Towards Prediction of Stoichiometry in Crystalline Multicomponent Complexes

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Abstract: We report on the crystal structure of urea (U) with acetic acid (A), its physical stability and its predictability using computational methods. The crystal structure of urea:acetic acid (U:A) shows hydrogen-bond ribbons and a 1:2 stoichiometry. Crystal structure prediction calculations are presented for two sets of U:A stoichiometries: 1:1 and 1:2. A 1:3 stoichiometry is also partially explored by means of a synthon approach. The calculated lattice energies, along with hydrogen-bond patterns, of crystal structures predicted with the three stoichiometries are presented and analysed to provide a rationalisation for the stoichiometry observed. Exploring stoichiometric diversity using computational methods provides a tool for the rationalisation of stoichiometry preferences in crystalline multicomponent systems and a first step towards their prediction.

Keywords: acetic acid · cocrystals · crystal structure prediction · solvates · stoichiometry · urea

Introduction

The "expected stoichiometries" in multicomponent crystals (cocrystals, hydrates and solvates)[1] refer to the stoichiometric ratios observed as a result of reliable donor–acceptor interactions between components.[1] However, the weaker these interactions, the less predictable will be the formation of multicomponent complexes, and the stoichiometric ratio of components in the resulting crystal. The formation of solvates, and their stoichiometries, appears particularly uncertain.[2] Although binary cocrystals are often designed[3] and generally obtained under stoichiometric conditions, solvates often appear by chance as undesirable results of crystallisations. Stoichiometric ratios are also known to vary in some systems, depending on the experimental conditions of crystallisation (e.g. caffeine crystallises with acetic acid in both 1:1 and 1:2 stoichiometries).[4] Little has been discussed in the literature about stoichiometric preferences in multicomponent complexes, owing, in part, to the lack of representative data. Although the number of crystal structures of cocrystals and solvates is constantly growing in the Cambridge Structural Database (CSD),[5] there is generally little stoichiometric diversity amongst them. The use of computational methods, however, may provide valuable insight since crystal structure prediction (CSP) calculations can be used to generate and assess hypothetical crystal structures with stoichiometries different to those obtained experimentally. In this way, the crystal structures of observed and unobserved stoichiometries may be compared both structurally and energetically to provide answers as to why certain stoichiometries are preferred over others.

The computational cost involved in performing CSP calculations for systems with more than one independent molecule can be very high[6–9] (here, following van Eijck and Kroon,[6] we denote the number of independent molecules in the unit cell as Z''). To keep the computational cost low, and to afford CSP calculations for multiple systems with different ratios of components, we have chosen to study a system of two small, rigid molecules: urea (U) and acetic acid (A), Figure 1. Surprisingly, urea clathrates aside, only one crystal structure of urea with a small common solvent molecule was found in the CSD: urea with hydrogen peroxide (1:1, CSD refcode UREXPO).[10,11] Except for this struc-

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📰 Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200800668.
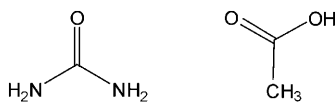
Figure 1. Chemical diagrams of urea and acetic acid.

ture, reported over 60 years ago, we are only aware of one other report of a urea solvate, in which urea was reported to crystallise with dioxane.[12] For this study, we chose acetic acid as solvent because of its molecular similarity with urea (both are small molecules of comparable shape, with complementary functional groups) and to follow up on earlier studies on the predictability of acetic acid solvates.[13] Other urea cocrystals with larger carboxylic acids are known,[14] and provide a valuable source of information in rationalising an initial choice of stoichiometries to be explored computationally. This work was aimed at i) attempting the experimental growth of an acetic acid solvate of urea, ii) computationally exploring the phase space of acetic acid solvates of urea with different stoichiometries and iii) rationalising the experimental observations: stoichiometry and crystal structure.

Results and Discussion

Stoichiometry of known urea-carboxylic acids cocrystals: The CSD was searched for cocrystals of urea (U) with carboxylic acids (A) to assess the stoichiometric tendencies in this family of crystal structures. (Urea inclusion compounds and urea complexes with carboxylic acid crown ethers were excluded, as the dominant interactions in these crystal structures are of a different nature to those expected in a urea:AcOH solvate.) A total of 18 entries were found: 6 entries for mono- and 12 for di-carboxylic acids (Table S1 in the Supporting Information). Amongst the urea:monocarboxylic acid cocrystals, stoichiometries of 1:1 and 1:2 were observed in similar numbers. For dicarboxylic acids, three stoichiometries are reported: 1:1, 1:2 and 2:1, the latter only occurring if the dicarboxylic acid crystallises on an inversion centre. It is most likely, therefore, that the crystal structure that urea forms with acetic acid would show a stoichiometric ratio of 1:1 or 1:2. However it is uncertain[14] which of the two possibilities would occur on the basis of the information accumulated in the CSD alone.

Structure and stability of an acetic acid solvate of urea: A single crystal of urea:acetic acid was obtained from a solution of urea in acetic acid under slow evaporation conditions. The structure was solved using single crystal XRD methods (Table 1). Urea crystallises with acetic acid in the monoclinic space group $P2_1/n$ in a 1:2 U:A stoichiometric ratio. The primary hydrogen-bond motif in the structure consists of a three-component motif of the type: U−A−A (Figure 2a). These trimers assemble into hydrogen-bonded ribbons (Figure 2b) that stack in the crystal structure

Table 1. Crystallographic data for the urea:acetic acid 1:2 solvate.

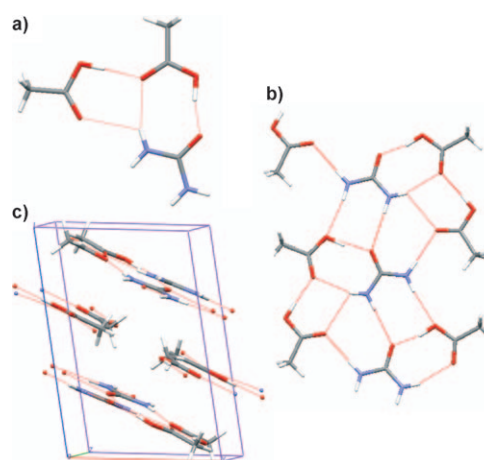|	1:2 urea:acetic acid
empirical formula	$C_5H_{12}N_2O_5$
formula weight	180.17
space group	$P2_1/n$
a [Å]	7.6549(3)
b [Å]	10.1351(4)
c [Å]	11.5219(5)
β [°]	99.570(2)
V [Å^3]	881.47(6)
T [K]	180(2)
Z	4
ρ_c [mg m^{-3}]	1.358
Θ range [°]	4.02–32.07
data/restraints/parameters	3013/2/117
final R indices	$R1 = 0.0427, wR2 = 0.1119$
R indices all data	$R1 = 0.0546, wR2 = 0.1222$

Figure 2. a) U−A−A motif, b) hydrogen-bond ribbon and c) unit cell representation in the urea:acetic acid 1:2 solvate.
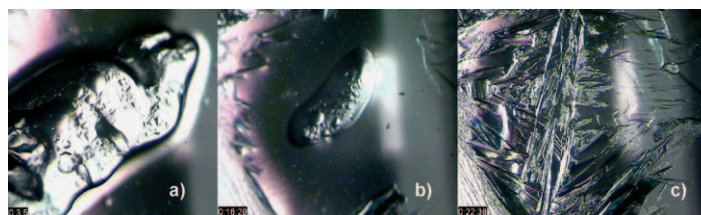

Figure 3. Micrographs of a urea:acetic acid single crystal a) immediately after removed from solution, b) after 16 minutes in air and c) after release and evaporation of all the solvent from the lattice.

(Figure 2c). The primary trimer motif observed here is frequently found in 1:2 acetic acid solvates.[4]

The crystals were found to be unstable when removed from the mother liquor: we were able to monitor the escape of lattice solvent from the crystals using optical microscopy (Figure 3a). As urea is highly soluble in acetic acid, the released solvent redissolved the resulting material (Figure 3b), which, after evaporation of the acetic acid, solidified as urea (Figure 3c). The acetic acid molecules are aligned within the
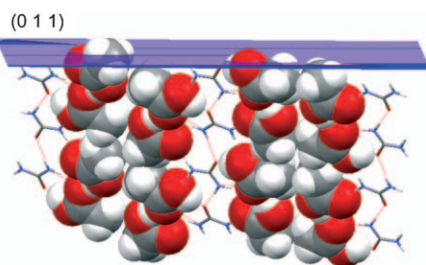
Figure 4. "Solvent columns" formed by the acetic acid molecules (space-fill represenation) and (0 1 1) face in the urea:acetic acid crystal structure.

crystal forming a "solvent column" (Figure 4). In those cases in which these solvent columns are cut by the dominant faces of the crystal morphology (Figure 4), solvent release is likely to be rapid. As a quick test, growth morphologies were calculated by using an attachment energy model. Around 88% of the surface area of the calculated morphology corresponded with crystal faces that would allow a relatively facile loss of solvent molecules. When the crystals are in solution, the interaction of the solvent with the crystal faces stabilises the crystal morphology (the crystals remain

intact in solution after several months). There is also an equilibrium between crystal, liquid and vapour such that if the crystals are isolated in a sealed container, as soon as the crystal-vapour equilibrium is established, solvent release also stops. However, if the crystals are left in an open atmosphere the equilibrium is shifted towards the liquid and vapour and the solvent easily leaves the lattice.

Crystal Structure Prediction Calculations

Prediction for 1:1 urea:acetic acid ($Z'' = 2$): From a 1:1 computational search carried out for crystal structures of urea:acetic acid in five of the most common space groups, 153 distinct crystal structures were found within 10 kJmol^{-1} of the global minimum. Of these, 101 belong to $P2_1/c$, 26 to $C2/c$, 15 to $P\bar{1}$, 9 to $P2_12_12_1$, and 2 to the $P2_1$ space group. The lattice energies and packing coefficients of these structures classified by hydrogen bonding are shown in Figure 5a. Almost all of the computer-generated crystal structures contain either heteromolecular (U–A, 83 structures) or homomolecular (U–U and A–A, 54 structures) motifs. Although the predicted crystal structures show favourable lattice energies, it is noteworthy that one of the urea anti-NH hydrogen
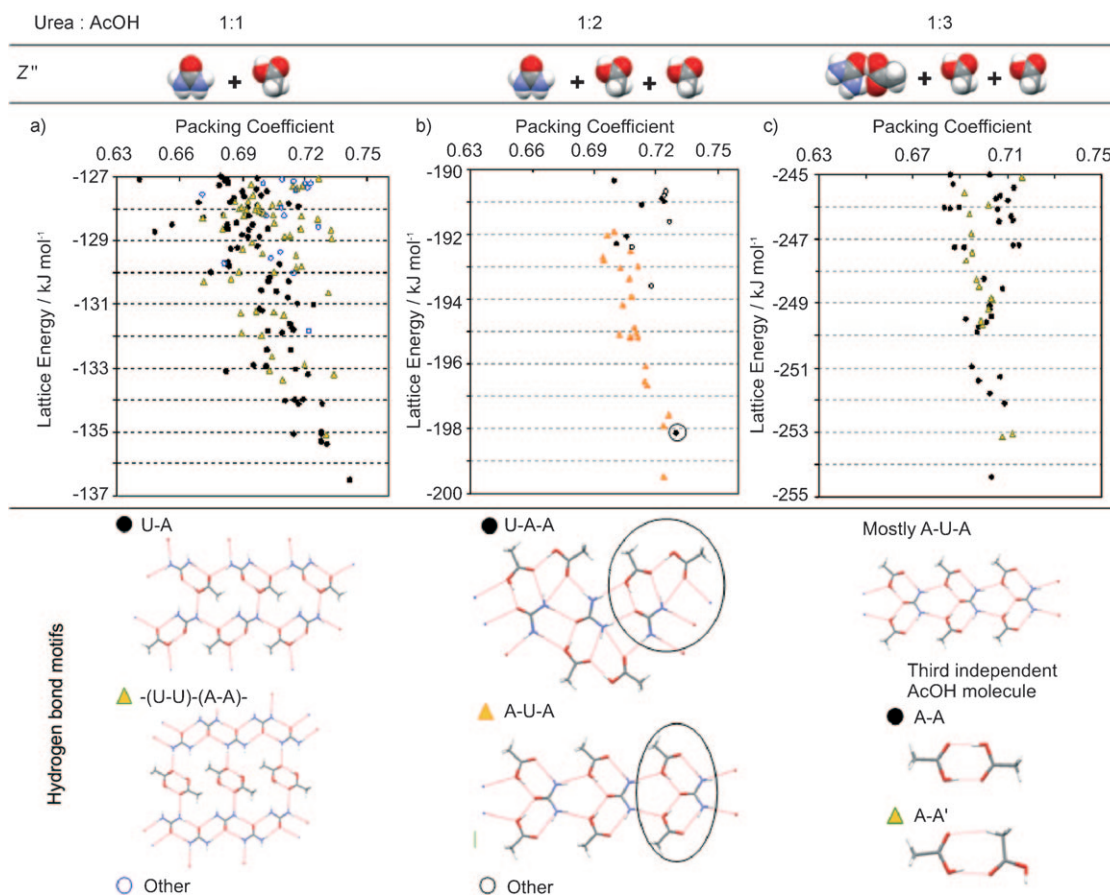

Figure 5. Lattice energy versus packing coefficients of the generated urea:acetic acid crystal structures in stoichiometries 1:1, 1:2 and 1:3. The structures are classified according to their hydrogen bonding.

atoms is not efficiently utilised for hydrogen bonding in any of the predicted 1:1 crystal structures (Figure 5a).

Prediction for 1:2 urea:acetic acid ($Z'' = 3$): 1:2 crystal structures (with $Z'' = 3$ independent molecules in the asymmetric unit) were generated in two space groups, resulting in 47 distinct crystal structures within $10 \, kJ \, mol^{-1}$ of the global minimum: 25 in $P2_1/c$ and 22 in $P\bar{1}$. Figure 5b shows the lattice energies vs packing coefficients of these low energy structures, classified by hydrogen-bond motifs. Two main types of primary motifs were found: U−A−A (8 structures) and A−U−A (30 structures). All hydrogen-bond donors and acceptors are satisfied in all of these structures. The experimentally observed structure was generated as the second most stable 1:2 structure in the search (circled structure located $1.3 \, kJ \, mol^{-1}$ above the global minimum), and the lowest energy U−A−A structure by almost $6 \, kJ \, mol^{-1}$.

Prediction for 1:3 urea:acetic acid ($Z'' = 4$): Crystal structures were also generated for a 1:3 stoichiometry. Because of the complexity of CSP calculations with four independent molecules ($Z'' = 4$), a partial synthon approach was used: we treated one U−A pair as a rigid dimer unit, in the hydrogen-bonded geometry commonly observed amongst the stable 1:1 and 1:2 predicted structures. This synthon approach reduces the computational demand of the calculations by transforming a $Z'' = 4$ problem to a $Z'' = 3$ problem, in which the independent units are a U−A dimer and two A molecules. Furthermore, only one of the most commonly observed space groups was searched ($P\bar{1}$), with five independent simulated annealing searches.[21] Therefore, the 1:3 set of structures will be incomplete, but we hoped that this restricted search would give a preliminary picture of the possible crystal structures with this stoichiometry.

Over 50 crystal structures were generated in $P\bar{1}$. The structures are classified by hydrogen-bond motifs in Figure 5c. In most of these structures, the -(A−U−A)- motif is observed (as in the 1:2 set). However, the third acetic acid molecule in the asymmetric unit can either: i) hydrogen bond to itself, forming a dimer motif or ii) hydrogen bond to another acetic acid molecule of the A−U−A motif through one strong (OH⋯O) and one weak (O⋯HC) interaction. In summary, in the 1:3 U:A crystal structures two molecules of acetic acid are tightly bound to urea forming extensive motifs, whereas the third independent molecule forms isolated dimers in the structure or hydrogen bonds to the sides of the main-ribbon motif through weaker interactions.
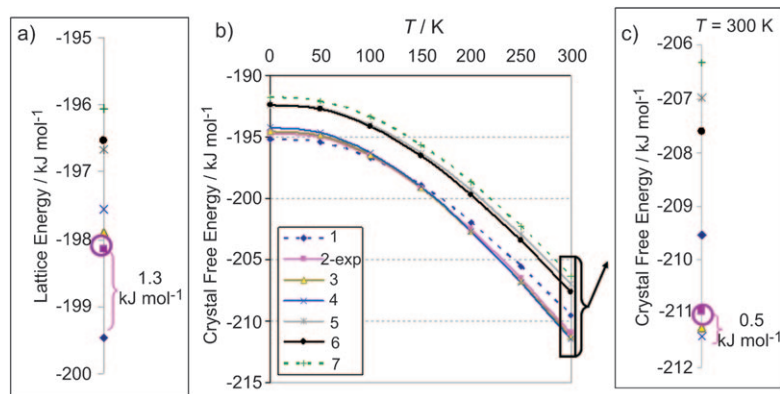

Figure 6. Crystal structure stability ranking based on a) lattice energy, b) plot of the temperature dependence of the crystal free energy and c) stability ranking based on crystal free energy at 300 K; for the seven most stable generated 1:2 urea:acetic acid crystal structures. The pink square corresponds to the experimental crystal structure.

Lattice dynamics calculations: Lattice dynamics calculations were carried out to evaluate the energetic contributions from lattice vibrations to the crystal free energy. These calculations were only performed for the 1:2 set of crystal structures, the experimentally observed stoichiometry. The structure ranking based on lattice energies only is plotted in Figure 6a. In Figure 6b, the temperature dependence of the crystal free energy is shown[2] and the final ranking of structures based on crystal free energy at 300 K is plotted in Figure 6c. The lattice-vibration contribution was found to be greatest for the structures initially ranked as second (the experimentally observed structure), third and fourth most stable, all of which decreased in free energy more quickly with temperature and became the most stable above 200 K. At 300 K, the experimental structure was ranked number 3, but only $0.5 \, kJ \, mol^{-1}$ from the global minimum (Figure 6c).

Predictability of the crystal structure of urea:acetic acid: Although CSP calculations become computationally demanding for structures with $Z'' > 1$, they can still be affordable by limiting the sampling phase space to only the most relevant space groups.[15] Despite the computational challenge, the experimental structure was successfully generated and predicted as the second most stable of all the possibilities in those two space groups. Furthermore, the lattice vibration calculations showed how the contribution of phonon vibrations to the crystal free energy may be important. The experimental structure became much closer to the global minimum at 300 K ($0.5 \, kJ \, mol^{-1}$, within the range of modelling inaccuracies), and there was a significant re-ranking of the remaining structures.

Rationalisation of stoichiometry: Various sets of CSP calculations have been presented to propose a rationalisation of the observed 1:2 stoichiometry in the urea:acetic acid sol-

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[2] The ranking of structures based on crystal free energy at $T = 0$ K (Figure 6b) differs from the ranking of structures based on lattice energies because of the contribution of vibrational zero point energy.

vate. The first observation we can appreciate from the CSP results presented above is that, of all three stoichiometries attempted, the 1:2 crystal structures showed the best hydrogen-bonding networks: all hydrogen-bond donors and acceptors of urea and acetic acid are satisfied and form strong and reliable hydrogen-bonded arrangements. In contrast, in the 1:1 structures, not all donors of the urea molecule are satisfied, and in the 1:3 structures, the third acetic acid does not hydrogen bond to the urea molecule and it is only filling space as part of an independent dimer. As acetic acid is free to form such dimers in solution, it is unlikely that incorporation of an acetic acid dimer into the urea:acetic acid solvate would provide sufficient enthalpic stabilisation to balance the loss of entropy associated with removing the molecules from solution.

As well as a rationalisation based on hydrogen bonding, we expected that the calculated lattice energies would reflect a thermodynamic reason for i) solvate formation and ii) the observation of a particular stoichiometry. The lattice energies of the 1:1, 1:2 and 1:3 sets of crystal structures (the lowest of which are given in Table 2) cannot be compared directly, as the composition of the crystals is different in the different crystal stoichiometries. However, we can compare all possible combinations of phases that may result from mixing 1 mol of urea and 3 mols of acetic acid at $T = 0$ K. By using the same model potential, the lattice energies of crystalline urea and the most stable polymorph of acetic acid were calculated to be $-71.97 \text{ kJ mol}^{-1}$ and $-58.09 \text{ kJ mol}^{-1}$ respectively. Four cases are possible for a 1:3 combination of urea with acetic acid (Figure 7): a) 1 mol of crystalline urea and 3 mols of crystalline acetic acid, b) 1 mol of crystalline 1:1 urea:acetic acid and 2 mols of crystalline acetic acid, c) 1 mol of crystalline 1:2 urea:acetic acid and 1 mol of crystalline acetic acid or d) 1 mol of crystalline 1:3 urea:acetic acid. The total configurational energy of the four different situations can be calculated completely ab initio, from the calculated lattice energies of the predicted crystal structures. Although the 1:3 urea:acetic acid crystal structure considered may not correspond to the global minimum possibility with this stoichiometry (as we only performed a limited sampling of one space group), we would expect a more stable structure, in the same or a different space group, to be in the range of polymorphic energy differences (within a few kJ mol^{-1}).

Table 2. Information on the four most stable predicted urea:acetic acid crystal structures for each of the 1:1, 1:2 and 1:3 stoichiometries.

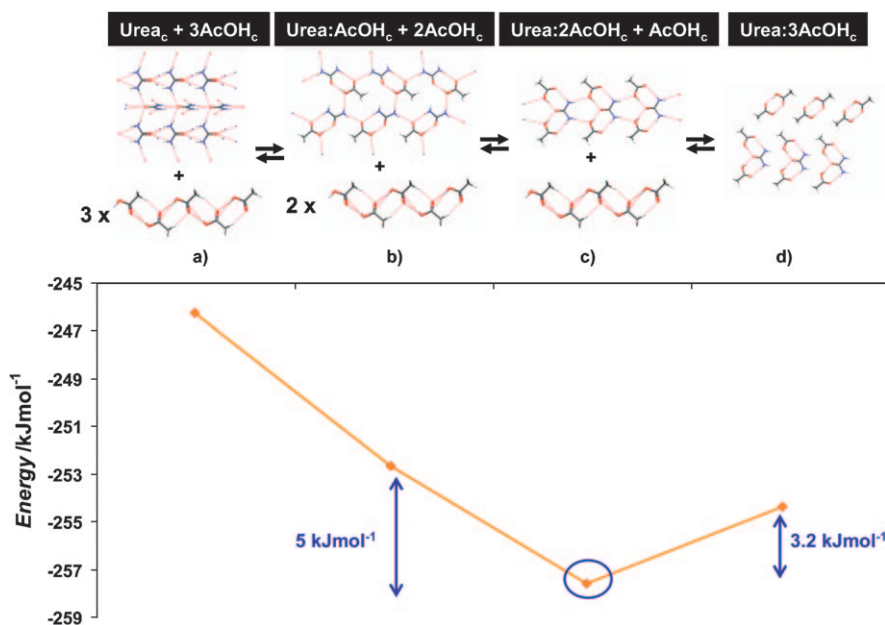|	DMA Ranking [0 K]	Space Group	Packing Coefficient	Lattice Energy [kJ mol^{-1}]
1:1	1	$P2_1/c$	0.742	−136.48
	2	$C2/c$	0.731	−135.39
	3	$P\bar{1}$	0.728	−135.34
	4	$P\bar{1}$	0.728	−135.29
1:2	1	$P\bar{1}$	0.724	−199.46
	2	$P2_1/c$	0.730	−198.15
	3	$P2_1/c$	0.723	−197.89
	4	$P2_1/c$	0.726	−197.56
1:3	1	$P\bar{1}$	0.704	−254.37
	2	$P\bar{1}$	0.708	−253.14
	3	$P\bar{1}$	0.712	−253.04
	4	$P\bar{1}$	0.709	−252.13

Figure 7. Possible combinations of crystal systems of urea and acetic acid in a 1:3 stoichiometry at $T = 0$ K.

This approach leads to combination c) (Figure 7) as the most stable.[3] Therefore, the calculations do suggest the 1:2 stoichiometry as the lowest energy possibility at 0 K. However, the results do highlight the very small energy differences involved in discriminating amongst the various possibilities with the differences between combinations of b), c) and d) (Figure 7) being only 5 and 3 kJ mol^{-1}. We used the lattice energy of the structure at the global minimum of the Urea: 2 AcOH search, since that would have been the choice for a true blind prediction. Had the lattice energy of the experimentally observed Urea:2 AcOH structure been used instead, the energy differences between the combinations b),

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[3] Had the global lattice energy minimum of similar CSP searches been used for urea and AcOH instead of the minimised lattice energies of the observed crystal structures, we would have arrived at the same conclusions (see Supporting Information).

c) and d) would have been even smaller (≈ 4 and $2\,\mathrm{kJ\,mol^{-1}}$).

The agreement here of this simplified $T=0$ K model with the experimentally observed outcome of crystallisation is encouraging, although the results also demonstrate that stoichiometry prediction will be very challenging for lattice energy based methods. The hydrogen-bond analysis adds confidence to the lattice energy argument in this case. Such visual assessment of the computer generated structures with different stoichiometries might be equally useful as an initial guide to the most likely outcome of crystallisation as lattice energies, bearing in mind that subjective visual assessment of crystal structures can be unreliable.[16]

Towards the prediction of stoichiometry: The study presented here may prove valuable in future CSP studies of crystal structures with unknown and uncertain stoichiometry—perhaps even as challenges for future CSP blind tests.[17–19] Firstly, we have utilised the information embedded in the CSD for simplifying the problem by analysing the observed urea:monocarboxylic acid stoichiometries and by limiting the searches to the most relevant space groups. Secondly, it may not be necessary to carry out complete searches with all possible stoichiometries, as analysis of some independent searches may provide a first insight into which stoichiometries may allow formation of crystal structures with optimised hydrogen bonding. These two points combined with thermodynamic arguments, built from predictions and evaluations of lattice energies, may provide a way of anticipating stoichiometries in crystal structures ab initio.

Conclusion

The generation of crystal structures with differing stoichiometries, presented here for the urea:acetic acid system, has aimed at sampling stoichiometric diversity by using computational methods. An analysis and comparison of these hypothetical structures with different stoichiometries points to the 1:2 stoichiometry as the most favoured, in agreement with the experimental findings. Furthermore, the observed structure was predicted as one of the most stable of the 1:2 possibilities, an encouraging result given the computational challenge associated with the prediction of structures with three independent molecules in the asymmetric unit. Lattice dynamics calculations on the system highlight the importance of considering vibrational energy effects for a more realistic ranking of structures at temperatures closer to the experimental conditions. This study may constitute the first step for future prediction of stoichiometries in solvates, a complex problem with relevant pharmaceutical applications.

Experimental Section

A single crystal of urea with acetic acid was obtained by slow evaporation of a saturated solution of urea in acetic acid at ambient temperature.

Plate-like 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 MoKα radiation ($\lambda=0.71073$ Å).

Computational methods: Molecular models of urea and acetic acid were taken from density functional theory (PW91/dnp) isolated molecule geometry optimisations using the code DMol3 as implemented in the Accelrys package Materials Studio.[20] Crystal structures were generated using the simulated annealing algorithm of Karfunkel and Gdanitz,[21–23] as implemented in the Accelrys Polymorph Predictor (PP) module of the Cerius^2 software suite[24] with the adjustable parameters taken from our previous work.[25] Three sets of calculations were performed with urea:-acetic acid stoichiometries of i) 1:1 ($Z''=2$), ii) 1:2 ($Z''=3$) and iii) 1:3 ($Z''=3$, using a synthon approach). The five most common space groups ($P2_1/c$, $P\bar{1}$, $P2_12_12_1$, $P2_1$ and $C2/c$) were searched for case i) and the two most popular for case ii) ($P2_1/c$ and $P\bar{1}$)[15] until searches were complete. Our choice of space groups was based on specific space group statistics for AcOH solvates.[15] One space group ($P\bar{1}$) was searched for case iii) (five independent simulated annealing runs) for comparison. Searches were performed by using an empirically derived atom-atom exp-6 potential (W99)[26–28] with an atomic point charge model (ESP charges fitted to the DMol calculated molecular electrostatic potential). Finally, the structures were reminimised using the W99 potential and atomic multipoles (derived from distributed multipole analysis of a B3P91/6-31G(d,p) calculated wavefunction) with the program *DMAREL*;[29] a 15 Å atom–atom cutoff was used for summing exp-6 interactions, Ewald for the poorly converging charge–charge, charge–dipole and dipole–dipole interactions, and a 15 Å cutoff on whole molecules for all other electrostatic interactions. The contributions of lattice vibrations to the crystal free energies at temperatures other than 0 K were calculated for the 1:2 set of crystal structures from harmonic $k=0$ phonons, as described elsewhere.[30–31] Further computational details are also provided as Supporting Information.

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