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Towards Prediction of Stoichiometry in Crystalline Multicomponent Complexes

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S1. Cocrystals of urea and carboxylic acids reported in the CSD

Table S1 Summary of the different urea: carboxylic acid cocrystals in the CSD. Urea:crown ether carboxylic acids are not included.

Type	Acid	Sketch	CSD refcode Space Group	Stoichiometry Urea:Acid	Motif*	Ref
Monocarboxylic acids	Salicylic		SLCADC10 $C2/c$	1:1	A-U-U-A	[1]
	5-nitro salicylic		NUNXUJ $P\bar{1}$	1:2	A-U-A	[2]
	3,5-dinitro salicylic		NUHYAQ $P2_1/c$	1:1	U-A	[2]
	4-amino benzoic		NUHYEU <i>Pnab</i>	1:2	(U-U)(A-A)	[2]
Dicarboxylic acids	Oxalic		UROXAM $C2/c$	1:1	U-A	[3]
			UROXAL $P2_1/c$	2:1	U-A-U	[4]
	Malonic		URMALN $P2_1/c$	1:1	U-A-U	[5]
	Maleic		CEKRUF Cc	1:1	U-A	[6]
			CEKSAM $P2_1/c$	1:2	A-U-A	[6]
	Fumaric		TIPWIY $P2_1/c$	2:1	U-A-U	[7]
	DL-Tartaric		NEHPIZ $P2_1$	1:1	No coordinates	[8]
	D-Tartaric		NEZDAX $P2_12_12_1$	1:1	No coordinates	[9]
	Succinic		VEJXAJ $P2_1/c$	2:1	U-A-U	[10] [6]
	Glutaric		TONGOS $P2_1/c$	1:1	U-A	[11]
	Itanoi		PANVAB $P2_1/c$	1:1	U-A	[12]
	o-Phthalic		NUHYIY01 $P\bar{1}$	1:1	U-A	[6]
	Pyrazine-2,3-dicarboxylic		NUHYOE $P2_1/c$	1:1	U-A	[2]
	Pyridine-2,6-dicarboxylic		NUHYUK $C2/c$	2:1	A-U-U-A	[2]

*A=acid, U=urea

S2. Experimental Methods

Materials preparation. A single crystal of urea with AcOH was obtained by slow evaporation of a solution of urea in AcOH at ambient temperature.

Single crystal XRD. Single crystals were cooled to 180 K immediately after removal from the solution and single crystal X-ray diffraction data was collected at 180 K on a Nonius Kappa CCD diffractometer using MoKa radiation ($\lambda = 0.71073 \text{ \AA}$) equipped with an Oxford Cryosystem cryostream. Data reduction and cell refinement were performed with the programs *DENZO* (University of Texas Southwestern Medical Center at Dallas, HKL Denzo and Scalepack, USA, 1997) and *COLLECT* (Nonius, B. V. Delft, The Netherlands, 1998). Multiscan absorption corrections were applied with the program *SORTAV*.^[13] Structures were solved by direct methods using *SHELXS-97* (University of Göttingen, Germany, 1997) and refined on F^2 against all data using *SHELXL-97* (University of Göttingen, Germany, 1997). All non-hydrogen atoms were refined with anisotropic displacement parameters. The OH hydrogen atoms were located in difference Fourier maps and refined isotropically. All other hydrogen atoms were placed geometrically and were allowed to ride during subsequent refinement. Experimental details of the structure determinations are given in table 2.

Table s2. Crystal data and structure refinement for the urea:AcOH1:2 solvate.

Empirical formula	C5 H12 N2 O5
Formula weight	180.17
Temperature	180(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 7.6549(3) Å b = 10.1351(4) Å c = 11.5219(5) Å
Volume	881.47(6) Å ³
Z	4
Density (calculated)	1.358 Mg/m ³
Absorption coefficient	0.121 mm ⁻¹
F(000)	384
Crystal size	0.25 x 0.23 x 0.23 mm ³
Theta range for data collection	4.02 to 32.07°
Index ranges	-11 ≤ h ≤ 11, -13 ≤ k ≤ 15, -15 ≤ l ≤ 17
Reflections collected	6288
Independent reflections	3013 [R(int) = 0.0277]
Completeness to theta = 32.07°	97.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.981 and 0.909
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3013 / 2 / 117
Goodness-of-fit on F ²	1.060
Final R indices [I > 2σ(I)]	R1 = 0.0427, wR2 = 0.1119
R indices (all data)	R1 = 0.0546, wR2 = 0.1222
Largest diff. peak and hole	0.256 and -0.226 e.Å ⁻³

Microscopy. Video recordings and photographs of the solvent release from the crystals were recorded at ambient temperature with a JVC digital video camera coupled to a Leica DM1000 microscope.

S3. Computational Methods

Molecular models. Molecular models of urea 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*,^[14] using the PW91 functional^[15] and the double numerical polarised (DNP) basis set.^[16]

Model potentials. Lattice energies were evaluated using an empirically derived atom-atom potential (W99)^[17-19] 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)^[20, 21] using the fitting procedure implemented in *Dmol3*. Atomic multipoles were derived from a distributed multipole analysis^[22] of a B3P91/6-31G(d,p) electron density using the *CADPAC* code^[23] 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. In the prediction of crystal structure and stoichiometry of the urea:AcOH crystalline complex we have performed crystal structure prediction calculations in both the 1:1 ($Z''=2$) and 1:2 ($Z''=3$) urea:AcOH stoichiometries. Crystal structures were generated in the five most common space groups ($P2_1/c$, $P\bar{1}$, $P2_12_12_1$, $P2_1$ and $C2/c$) for the 1:1 urea:AcOH stoichiometry. In the 1:2 case however, because of the large computational requirements in sampling the phase space of crystal structures with three independent molecules in the asymmetric unit, the searches were limited to two space groups: $P2_1/c$ and $P\bar{1}$ (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^[24]). Additionally, a 1:3 stoichiometry was also sampled for comparison purposes in the space group $P\bar{1}$. In order to reduce the complexity of the $Z''=4$, a synthon approach using a rigid urea-AcOH dimer (previously predicted in all the structures of the 1:1 and 1:2 stoichiometries) was used with an extra two independent AcOH molecules. Crystal structures were generated using the simulated annealing algorithm of Karfunkel and

Gdanitz,^[25-27] as implemented in the Accelrys *Polymorph Predictor* (PP) module of the Cerius² software suite^[28] with the adjustable parameters taken from our previous work.^[29] 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 $Z''=3$). For the 1:3 stoichiometry set, five independent searches were carried out and, although the sampling was far from being complete, at least the predicted global minimum was generated twice. The *COMPACT* algorithm was used for the final clustering of structures.^[30] Finally, the computer generated crystal structures were energy minimized using the atomic multipole model potential with the program *DMAREL*.^[31]

Lattice Vibrations. The second derivative matrix at the minimum was used to calculate the corresponding T = 0 K elastic constants^[32] and the $\mathbf{k} = 0$ harmonic phonon frequencies.^[33] These rigid molecule frequencies were used to estimate the intermolecular contribution to the vibrational free energy, F_{vib} , of the crystal using a hybrid Debye–Einstein model of phonon dispersion, as described in reference^[34].

$$F_{vib} = \frac{1}{2} \sum_{i>3} h\omega_i + \frac{9}{8} h\omega_D + kT \sum_{i>3} \ln[1 - \exp(-h\omega_i / kT)] + 3kT \ln[1 - \exp(-h\omega_D / kT)] - kTD \left(\frac{h\omega_D}{kT} \right)$$

The first two terms on the right-hand side of eqn. (1) give the vibrational zero point energy and the final three terms describe the thermal contributions to the free energy. ω_i are the optic mode frequencies, which are assumed to have no dispersion across the Brillouin zone, and ω_D (the Debye frequency) is the average acoustic mode frequency at the zone boundary, which is estimated by extrapolating the acoustic modes along several high symmetry directions using their gradients at $\mathbf{k} = 0$ calculated from the elastic constant tensor. $D(x)$ is the Debye function:

$$D(x) = \frac{3}{x^3} \int_0^x \frac{t^3 dt}{\exp(t) - 1}$$

Morphology predictions. Growth morphology calculations were performed using the attachment energy method^[35, 36] implemented in the *Morphology Predictor* module of the Cerius² software suite.^[28] The W99 plus the atomic point charge model was used for the evaluation of attachment energies. The percentage of surface area of the crystal morphology that would allow solvent release was calculated by adding up the percentage of surface area of the crystal faces in the predicted morphology that cut the AcOH solvent columns.

Table S3 Contribution of the different crystal faces (in %) to the total surface area of the predicted morphology of urea:AcOH.

Face	% total surface area	Easy solvent release?
(0 1 1)	49.10	Yes
(1 1 -1)	19.76	Yes
(1 0 0)	18.09	Yes
(1 0 -2)	9.86	No
(0 0 2)	2.02	No
(1 1 0)	1.17	Yes
Total % of surface area for solvent release	88.12	

S4 On the different models used for the prediction of stoichiometry

The graph presented in figure 7 in the main paper is here repeated using three different sets of crystal structures as reference (figure S1):

- The minimised experimental crystal structures for urea and AcOH, and the global minimum of the 1:2 solvates (as in figure 7, orange line in the graph),
- All the experimentally observed crystal structures (green line in the graph)
- All structures at the global minimum obtained after a CSP search for urea, AcOH and the 1:2 urea:AcOH solvate (blue line in the graph).

All models are consistent and would have suggested the 1:2 stoichiometry as most favoured. However, the energy differences between the situations are really small (a few kJ/mol). This suggests that stoichiometry prediction will be very challenging for lattice energy based methods and that more accurate models for the evaluation of lattice energies will probably be needed for more complex systems.

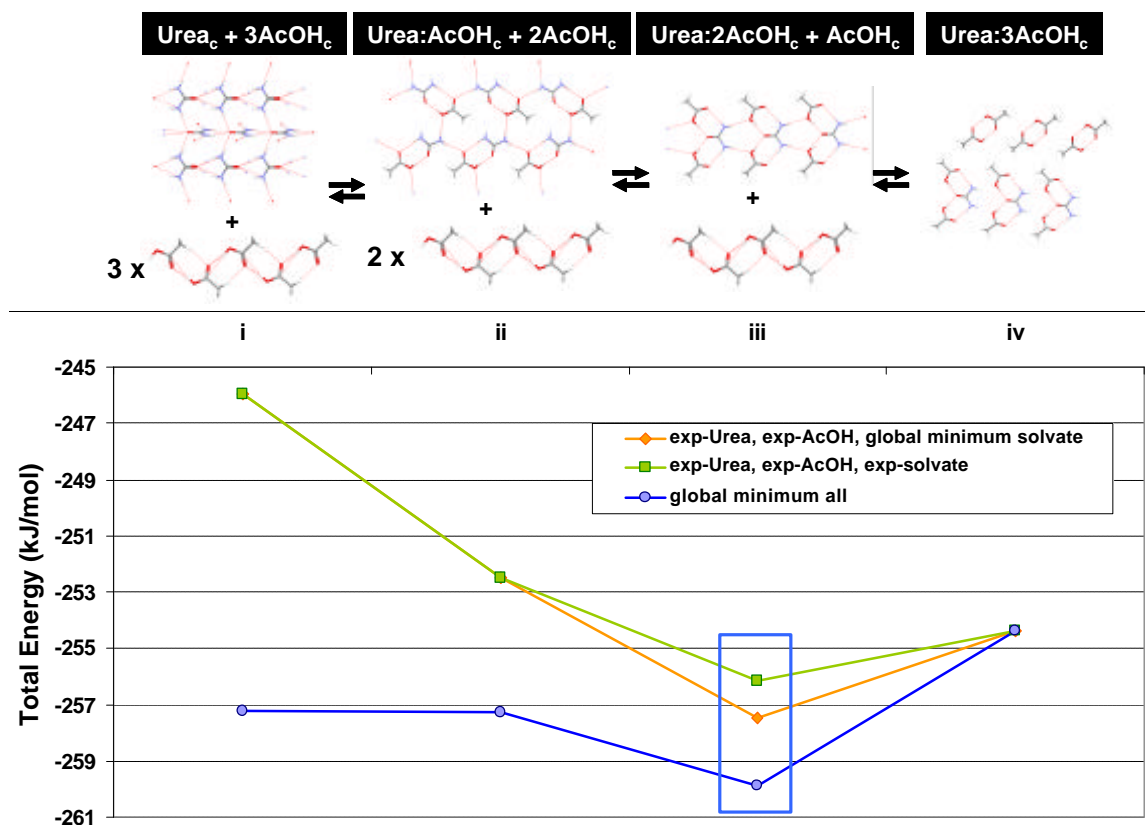


Figure S1. Possible combinations of crystal systems of urea and acetic acid in a 1:3 stoichiometry at 0 K and lattice energies when different models were used as reference. All models agree on the 1:2 stoichiometry as being the most favoured.

S5. References

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