Co-crystals of caffeine and piracetam with 4-hydroxybenzoic acid: unravelling the hidden hydrates of 1:1 co-crystals

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Electronic Supplementary Information

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Experimental

Materials

All the chemicals were purchased from Sigma-Alrdich Singapore. Analytical grade solvents were used for the crystallization experiments.

Single crystal X-ray diffraction

X-ray reflections were collected on a Rigaku Saturn CCD area detector with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were collected and processed using CrystalClear (Rigaku) software. Structures were solved by direct methods and SHELX-TL was used for structure solution and least-squares refinement. Non-hydrogen atoms were refined anisotropically. All hydrogen atoms were fixed at idealized positions except for the N-H hydrogens which were located from the difference Fourier map and allowed to ride on their parent atoms in the refinement cycles. All O-H and C-H distances were neutron normalized to 0.983 and 1.083 Å, respectively. Details of hydrogen bond parameters in the crystal structures are given in Table 1.

Powder X-ray diffraction (PXRD)

The powder materials of the grinding experiments were identified by D8 Advance powder X-ray diffractometer (Bruker AXS GmbH, Germany) with Cu-Kα radiation (λ = 1.54056 Å). The voltage and current applied were 35 kV and 40 mA, respectively. Samples were placed on the sample holder which has 1 mm thickness and 1.5 cm diameter. The sample was scanned within the scan range of 2θ = 5° to 50° continuous scan, with a scan rate of 2 deg min^{-1}. The PXRD patterns were plotted using OriginPro 7.5.

Thermogravimetric analysis (TGA)

TGA was performed on a TA instruments, TGA Q500 thermogravimetric analyzer. Approximately 15 mg of the sample was added to an alumina crucible. The samples were

heated over the temperature range of 25 to 300 °C at a constant heating rate of 5 °C min^{-1}. The samples were purged with a stream of flowing nitrogen throughout the experiment at 40 ml min^{-1}.

Differential scanning calorimetry (DSC)

DSC was performed with a Perkin Elmer Diamond DSC with an autosampler. Crystals taken from the mother liquor were blotted dry on a filter paper and placed in crimped but vented aluminium sample pans. The sample size was 2–5 mg and the temperature range was typically 30–150 °C at a heating rate of 10 °C min^{-1}. The samples were purged with a stream of flowing nitrogen (20 ml min^{-1}). The instrument was calibrated using indium as the reference material.

Hot-stage microscopy (HSM)

Thermomicroscopic investigations were performed with an optical polarizing microscope (Olympus, BX51) equipped with a Linkam hot-stage THMS 600 connected to a TMS 94 temperature controller and a LNP 94/2 liquid nitrogen pump (Linkam Scientific Instruments Ltd., Tadworth, Surrey, UK). The microscopic images were recorded with a CCD camera attached to the Olympus BX-51 microscope (Olympus Optical GmbH, Vienna, A) at every 12 sec time intervals using Soft Imaging System's Analysis image capture software. Samples were heated over the temperature range of 30 to 200 °C at a constant heating rate of 5 °C min^{-1}. The hot-stage was calibrated using USP melting point standards.

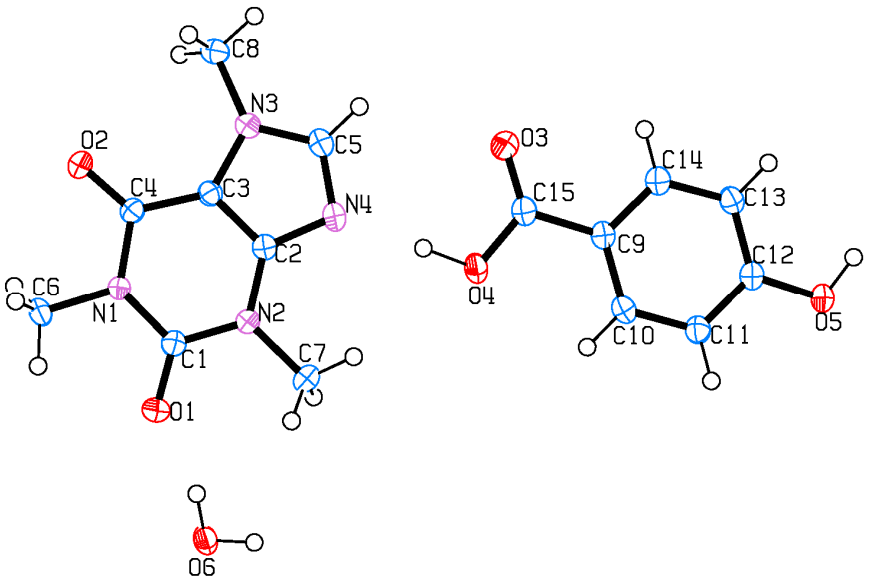
Cambridge Structural Database (CSD)

CSD Conquest November 2011 release was searched for crystal structures involving caffeine and piracetam. Crystal structures determined from X-ray powder diffraction data were omitted. Duplicate refcodes were manually removed and only one refcode was counted for each polymorphic set. All the crystal structures were analyzed by visuallizing in Mercury 2.4.

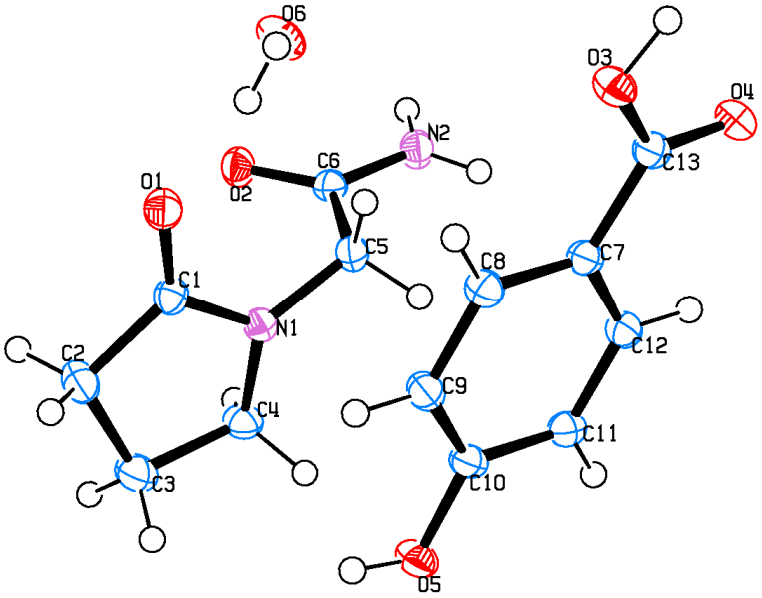
Table S1. The geometric parameters for the intermolecular interactions in the co-crystal hydrates of CAF and PA with 4HBA (neutron normalized).

Co-crystal hydrate	D–H···A[a]	H···A/Å	D···A/Å	D–H···A/°	Symmetry code
CAF-4HBA-Hydrate	O4–H1···N4	1.72	2.701(2)	176	
	O5–H2···O6	1.63	2.616(2)	177	1+x,y,1+z
	O6–H3···O1	1.74	2.707(2)	165	
	O6–H4···O2	1.81	2.780(2)	168	x,-1+y,z
	C6–H6A···O1	2.22	2.700(2)	104	
	C6–H6B···O2	2.27	3.345(2)	172	1-x,2-y,-z
	C7–H7A···O5	2.46	3.410(2)	146	1-x,-y,1-z
	C7–H7B···N4	2.54	2.947(2)	101	
	C8–H8A···O3	2.57	3.260(2)	121	2-x,2-y,1-z
PA-4HBA-Hydrate	N2–H1···O1	1.97	2.934(2)	159	-1+x,y,z
	N2–H6···O2	1.91	2.917(1)	172	-x,-y,-z
	O3–H7···O4	1.67	2.648(1)	173	-x,-y,1-z
	O5–H10···O6	1.67	2.641(2)	169	x,1+y,z
	O6–H13···O1	1.74	2.717(1)	170	
	O6–H14···O4	1.84	2.819(1)	171	1+x,y,z
	C2–H2A···O2	2.59	3.282(2)	121	1-x,1-y,-z
	C11–H11···O6	2.52	3.524(2)	154	-1+x,1+y,z

[a] D = Donor, A = Acceptor



CAF-4HBA (1:1) hydrate



PA-4HBA (1:1) hydrate

Fig. S1 ORTEP diagrams of crystal structures of the hydrates of 1:1 co-crystals of CAF, and PA with 4HBA.

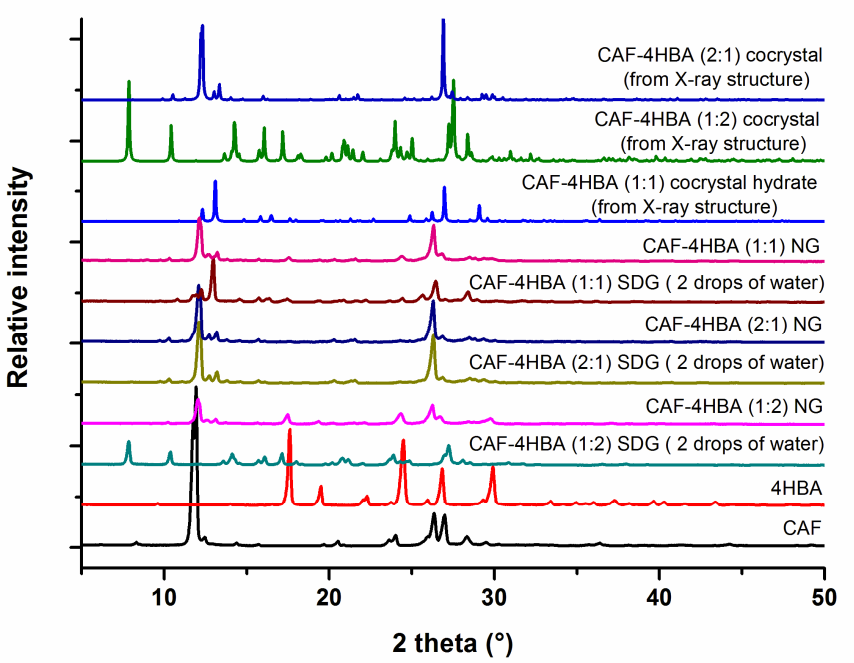


Fig. S2 Comparison of the PXRD patterns of the samples obtained in the grinding experiments on 1:2, 2:1, and 1:1 CAF and 4HBA with water. Simulated PXRD patterns from the single crystal X-ray data are also provided for comparison. Notice that the NG grinding of 1:1 CAF and 4HBA did not produce the co-crystal hydrate.

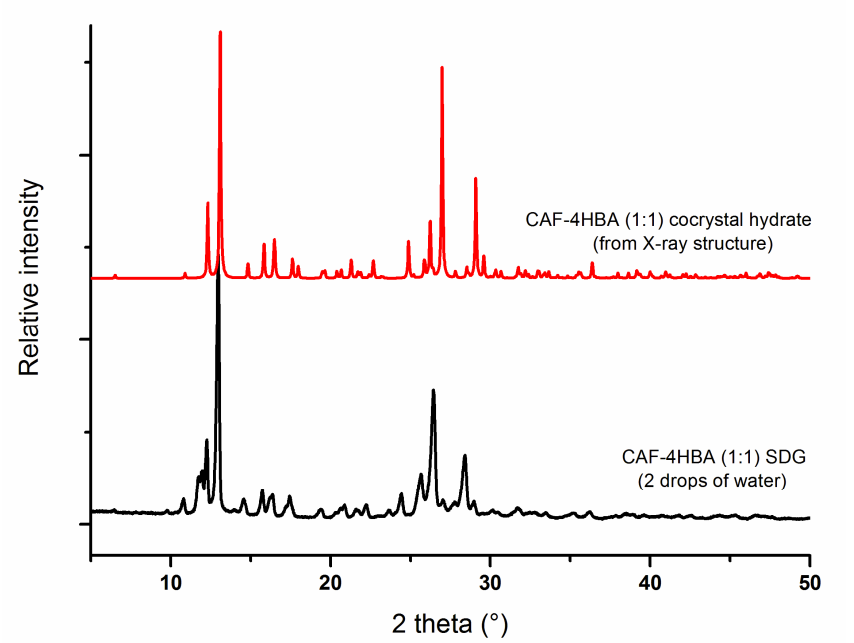


Fig. S3 Comparison of the PXRD pattern of the sample obtained in the grinding experiment on 1:1 CAF and 4HBA with water and simulated PXRD pattern of the 1:1 CAF and 4HBA co-crystal hydrate. Notice that the SDG experiment with water produced the 1:1 co-crystal hydrate.

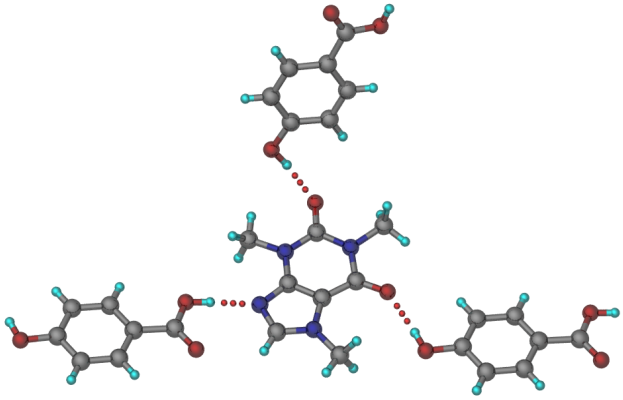


Fig. S4 Hydrogen bonding in the 1:2 CAF and 4HBA co-crystal.

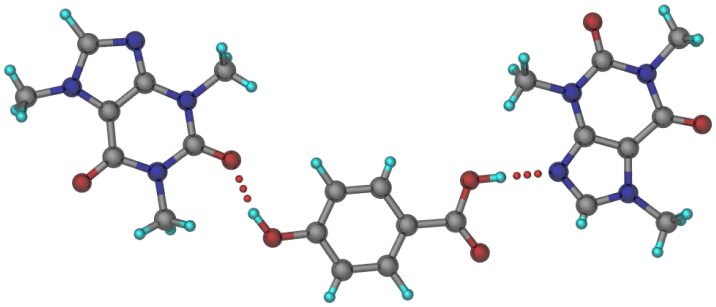


Fig. S5 Hydrogen bonding in the 2:1 CAF and 4HBA co-crystal.

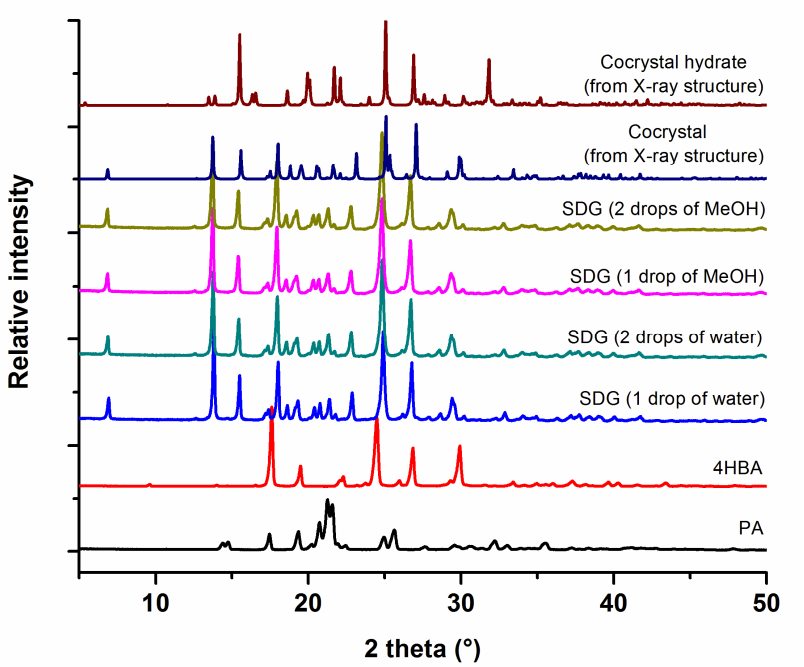


Fig. S6 Comparison of the PXRD patterns of the samples obtained in the grinding experiments on 1:1 PA and 4HBA with methanol and water. Simulated PXRD patterns from the single crystal X-ray data are also provided for comparison. Notice the formation of anhydrous co-crystal in all the grinding experiments.

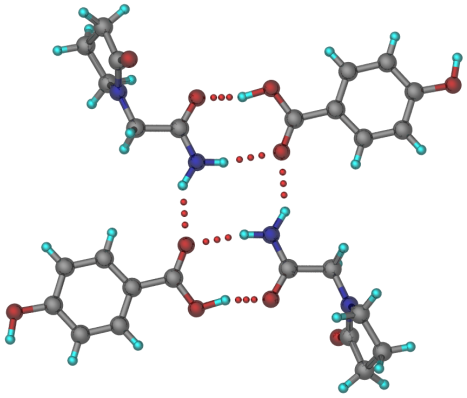


Fig. S7 Hydrogen bonding in the 1:1 PA and 4HBA co-crystal.

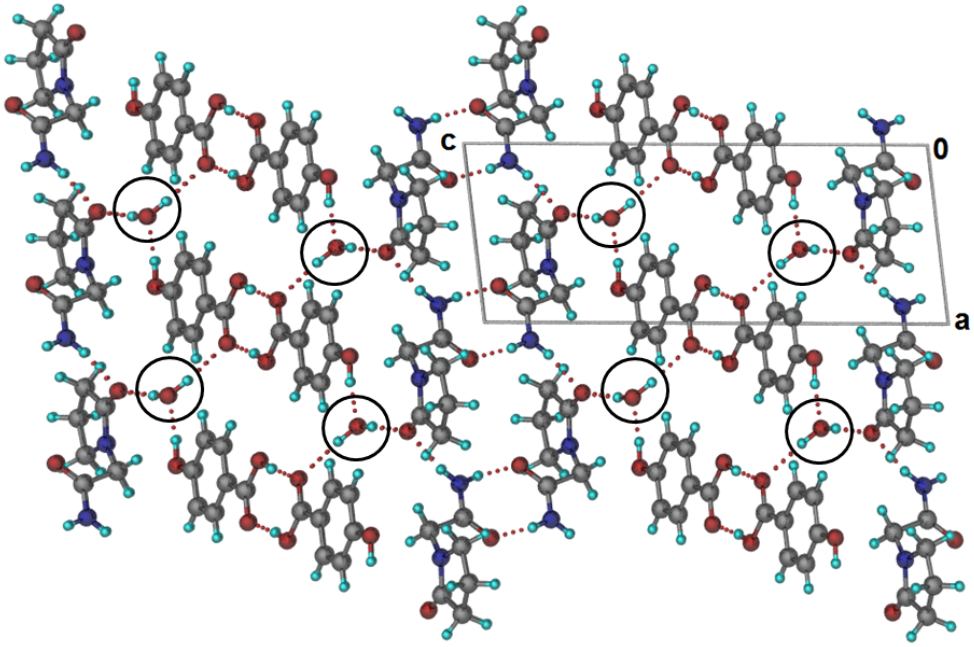


Fig. S8 Packing diagram of PA-4HBA (1:1) co-crystal hydrate showing the hydrogen bonded water molecules located in the channels along the crystallographic *b*-axis. Water molecules are circled for clarity.

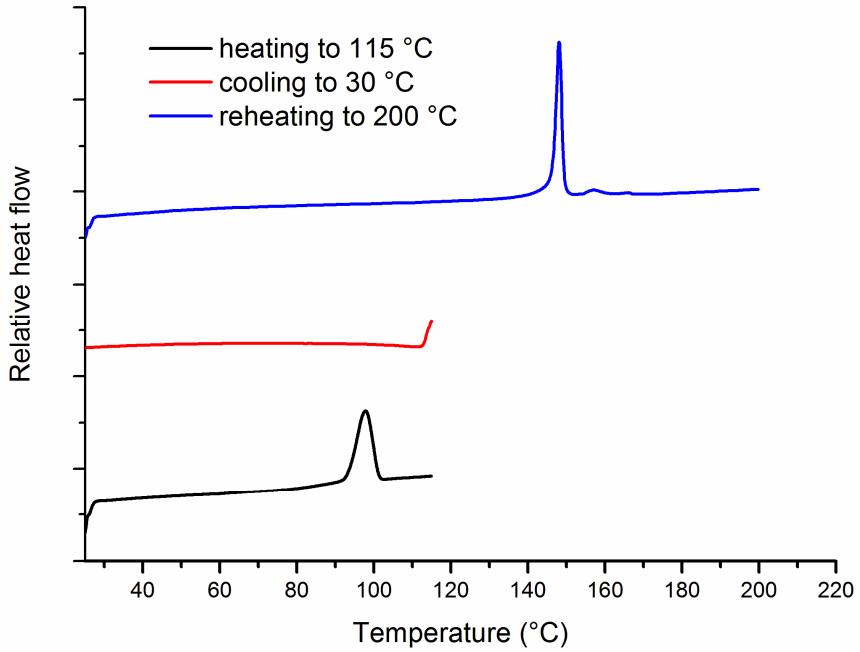


Fig. S9 A DSC heat-cool-heat cycle of the CAF-4HBA (1:1) co-crystal hydrate showing the dehydration in the first heating and a single endotherm in the reheating for melting of the dehydrated solid.

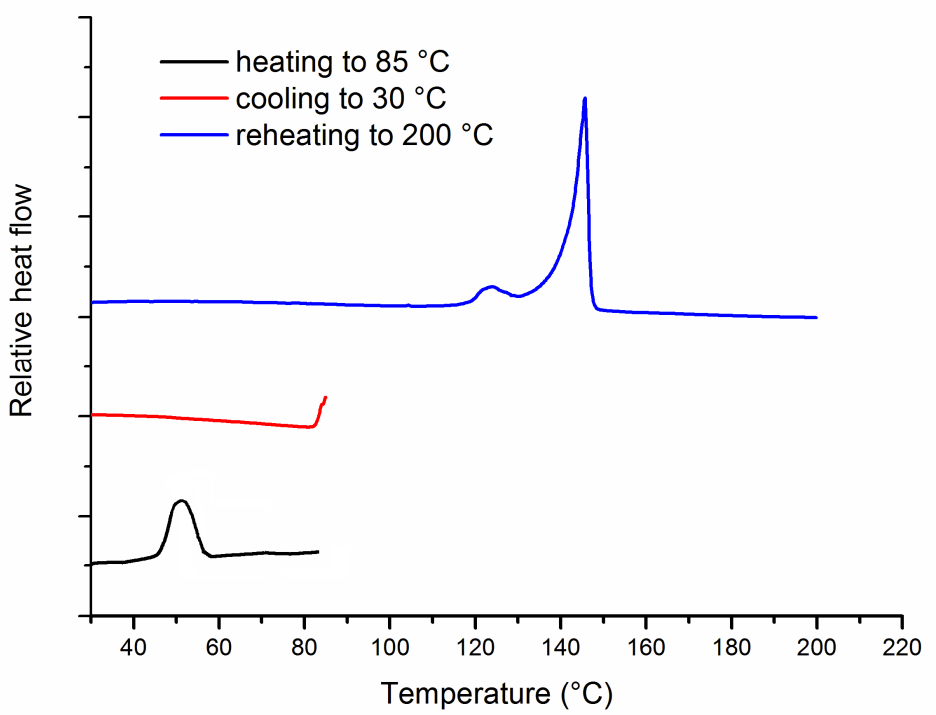


Fig. S10 A DSC heat-cool-heat cycle of the PA-4HBA (1:1) co-crystal hydrate showing the dehydration in the first heating and a single endotherm in the reheating for melting of the dehydrated solid. A small endotherm just before the melting endotherm in the reheating could be due to an unknown phase transformation of the dehydrated sample.