Prediction and Observation of Isostructurality Induced by Solvent Incorporation in Multicomponent Crystals

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The prediction of crystal structures with more than one molecule in the asymmetric unit ($Z' > 1$) represents a major challenge in the field of crystal structure prediction (CSP).[1] The increasingly complex searchable phase space for crystal structures with multiple crystallographically independent molecules results in a much higher computational cost than for $Z' = 1$. This is the case for even the simplest multicomponent systems. As a result, although the properties of such systems (which include cocrystals, solvates,[2] and salts)[3,4] are of key importance to the pharmaceutical industry, as well as other areas of materials chemistry, their study has been principally experimental—with the exception of only three studies on the prediction of various sugar hydrates[5] and diastereoisomeric salts.[6,7]

Carbamazepine (CBZ), a first generation antiepileptic drug, is a well-studied crystal system known to crystallize in various polymorphic forms.[8] CBZ is also well-known for its promiscuity in forming cocrystals and solvates;[9] CBZ:acetic acid (AcOH) is one of many. On the other hand, its 10,11-dihydro derivative (DHCBZ) has very rarely been investigated, with no studies addressing its cocrystallization/solvation tendencies. In a recent study,[10] we rationalized how the small difference in molecular shape between CBZ and DHCBZ induces the systems to hydrogen bond in completely different manners: dimers are consistently observed in all CBZ polymorphs,[8] whereas chains are preferred in the DHCBZ ones.[11,12] In this context, two main points are addressed in this study: first, on the predictability of the crystal structures of these two pharmaceutical molecules with AcOH, and second, on the influence of the incorporation of AcOH in the crystal lattices on the observed hydrogen bonding and crystal structures of these, to date, very different crystal systems.

We initially generated crystal structures of 1:1 CBZ:AcOH in six of the most common space groups ($C2/c$, $P2_1$, $P2_12_12_1$, $P2_1/c$, $P\bar{1}$, and $R\bar{3}$) using a Monte Carlo simulated annealing sampling of packing space, as implemented in the Polymorph Predictor package in Cerius2.[13] Because of the stochastic nature of the Monte Carlo algorithm, independent searches in each space group were repeated until no new structures were generated, requiring up to 15 independent runs in some space groups. Such calculations required approximately 2 months of computer time (on a single 600 MHz SGI machine). Meanwhile, an assessment of the space group occurrences using the Cambridge Structural Database[14] (CSD) was also undertaken. This assessment showed that more than 85% of the observed multicomponent systems of nonchiral molecules with AcOH crystallize within either $P2_1/c$ or $P\bar{1}$ space groups.[15] This information was then used for the prediction of our second system, DHCBZ:AcOH. Limiting the calculations to these two space groups reduced computational time significantly. Ranking of the crystal structures was on the basis of lattice energy, using the W99 potential and an atomic multipole model for the evaluation of intermolecular

Table 1. Crystal Structure Information for the Experimental and Predicted CBZ:AcOH and DHCBZ:AcOH Crystal Structures. Both Systems Belong to the $P2_1/c$ Space Group

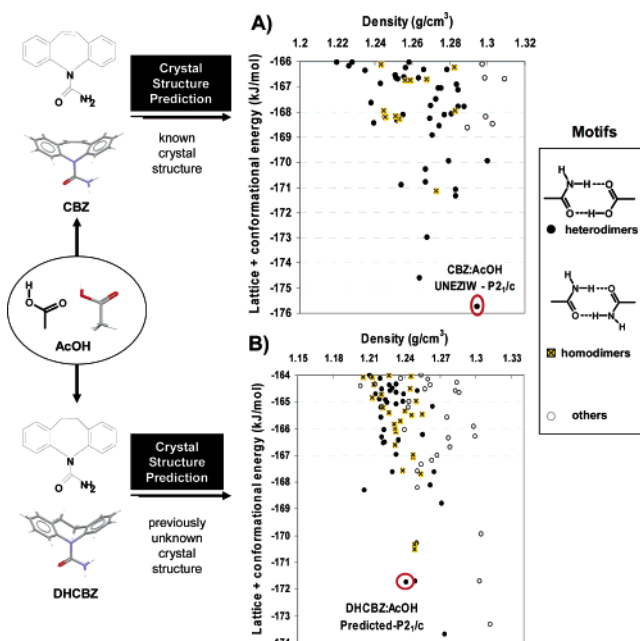|	CBZ:AcOH		DHCBZ:AcOH	
	predicted	exp, $T = 100$ K	predicted	exp, $T = 120$ K
E_{tot} (kJ/mol)	−175.75		−171.71	
ρ (g/cm³)	1.295	1.331	1.241	1.300
a (Å)	19.135	18.499	19.163	18.720
b (Å)	15.808	15.714	16.043	15.425
c (Å)	5.034	5.121	5.215	5.299
β (°)	93.49	96.55	94.78	95.17

Figure 1. Crystal structure prediction results for the two multicomponent systems CBZ:AcOH (A) and DHCBZ:AcOH (B). Structures are classified by hydrogen bond motif: black dots show heterodimers, crossed squares homodimers, and open circles other motifs (e.g., homo- or heterochains).

repulsion—dispersion and electrostatic interactions, respectively. Molecular flexibility due to amide pyramidalization was taken into account during energy minimization in the same manner as reported for our study of the pure CBZ polymorphs.[16]

An experimental crystal structure of CBZ:AcOH (CSD refcode UNEZIW)[9] was known beforehand. For the DHCBZ:AcOH system, no experimental work was undertaken until all calculations were completed and a set of possible structures was established. Subsequently, possible formation of crystals of DHCBZ with AcOH was assessed by simple grinding[17] of the two components. The resulting structure was identified by comparison of the experimental PXRD pattern with the simulated ones for the most stable predicted
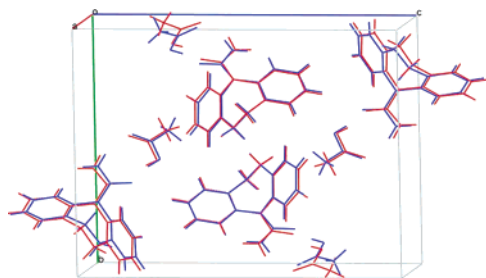
Figure 2. Overlay of the predicted (red) and experimentally determined (blue) DHCBZ:AcOH crystal structures.

crystal structures of the system. As final confirmation, single crystals were grown from a solution of DHCBZ in AcOH, and the structure was confirmed by single-crystal XRD at 120 K (Table 1).

Excellent agreement between prediction and experiment was obtained for the CBZ:AcOH system (Figure 1A). Not only was the experimental structure found by the search method, but it also emerged as the most stable among the thousands of possibilities generated during the sampling of packing space. Upon analysis of the DHCBZ:AcOH prediction results (Figure 1B), it was noticed that the third most stable generated structure for DHCBZ:AcOH was isomorphic with the experimental CBZ:AcOH. Furthermore, the energy gain predicted upon formation of the DHCBZ:AcOH multicomponent crystal ($E_{DHCBZ:AcOH} - E_{DHCBZ} = -52.7$ kJ/mol) was of comparable magnitude to that of the known CBZ:AcOH system ($E_{CBZ:AcOH} - E_{CBZ} = -60.8$ kJ/mol),[18] thereby suggesting a high likelihood of formation. The subsequent grinding experiment revealed the formation of a DHCBZ:AcOH crystal structure which was readily identified as the third most stable predicted structure, the structure isomorphic with CBZ:AcOH (Figure 2). Although the structure observed would not have been first choice in terms of calculated stability, falling within the lowest three was encouraging, and it still remains to be seen whether additional polymorphs, corresponding to the two lower energy structures, may be produced.

From a crystal engineering point of view,[20] analysis of the hydrogen bond motifs in all of the hypothetical structures (Figure 1) may be considered a way of assessing the synthon preferences in this type of multicomponent system. The amide—carboxylic acid heterosynthon is notably most favored within the low-energy structures of both systems (Figure 1); the calculations agree with the synthon rationalization proposed by Fleischman et al.[9] for the design of a series of CBZ cocrystals and solvates.

Remarkably, we noticed that even though small changes in molecular shape appear to dictate the preference between chain and dimer motifs for the CBZ and DHCBZ single-component crystals, incorporation of AcOH resulted not only in the formation of identical heterosynthons but also in isomorphic crystal structures (Table 1 and Figure 3) for the two systems. In this case, the presence of the second component overrides the influence of the change in molecular shape on crystal packing and hydrogen bonding.

In conclusion, we have reported the first successful prediction of the crystal structures of multicomponent crystals of two pharmaceutically active molecules, demonstrating that CSP methods are useful in understanding multicomponent crystals; the methods are, of course, subject to the same limitations as single-component studies—limited accuracy of model potentials and our lack of understanding of kinetic influences on crystal structure. Further-
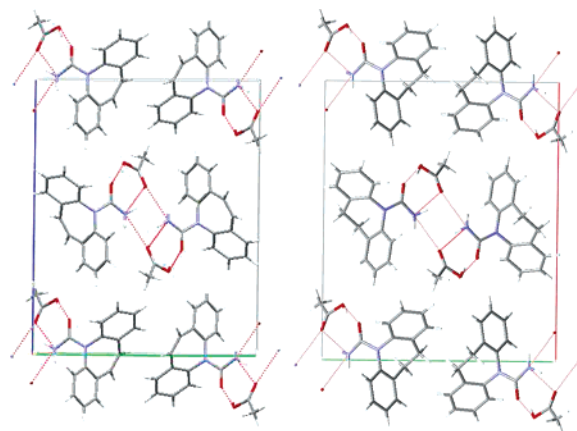

Figure 3. Unit cell representations of the isomorphic CBZ:AcOH (left) and DHCBZ:AcOH (right) crystal structures.

more, we stress the fact that, although CBZ and DHCBZ show very different hydrogen bonding and packing arrangements in their respective single-component polymorphs, formation of a multi-component crystal with AcOH results in isomorphic structures.

Supporting Information Available: Crystallographic data of the DHCBZ:AcOH crystal structure. CIFs and further information of the 10 most stable predicted crystal structures of CBZ:AcOH and DHCBZ: AcOH. Complete list of authors for ref 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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