S1 Rietveld refinement details

The predicted structure was transformed to its reduced cell representation by using the program Platon. The refinement was performed by using the EXPGUI interface to the program GSAS. All covalent bond lengths and bond angles were restrained to their values in the predicted structure, i.e., to DFT optimised values. Planar group restraints were applied for both the theobromine and acetic acid molecules (except for the methyl H atoms). All atoms that belong to the same molecule were constrained to have the same isotropic displacement parameter. The background was modelled by a 15 term shifted Chebyshev polynomial of the first kind, while peak profiles were described by pseudo-Voigt functions with asymmetry correction. A March-Dollase preferred orientation correction was applied along the [-1 1 3] axis with a refined ratio of 0.92. (This axis is perpendicular to the mean plane of the molecules.) Complete convergence was achieved with a mean shift/s.u. ratio < 0.01 and a maximum shift/s.u. value of 0.02. The refined model and the experimental data show a good agreement (Figure S1, $R_p = 0.0366$, $R_{wp} = 0.0458$, $R_{exp} = 0.0503$, $R_I = 0.0734$, $\chi^2 = 0.898$).

**Figure S1.** Final observed (crosses), calculated (red) and difference (blue) profiles for the Rietveld refinement.
S2. Computational Methods

**Molecular models.** Molecular models of theobromine, caffeine and AcOH were taken from density functional theory (DFT) isolated molecule geometry optimisations using the code Dmol3 as implemented in the Accelrys package Materials Studio,\(^8\) using the PW91 functional\(^9\) and the double numerical polarised (DNP) basis set.\(^10\)

**Model potentials.** Lattice energies were evaluated using an empirically derived atom-atom potential (W99)\(^{11-13}\) for the description of repulsion-dispersion contributions and atomic point charges or multipoles for the electrostatics. In the simplest electrostatic model, atom centred charges were derived to reproduce the molecular electrostatic potential (ESP charges)\(^{14,15}\) using the fitting procedure implemented in Dmol3. Atomic multipoles were derived from a distributed multipole analysis\(^16\) of a B3LYP/6-31G(d,p) electron density using the CADPAC code\(^17\) up to \(l=4\) (charge, dipole, quadrupole, octupole and hexadecapole) on each atom. The centre of interaction for all hydrogen atoms was shifted 0.1 Å along the X-H bond (X= C, N, O) towards the heavy atom; X-H distances were shortened by 0.1 Å after DFT optimization. All charge-charge, charge-dipole and dipole-dipole contributions to the lattice energy were evaluated using Ewald summation, while higher order terms (up to \(R^{-5}\)) and the repulsion-dispersion interactions were summed to a 15 Å cutoff.

**Crystal structure prediction.** For the prediction of crystal structure and stoichiometry of the theobromine:AcOH, we performed crystal structure prediction calculations in both the 1:1 (Z'='2) and 1:2 (Z'='3) theobromine:AcOH stoichiometries. Crystal structures were generated in the two most common space groups for AcOH solvates (\(P2_1/c\), \(PT\)) -we have reported elsewhere that 85.5 % of the known AcOH solvates of achiral molecules crystallise in one or other of these two space groups.\(^18\) Crystal structures were generated using the simulated annealing algorithm of Karfunkel and Gdanitz,\(^19-21\) as implemented in the Accelrys Polymorph Predictor (PP) module of the Cerius\(^2\) software suite\(^22\) with the adjustable parameters taken from our previous work.\(^23\) The computer generated crystal structures were lattice energy minimized (using the atomic point charge model potential described above) and clustered, to remove duplicates. Independent searches in each space group were performed until no new structures were generated (up to five times for \(Z'='2\) and fifteen times for \(Z'='3\)). The COMPACK algorithm was used for the final clustering of structures.\(^24\) Finally, the computer generated crystal structures were energy minimised using the atomic multipole model potential with the program DMAREL.\(^25\)