

† *Electronic Supplementary Information*

On the Hydrates of Codeine Phosphate: Remarkable Influence of Hydrogen Bonding on the Crystal Size

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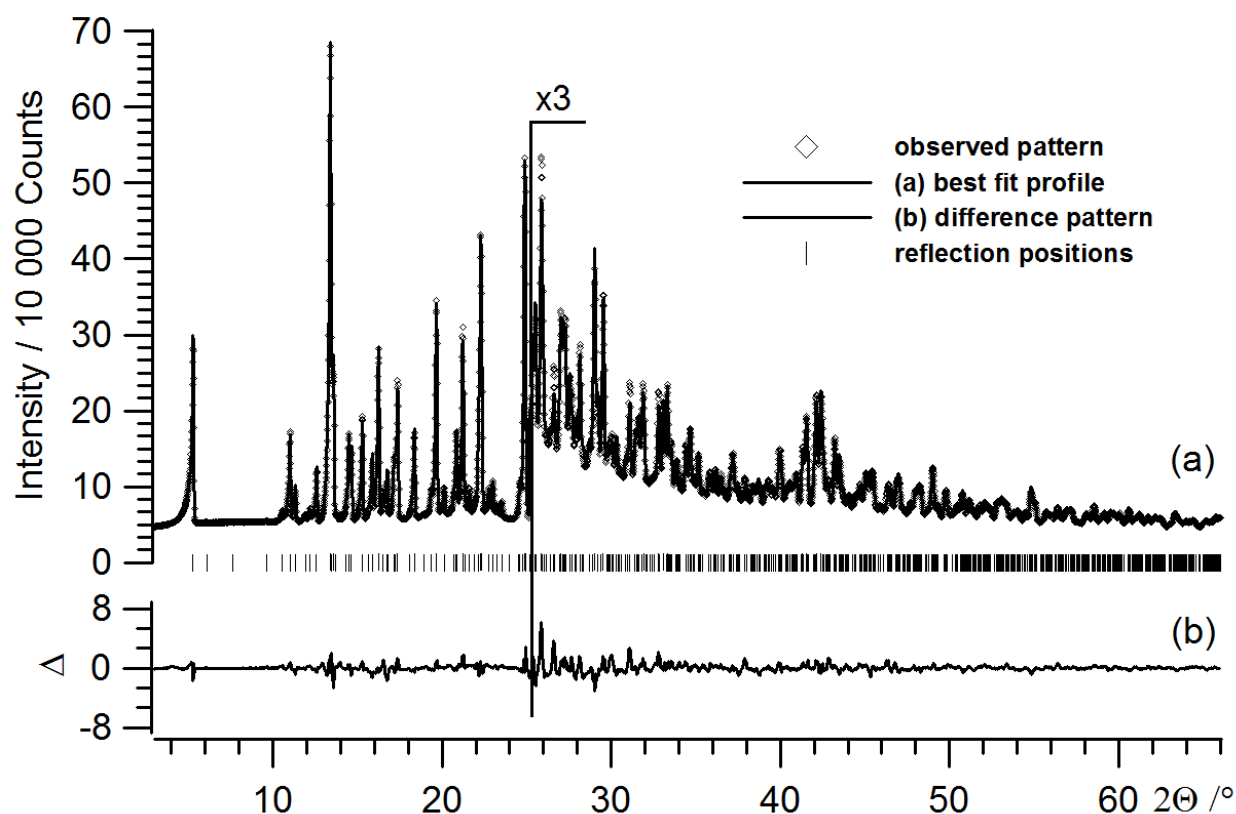
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1. Sample preparation

The commercial hydrates of codeine phosphate (hemihydrate and sesquihydrate) are routinely produced by a reaction of pure codeine with stoichiometric portions of phosphoric acid and water in ethanol solution. Alternatively, our previous studies (reference No. 2 in the current manuscript) have confirmed that codeine phosphate hemihydrate is obtained in a controlled and repeatable manner upon recrystallization of codeine phosphate sesquihydrate from hot DMF solution. An anhydrous codeine phosphate can be also obtained by controlled recrystallization of codeine phosphate sesquihydrate from several solvents (anhydrous ethanol, acetone, ethyl acetate and acetonitrile).

2. Crystallographic details

High-resolution XRPD patterns were collected on laboratory powder diffractometer *Stoe Stadi-P* with $\text{CuK}\alpha_1$ radiation from primary Ge(111)-Johannson-type monochromator and Dectris-MYTHEN 1K strip PSD with an opening angle of 12° in 2θ , in Debye-Scherrer geometry. Prior to measurement the samples were manually powdered in a mortar and pestle and sealed in borosilicate glass capillaries of 0.5 mm diameter (Hilgenberg glass No. 50). The samples were spun during data collection for better particle statistics. For the temperature-resolved measurements, hot/cold air blower (Oxford Cryosystems) was used for temperature control. *In situ* XRPD patterns were collected at each degree on heating, in 2θ range of $10\text{--}13^\circ$, with data collection time of 2 min. The powder pattern used for structure solution (Figure S1) was collected over one day (24h).



ESI Figure S1. Scattered X-ray intensities as a function of diffraction angle of the pattern of **COP-S**. The observed pattern (diamonds) measured in Debye-Scherrer geometry, the best Rietveld fit profile (line) and the difference curve between the observed and the calculated profiles (below) are shown. The Bragg reflections positions of the three present phases are given.

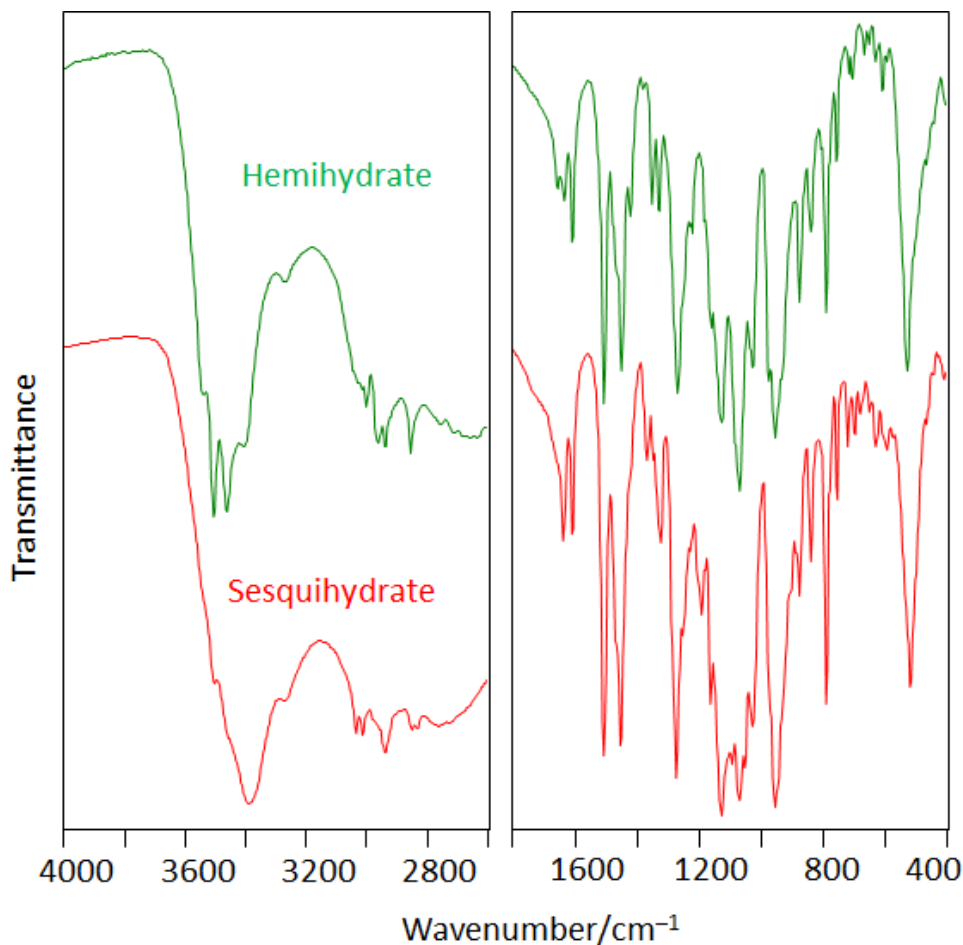
The powder data analyses (pattern indexing, profile fitting, crystal structure solution and refinement) were performed with the program TOPAS 4.2. (S1) The pattern of **COP-S** was indexed with the singular value decomposition method, (S2) resulting in orthorhombic unit cells. Precise lattice parameters were determined by Pawley fit, (S3) using the fundamental parameter approach for peak fitting. (S4) During the full profile decomposition, the lattice parameters, stain and crystal size contributions were refined. In addition, Chebyshev polynomials were used to model the background.

The crystal structure of **COP-S** was solved by the global optimization method of simulated annealing (SA) in real space. The structure solution was performed in the $P2_12_12_1$ space group using two rigid bodies in the asymmetric units. For the definition of the connectivity between the atoms within the rigid bodies, the z matrix notation was used. The rigid bodies were built based on the related crystal structure of **COP-H** (reference 3 in the main text). During the SA runs, three rotations, three translations for each rigid body together with all possible torsion angles were set flexible. An overall temperature factor for each atom type was included in the SA process. Once a global minimum was found, the crystal structures were subjected to Rietveld refinement. (S5) Free refinement of all profile and lattice parameters was used. Unconstrained and unrestrained refinement lead to longer P–O bonds than expected, without significant influence on the overall hydrogen bonding scheme. The anisotropy of width and asymmetry of

the Bragg reflections was successfully modelled by applying symmetry adapted spherical harmonics of low order to Gaussian, Lorentzian and exponential distributions which are then convoluted with geometrical and instrumental contributions to the final peak profile. Despite the use of capillaries in Debye-Scherrer geometry, a small amount of preferred orientation originating from the plate-like crystals (Figure 1 in the main text) was detected and was adequately described by the use of symmetry adapted spherical harmonics (affecting the R_{wp} value for less than 0.5%). The final Rietveld plot is given in Figure S1. The unit cell axes parameters were refined to values of $a = 33.4761(7)$ Å, $b = 16.0612(3)$ Å, $c = 7.1921(2)$ Å; and the figures of merit to values of $R_{Bragg} = 2.25$ %, $R_{exp} = 0.99$ %, $R_{wp} = 3.48$ %, $R_p = 2.85$ %. 89 parameters were refined. The hydrogen atoms were normalized using the program *Mercury*. (S6)

3. FTIR Spectra

Further information on the infrared spectroscopy measurements (sample preparation, instrumentation used, etc.) are given in reference 2 in the main text.



ESI Figure S2. FT-IR spectra of COP-H and COP-S recorded in transmittance mode.

References:

- (S1) Bruker AXS, *Topas*, version 4.2. 2007.
- (S2) A. A. Coelho, *J. Appl. Cryst.*, 2003, **36**, 86.
- (S3) G. S. Pawley, *J. Appl. Cryst.*, 1981, **14**, 357.
- (S4) A. A. Coelho, *J. Appl. Cryst.*, 2000, **33**, 899.
- (S5) H. M. Rietveld, *J. Appl. Cryst.*, 1969, **2**, 65.
- (S6) CCDC, *Mercury CSD 3.1 Development (Build RC5)*, Cambridge, 2012.