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Supporting information for article:

Structural basis for the transformation pathways of the sodium naproxen anhydrate–hydrate system

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Corresponding author. E-mail: andrew.bond@sund.ku.dk

Supporting Information

S1. Solid-state NMR: experimental details

Solid-state NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at Larmor frequencies of 100.62, 105.85 and 400.13 MHz for ^{13}C, [23]Na and ^{1}H, respectively, using a double-tuned CP/MAS probe equipped for 4 mm (o.d.) rotors.

[13]C CP/MAS spectra were recorded using a contact time of 8.5 ms, a spin-rate of 12 kHz, a recycle delay of 8s, an acquisition time of 40.9 ms during which ^{1}H TPPM decoupling [Bennett, 1995] (80 kHz rf-field strength) was employed, 256 scans and a temperature of 313K. Cross polarization was carried out using variable amplitude CP [Peersen, 1993] with a maximum rf-field strength of 80 kHz for both ^{1}H and [13]C.[13]C chemical shifts were referenced to an external sample of α-glycine (carbonyl group) at 176.5 ppm.

Single-pulse ^{23}Na MAS NMR spectra were recorded using a 1.8 μs pulse (69.4 kHz rf-field strength), spin-rate of 12 kHz, a recycle delay of 16 s, 32 scans, a temperature of 313 K, an acquisition time of 40.9 ms during which ^{1}H TPPM decoupling (80 kHz rf-field strength) were employed. [23]Na chemical shifts were referenced to an external sample of 1.0 M NaCl (aq) (0.0 ppm).

[23]Na 3Q-MAS spectra were recorded using a z-filtered split-t1 3Q-MAS exp [Brown, 1997] employing a 3Q-excitation pulse of 18.7 μs, a 3Q-to-1Q conversion pulse of 37.1 μs (rf-field strength of 69.4 kHz for both) and two 5.0 μs (rf-field strength of 25 kHz) pulses for the z-filter, a recycle delay of 4 s, a spin-rate of 12 kHz, a temperature of 313 K and 192 or 768 scans for each of the 72 t1-increments of 83.33 μs in the isotropic dimension. Subsequently data were processed using the *NMRpipe* software [Delaglio, 1995].

One single-pulse [23]Na MAS spectrum of NSAH was recorded on a Bruker Avance-III 700 spectrometer operating at a Larmor frequency of 185.15 MHz for [23]Na using a triple-tuned probe equipped for 4 mm (o.d.) rotors. This spectrum was recorded using a pulse width of 1.0 μs (rf-field strength: 41.7 kHz), a recycle delay of 4 s, a spin-rate of 12 kHz, 1024 scans, and an acquisition time of 8.24 ms.

S2. Experimental and calculated ²³Na MAS NMR spectra

[Calculated spectra employ the parameters listed in Table 2 of the main manuscript]
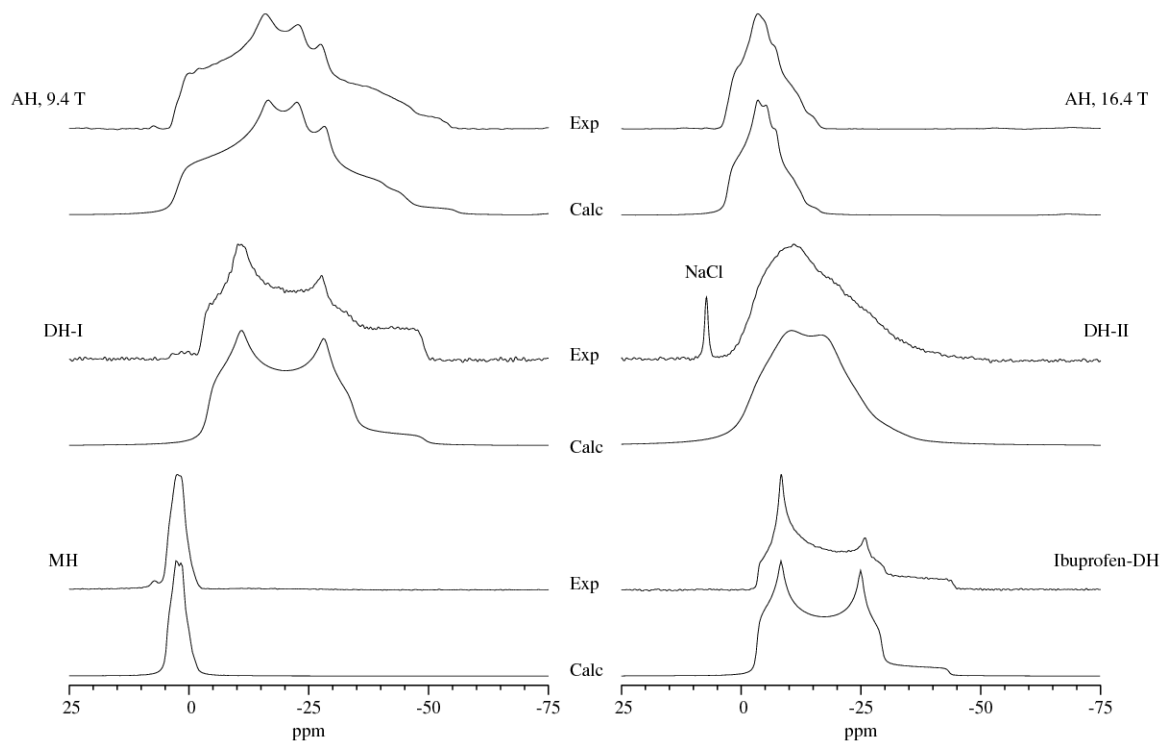
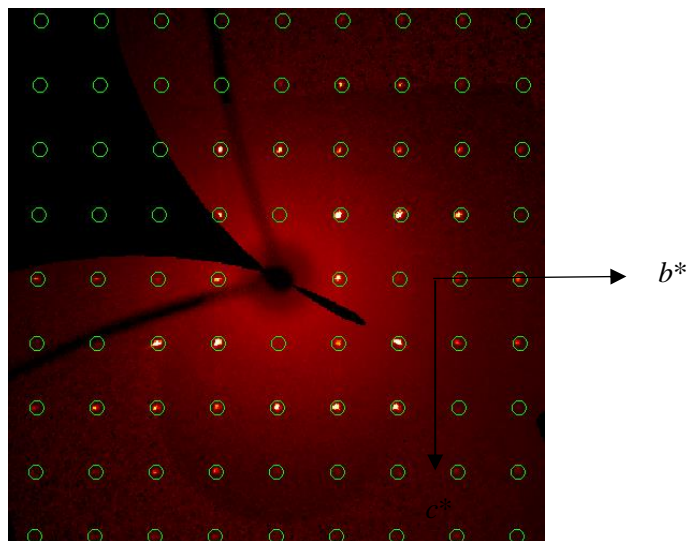## S3. ²³Na 3Q-MAS NMR spectra of sodium (*S*)-ibuprofen dihydrate (A) and DH-II (B)

[A horizontal line at the shift of Ibuprofen-DH in the isotropic dimension is inserted as a guide to the eye. The asterisk denotes an MH impurity in the DH-II sample]
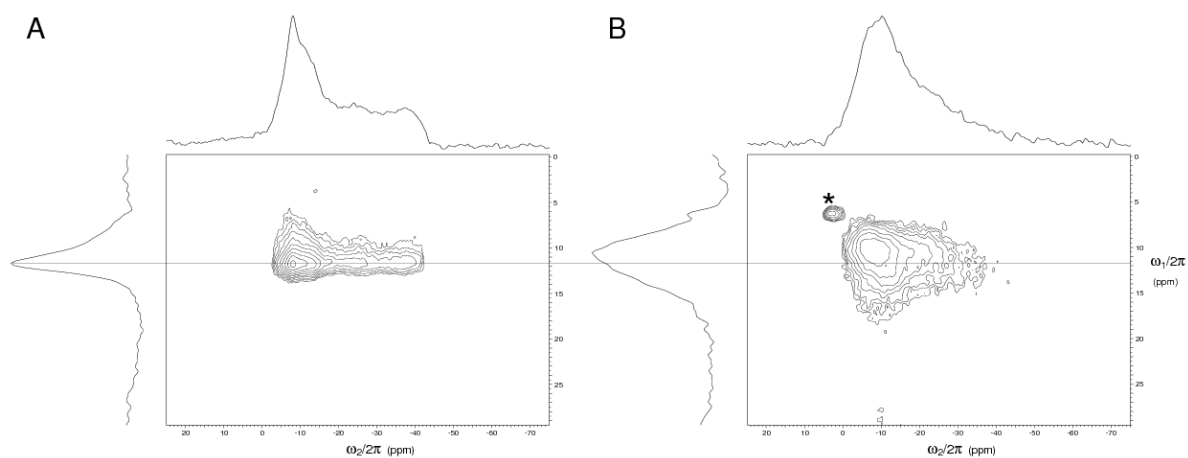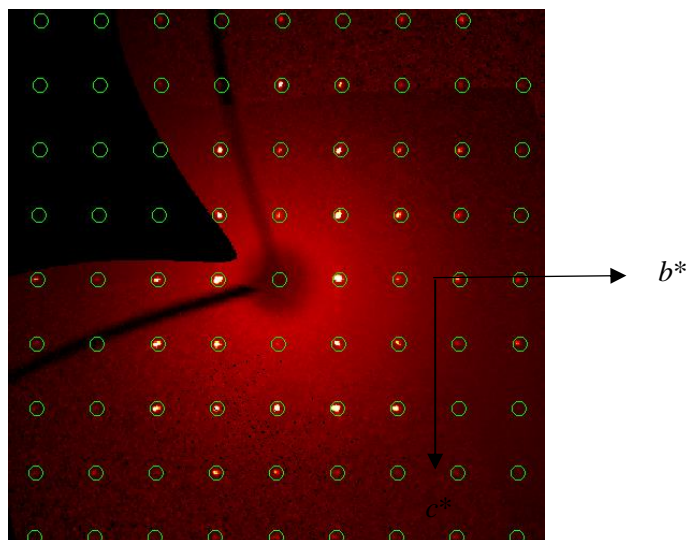
S4. Reconstructed precession images for single-crystal data of DH-I

[Peak predictions correspond to: a = 22.281, b = 5.811, c = 5.435 Å, α = 89.5, β = 85.5, γ = 92.6°]
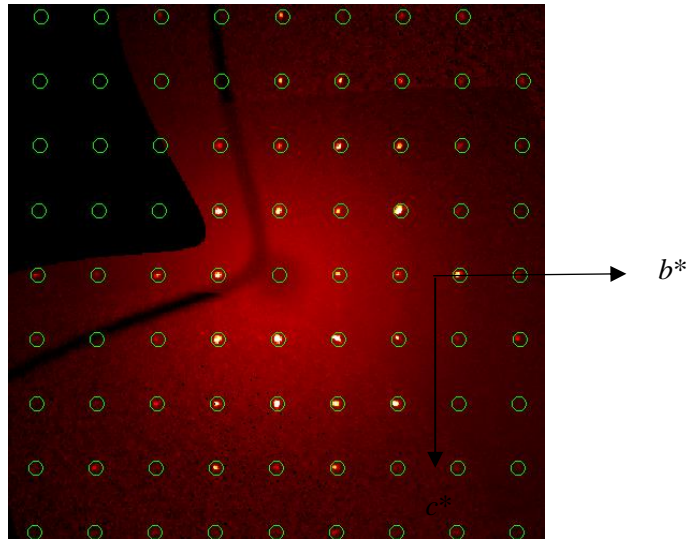
(0kl)

(1kl)

($2kl$)

S4. Reconstructed precession images for single-crystal data of DH-I

[Peak predictions correspond to: a = 22.281, b = 5.811, c = 5.435 Å, α = 89.5, β = 85.5, γ = 92.6°]
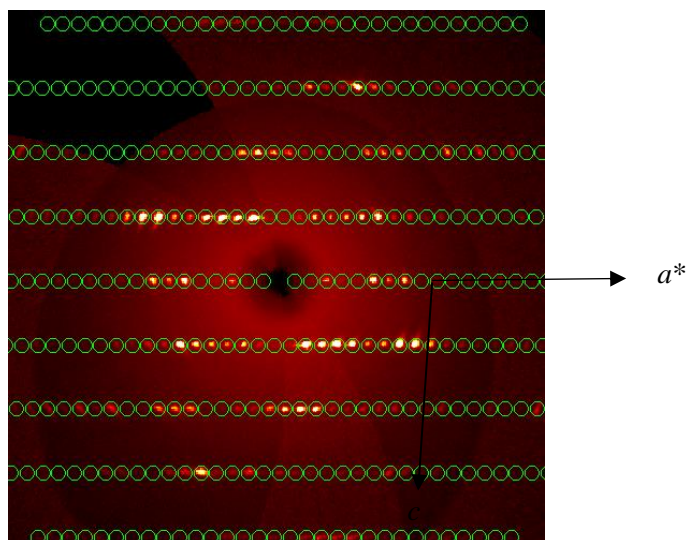

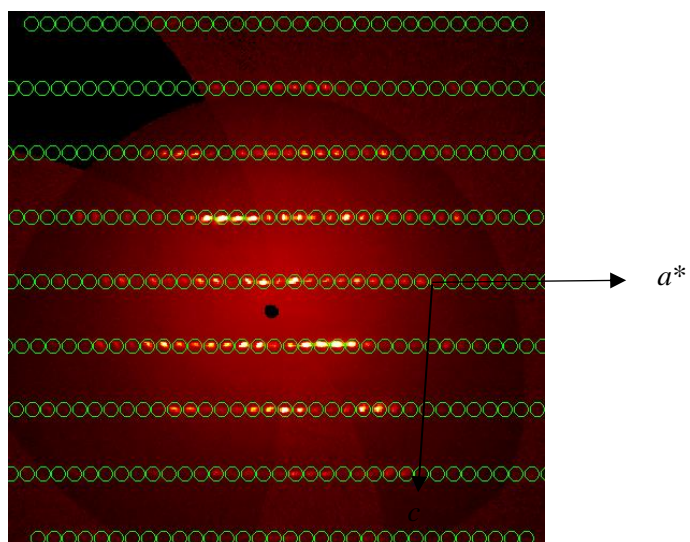($h0l$)

($h1l$)

(*h2l*)

S4. Reconstructed precession images for single-crystal data of DH-I

[Peak predictions correspond to: $a = 22.281$, $b = 5.811$, $c = 5.435$ Å, $\alpha = 89.5$, $\beta = 85.5$, $\gamma = 92.6°$]

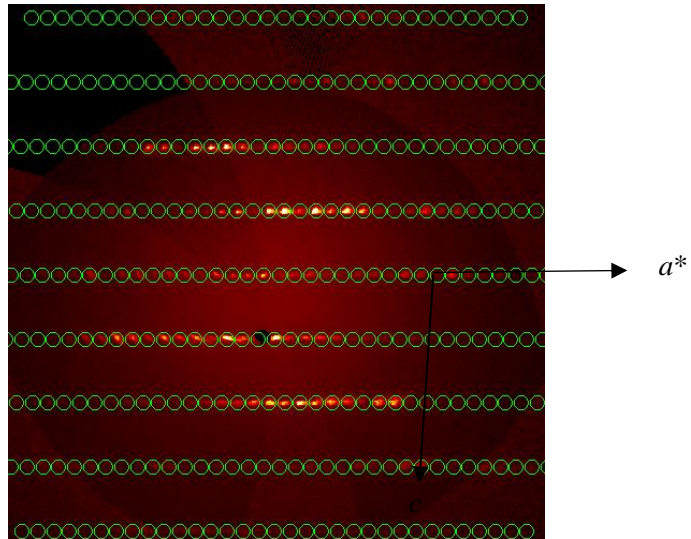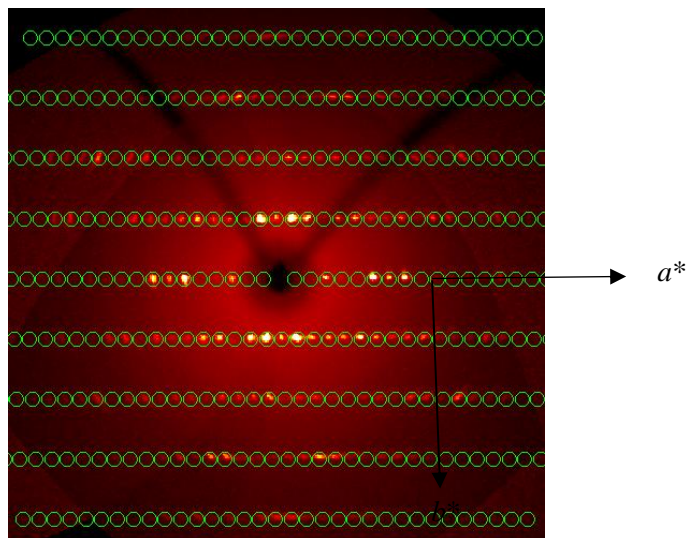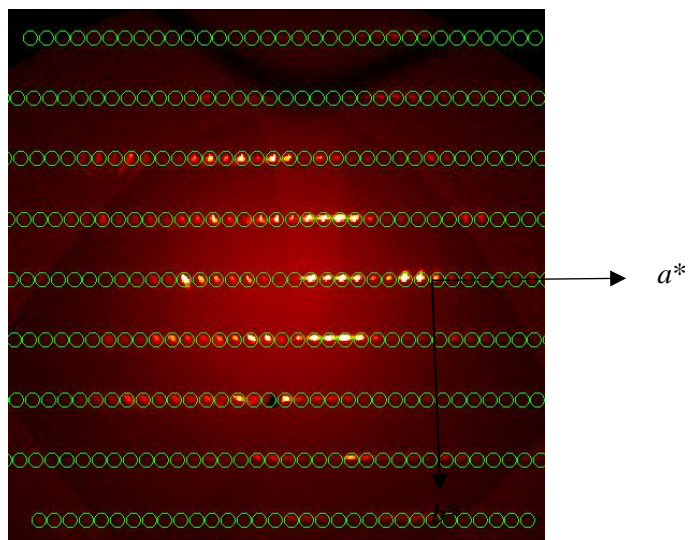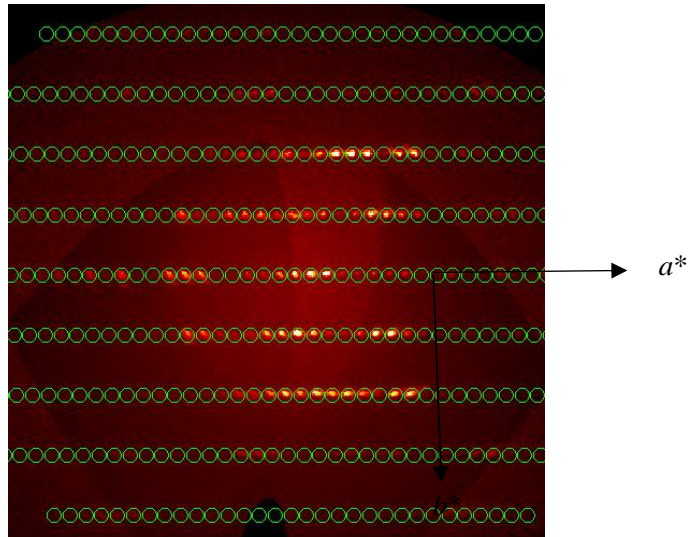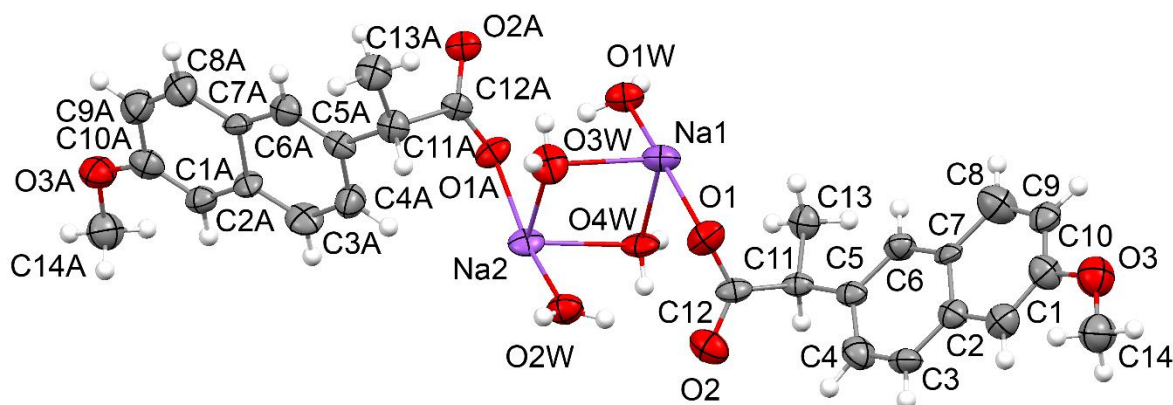(hk0)

$a*$

(hk1)

$a*$

(*hk*2)

$a*$

S5. Displacement ellipsoid plot for single-crystal structure of DH-I
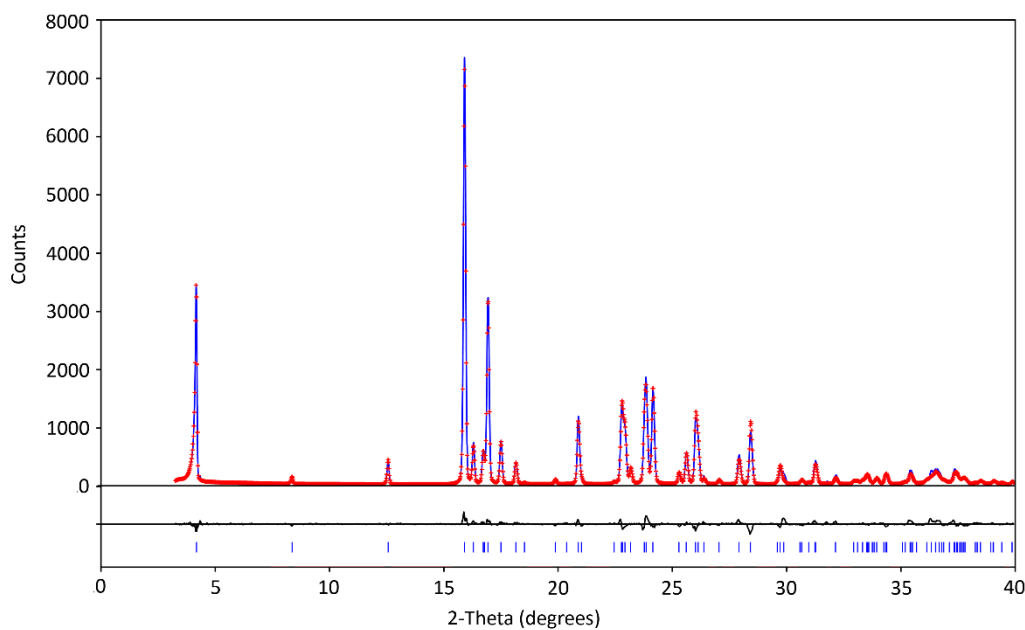

S6. Rietveld refinement

Rietveld refinements were carried out using *TOPAS* Academic ver. 4.1 (Coelho, 2007). The interface in *DASH* (David et al., 2006) was used to construct the initial input files. The starting point for each refinement was the DFT-D minimized structure. Tight restraints were generated for all bond distances and angles, and the naphthalene rings of the naproxen molecules were also tightly restrained to be planar. All coordinates (including H atoms) were refined with a common isotropic displacement parameter for non-H atoms, and with U(iso) for the H atoms equal to 1.2 times the refined parameter. The background was modelled with a 20-term Chebyshev polynomial and peak asymmetry was refined using spherical harmonics. A correction for preferred orientation was applied in each case using the March-Dollase model. The refinement strategy allows the fit to the experimental PXRD pattern to be optimized, while keeping the structure close to the DFT-D optimized structure. The result is a sensible model, close to that expected from a single-crystal refinement, with a measure of how well that model fits the experimental data.

S6.1. Rietveld refinement for AH
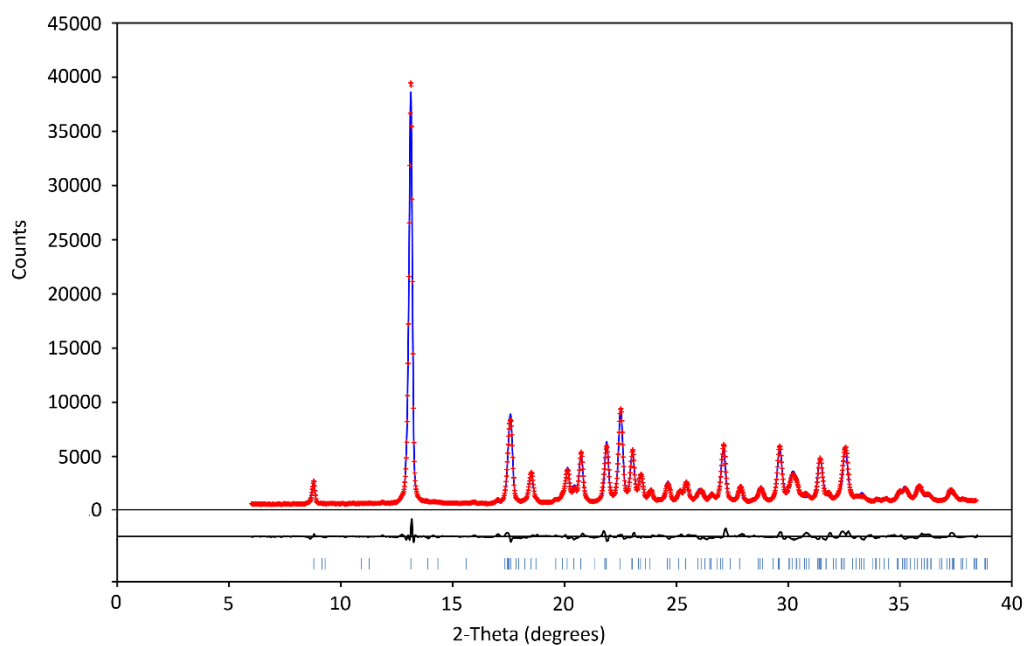
	Rp (%)	Rwp (%)	χ^2
Before background subtraction	4.922	6.600	2.98
After background subtraction	8.346	9.990	

S6.2. Rietveld refinement for MH

	Rp (%)	Rwp (%)	χ^2
Before background subtraction	5.021	7.496	1.03
After background subtraction	6.800	9.313	

S6.3. Rietveld refinement for DH-I
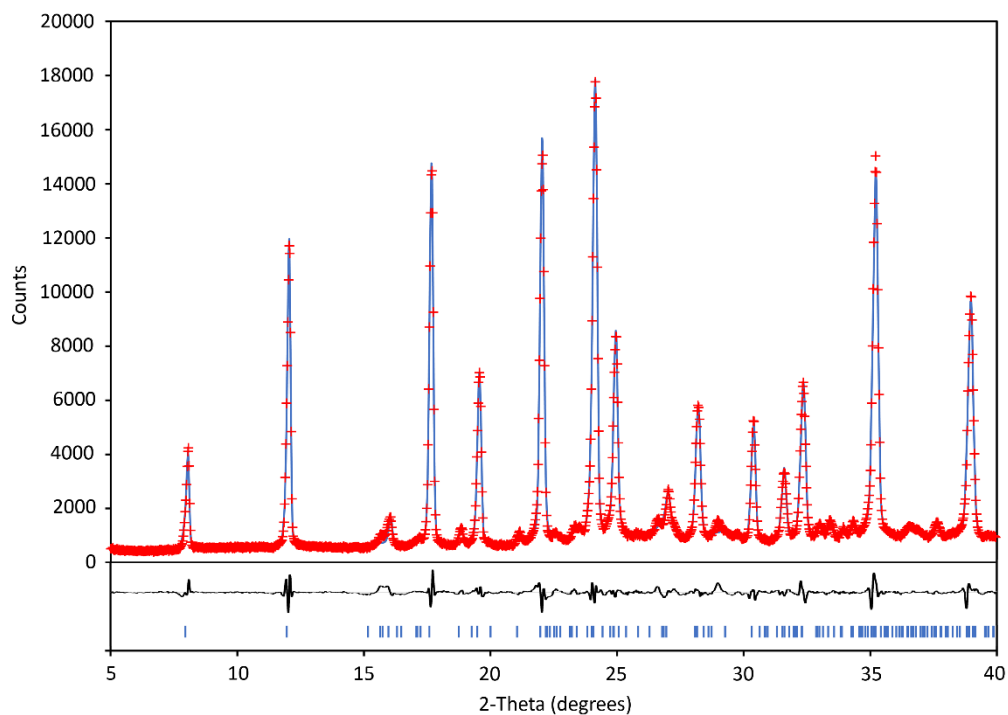
	Rp (%)	Rwp (%)	χ^2
Before background subtraction	4.774	6.800	2.99
After background subtraction	3.700	4.888	

S6.4. Rietveld refinement for DH-II [difference curve also shown in the main paper]

	Rp (%)	Rwp (%)	χ^2
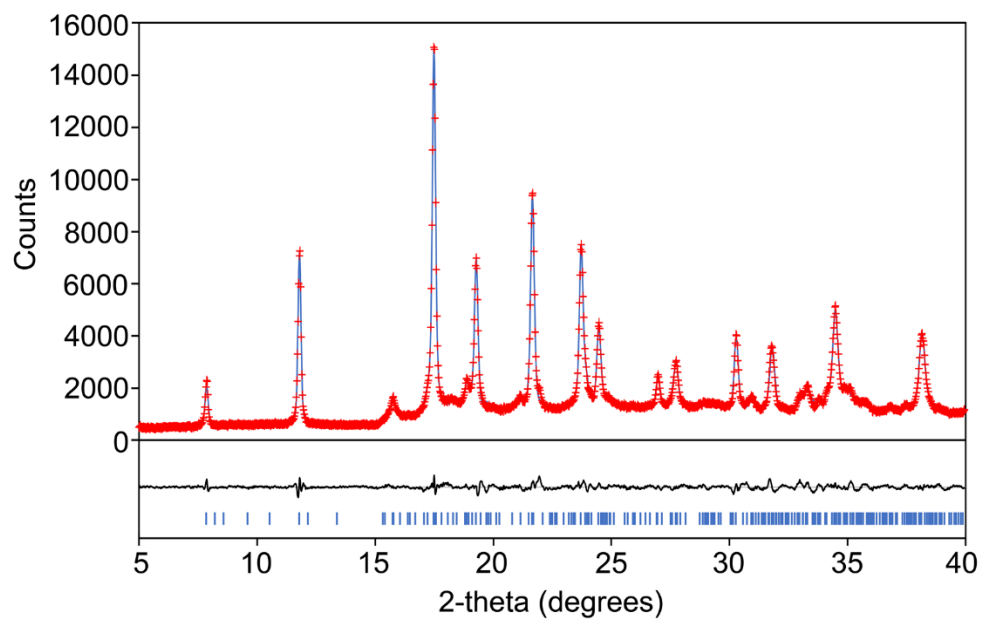
|			
Before background subtraction	3.916	5.267	2.582
After background subtraction	5.438	7.031	

S7. Relationship between DH-II and sodium (*S*)-ibuprofen dihydrate

[CSD: KATNOJ (enantiomeric ibuprofen) and KASVEG (racemic) are isostructural]

Overlay of DH-II (red) and KASVEG (green). Only Na, H_2O and carboxylate groups are shown. The right-hand diagram shows that the Na/H_2O/carboxylate region of DH-II conforms to space group *P*−1, as for KASVEG. [In the DH-II cell, space group is formally *A*−1]:
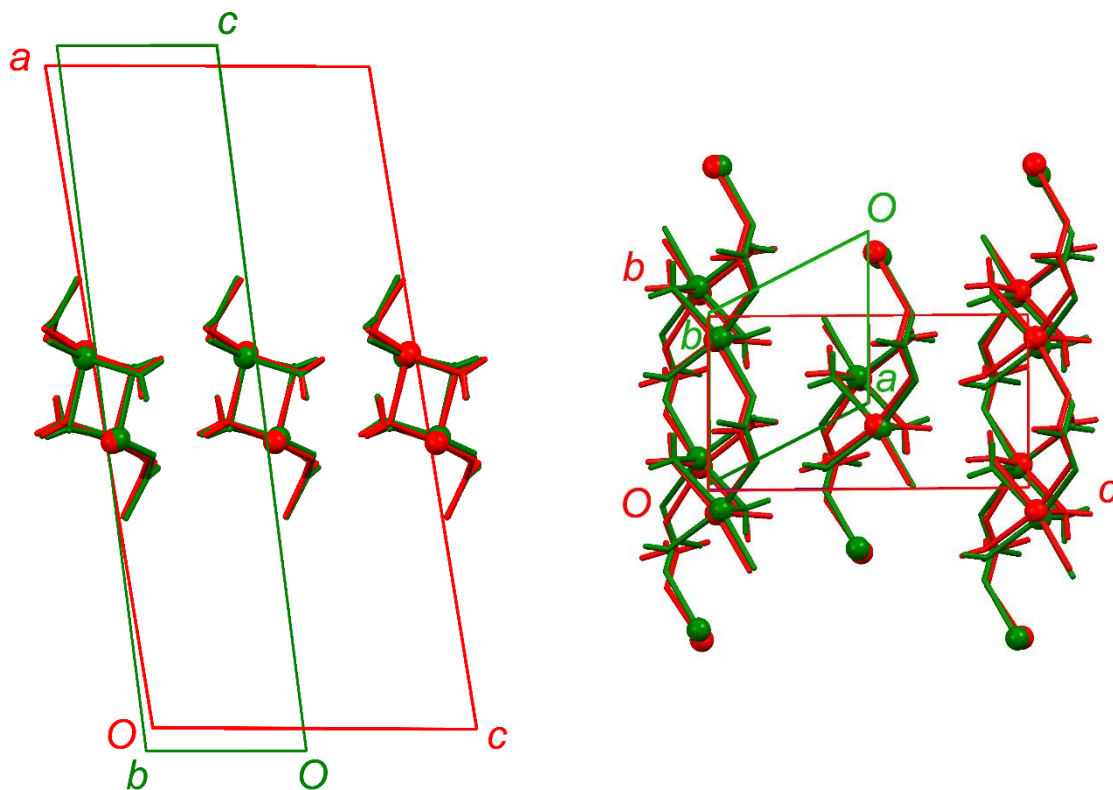
Relationship between the unit cells:

$$\begin{pmatrix} 0 & 0 & -1 \\ 1 & 0 & 0 \\ -1 & 2 & 0 \end{pmatrix}$$

KASVEG	5.740	6.028	23.830
	83.46	89.24	63.15

23.830	5.740	10.761
91.57	96.93	90.76

DH-II	22.750	5.747	10.866
	89.61	98.20	92.11

References

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