Supporting Information:
Efficient Screening of Coformers for Active Pharmaceutical Ingredient Cocrystallization

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1 CPU cost breakdown

1.1 Single component investigations

Breakdown of CPU cost (CPU hours)

| API          | CrystPred | LAMs | Global | Analysis | Clustering | CrystOpt refinements | Total   |
|--------------|-----------|------|--------|----------|------------|----------------------|---------|
| PARACETAMOL  | 1086.05   |      | 827.23 | 9.77     | 1.10       | 4132.59              | 6056.75 |
| ASPIRIN      | 3837.39   |      | 463.20 | 10.79    | 3.80       | 2763.00              | 7078.18 |
| CARBAMAZAPENE| 37.22     |      | 729.36 | 4.86     | 1.00       | 4342.00              | 5114.45 |

1.2 Cocrystal investigations

| structure  | Global | Analysis | Clustering | Aspirin refinements | refinement | Total |
|------------|--------|----------|------------|--------------------|------------|-------|
| OXALAC     | 804    | 2        | 1          | 472                | 1717       | 2524  |
| DUPKAB     | 4854   | 0        | 3          | 492                | 5445       | 10302 |
| SUCACB     | 1129   | 0        | 0          | 497                | 2595       | 3724  |
| CEBGOF     | 868    | 0        | 0          | 492                | 3444       | 4312  |
| PYRDNIA    | 954    | 2        | 1          | 499                | 1780       | 2737  |
| TELZOS     | 1292   | 0        | 0          | 498                | 3852       | 5144  |
| NICOMA     | 1246   | 1        | 1          | 490                | 4075       | 5323  |
| BITZAF     | 3130   | 0        | 3          | 491                | 1568       | 4701  |
| NICOAC     | 1673   | 0        | 0          | 499                | 5556       | 7230  |
| ESALUF     | 2317   | 17       | 2          | 495                | 3010       | 5347  |

Carbamazepine
### 1.3 Computing quantity $\Delta \Delta U_c$

| System | lowest experimental energy (kJ/mol) | Global Minimum (kJ/mol) |
|--------|----------------------------------|-------------------------|
| PARA   | -114.405                         | -114.405                |
| ASPI   | -114.058                         | -114.058                |
| CARB   | -128.32                          | -129.947                |
| BITZ   | -127.253                         | -133.198                |
| CEBG   | -99.6216                         | -99.6216                |
| DUPK   | -112.607                         | -112.607                |
| ESAL   | -91.448                          | -94.3638                |
| NICC   | -100.044                         | -100.044                |
| NICM   | -100.317                         | -100.317                |
| OXAL   | -70.5857                         | -70.5857                |
| PYRD   | -60.4391                         | -58.9266                |
| SUCA   | -102.046                         | -102.046                |
| TELZ   | -114.033                         | -115.753                |

| System | API expal energy | API expal energy + coformer | Cocystal energy | solvate correction | $\Delta \Delta U_c$ (approach 1) | $\Delta \Delta U_c$ (approach 2) |
|--------|------------------|-----------------------------|-----------------|---------------------|-------------------------------|-------------------------------|
| OXALAC |                 |                             |                 |                     |                               |                               |
| DUPKAB |                 |                             |                 |                     |                               |                               |
| SUCACB |                 |                             |                 |                     |                               |                               |
| CEBGOF |                 |                             |                 |                     |                               |                               |
| PYRDN |                 |                             |                 |                     |                               |                               |
| TELZ |                 |                             |                 |                     |                               |                               |
| NICOAM |                 |                             |                 |                     |                               |                               |
| BITZAF |                 |                             |                 |                     |                               |                               |
| NICOAC |                 |                             |                 |                     |                               |                               |
| ESALUF |                 |                             |                 |                     |                               |                               |
| ASPIRIN |                |                             |                 |                     |                               |                               |
|                  | GM energy       |                  |                  |  
|------------------|-----------------|-----------------|-----------------|  
| PARA-BITZ       | -241.659        | -247.604        | -239.915        | 0         | 1.7434 | 7.6887 |  
| PARA-CEBG       | -214.027        | -214.027        | -209.705        | 0         | 4.3225 | 4.3225 |  
| PARA-DUPK       | -227.012        | -227.012        | -219.217        | 0         | 7.7957 | 7.7957 |  
| PARA-ESAL       | -205.853        | -208.769        | -196.186        | 0         | 9.6675 | 12.5833 |  
| PARA-NICC       | -214.45         | -214.45         | -204.907        | 0         | 9.5424 | 9.5424 |  
| PARA-NICM       | -214.723        | -214.723        | -214.198        | 0         | 0.5248 | 0.5248 |  
| PARA-OXAL       | -184.991        | -184.991        | -188.554        | 0         | -3.5631 | -3.5631 |  
| PARA-PYRD       | -171.774        | -173.332        | -177.185        | 2.5       | -2.9104 | -1.3525 |  
| PARA-SUCA       | -216.452        | -216.452        | -198.819        | 0         | 17.6324 | 17.6324 |  
| PARA-TELZ       | -228.438        | -230.158        | -232.549        | 0         | -4.1106 | -2.3908 |  
| ASPI-BITZ       | -241.311        | -247.256        | -203.893        | 0         | 37.4178 | 43.3631 |  
| ASPI-CEBG       | -213.68         | -213.68         | -203.994        | 0         | 9.686   | 9.686   |  
| ASPI-DUPK       | -226.665        | -226.665        | -213.887        | 0         | 12.7779 | 12.7779 |  
| ASPI-ESAL       | -205.506        | -208.422        | -195.11         | 0         | 10.3959 | 13.3117 |  
| ASPI-NICC       | -214.102        | -214.102        | -200.377        | 0         | 13.725  | 13.725  |  
| ASPI-NICM       | -214.375        | -214.375        | -207.614        | 0         | 6.7613  | 6.7613  |  
| ASPI-OXAL       | -184.644        | -184.644        | -189.181        | 0         | -4.5378 | -4.5378 |  
| ASPI-PYRD       | -171.427        | -172.985        | -181.3          | 2.5       | -7.3737 | -5.8158 |  
| ASPI-SUCA       | -216.104        | -216.104        | -202.182        | 0         | 13.9226 | 13.9226 |  
| ASPI-TELZ       | -228.091        | -229.811        | -222.617        | 0         | 5.4738  | 7.1936  |  
| CARB-BITZ       | -255.573        | -261.518        | -251.738        | 0         | 3.8348  | 9.7801  |  
| CARB-CEBG       | -227.941        | -227.941        | -230.526        | 0         | -2.5843 | -2.5843 |  
| CARB-DUPK       | -240.927        | -240.927        | -243.73         | 0         | -2.8036 | -2.8036 |  
| CARB-ESAL       | -219.768        | -222.684        | -219.803        | 0         | -0.035  | 2.8808  |
| CARB-NICC | 228.364 | 228.364 | 224.067 | 0 | 4.297 | 4.297 |
|----------|---------|---------|---------|---|-------|-------|
| CARB-NICM| 228.637 | 228.637 | 226.569 | 0 | 2.0674 | 2.0674 |
| CARB-OXAL| -198.905| -198.905| -211.832| 0 | -12.9269 | -12.9269 |
| CARB-PYRD| -185.688| -187.246| -192.044| 2.5 | -3.8559 | -2.298 |
| CARB-SUCA| -230.366| -230.366| -230.978| 0 | -0.612 | -0.612 |
| CARB-TELZ| -242.353| -244.073| -250.954| 0 | -8.6016 | -6.8818 |
| CARB-ASPI| -242.378| -244.005| -237.386| 0 | 4.9916 | 6.6193 |

## 2 EXPERIMENTAL

### 2.1 cis Aconitic acid (form II)

Slurry experiments of the commercial sample in \( n \)-heptane, dichloromethane or diethyl ether resulted in form II. The experimental PXRD pattern of the \( cis \) aconitic acid form II indexed to the monoclinic space group \( C2/c \), with \( Z'\)=1 (Figure 1.a). The unit cell and space group symmetry are distinct from the already known structure of \( cis \) aconitic acid form I (\( Pbca, Z'\)=1). The molecular conformations present in the two \( cis \) aconitic acid polymorphs differ substantially. In form I one of the acid groups forms an intramolecular O−H⋯O hydrogen bonding interaction to a second carboxylic acid function (Figure 1.b). This is in contrast to form II, where all three of the carboxylic acid protons form intermolecular interactions. Five strong hydrogen bonding interactions are formed in form I, one carboxylic acid dimer [\( R2_2(8) \)] ¹, one \( C1(7) \) chain and the intramolecular hydrogen bond. The second polymorph forms six hydrogen bonding interactions, two \( R2_2(8) \) dimers one \( C1(7) \) chain motif with all interactions being O−H⋯O (Figure 1.c). Furthermore, C−H⋯O close contacts stabilise the structure.
Figure 1. (a) Observed (black points), calculated (red line) and difference profiles (green) for the Rietveld refinements of *cis* aconitic acid form II. Blue tick marks denote the peak positions. (b) Conformation found in the two *cis* aconitic acid polymorphs. Note one of the COOH function of form II might be disordered, i.e. 180° flip of the acid function marked with an ellipsoid. (c) Packing diagram of *cis* aconitic acid form II viewed along the *b* crystallographic axis.

Finally, the *cis* aconitic acid pure form investigation is slightly different. Experimental indications suggested that the intramolecular hydrogen bond may be broken, necessitating broadening the search ranges, as the initial investigation had assumed the intramolecular hydrogen bond was maintained.

2.2 Paracetamol (PARA) cocrystal screen

The oxalic acid cocrystal (PARA-OXAL) and pyridine solvate (PARA-PYRD) were both successfully reproduced.

An overview over the paracetamol crystallization experiments is given in Table S1 and selected PXRD diffractograms are shown in Figure S1 - Figure S10.

Table S1. Overview paracetamol crystallization results.

| Coformer | Contact | Slurry experiments | Liquid-assisted grinding | Co-sublimation |
|----------|---------|--------------------|--------------------------|---------------|
|          |         |                    |                          |               |

| Preparation | n-Heptane | Pyridine | Diethyl ether | n-heptane | Diethyl ether |
|-------------|-----------|----------|---------------|-----------|---------------|

5
| Compound                  | Paracetamol | Pyridoxine | Methyl paraben | Propyl paraben | t-Butyl-4-<br>hydroxyanisole | Nicotinic Acid | Nicotinamide | Oxalic Acid | Succinic Acid | cis-Aconitic Acid | Pyridine |
|--------------------------|-------------|------------|----------------|----------------|-------------------------------|----------------|--------------|-------------|---------------|-------------------|-----------|
|                          | x           | x          | x              | x              | x                             | n. a.          | x            | yes         | x             | x                 | n. a.     |
|                          |             |            |                |                |                               | n. a.          | x            | yes         | yes           | yes               | n. a.     |
|                          |             |            |                |                |                               |                | x            | yes         | yes           | yes               |           |
|                          |             |            |                |                |                               |                | n. a.        | n. a.       | n. a.         | n. a.            | n. a.     |

n.a. – not attempted, yes – cocrystal/solvate formation, x – physical mixture of the two compounds.

**Figure S1.** Comparison of experimental and from single crystal structure data simulated PXRD patterns of paracetamol (red), **pyridoxine** and a physical mixture obtained from LAG grinding experiments.
Figure S2. Comparison of experimental and from single crystal structure data simulated PXRD patterns of paracetamol (red), methyl paraben and a physical mixture obtained from LAG grinding experiments.

Figure S3. Comparison of experimental and from single crystal structure data simulated PXRD patterns of paracetamol (red), propyl paraben and a physical mixture obtained from LAG grinding experiments.
Figure S4. Comparison of experimental and from single crystal structure data simulated PXRD patterns of paracetamol (red), t-butyl-4-hydroxyanisole and a physical mixture obtained from LAG grinding experiments.

Figure S5. Comparison of experimental and from single crystal structure data simulated PXRD patterns of paracetamol (red), nicotinic acid and a physical mixture obtained from LAG grinding experiments.
Figure S6. Comparison of experimental and from single crystal structure data simulated PXRD patterns of paracetamol (red), nicotinamide and a physical mixture obtained from LAG grinding experiments.

Figure S7. Comparison of experimental and from single crystal structure data simulated PXRD patterns of paracetamol (red), oxalic acid and the cocrystal obtained in co-sublimation experiments.
Figure S8. Comparison of experimental and from single crystal structure data simulated PXRD patterns of paracetamol (red), succinic acid and a physical mixture obtained from LAG grinding experiments.

Figure S9. Comparison of experimental and from single crystal structure data simulated PXRD patterns of paracetamol (red), cis-aconitic acid and a physical mixture obtained from LAG grinding and crystallisation experiments.
Figure S10. Comparison of experimental and from single crystal structure data simulated PXRD patterns of paracetamol (red) and the pyridine solvate of APAP.
2.3 Acetylsalicylic Acid (ASPI) cocrystal screen

No multicomponent forms were obtained using the chosen coformers/solvents (Table S2, Figure S11 - Figure S19).

Table S2. Overview acetylsalicylic acid crystallisation results.

| Coformer               | Contact Preparation | Slurry experiments                  | Liquid-assisted grinding          | Co-sublimation           |
|------------------------|---------------------|-------------------------------------|----------------------------------|--------------------------|
|                        |                     | n-Heptane  | Pyridine       | Diethyl ether | n-heptane | Diethyl ether |                     |
| Pyridoxine             | x                   | x         | n. a.          | x            | x         | x             | x                   |
| Methyl parabene        | x                   | x         | n. a.          | x            | x         | x             | x                   |
| Propyl parabene        | x                   | x         | n. a.          | x            | x         | x             | x                   |
| t-Butyl-4-hydroxyanisole| n. a.              | x         | n. a.          | x            | x         | x             | x                   |
| Nicotinic Acid         | n. a.              | x         | n. a.          | x            | x         | x             | x                   |
| Nicotinamide           | x                   | x         | n. a.          | x            | x         | x             | x                   |
| Oxalic Acid            | n. a.              | x         | n. a.          | x            | x         | x             | x                   |
| Succinic Acid          | n. a.              | x         | n. a.          | x            | x         | x             | x                   |
| cis-Aconitic Acid      | x                   | x         | n. a.          | x            | x         | x             | x                   |
| Pyridine               | n. a.              | n. a.     | x              | n. a.        | n. a.     | n. a.         | n. a.               |

n.a. – not attempted, x – physical mixture of the two compounds.

Figure S11. Comparison of experimental and from single crystal structure data simulated PXRD patterns of acetylsalicylic acid (red), pyridoxine and a physical mixture obtained from LAG grinding experiments.
Figure S12. Comparison of experimental and from single crystal structure data simulated PXRD patterns of acetylsalicylic acid (red), methyl paraben and a physical mixture obtained from LAG grinding experiments.

Figure S13. Comparison of experimental and from single crystal structure data simulated PXRD patterns of acetylsalicylic acid (red), propyl paraben and a physical mixture obtained from LAG grinding experiments.
Figure S14. Comparison of experimental and from single crystal structure data simulated PXRD patterns of acetylsalicylic acid (red), t-buty1-4-hydroxyanisole and a physical mixture obtained from LAG grinding experiments.

Figure S15. Comparison of experimental PXRD patterns of acetylsalicylic acid (red), nicotinic acid and a physical mixture obtained from LAG grinding experiments.
**Figure S16.** Comparison of experimental and from single crystal structure data simulated PXRD patterns of acetylsalicylic acid (red), nicotinamide and a physical mixture obtained from LAG grinding experiments.

**Figure S17.** Comparison of experimental PXRD patterns of acetylsalicylic acid (red), oxalic acid and a physical mixture obtained from LAG grinding experiments.
Figure S18. Comparison of experimental and from single crystal structure data simulated PXRD patterns of acetylsalicylic acid (red), succinic acid and a physical mixture obtained from LAG grinding experiments.

Figure S19. Comparison of experimental PXRD patterns of acetylsalicylic acid (red), cis-aconitic acid and a physical mixture obtained from LAG grinding experiments.
2.4 Carbamazepine (CARB) cocrystal screen

All experimental cocrystals (nicotinamide, oxalic acid, succinic acid) were reproduced in the experimental screen. Furthermore, new cocrystals were found with methyl parabene, t-butyl-4-hydroxyanisole and cis-aconitic acid (Table S3, Figure S21 - Figure S29). In case of propyl paraben one experiment resulted in a new pattern.

Table S3. Overview carbamazepine crystallization results.

| Coformer                  | Contact Preparation | Slurry experiments | Liquid-assisted grinding | Co-sublimation |
|---------------------------|---------------------|--------------------|--------------------------|---------------|
|                           |                     | n-Heptane          | Pyridine                 | Diethyl ether | n-heptane | Diethyl ether |
| Pyridoxine                | x                   | x                  | n. a.                    | x             | x         | x             |
| Methyl parabene           | yes                 | yes                | n. a.                    | yes           | yes       | yes           |
| Propyl parabene           | x                   | Inconclusive       | n. a.                    | x             | x         | x             |
| t-Butyl-4-hydroxyanisole  | n. a.               | yes                | n. a.                    | yes           | yes       | yes           |
| Nicotinic Acid            | n. a.               | x                  | n. a.                    | x             | x         | x             |
| Nicotinamide              | yes                 | yes                | n. a.                    | yes           | yes       | yes           |
| Oxalic Acid               | n. a.               | yes                | n. a.                    | yes           | yes       | yes           |
| Succinic Acid             | n. a.               | yes                | n. a.                    | yes           | yes       | yes           |
| cis-Aconitic Acid         | x                   | yes                | n. a.                    | yes           | yes       | yes           |
| Pyridine                  | n. a.               | n. a.              | x                        | n. a.         | n. a.     | n. a.         |

n.a. – not attempted, x – physical mixture of the two compounds. Inconclusive refers to the ambiguous PXRD pattern observed in Figure S22

Figure S20. Contact preparation of nicotinamide-cocrystal-carbamazepine. At 126 °C and 160 °C the eutectic temperatures between nicotinamide and the cocrystal and carbamazepine and the cocrystal, respectively, can be seen.
Figure S21. Comparison of experimental and from single crystal structure data simulated PXRD patterns of carbamazepine (red), pyridoxine and a physical mixture obtained from LAG grinding experiments.

Figure S22. Comparison of experimental and from single crystal structure data simulated PXRD patterns of carbamazepine (red), methyl parabene and a cocrystal.
Figure S23. Comparison of experimental and from single crystal structure data simulated PXRD patterns of carbamazepine (red), propyl parabene and a physical mixture obtained from LAG grinding experiments.

Figure S24. Comparison of experimental and from single crystal structure data simulated PXRD patterns of carbamazepine (red), t-butyl-4-hydroxyanisole and a cocrystal.
Figure S25. Comparison of experimental and from single crystal structure data simulated PXRD patterns of carbamazepine (red), **nicotinic acid** and a physical mixture obtained from LAG grinding/slurry experiments.

Figure S26. Comparison of experimental and from single crystal structure data simulated PXRD patterns of carbamazepine (first), **nicotinamide** and a cocrystal (SDG and slurry).
Figure S27. Comparison of experimental and from single crystal structure data simulated PXRD patterns of carbamazepine (first), oxalic acid and a cocrystal (SDG and slurry).

Figure S28. Comparison of experimental and from single crystal structure data simulated PXRD patterns of carbamazepine (first), succinic acid and a cocrystal (slurry experiment).
Figure S29. Comparison of experimental and from single crystal structure data simulated PXRD patterns of carbamazepine (first), cis aconitic acid and a cocrystal (SDG and slurry).

Additional cocrystallization experiments were undertaken for the combination carbamazepine and propyl parabene (Table S4) with the aim to reproduce the phase seen in the initial $n$-heptane slurry experiments (Figure S23). Therefore, the range of solvents, molar ratios and crystallisation techniques was extended. None of the additional experiments resulted in a cocrystal.
**Table S4.** Overview additional carbamazepine and propyl paraben cocrystallization results.

| Solvent / molar ratio (CBZ:PP) | 1:1 | 2:1 | 1:2 |
|-------------------------------|-----|-----|-----|
| **Grinding (dry or liquid-assisted)** |     |     |     |
| dry                           | x   | x   | x   |
| dichloromethane               | x, x\(^a\) | x | x |
| dichloroethane                | x   | x   | x   |
| diethyl ether                 | x   | x   | x   |
| diisopropyl ether             | x   | x   | x   |
| acetone                       | x   | x   | x   |
| methanol                      | x   | x   | x   |
| n-butanol                     | x   | x   | x   |
| ethyl acetate                 | x   | x   | x   |
| n-heptane                     | x   | x   | x   |
| **Slurry experimentes (10 °C – 30 °C)** |     |     |     |
| Diethyl ether                 | x   | n. a. | n. a. |
| diisopropyl ether             | x   | n. a. | n. a. |
| n-butanol                     | x   | n. a. | n. a. |
| n-heptane                     | x, x\(^a\) | n. a. | n. a. |
| **Solvent evaporation experiments (RT)** |     |     |     |
| acetone                       | x   | n. a. | n. a. |
| methanol                      | x   | n. a. | n. a. |
| ethanol                       | x   | n. a. | n. a. |
| n-butanol                     | x   | n. a. | n. a. |
| ethyl acetate                 | x   | n. a. | n. a. |
| acetonitrile                  | x   | n. a. | n. a. |
| **Cooling crystallisation experiments** |     |     |     |
| acetone                       | x   | n. a. | n. a. |
| methanol                      | x   | n. a. | n. a. |
| ethanol                       | x   | n. a. | n. a. |
| n-butanol                     | x   | n. a. | n. a. |
| ethyl acetate                 | x   | n. a. | n. a. |
| acetonitrile                  | x   | n. a. | n. a. |

n.a. – not attempted, x – physical mixture of the two compounds. \(^a\)Two additional peak positions, otherwise physical mixture.
2.5 Rietveld refinements

DFT-d calculations (fixed cell and full optimization) were carried out with the CASTEP plane wave\(^2\) code using the Perdew-Burke-Ernzerhof (PBE) generalized gradient approximation (GGA) exchange-correlation density functional and ultrasoft pseudopotentials, with the addition of the Tkatchenko and Scheffler (TS) semi-empirical dispersion corrections.\(^20\) Brillouin zone integrations were performed on a symmetrized Monkhorst–Pack k-point grid with the number of k-points chosen to provide a maximum spacing of 0.07 Å\(^{-1}\) and a basis set cut-off of 560 eV. The self-consistent field convergence on total energy was set to 1x10\(^{-5}\) eV per atom. Energy minimizations were performed using the Broyden–Fletcher–Goldfarb–Shanno optimisation scheme within the space group constraints. The optimizations were considered complete when energies were converged to better than 2x10\(^{-5}\) eV per atom, atomic displacements converged to 1x10\(^{-3}\) Å, maximum forces to 5x10\(^{-2}\) eV Å\(^{-1}\), and maximum stresses were converged to 1x10\(^{-3}\) GPa.

**Carbamazepine: 3-t-butyl-4-hydroxyanisole BHA cocrystals (CARB:ESAL-A)**

The fixed cell PBE-TS structure was used as the starting point for rigid body Rietveld refinements in TOPAS academic.\(^3\) The final refinements included a total of 54 parameters (28 profile, 4 cell, 1 scale, 1 isotropic temperature factor, 6 position and 6 rotation, 8 preferred orientation) yielding a final \(R_{wp} = 8.35\%\).

```
TITL CARB:ESAL-A
CELL 0.71073 9.5920 23.9589 10.6474 90 110.029 90
ZERR 4 0.0004 0.0007 0.0003 0 0.002 0
LATT 1
SYMM 1/2-x,1/2+y,1/2-z
SFAC C H N O
UNIT 104 112 8 12
FVAR 1.00
O1 O Uiso 0.4853(5) -0.0337(3) 0.1643(10) 1.000 0.062(2)
N1 N Uiso 0.4724(5) 0.0564(4) 0.2301(9) 1.000 0.062(2)
N2 N Uiso 0.2621(5) -0.0007(3) 0.1612(8) 1.000 0.062(2)
C1 C Uiso 0.3951(6) 0.0993(4) 0.2734(9) 1.000 0.062(2)
C2 C Uiso 0.4092(5) 0.0052(3) 0.1843(9) 1.000 0.062(2)
O2 O Uiso 0.342(3) 0.3803(6) 0.346(3) 1.000 0.062(2)
O3 O Uiso 0.902(2) 0.3649(8) 0.308(3) 1.000 0.062(2)
C3 C Uiso 0.6289(5) 0.0634(4) 0.2600(11) 1.000 0.062(2)
C4 C Uiso 0.2887(6) 0.1316(3) 0.1789(10) 1.000 0.062(2)
C5 C Uiso 0.4247(8) 0.1071(4) 0.4117(9) 1.000 0.062(2)
C6 C Uiso 0.7245(6) 0.0614(5) 0.3943(12) 1.000 0.062(2)
C7 C Uiso 0.6845(5) 0.0713(4) 0.1563(12) 1.000 0.062(2)
C8 C Uiso 0.2061(7) 0.1799(3) 0.2199(10) 1.000 0.062(2)
C9 C Uiso 0.3376(9) 0.1463(4) 0.4503(10) 1.000 0.062(2)
C10 C Uiso 0.5423(8) 0.0785(5) 0.5144(9) 1.000 0.062(2)
C11 C Uiso 0.6717(7) 0.0583(5) 0.5067(10) 1.000 0.062(2)
C12 C Uiso 0.8785(6) 0.0647(5) 0.4197(13) 1.000 0.062(2)
C13 C Uiso 0.8370(5) 0.0760(4) 0.1843(14) 1.000 0.062(2)
```
C14 C Uiso 0.2302(9) 0.1779(4) 0.3560(10) 1.000 0.062(2)
C15 C Uiso 0.9340(5) 0.0722(5) 0.3162(15) 1.000 0.062(2)
C16 C Uiso 0.691(2) 0.3169(7) 0.330(3) 1.000 0.062(2)
C17 C Uiso 0.763(2) 0.3667(7) 0.314(3) 1.000 0.062(2)
C18 C Uiso 0.548(2) 0.3219(6) 0.337(3) 1.000 0.062(2)
C19 C Uiso 0.768(2) 0.2597(7) 0.347(3) 1.000 0.062(2)
C20 C Uiso 0.479(3) 0.3735(6) 0.333(3) 1.000 0.062(2)
C21 C Uiso 0.692(3) 0.4183(7) 0.308(3) 1.000 0.062(2)
C22 C Uiso 0.902(2) 0.2594(8) 0.479(3) 1.000 0.062(2)
C23 C Uiso 0.6649(19) 0.2121(7) 0.355(2) 1.000 0.062(2)
C24 C Uiso 0.822(2) 0.2465(7) 0.229(3) 1.000 0.062(2)
C25 C Uiso 0.552(3) 0.4221(6) 0.318(3) 1.000 0.062(2)
C26 C Uiso 0.263(2) 0.3314(6) 0.359(3) 1.000 0.062(2)
H1 H Uiso 0.2197(5) -0.0401(3) 0.1443(8) 1.000 0.074(3)
H2 H Uiso 0.2012(5) 0.0307(3) 0.1793(7) 1.000 0.074(3)
H3 H Uiso 0.2708(6) 0.1253(3) 0.0733(10) 1.000 0.074(3)
H4 H Uiso 0.6076(6) 0.0722(3) 0.0537(12) 1.000 0.074(3)
H5 H Uiso 0.1228(7) 0.1955(3) 0.1453(11) 1.000 0.074(3)
H6 H Uiso 0.3565(10) 0.1517(5) 0.5566(10) 1.000 0.074(3)
H7 H Uiso 0.5290(10) 0.0762(6) 0.6119(9) 1.000 0.074(3)
H8 H Uiso 0.7522(8) 0.0425(6) 0.5991(11) 1.000 0.074(3)
H9 H Uiso 0.9540(6) 0.0628(6) 0.5228(14) 1.000 0.074(3)
H10 H Uiso 0.8798(6) 0.0822(4) 0.1028(15) 1.000 0.074(3)
H11 H Uiso 0.1640(10) 0.2078(4) 0.3885(11) 1.000 0.074(3)
H12 H Uiso 1.0534(5) 0.0757(5) 0.3391(16) 1.000 0.074(3)
H13 H Uiso 0.941(3) 0.4036(8) 0.312(3) 1.000 0.074(3)
H14 H Uiso 0.491(2) 0.2841(6) 0.348(3) 1.000 0.074(3)
H15 H Uiso 0.750(3) 0.4561(7) 0.297(3) 1.000 0.074(3)
H16 H Uiso 0.958(2) 0.2186(9) 0.493(3) 1.000 0.074(3)
H17 H Uiso 0.865(2) 0.2660(9) 0.565(3) 1.000 0.074(3)
H18 H Uiso 0.983(2) 0.2920(9) 0.480(3) 1.000 0.074(3)
H19 H Uiso 0.626(2) 0.2164(7) 0.440(2) 1.000 0.074(3)
H20 H Uiso 0.5677(19) 0.2082(6) 0.264(2) 1.000 0.074(3)
H21 H Uiso 0.7262(18) 0.1727(7) 0.369(2) 1.000 0.074(3)
H22 H Uiso 0.8656(19) 0.2037(7) 0.239(3) 1.000 0.074(3)
H23 H Uiso 0.910(2) 0.2751(8) 0.226(3) 1.000 0.074(3)
H24 H Uiso 0.730(2) 0.2493(7) 0.133(3) 1.000 0.074(3)
H25 H Uiso 0.501(3) 0.4628(6) 0.316(3) 1.000 0.074(3)
H26 H Uiso 0.326(2) 0.3072(6) 0.449(3) 1.000 0.074(3)
H27 H Uiso 0.159(2) 0.3456(6) 0.368(3) 1.000 0.074(3)
H28 H Uiso 0.239(2) 0.3047(5) 0.270(3) 1.000 0.074(3)
END
Figure S30. Overlay of the 30-molecule cluster of the observed structure of CARB:ESAL-A (colored by element, main disorder component only) and calculated PBE-TS structure (green, cell parameters fixed, atom positions optimized), rmsd_{30}=0.07 Å.

Carbamazepine: 3-t-butyl-4-hydroxyanisole BHA cocrystals (CARB:ESAL-B)

The PBE-TS structure (fixed cell parameters) were used as the starting point for rigid body Rietveld refinements in TOPAS academic.\textsuperscript{3} The final refinements included a total of 61 parameters (28 profile, 4 cell, 1 scale, 1 isotropic temperature factor, 6 position and 6 rotation, 15 preferred orientation) yielding a final R_{wp}= 6.56%.

TITL CARB:ESAL-B
CELL 0.71073 12.6807 7.7880 23.3619 90 96.927 90
ZERR 4 0.0005 0.0003 0.0010 0 0.002 0
LATT 1
SYMM -x,1/2+y,1/2-z
SFAC C H N O
UNIT 104 112 8 12
FVAR 1.00
O1 O Uiso 0.0278(12) 0.079(2) 0.2212(3) 1.000 0.076(4)
N1 N Uiso 0.2087(12) 0.073(3) 0.2390(3) 1.000 0.076(4)
N2 N Uiso 0.1116(13) 0.289(3) 0.2778(3) 1.000 0.076(4)
C1 C Uiso 0.1886(11) -0.230(2) 0.2127(4) 1.000 0.076(4)
C2 C Uiso 0.2054(10) -0.322(2) 0.1155(4) 1.000 0.076(4)
O2 O Uiso 0.8398(12) 0.688(4) 0.0029(14) 1.000 0.076(4)
O3 O Uiso 0.8505(9) 0.124(4) 0.1485(13) 1.000 0.076(4)
C3 C Uiso 0.1851(11) -0.360(2) 0.1717(4) 1.000 0.076(4)
C4 C Uiso 0.2315(9) -0.156(2) 0.1011(4) 1.000 0.076(4)
C5 C Uiso 0.2388(9) -0.022(2) 0.1422(4) 1.000 0.076(4)
C6 C Uiso 0.2788(9) 0.145(2) 0.1275(4) 1.000 0.076(4)
C7 C Uiso 0.3359(10) 0.258(2) 0.1635(5) 1.000 0.076(4)
C8 C Uiso 0.3671(11) 0.242(3) 0.2253(5) 1.000 0.076(4)
C9 C Uiso 0.4613(12) 0.321(3) 0.2504(6) 1.000 0.076(4)
C10 C Uiso 0.4969(14) 0.302(3) 0.3087(6) 1.000 0.076(4)
C11 C Uiso 0.4373(15) 0.208(3) 0.3443(5) 1.000 0.076(4)
C12 C Uiso 0.3420(14) 0.133(3) 0.3211(4) 1.000 0.076(4)
C13 C Uiso 0.3074(12) 0.149(3) 0.2622(4) 1.000 0.076(4)
C14 C Uiso 0.2128(11) -0.062(2) 0.1979(3) 1.000 0.076(4)
C15 C Uiso 0.1115(12) 0.149(3) 0.2622(4) 1.000 0.076(4)
C16 C Uiso 0.9249(13) 0.809(4) 0.0089(15) 1.000 0.076(4)
C17 C Uiso 0.7588(10) 0.444(4) 0.0388(13) 1.000 0.076(4)
C18 C Uiso 0.8473(11) 0.553(4) 0.0412(14) 1.000 0.076(4)
C19 C Uiso 0.9358(10) 0.519(4) 0.0810(15) 1.000 0.076(4)
C20 C Uiso 0.9350(9) 0.375(4) 0.1164(14) 1.000 0.076(4)
C21 C Uiso 0.8477(9) 0.265(4) 0.1133(13) 1.000 0.076(4)
C22 C Uiso 0.7555(9) 0.299(4) 0.0742(13) 1.000 0.076(4)
C23 C Uiso 0.6554(8) 0.186(4) 0.0719(12) 1.000 0.076(4)
C24 C Uiso 0.5648(8) 0.254(3) 0.0278(11) 1.000 0.076(4)
C25 C Uiso 0.4643(16) 0.195(4) 0.3902(5) 1.000 0.091(4)
C26 C Uiso 0.2929(15) 0.062(3) 0.3484(4) 1.000 0.091(4)
H1 H Uiso 0.0425(14) 0.354(3) 0.2807(4) 1.000 0.091(4)
H2 H Uiso 0.2008(10) -0.423(2) 0.0830(5) 1.000 0.091(4)
H3 H Uiso 0.1650(12) -0.490(2) 0.1835(5) 1.000 0.091(4)
H4 H Uiso 0.2487(8) -0.128(2) 0.0574(4) 1.000 0.091(4)
H5 H Uiso 0.3699(10) 0.368(2) 0.1435(5) 1.000 0.091(4)
H6 H Uiso 0.5074(12) 0.397(3) 0.2231(7) 1.000 0.091(4)
H7 H Uiso 0.5710(14) 0.362(3) 0.3265(7) 1.000 0.091(4)
H8 H Uiso 0.6904(10) 0.368(2) 0.1435(5) 1.000 0.091(4)
H9 H Uiso 0.6080(7) 0.078(4) 0.0860(12) 1.000 0.091(4)
END
Figure S31. Overlay of the 30-molecule cluster of the observed structure of CARB:ESAL-B (colored by element, main disorder component only) and calculated PBE-TS structure (green, cell parameters fixed, atom positions optimized), rmsd$_{30}$=0.08 Å.

Carbamazepine:methyl paraben CEBG cocrystals (CARB-CEBG-A)
The fixed cell PBE-TS structure was used as the starting point for rigid body Rietveld refinements in TOPAS academic.\textsuperscript{3} The final refinements included a total of 54 parameters (26 profile, 6 cell, 1 scale, 1 isotropic temperature factor, 6 position and 6 rotation, 8 preferred orientation) yielding a final R$_{wp}$= 7.62%.

TITL CARB-CEBG-A
CELL 0.71073 6.6607 8.4157 17.7876 89.651 87.906 87.519
ZERR 2 0.0002 0.0003 0.0006 0.003 0.003 0.004
LATT 1
SFAC C H N O
UNIT 46 40 4 8
FVAR 1.00
O1 O Uiso 0.6188(17) -0.201(2) 0.2401(8) 1.000 0.076(4)
N1 N Uiso 0.7326(15) 0.019(2) 0.1784(8) 1.000 0.076(4)
N2 N Uiso 0.6140(19) 0.035(3) 0.3037(8) 1.000 0.076(4)
C1 C Uiso 0.6826(12) -0.126(2) 0.0617(8) 1.000 0.076(4)
C2 C Uiso 0.9581(13) -0.279(3) 0.0018(10) 1.000 0.076(4)
O2 O Uiso 0.558(11) 0.126(5) 0.571(2) 1.000 0.076(4)
O3 O Uiso 0.362(10) 0.599(4) 0.299(2) 1.000 0.076(4)
C3 C Uiso 0.7560(13) -0.227(2) 0.0042(9) 1.000 0.076(4)
O4 O Uiso 0.871(11) 0.198(6) 0.534(2) 1.000 0.076(4)
C4 C Uiso 1.0863(13) -0.227(3) 0.0556(10) 1.000 0.076(4)
C5 C Uiso 1.0169(13) -0.123(3) 0.1136(10) 1.000 0.076(4)
C6 C Uiso 1.1568(14) -0.068(3) 0.1680(10) 1.000 0.076(4)
C7 C Uiso 1.1487(16) 0.073(3) 0.2053(10) 1.000 0.076(4)
C8 C Uiso 1.0000(17) 0.204(3) 0.1981(10) 1.000 0.076(4)
C9 C Uiso 1.056(2) 0.362(3) 0.2065(10) 1.000 0.076(4)
C10 C Uiso 0.921(2) 0.490(3) 0.1935(10) 1.000 0.076(4)
C11 C Uiso 0.726(2) 0.462(2) 0.1712(9) 1.000 0.076(4)
C12 C Uiso 0.6652(17) 0.490(3) 0.1935(10) 1.000 0.076(4)
C13 C Uiso 0.7944(16) 0.178(3) 0.1800(9) 1.000 0.076(4)
C14 C Uiso 0.8106(13) -0.077(3) 0.1167(9) 1.000 0.076(4)
C15 C Uiso 0.6538(17) -0.056(2) 0.2420(8) 1.000 0.076(4)
C16 C Uiso 0.952(11) 0.1137(7) 0.5982(8) 1.000 0.076(4)
C17 C Uiso 0.598(10) 0.299(5) 0.465(2) 1.000 0.076(4)
C18 C Uiso 0.669(11) 0.199(5) 0.528(2) 1.000 0.076(4)
C19 C Uiso 0.395(10) 0.296(4) 0.4458(19) 1.000 0.076(4)
C20 C Uiso 0.724(10) 0.404(5) 0.425(2) 1.000 0.076(4)
C21 C Uiso 0.649(10) 0.503(5) 0.369(2) 1.000 0.076(4)
C22 C Uiso 0.445(10) 0.501(4) 0.351(2) 1.000 0.076(4)
C23 C Uiso 0.320(10) 0.394(4) 0.3893(19) 1.000 0.076(4)
H1 H Uiso 0.550(2) -0.017(3) 0.3506(8) 1.000 0.091(4)
H2 H Uiso 0.648(2) 0.152(3) 0.3051(8) 1.000 0.091(4)
H3 H Uiso 0.5250(12) -0.086(2) 0.0657(7) 1.000 0.091(4)
H4 H Uiso 1.0152(15) -0.361(3) -0.0419(10) 1.000 0.091(4)
H5 H Uiso 0.6555(13) -0.266(2) -0.0384(8) 1.000 0.091(4)
H6 H Uiso 1.2442(13) -0.268(3) 0.0555(11) 1.000 0.091(4)
H7 H Uiso 1.2904(15) -0.146(3) 0.1754(11) 1.000 0.091(4)
H8 H Uiso 1.2757(17) 0.098(3) 0.2400(11) 1.000 0.091(4)
H9 H Uiso 1.208(2) 0.386(3) 0.2226(11) 1.000 0.091(4)
H10 H Uiso 0.966(3) 0.611(3) 0.2012(11) 1.000 0.091(4)
H11 H Uiso 0.623(2) 0.563(2) 0.1606(9) 1.000 0.091(4)
H12 H Uiso 0.5125(16) 0.281(2) 0.1505(8) 1.000 0.091(4)
H13 H Uiso 0.462(10) 0.676(4) 0.278(2) 1.000 0.091(4)
H14 H Uiso 0.896(11) 0.169(7) 0.650(2) 1.000 0.091(4)
H15 H Uiso 1.115(11) 0.122(7) 0.591(3) 1.000 0.091(4)
H16 H Uiso 0.914(11) 0.025(6) 0.597(2) 1.000 0.091(4)
H17 H Uiso 0.298(10) 0.216(4) 0.4768(18) 1.000 0.091(4)
H18 H Uiso 0.880(10) 0.410(6) 0.440(2) 1.000 0.091(4)
H19 H Uiso 0.746(10) 0.587(5) 0.339(2) 1.000 0.091(4)
H20 H Uiso 0.163(10) 0.392(4) 0.3746(18) 1.000 0.091(4)
END
Figure S32. Overlay of the 30-molecule cluster of the observed structure of CARB-CEBG-A (colored by element, main disorder component only) and calculated PBE-TS structure (green, cell parameters fixed, atom positions optimized), $\text{rmsd}_{30}=0.09$ Å.

cis Aconitic acid (form II)

The PBE-TS structure (fixed cell parameters) were used as the starting point for rigid body Rietveld refinements in TOPAS academic. The final refinements included a total of 58 parameters (38 profile, 4 cell, 1 scale, 1 isotropic temperature factor, 3 position and 3 rotation, 8 preferred orientation) yielding a final $R_{wp}=8.02\%$. Note that only one position of the likely disordered COOH function was refined.

TITL cis Aconitic acid (form II)
CELL 0.71073 25.2072 4.91846 11.5654 90 97.8134 90
ZERR 8 0.0008 0.00014 0.0004 0 0.0015 0
LATT 7
SYMM -x,y,1/2-z
SFAC C H O
UNIT 48 48 48
FVAR 1.00
O1 O Uiso 0.2531(2) 0.9545(14) 0.4151(6) 1.000 0.0414(14)
O2 O Uiso 0.1331(2) 0.8155(11) 0.4378(5) 1.000 0.0414(14)
O3 O Uiso 0.2015(3) 1.3319(12) 0.3931(6) 1.000 0.0414(14)
O4 O Uiso 0.08025(18) 0.5533(8) 0.3086(4) 1.000 0.0414(14)
O5 O Uiso 0.0450(2) 1.0372(6) 0.1224(5) 1.000 0.0414(14)
O6 O Uiso 0.03986(17) 0.7218(5) -0.0199(4) 1.000 0.0414(14)
C1 C Uiso 0.1862(2) 0.9939(10) 0.2485(6) 1.000 0.0414(14)
C2 C Uiso 0.11915(17) 0.7286(7) 0.1166(5) 1.000 0.0414(14)
C3 C Uiso 0.14327(19) 0.8300(9) 0.2343(5) 1.000 0.0414(14)
C4 C Uiso 0.2157(2) 1.0876(12) 0.3623(6) 1.000 0.0414(14)
C5 C Uiso 0.11900(19) 0.7359(9) 0.3379(4) 1.000 0.0414(14)
C6 C Uiso 0.06459(18) 0.8433(6) 0.0747(5) 1.000 0.0414(14)
H1 H Uiso 0.06791(18) 0.4772(9) 0.3800(4) 1.000 0.0498(16)
H2 H Uiso 0.00379(18) 0.8190(5) -0.0516(4) 1.000 0.0498(16)
H3 H Uiso 0.2033(2) 1.0697(10) 0.1726(6) 1.000 0.0498(16)
H4 H Uiso 0.14402(18) 0.7875(8) 0.0499(5) 1.000 0.0498(16)
H5 H Uiso 0.11660(15) 0.5053(7) 0.1146(4) 1.000 0.0498(16)
H6 H Uiso 0.2231(3) 1.3950(13) 0.4704(7) 1.000 0.0498(16)
END

Figure S33. Overlay of the 15-molecule cluster of the observed structure of cis Aconitic acid form II (colored by element, main disorder component only) and calculated PBE-TS structure (green, cell parameters fixed, atom positions optimized), rmsd15=0.14 Å.

References
1. Etter, M. C.; MacDonald, J. C.; Bernstein, J., Graph-set analysis of hydrogen-bond patterns in organic crystals. Acta Crystallographica, Section B: Structural Science 1990, B46 (2), 256-262.
2. Clark, S. J.; Segall, M. D.; Pickard, C. J.; Hasnip, P. J.; Probert, M. J.; Refson, K.; Payne, M. C., First principles methods using CASTEP. Zeitschrift fur Kristallographie 2005, 220 (5-6), 567-570.
3. Coelho, A. A. Topas Academic V5, Coelho Software: Brisbane, 2012.