Tol                 | Needles and plates | II\(^\circ\), I |
| Ethyl methyl ketone | DCM               | Needles          | II\(^\circ\) |
| CH                  | Needles          | II\(^\circ\) |
| Tol                 | Needles and plates | II\(^\circ\), I |
| Ethylacetate        | DCM               | Needles and plates | II\(^\circ\), I |
| CH                  | Dehydration (HH) and form II\(^\circ\) (thinner needles) | HH, II\(^\circ\) |
| Tol                 | Needles and plates | II\(^\circ\), I |
| Nitromethane        | DCM               | Needles          | II\(^\circ\) |
| CH                  | Needles and few plates | II\(^\circ\), I |
| Pyridine            | DCM               | Yellow, melts at 154°C, embedded in silicon oil: after melting solvent escapes | Salt |
|                     | Tol               | Rectangular plates | HH |
| Tetrahydrofuran     | DCM               | Long thin needles | II\(^\circ\) |
| CH                  | Needles and platy crystals | HH, II\(^\circ\), I |
| Tol                 | Needles and plates | II\(^\circ\), I |
| Water               | Tol               | Rectangular plates | HH |

\(^a\) A Saturated solution (at RT) of \(\beta\)-RA was prepared in solvent 1 and after filtration ca. three times the amount of solvent 2 was added.
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**Table S4.** Results: solvent mediated transformation experiments\(^a\) (II° - form II°, HH – hemihydrate, SDX – dioxane hemisolvate, SDMF-II – DMF \(\frac{3}{4}\) solvate, SDMSO-II – dimethyl sulphoxide hemisolvate).

| Solvent          | Form       | Solvent          | Form       |
|------------------|------------|------------------|------------|
| \(n\)-Butanol    | II°        | Dioxane          | SDX        |
| \(i\)-Butanol    | II°        | Dimethyl formamide | SDMF-II   |
| \(n\)-Propanol   | HH         | Dimethyl sulphoxide | SDMSO    |
| \(i\)-Propanol   | II°        | Ethyl methyl ketone | II°      |
| Ethanol          | II°        | Ethylacetate     | HH         |
| Methanol         | II°        | Nitromethane     | II°        |
| Acetic acid      | II°        | Pyridine         | Pyridinium-Salt |
| Acetone          | II°        | Tetrahydrofurane | HH         |
| Acetonitrile     | II°        | Water            | HH         |
| Chloroform       | HH         | Toluene          | HH         |
| Dichloromethane  | HH         | Xylene           | HH         |
| Dichloroethane   | HH         | Cyclohexane      | HH, II°    |
| Diethyl ether    | II°        | Cyclohexanone    | II°        |
| Diisopropyl ether| HH         | Heptane          | HH         |

\(^a\)\(\beta\)RA and few drops of solvent were grinded in a grinding mill (Retsch Schwingmühle MM301) for 7.5 minutes.

**Table S5.** Results: Vapor diffusion experiments\(^b\) (II° – form II°, I - form I, HH – hemihydrate, SDMSO – DMSO solvate, SAA – acetic acid monosolvate, SDMF-II – dimethyl formamide \(\frac{3}{4}\) solvate).

| Solvent          | Description (HTM)          | Form       |
|------------------|----------------------------|------------|
| \(n\)-Butanol    | Needles and platy crystals | II°, I     |
| \(i\)-Butanol    | Rectangular plates         | HH         |
| \(n\)-Propanol   | Rectangular plates         | HH         |
| \(i\)-Propanol   | Needles and plates         | II°, I     |
| Ethanol          | Needles                    | II°        |
| Methanol         | Needles                    | II°        |
| Acetic acid      | Needles                    | II°        |
| Acetone          | Needles                    | II°        |
| Acetonitrile     | Needles and plates         | II°, I     |
| Chloroform       | Needles and few plates     | II°, I     |
| Diethyl ether    | Needles and plates         | II°, I     |
| Disopropyl ether | Needles and plates         | II°, I     |
| Dioxane          | Needles                    | II°        |
| Dimethyl formamide | Solvate (platy)           | SDMF-II    |
| Dimethyl sulphoxide | Needles                   | II°        |
| Ethyl methyl ketone | Needles and plates        | II°, I     |
| Ethylacetate     | Needles                    | II°        |
| Nitromethane     | Needles and plates         | II°, I     |
| Pyridine         | yellow crystals            | Pyridinium-Salt |
| Tetrahydrofurane | Needles                    | II°        |
| Water            | Rectangular plates         | HH         |

\(^b\)A saturated solution of \(\beta\)RA 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 anti-solvent had been added.
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1.2 Thermal analysis, thermodynamic and kinetic stability

Figure S1 shows the dehydration of βRA HHH embedded in silicon oil.

(a) 50 °C  (b) 70 °C  (c) 90 °C
(d) 94 °C  (e) 96 °C  (f) 100 °C

Figure S1. Photomicrographs (embedded in silicon oil) showing the dehydration process of βRA HHH.

The thermodynamic relationship of the two βRA modifications is displayed in a semi-schematic energy/temperature diagram (Figure S2).^{1,2}

Figure S2. Semi-schematic energy/temperature diagram of βRA 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).
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1.3 X-ray diffractometry

1.3.1 Powder X-ray diffraction data for structure determination of form I

Table S6. Variable count time scheme for powder X-ray data collection used for form I structure determination.

| 2θ range (°) | Count time (s per step) |
|--------------|-------------------------|
| 3 to 22      | 2                       |
| 22 to 40     | 5                       |
| 40 to 55     | 12                      |
| 55 to 70     | 24                      |

1.3.2 Identification of βRA phases

The powder X-ray diffraction patterns (Figure S3, Table S7) were obtained using a 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-Kα₁,₂ radiation source with a focusing mirror, a 0.5° divergence slit and a 0.02° Soller slit collimator on the incident beam side, a 2 mm anticluttering 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 2θ = 0.013° with 20 s or 40 s per step in the 2θ range between 2° and 40°.

The mechanical instability of all βRA phases except form II° and HH allowed the samples only to be ground gently and variations in intensities in the powder patterns due to preferred orientation could not be prevented.
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Figure S3. Powder X-ray diffraction patterns of the βRA polymorphs (I, II°), hydrates (HH, MH), solvates (S_{AA}, S_{DMF-II}, S_{DMF-I}, S_{DMSO} and S_{DX}) and the pyridinium salt.

| Form II° | Form I | HH | MH | S_{AC} | S_{DMF-II} | S_{DMF-I} | S_{DMSO} | S_{DX} | Pyridine |
|----------|--------|----|----|--------|------------|-----------|----------|-------|----------|
| 7.87     | 15.27  | 13.52 | 10.30 | 12.39 | 10.13 | 11.08 | 14.96 | 15.67 | 13.07 |
| 13.68     | 16.42  | 16.39 | 14.52 | 16.92 | 14.13 | 16.85 | 20.73 | 16.09 | 16.66 |
| 16.28     | 17.71  | 18.06 | 23.57 | 18.10 | 15.18 | 18.52 | 21.34 | 16.91 | 17.54 |
| 22.78     | 23.65  | 19.28 | 24.71 | 21.76 | 16.59 | 22.08 | 21.84 | 17.47 | 24.77 |
| 25.38     | 24.88  | 20.93 | 27.37 | 23.29 | 20.35 | 25.71 | 23.46 | 24.00 | 25.42 |
| 26.92     | 26.50  | 22.57 | 28.18 | 23.63 | 24.81 | 26.98 | 24.66 | 25.30 | 26.65 |
| 28.17     | 28.22  | 28.45 | 29.20 | 27.07 | 27.02 | 27.21 | 27.74 | 25.65 | 27.01 |
|          |        |      |      | 27.53 |      |      |        |       | 30.40 |

1.3.3 Variable temperature and moisture PXRD measurements

Temperature and moisture dependent measurements (Figure S4 and S5) were conducted on a Siemens D-5000 diffractometer equipped with a theta/theta goniometer, a Cu-K\(\alpha_{1,2}\) radiation source, a Göbel mirror (Bruker AXS, D), a 0.15° Soller slit collimator and a scintillation counter, equipped with a low temperature chamber (TTK, Anton Paar, A)
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interfaced with a SETARAM-WETSYS humidity generator (KEP-technologies, USA) to control the relative humidity (RH) in the chamber. The patterns were recorded at a tube voltage of 40 kV and a tube current of 40 mA, applying a scan rate of 0.05° $2\theta$ s$^{-1}$ in the angular range of 2 to 40° $2\theta$.

$HH$ dehydration was monitored at 0% relative humidity and RT. The dehydration led to a mixture of the two polymorphs. $MH$ was monitored at ambient conditions (ca. 40% RH and RT) and resulted in pure form II°. Scan number corresponds to time in the figures.

Figure S4. PXRD temperature-scan showing the dehydration of $\beta$RA $HH$ (front – hemihydrate, back – form II° and I) at RT and 0% RH. Time range: 5 days

Figure S5 PXRD temperature-scan showing the dehydration of $\beta$RA $MH$ in the range from 9 to 31 $2\theta$ recorded at ambient conditions (front – monohydrate, back – form II°). Time range: 2 hours
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1.3.4 Pyridinium salt: hydrogen bonding motif

The pyridinium cation interacts with the $\beta$RA anion via an ionic $N^+\text{–H}⋯\text{O}$ hydrogen bond. The anion forms a helix along $b$, mediated by $2_1$ symmetry (Figure S6).

![Figure S6. Hydrogen bonding motif present in the $\beta$RA pyridinium salt.](image)
2 THEORETICAL

2.1 Conformational analysis of βRA and the choice of method for ΔE$_{\text{intra}}$

The conformational energy scans for isolated βRA given in Figure S7 show that there are eight distinct planar minima, separated by significant barriers. The p-OH group can rotate significantly for minimal energy cost, in agreement with the experimental conformations. The relative energies of the eight fully optimized conformations (Table S8) depend slightly on the level of theory, but there is a clear pattern of having pairs of conformations of similar energy differing in the orientation of the p-OH proton. There is a significant energy difference for swapping the position of the carboxylic acid proton and an even larger penalty of ca. 50 kJ mol$^{-1}$ for breaking the intramolecular hydrogen bond. The PBE0/6-31G(d,p) method was chosen to model ΔE$_{\text{intra}}$ in the final lattice energy minimization (stage 3 ESI 2.4.1) as the best compromise between accuracy and computational cost.

The most stable crystal structures generated with each conformation 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 (Table S8). Our lattice energy model may be incorrectly modeling the balance between intra- and intermolecular hydrogen bonds, as ΔE$_{\text{intra}}$ was derived from isolated gas phase optimizations and is quite sensitive to the method of calculation.$^{3}$ However the energy differences are so large that we can exclude the possibility of crystal structures without the intramolecular H-bond.
Figure S7. Potential energy surface scans for βRA with respect to (a) $\theta_3$ (1D scan) and (b) $\theta_1$ and $\theta_2$ at the HF level of theory with the 6-31G(d,p) basis set. The range of experimentally observed torsion angles for the $p$-OH group is denoted on (a) with yellow bands.
Table S8. βRA conformational energy minima and their ΔE_{intra} values with respect to the global conformational minimum (conf_p1); summary of rigid-body (stage 2) search results. $E_{intra}$: lattice energy, where $E_{intra}$= the sum of the intermolecular lattice energy ($U_{inter}$) and the conformational energy penalty ($ΔE_{intra}$).

| Level of theory for calculating $ΔE_{intra}$/ conformations | conf_p1 | conf_p2 | Conf_o_p1 | Conf_o_p2 |
|-------------------------------------------------------------|---------|---------|-----------|-----------|
| HF/6-31G(d,p) / kJ mol$^{-1}$ | 0       | 2.72    | 50.96     | 48.44     |
| MP2/6-31G(d,p) / kJ mol$^{-1}$ | 0       | 2.27    | 50.30     | 47.69     |
| PBE0/6-31G(d,p) / kJ mol$^{-1}$ | 0       | 2.22    | 57.99     | 55.35     |
| DMACRYS minima within 5/10 kJ mol$^{-1}$ of overall global minimum | 24/107  | 0/19    | 0/0       | 0/0       |
| $U_{inter}$ / kJ mol$^{-1}$ | -116.18 | -112.28 | -130.67   | -132.37   |
| $E_{lat}$ (lowest), stage 2 / kJ mol$^{-1}$ | -116.18 | -109.56 | -71.71    | -83.93    |
| HF/6-31G(d,p) / kJ mol$^{-1}$ | 16.15   | 17.96   | 47.87     | 44.67     |
| MP2/6-31G(d,p) / kJ mol$^{-1}$ | 17.72   | 18.09   | 48.97     | 45.61     |
| PBE0/6-31G(d,p) / kJ mol$^{-1}$ | 19.51   | 20.81   | 55.12     | 51.88     |
| DMACRYS minima within 5/10 kJ mol$^{-1}$ of overall global minimum | 0/0     | 0/0     | 0/0       | 4/201     |
| $U_{inter}$ / kJ mol$^{-1}$ | -121.43 | -116.78 | -130.97   | -132.16   |
| $E_{lat}$ (lowest), stage 2 / kJ mol$^{-1}$ | -105.29 | -98.82  | -83.10    | -87.49    |
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2.2 Testing the model for the intermolecular forces for $U_{\text{inter}}$

The modeling of the intermolecular forces was tested by the reproduction of the crystal structures of form II$^p$, the hemihydrate and 19 related molecules (phenols, benzoic acid derivatives and their hydrates) chosen to also be single crystal determinations with the proton positions located from the Fourier difference maps. The subset of results for $\beta$RA form II$^p$ and the hemihydrate ($HH$) are shown in Table S9. We considered various parameterizations of the atom-atom exp-6 repulsion-dispersion potential of the form:

$$U = \sum_{i,j=k+2}^{\text{i.e., } 2} \left( A_{ii} A_{kk} \right)^{1/2} \exp(-\left( B_{nn} + B_{kk} \right) R_{ik} / 2) - \left( C_{ii} C_{kk} \right)^{1/2} \frac{1}{R_{ik}^6},$$

where atom $i$ in molecule 1 is of type $\iota$ and separated by $R_{ik}$ from atom $k$, of type $\kappa$, in molecule 2. The various sets of parameters were tested in conjunction with an MP2/6-31G(d,p) distributed multipole model for the electrostatic contribution.

The use of the recent Williams parameterization$^4$ (W01) gave very short intermolecular hydrogen bonds in the carboxylic acid $R_2^2(8)$ dimers. The older FIT$^{5-7}$ parameterization, in contrast resulted in these hydrogen bonds being somewhat too long in a number of the structures. An attempt to improve this by modifying (FIT$\text{COOH}$) the pre-exponential term $A_{ii}$ for the polar hydrogen in the COOH group, gave an excellent reproduction of all hydrogen bond lengths with an optimized value of 3018 kJ mol$^{-1}$ (compared to 5030 kJ mol$^{-1}$ in the FIT parameterization).

Since the FIT$\text{COOH}$ used in conjunction with the MP2/6-31G(d,p) distributed multipoles appeared to satisfactorily reproduce the large set of crystal structures, it was used initially in stage 2 of the search. Although this found form II$^p$ of $\beta$RA, it was ca. 5 kJ mol$^{-1}$ above the global lattice energy minimum. This search also found a chain (ch) structure (Figure 13) that is not observed at all in the CSD as the global minimum and in the majority of low energy crystal structures. This prompted an investigation into the sensitivity of the intermolecular potential to the charge density used to define the electrostatic contribution to the lattice energy.

The electrostatic potential around $\beta$RA in the two lowest energy conformations, as calculated from the distributed multipoles shows marked differences (Figure S8) when calculated from the MP2/6-31G(d,p) or PBE0/aug-cc-pVTZ charge densities. There is a clear difference in that the carbonyl oxygen region becomes more negative and the $p$-OH oxygen region less negative with the better PBE0/aug-cc-pVTZ charge density. This resulted in a change in the favorability of the different hydrogen bonding motifs.

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Thus the final model (FINAL) used in the stage 2 and 3 for the lattice energy landscapes (Figure 13, Tables S9 - S12) used the FIT parameters and the distributed multipole of the PBE0/aug-cc-pVTZ charge density. This gave satisfactory reproduction of 14 carboxylic acid structures, in addition to those of βRA shown in Table S9.

### Table S9.
The reproduction of experimental βRA crystal structures following stage 3 minimization of $E_{\text{lat}} = U_{\text{inter}} + \Delta E_{\text{intra}}$ using different repulsion-dispersion potential parameters and ab initio charge densities.

| potential | Lattice parameters (cell vectors/Å, angles/°) | cell density g/cm$^3$ | rmsd$^1_{15}$ (Å) |
|-----------|---------------------------------------------|-----------------------|-------------------|
|           | (Δ/ Å, °)                                    |                       |                   |
| Form Ao (ZZZEU03) | |                       |                   |
| Expt$^a$ | 3.674 22.341 8.007 90 99.57 90 1.580 | 0.280 |
| W01$^b$ | (0.139) (-0.124) (-0.157) (3.02) (-0.148) | 0.261 |
| FIT$^b$ | (0.050) (0.447) (-0.154) (2.88) (-0.410) | 0.221 |
| FITCOOH$^c$ | (0.078) (0.257) (-0.171) (3.00) (-0.063) | 0.158 |
| FINAL$^d$ | (0.089) (0.040) (0.032) (1.93) (-2.33) | |
| Hemihydrate (QIVTUK) | |                       |                   |
| Expt$^e$ | 7.026 9.547 11.199 96.78 104.34 98.85 1.527 | 0.220 |
| FITCOOH$^c$ | (-0.165) (-2.686) (-0.105) (-1.25) (2.36) (0.89) (2.13) | |
| FINAL$^d$ | (-0.072) (0.337) (-0.272) (-2.29) (1.27) (2.82) (1.16) | 0.237 |

$^a$The experimental structures (expt) are compared with the minimum in the lattice energy found for the conformationally relaxed structure (stage 3), using the $^{b,c}$MP2/6-31G(d,p) or $^{d}$PBE0/aug-cc-pVTZ for DMA + exp-6 potential and the $^{b,c}$FIT/modified FIT repulsion-disperion parameters and $^{d}$ΔE_{intra} derived form $^{b,c}$HF/6-31G(d,p) or $^{d}$PBE0/6-31G(d,p). $^c$Quantities in parentheses are percentage error, Δ%/ = 100((stage3 – expt)/expt). $^d$The quality of the reproduction of the crystal structures was evaluated by the optimal root-mean square overlay of all non-hydrogen atoms and non-water molecules in a 15 molecule coordination cluster (rmsd$^1_{15}$).
Figure S8. Electrostatic potential (V) maps for β-RA on a surface defined by twice the atomic van der Waals radii calculated from the distributed multipoles of the MP2/6-31G(d,p) and PBE0/aug-cc-pVTZ molecular charge densities for conf_p1 and conf_p2, drawn with ORIENT. The van der Waals radii were those of Bondi, except there was an effectively zero radius for polar hydrogen atoms to reflect the close distances in hydrogen bonds.
2.3 Modeling of form I

The final computational model was successful in modeling all well-determined experimental crystal structures and produced a plausible lattice energy landscape. However, modeling of the anhydrous form I gave significant errors (Table S10). The lattice energy minima predicted that the anhydrous form I was denser than form II°, in marked contrast to the observed and usual situation where the high temperature form is less dense. The lattice energy minima nominally correspond to static 0 K structures, but the empirical parameterization of the FIT potential to crystal structures implies that some thermal effects have been absorbed. Contrasting the experimental structures for form II° and HH at a range of temperatures (Table S10), shows normal thermal expansion, and that the potential is slightly underestimating the density for II°. Hence the 6% overestimate of the density of form I is not due to normal thermal expansion effects.

Table S10. Experimentally measured temperature dependent change of lattice parameters and densities for form II° and HH, along with the quality of representation of the crystal structures.

| Lattice parameters (cell vectors/Å, angles/°) | cell density |
|---------------------------------------------|-------------|
| a   b   c   α   β   γ    g cm⁻³    Δ%/a    |
| Form II°b                                   |
| Stage 3 3.763 22.381 8.170 105.35 1.543 |
| 20K    3.656 22.329 8.221 106.23 1.589 -2.90 |
| 90K    3.669 22.333 8.229 106.45 1.583 -2.53 |
| 90K    3.669 22.347 8.235 106.43 1.581 -2.40 |
| 100K   3.672 22.341 8.233 106.49 1.581 -2.40 |
| 110K   3.672 22.341 8.236 106.53 1.580 -2.34 |
| 150K   3.685 22.367 8.248 106.71 1.572 -1.85 |
| 150K   3.686 22.368 8.254 106.70 1.571 -1.78 |

| Hemihydrate                                  |
|---------------------------------------------|-------------|
| Stage 3 6.954 9.884 10.927 94.49 105.61 101.67 1.545 |
| 173K   7.027 9.545 11.176 96.68 104.32 98.90 1.530 +0.98 |
| RT     7.026 9.547 11.199 96.78 104.34 98.85 1.527 +1.18 |

| Form I                                       |
|---------------------------------------------|-------------|
| Stage 3 20.872 4.993 6.057 92.96 1.624 |
| 298K   23.198 5.547 5.198 92.22 1.532 +6.01 |

Δ%/a = 100*(Stage 3 – experimental)/experimental; experimental crystal structures transformed to P2₁/c using Powder Cell.¹²

We computationally generated three alternative ordered versions of form I differing only in the proton positions which were kept fixed: two Z’=1 with the p-OH proton pointing either to the o-OH oxygen or the p-OH oxygen of an adjacent βRA molecule and a Z’=2 structure, Pc, with one p-OH proton pointing to the o-OH oxygen and the second to the p-OH oxygen. Table S11 gives detailed results for the anhydrate modeling, including the computational investigations of proton disorder in form I. The lattice energies for the alternative form I...
structures were ca. 8 kJ mol\(^{-1}\) less stable than these for the experimental proton position. The lower stability can be attributed mainly to the less favorable βRA conformation (\(\Delta E_{\text{intra}}\) contribution) c.f. Figure S7a. Allowing a change in conformation in these alternative crystal structures (stage 3) led to the same computational minima independent of where the p-OH proton was initially pointing. It has to be noted that we could not have found the alternative form I structures in our rigid-body searches (step 2) as we did not consider these conformations as rigid-body input conformations.
### Table S11. Computational modeling of β-RA forms II° and I.

|                | a/Å  | b/Å  | c/Å  | β/°   | Density /g cm⁻³ | δ₁ /Å  | O4···O4 /Å  | O4···O3 /Å  | rmsd 15 Å | U_inter /kJ mol⁻¹ | ΔE_inter /kJ mol⁻¹ | E_latt /kJ mol⁻¹ | ZPE /kJ mol⁻¹ | Total thermal Energy | Free energy at 289K /kJ mol⁻¹ |
|----------------|------|------|------|-------|------------------|-------|-------------|-------------|------------|------------------|-------------------|-----------------|-----------------|-------------------|-------------------------|
| **Form II°**   |      |      |      |       |                  |       |             |             |            |                  |                   |                 |                 |                   |                          |
| Exp.           | 3.656| 22.329| 8.221| 106.23| 1.589            | -     | -           | -           | -          | -114.20         | 0                 | -114.20         | 3.06            | -17.97           | -129.11                      |
| Stage 2        | 3.782| 22.317| 8.233| 106.20| 1.532            | -     | -           | -           | 0.169      | -115.46         | 0.65              | -114.81         | 3.10            | -17.85           | -129.56                      |
| Stage 3        | 3.763| 22.381| 8.170| 105.35| 1.543            | -     | -           | -           | 0.162      | -115.46         | 0.65              | -114.81         | 3.10            | -17.85           | -129.56                      |
| **Form I**     |      |      |      |       |                  |       |             |             |            |                  |                   |                 |                 |                   |                          |
| Exp.           | 5.198| 5.547| 23.198| 92.21| 1.532            | 180   | 3.244       | 2.827       | -          | -115.36         | 0                 | -115.36         | 3.24            | -17.30           | -129.42                      |
| Stage 2        | 5.868| 5.072| 21.428| 93.50| 1.608            | 180   | 2.947       | 2.931       | 0.873      | -116.13         | 6.81              | -109.32         | 3.12            | -18.00           | -124.20                      |
| RB° pointing to | 5.396| 5.492| 22.049| 97.34| 1.580            | 151   | 3.175       | 2.839       | 0.539      | -116.13         | 6.81              | -109.32         | 3.12            | -18.00           | -124.20                      |
| o-OH           |      |      |      |       |                  |       |             |             |            |                  |                   |                 |                 |                   |                          |
| RB° pointing to | 6.167| 4.837| 21.701| 90.17| 1.582            | -151  | 2.843       | 3.009       | 1.089      | -114.75         | 6.76              | -107.99         | 3.27            | -17.38           | -122.10                      |
| RB° pointing to | 5.405| 5.457| 22.216| 95.82| 1.571            | 151/- | 2.980/     | 2.792/      | 0.567      | -112.19         | 4.89              | -107.30         | 3.09            | -18.31           | -122.52                      |
| p-OH           |      |      |      |       |                  |       |             |             |            |                  |                   |                 |                 |                   |                          |
| Z'=2°          | 6.057| 4.993| 20.872| 92.96| 1.624            | -178  | 2.930       | 2.952       | 1.063      | -116.93         | 0.79              | -116.14         | 3.34            | -16.95           | -129.75                      |

*a*experimental crystal structures transformed to P2₁/c using Powder Cell.12 Rigid-body minimizations. The quality of the 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 (rmsd₁). dZero-point energy. The Helmholtz free energy as estimated from the lattice energy, zero point intermolecular energy, and temperature dependence of the rigid molecule internal energy and entropy, as derived from the k =0 second derivative properties.13
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2.4 Computational generation of the crystal energy landscape (CSP)

2.4.1 Methodology (additional information)

Stage 1 $Z' = 1$ and $Z' = 2$ crystal structures were generated (Crystal Predictor) in the following 25 space groups: $P1$, $P1\bar{1}$, $P2_1/c$, $P2_1/2_1$, $P2_1/2_1\bar{2}$, $Pna2_1$, $Pca2_1$, $Pbca$, $Pbcn$, $P2_1/c$, $C2/c$, $Cc$, $C2$, $Pc$, $Cm$, $P2_1/m$, $C2/m$, $P2/c$, $C22_1$, $Pmna$, $Pccn$, $Pbcm$, $Pmma$, and $Pnma$. For the $Z'=1$ structures all planar conformational minima (Table S8) were used. In addition $Z' = 2$ structures containing the global (conf_p1) and second lowest (conf_p2) energy conformational minima in the asymmetric unit were generated. The molecules were held rigid in their HF/6-31G(d,p) optimized conformations. The model for the intermolecular forces used the FIT$^{6,7,14}$ potential with modified $A_{ij}$ for the carboxylic acid proton, 3018 kJ mol$^{-1}$, and the atomic charges fitted to the MP2(fc)/6-31G(d,p) electrostatic potential using the CHELPG scheme.$^{15}$

Stage 2 All crystallographically distinct, $Z'$=1 generated crystal structures within 20 kJ mol$^{-1}$ from the corresponding search minimum (289 to 1822 structures) and the 7500 most stable unique $Z'$=2 structures (11.04 kJ mol$^{-1}$ energy range) were reminimized. The intermolecular lattice energy was calculated using the FIT$^{6,7,14}$ exp-6 potential parameters and the distributed multipoles$^{16}$ up to hexadecapole derived from the PBE0/aug-cc-pVTZ charge density using GDMA2.$^{17}$ Conformations were kept rigid at the HF/6-31G(d,p) optimized geometries.

Stage 3 In the final stage (CrystalOptimizer) the four flexible torsion angles shown in Figure 1 were minimized as a response to the packing forces, in addition to the cell geometry and relative position and orientation of all molecules in the lattice. All other intramolecular degrees of freedom were allowed to relax to their isolated molecule optimized values for the corresponding values of the flexible torsions. This was done by using CrystalOptimizer$^{18}$ by minimizing the lattice energy ($E_{\text{latt}}$), calculated as the sum of the intermolecular contribution ($U_{\text{inter}}$) and the conformational energy penalty ($\Delta E_{\text{intra}}$, with respect to the global conformational minimum) paid to improve the intermolecular interactions. Conformational energy penalties and isolated-molecule charge densities were computed at the PBE0/6-31G(d,p) and PBE0/aug-cc-pVTZ levels, respectively, in the on-the-fly quantum-mechanical calculations.
2.4.2 The Crystal Energy Landscape following relaxation of the conformation within the crystal structure (stage 3)

The hypothetical crystal structures are available in *.res from the authors on request.

### Table S12. Structurally Characterized and Hypothetical Low-energy Crystal Structures of βRA.

| Structure | Space group | Reduced cell parameters | $E_{un}$/ kJ mol$^{-1}$ | Density/ g cm$^{-3}$ |
|-----------|-------------|--------------------------|------------------------|---------------------|
|           | a/Å         | b/Å                      | c/Å                    | α/°                 |
|           | β/°         | γ/°                      |                        |                     |
| Experimentally observed Anhydrates minimized with CrystalOptimizer |
| II$^{a}$  | $P_2_1/c$   | 3.763                    | 22.381                 | 8.170               | 90                  |
|           |             |                          |                        | 105.347             | 90                  |
|           |             |                          |                        | -114.81             | 1.543               |
| I          | $P_2_1/c$   | 6.057                    | 4.994                  | 20.872              | 90                  |
|           |             |                          |                        | 92.964              | 90                  |
|           |             |                          |                        | -116.14             | 1.624               |
| Table S12. Structurally Characterized and Hypothetical Low-energy Crystal Structures of βRA. |
| 1 A7      | $P_2_1/c$   | 6.054                    | 4.994                  | 20.879              | 90                  |
|           |             |                          |                        | 92.964              | 90                  |
|           |             |                          |                        | -116.14             | 1.624               |
| 1 A540    | $P_2_1/c$   | 3.762                    | 22.398                 | 8.157               | 90                  |
|           |             |                          |                        | -114.83             | 1.544               |
| 1 A352    | $P_2_1/c$   | 4.182                    | 6.780                  | 24.320              | 90                  |
|           |             |                          |                        | 99.321              | -114.0              |
|           |             |                          |                        | 1.551               |
| 1 A A7    | $P_2_1/c$   | 11.482                   | 3.726                  | 16.550              | 90                  |
|           |             |                          |                        | 95.175              | 90                  |
|           |             |                          |                        | -114.50             | 1.551               |
| 1 A A4    | $P_2_1/c$   | 10.450                   | 3.762                  | 16.550              | 90                  |
|           |             |                          |                        | 105.646             | 90                  |
|           |             |                          |                        | -114.44             | 1.634               |
| 1 A A2    | $P_2_1/c$   | 4.182                    | 6.780                  | 24.320              | 90                  |
|           |             |                          |                        | 99.321              | -114.0              |
|           |             |                          |                        | 1.510               |
| 1 A A5    | $P_2_1/c$   | 10.446                   | 3.785                  | 16.734              | 90                  |
|           |             |                          |                        | 104.206             | 90                  |
|           |             |                          |                        | -114.14             | 1.645               |
| 1 A39     | $P_2_1/c$   | 11.093                   | 3.911                  | 15.109              | 90                  |
|           |             |                          |                        | 103.365             | 90                  |
|           |             |                          |                        | -113.77             | 1.605               |
| 1 A A45   | $C_2/c$     | 25.931                   | 3.843                  | 13.314              | 90                  |
|           |             |                          |                        | 108.209             | 90                  |
|           |             |                          |                        | -113.53             | 1.624               |
| 1 A A24   | $P_2_1/c$   | 11.673                   | 3.676                  | 16.709              | 90                  |
|           |             |                          |                        | 119.672             | 90                  |
|           |             |                          |                        | -113.32             | 1.643               |
| 1 A A33   | $P_2_1/c$   | 8.571                    | 7.917                  | 9.838               | 90                  |
|           |             |                          |                        | 95.634              | 90                  |
|           |             |                          |                        | -113.32             | 1.541               |
| 1 A A3    | $P_2_1/c$   | 11.673                   | 3.676                  | 16.708              | 90                  |
|           |             |                          |                        | 119.663             | 90                  |
|           |             |                          |                        | -113.31             | 1.643               |
| 1 A A157  | $Pbca$      | 16.635                   | 20.312                 | 3.721               | 90                  |
|           |             |                          |                        | 90                  | 90                  |
|           |             |                          |                        | -113.25             | 1.630               |
| 1 A A8    | $P_2_1/c$   | 8.415                    | 5.203                  | 14.573              | 90                  |
|           |             |                          |                        | 100.072             | 90                  |
|           |             |                          |                        | -113.07             | 1.629               |
| 1 A A9    | $P_2_1/c$   | 8.415                    | 5.203                  | 14.576              | 90                  |
|           |             |                          |                        | 100.074             | 90                  |
|           |             |                          |                        | -113.05             | 1.630               |
| 1 A A126  | $Pbca$      | 3.703                    | 16.692                 | 20.326              | 90                  |
|           |             |                          |                        | 90                  | 90                  |
|           |             |                          |                        | -112.78             | 1.629               |
| 1 A A93   | $C_2/c$     | 24.922                   | 4.322                  | 12.178              | 90                  |
|           |             |                          |                        | 97.924              | 90                  |
|           |             |                          |                        | -112.76             | 1.576               |
| 1 A A120  | $C_2/c$     | 16.165                   | 9.178                  | 10.633              | 90                  |
|           |             |                          |                        | 119.746             | 90                  |
|           |             |                          |                        | -112.70             | 1.495               |
| 1 A A52   | $P_2_1_2_1$ | 7.049                    | 8.718                  | 10.419              | 90                  |
|           |             |                          |                        | 90                  | 90                  |
|           |             |                          |                        | -111.84             | 1.599               |
| Anhydrate Search 3: $Z''$ = 2, conf_p1 and conf_p2 |
| 12 A3     | $P-1$       | 5.249                    | 8.505                  | 14.097              | 91.436              | 90 |
|           |             |                          |                        | 90                  |
|           |             |                          |                        | -113.82             | 1.627               |
| 12 A4     | $P_2_1/c$   | 8.510                    | 5.2452                 | 14.110              | 90                  |
|           |             |                          |                        | 91.644              | 90                  |
|           |             |                          |                        | -113.80             | 1.626               |
| 12 A2     | $P_2_1/c$   | 10.450                   | 3.762                  | 16.550              | 90                  |
|           |             |                          |                        | 105.646             | 90                  |
|           |             |                          |                        | -113.72             | 1.627               |
| 12 A91    | $P-1$       | 4.930                    | 6.278                  | 21.347              | 88.300              | 88.535 |
|           |             |                          |                        | 78.056              | -113.28             |
|           |             |                          |                        | 1.585               |

$^{a}$experimental structures transformed to conventional setting using PLATON.$^{19}$ Labels for hypothetical structures correspond to internal res file names, are of format conformation_search output name. The structures found in the search which correspond to the known forms are in bold text.
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