Solvent inclusion in form II carbamazepine

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We report on experimental and theoretical evidence for solvent inclusion in form II carbamazepine ($R\bar{3}$) and discuss the implications for the formation and stability of this form.

Carbamazepine (CBZ) is one of the most extensively studied drug molecules in the literature due, in part, to its propensity for polymorphism[1–5] and cocrystal/solvate formation.[6] To date, there are four known polymorphs of CBZ.[1–4] The crystal structure of form II, of trigonal symmetry ($R\bar{3}$), was first reported almost twenty years ago.[3] Although the authors noted significant voids in the crystal structure (Fig. 1),[3] the possibility of occluded solvent was ruled out as a result of thermogravimetric analysis. Since then, little attention has been paid to the possible role of solvent in the formation and stability of this crystal structure.

Recently, various computational studies have reported considerable success in predicting the crystal structures of forms III and IV of CBZ,[7] various CBZ derivatives,[8] as well as for the multicomponent system CBZ:AcOH.[9] In the case of form II CBZ, however, more than a hundred hypothetical polymorphs were predicted to be more stable than the observed structure (form II being 8.4 kJ mol^{-1} less stable than form III).[7] Motivated by the success with the remaining forms, we reconsidered the possibility of solvent inclusion being important in the stability, and therefore the formation, of this particular crystal form. We report herein theoretical calculations combined with a thorough experimental analysis that point to solvent inclusion during crystal growth. Based on these findings, we took advantage of the inclusion properties of form II CBZ to design an isomorphic pseudopolymorph with improved physical stability.

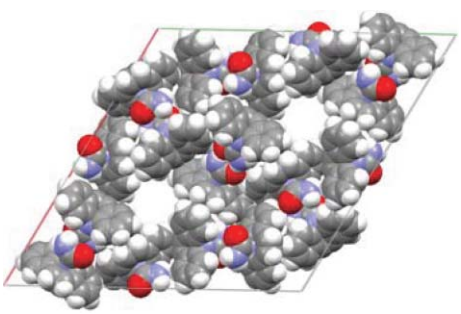

Fig. 1 Spacefill representation of form II CBZ, viewed down the *c* axis and showing the channel like structure.

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The solvent-accessible volume in form II CBZ was calculated with the program PLATON (using a van der Waals probe radius of 1.5 Å).[10] All molecular models were energy minimised and atomic charges were fitted to the molecular electrostatic potential (ESP) using the code Dmol3 (pw91/dnp) as implemented in *Materials Studio*.[11] A 1 × 1 × 4 supercell model of form II CBZ was built to evaluate the change in packing coefficient, unit cell volume and the overall gain in stability by inclusion of toluene in the crystal voids. The three independent pores contained in the supercell were filled with molecules of toluene at random positions – in increments of one molecule per pore. The whole system was then energy minimised with *Cerius2*,[12] treating the molecular models as rigid, using the atomic ESP charges and the W99[13–15] interatomic potential for the evaluation of the intermolecular electrostatics and van der Waals interaction energies respectively. As much as ~98% of the energy gain by solvent inclusion was found to be due to van der Waals interactions. The real stabilisation energy of the system (ΔE^{syst}) was calculated as follows: $\Delta E^{syst} = \Delta E^{cryst} - y\Delta H^{vap}_{exp}$ (*tol*), where ΔE^{cryst} is the calculated stabilisation energy of the crystal as a result of toluene inclusion,† ΔH^{vap}_{exp} (*tol*) is the experimental vaporisation enthalpy of toluene[16] (38 kJ mol^{-1}) and $y\Delta H^{vap}_{exp}$ (*tol*), therefore, the energy needed to remove *y* moles of toluene from the liquid.

Two solvents of very different nature were chosen for the experimental study: toluene and n-tridecane. Form II CBZ ($R\bar{3}$) was grown by cooling a boiling solution of CBZ in toluene to room temperature. As CBZ is highly insoluble in n-tridecane, a form II analog was prepared by melting form III CBZ in n-tridecane (the boiling point of n-tridecane, ~234 °C, is higher than the melting point of form III CBZ, ~175 °C) and cooling to room temperature. Needle-like crystals were obtained in both cases after 5 minutes. Crystals grown from n-tridecane were washed with n-hexane. After vacuum filtration of the samples, TGA and DSC analyses were carried out at heating rates of 2 °C min^{-1}. *In situ* hot stage PXRD was used for crystal structure identification and solution ^{1}H-NMR for identification and quantification of the inclusion solvent. Hot stage microscopy was used for visual inspection of the crystals at a heating rate of 5 °C min^{-1}.

The solvent-accessible volume per unit cell of form II CBZ was calculated to be less than 7%, with the pores aligned along the *c* unit cell direction and forming accessible channels to the crystal exterior. Using the model described above, inclusion of toluene in these channels resulted in an increase of packing coefficient (Fig. 2a). As the pores are filled, however, a convergence in the calculated packing coefficient is observed – the supercell volume expansion (Fig. 2a) becomes more important and comparable to the volume filled by included solvent. According to the simulations, a toluene : CBZ stoichiometry of 0.08–0.12 (3–4.5 wt.% solvent) is sufficient to fill the pores in form II CBZ.

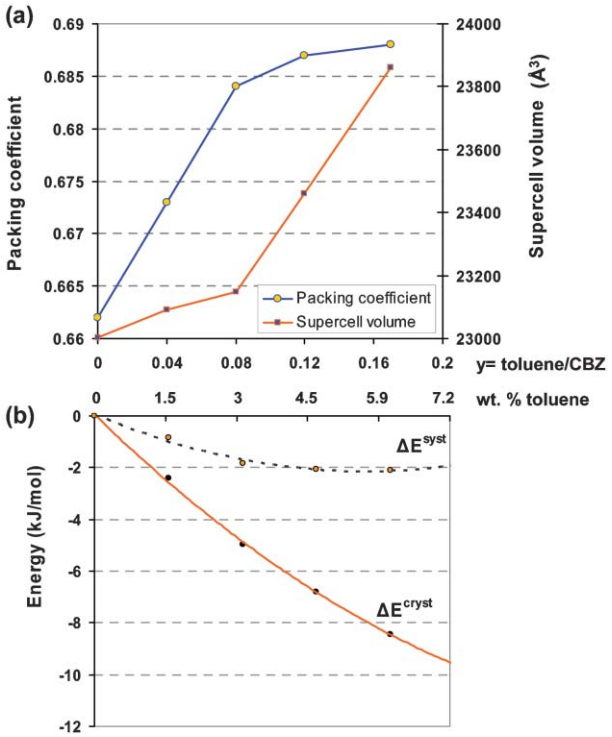

Fig. 2 (a) Packing coefficient and supercell volume, (b) total (ΔE^{cryst}, solid line) and real stabilisation energies (ΔE^{syst}, dashed line) as a function of y (included-toluene/CBZ stoichiometry).

The total calculated stabilisation energy (ΔE^{cryst}) for toluene inclusion in the voids of form II CBZ (Fig. 2b, solid line) becomes greater and of significant magnitude (up to 9 kJ mol^{-1} for y = 0.16) as the amount of solvent per pore is increased. However the real stabilisation energy of the system (ΔE^{syst} Fig. 2b, dashed line), which accounts for the energy needed to remove the same amount of toluene from the liquid, only increases until $y \sim 0.08$. After this, it levels off so there is no further overall enthalpy gain to balance the decrease in entropy of the uptaken solvent.

Due to solvent disorder within the structure, we were only able to observe some electron density within the pores of form II CBZ by single crystal X-ray diffraction, but not able to assign specific atom positions for the guest. The TGA analysis of the form II CBZ crystals grown from toluene, however, revealed a clear loss of weight‡ (2.7–3.7%), with a simultaneous darkening of the crystals, between 130–180 °C (Fig. 3a). This weight loss can be associated

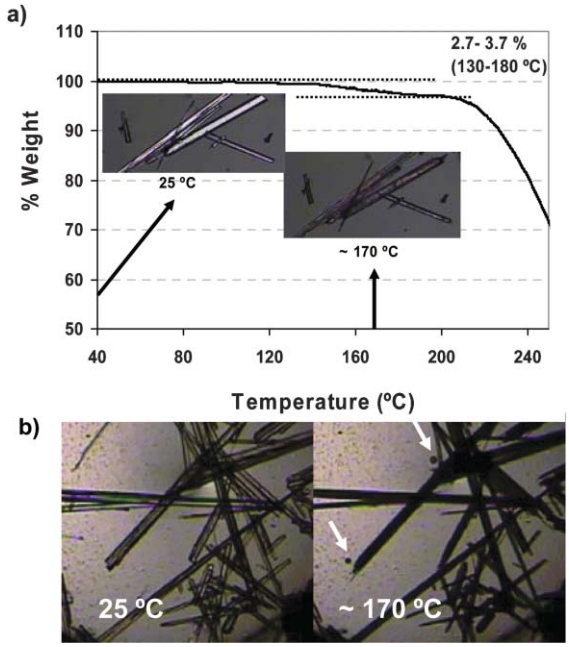

Fig. 3 (a) TGA curve (2 °C min^{-1}) and micrographs of form II CBZ from toluene and (b) micrographs of bubbles associated with solvent release in crystals immersed in silicone oil.

with a very small endothermic event in the DSC trace (Table 1). ^{1}H-NMR analysis identified toluene as the solvent included in form II. Visual observation of toluene release (Fig. 3b) was also recorded under the hot stage microscope by immersing the sample in silicone oil and heating to 190 °C. Bubbles of solvent were released from both ends of the needle-shaped crystal, showing that the channels are aligned in the same direction as the needles. The melting onset of the sample occurred at 190.4 °C (Table 1).

Whilst the choice of toluene as an inclusion solvent was arbitrary (but based on the fact that it is a common solvent that cannot form a hydrogen-bonded solvate with CBZ and from which form II can be easily grown), the choice of n-tridecane was carefully made. Once the inclusion properties of form II were established with toluene, we sought to engineer enhanced stability of the structure by inclusion of a large solvent molecule such as n-tridecane. When form II was prepared from this long chain hydrocarbon, a loss of solvent of comparable magnitude (3.7–4.8 wt.%, identified as n-tridecane by ^{1}H-NMR) was also observed but at a much higher temperature and showing a sharper weight

Table 1 Summary of events observed with microscopy, DSC and wt.% of included solvent (measured by TGA and NMR and calculated) in form II CBZ grown from toluene and n-tridecane

Solvent	T (°C)	Hot stage microscopy	Solvent wt. (%)	DSC	Event
Toluene	130–180	Crystals darken	TGA: 2.7–3.7[a] NMR: 4.2 Calcs: 3–4.5	Small[b] Endothermic	Solvent release and partial conversion to form I[c]
	190.4	Crystals melt	—	Endothermic	Melting
$C_{13}H_{28}$	150–170	Growth of small hair-like crystals	—	—	Growth of form I from vapour
	188.5	Hair-like crystals melt	—	—	Form I melts
	195.0	Mother crystals melt	TGA: 3.7–4.7 NMR: 5.4	Endothermic	Form II melting and n-tridecane release

[a] A range of values is given resulting from three independent measurements. [b] This endothermic event was very small and difficult to detect in consecutive measurements. [c] *In situ* hot stage PXRD indicated this to be only a partial transformation to form I.

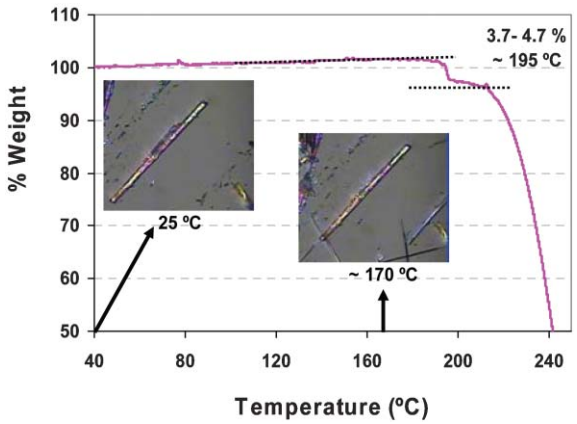

Fig. 4 TGA curve (2 °C min^{-1}) and micrographs of form II CBZ from n-tridecane.

loss than in the case of toluene (Fig. 4). Unlike the case with toluene, the sample retained its crystallinity and n-tridecane was only released upon melting of the crystals (at 195.0 °C).

Experimental evidence for solvent inclusion in form II CBZ has been provided by using combined TGA, DSC and hot stage microscopy. Because of the small percentage of solvent-accessible volume per unit cell in form II CBZ (7%), only small solvent/CBZ ratios are possible. Using our theoretical model, we calculated pore filling at 3–4.5 wt.% of toluene, in good agreement with the experimental measurements from both TGA and NMR (Table 1). It is perhaps because the amount of included solvent is so small that its presence has not previously been detected. It is also possible that under severe drying conditions, or by growing form II from more volatile solvents, release of inclusion solvent may rapidly occur at room temperature.§ Toluene release and crystal darkening were observed between 130–180 °C, the temperature range in which the form II → form I phase transition is reported.[3,5,17–19] Contrary to earlier reports,[5,20] we also recorded a small endothermic event by DSC, which we attribute to a combination of the onset of the phase transition and the release of solvent.

While toluene release occurred progressively over a wide temperature range (starting at 130 °C until the melting point), we observe that n-tridecane loss occurred only during crystal melting. Although some spontaneous growth of hair-like crystals (form I) from the vapour was observed at ~160 °C, inclusion of n-tridecane in form II completely prevented the transformation to form I. Furthermore, the melting point of the n-tridecane form II sample was almost 5 °C higher (195.0 °C) compared to the toluene form II. Additionally, form II left in the mother liquor was transformed into the most stable form III after a week in the case of toluene, whereas no such transformation occurred in n-tridecane even after one month.

In summary, despite considerable effort invested in the study of polymorphism in carbamazepine in recent years, we provide here the first experimental and computational evidence for the importance of solvent inclusion in the stability of the trigonal form. The presence of solvent in the pores appears to play a key role in the formation and therefore observation of this low density structure containing large voids and a high relative lattice energy. Finally, we note that the framework structure of form II was generated by computational methods.[7] While the structure was predicted to have a high energy relative to the thermodynamically stable polymorphs,[7] the inclusion of solvent and consequent stabilisation of the crystal structure might have been predictable through an analysis of void space and solvent inclusion calculations. This type of analysis of high energy structures resulting from crystal structure prediction calculations might be a way of predicting the formation of metastable polymorphs, whose growth can be templated or stabilised by solvent inclusion. Predicting which of the many high energy putative structures might form under a given set of conditions remains a great challenge.[21]

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Notes and references

† The stabilisation energy of the crystal was calculated as the difference between the minimised lattice energy of form II with toluene included in the channels and the lattice energy of the pure crystal: $\Delta E^{cryst} = E_{latt}(CBZ{:}tol) - E_{latt}(CBZ)$.

‡ Weight loss in TGA was not observed for different CBZ polymorphs.

§ In the original work,[3] the crystals were grown from boiling solutions in THF, $CHCl_3$, CCl_4 and cyclohexane. It has also been obtained from other solvents[5,22] and by freeze-drying the CBZ dihydrate.[23]

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