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COMMUNICATION

Mechanochemical synthesis and structural characterisation of a theophylline-benzoic acid cocrystal (1 : 1)†

Sebastian Heiden, Lisa Tröbs, Klaus-Jürgen Wenzel and Franziska Emmerling*

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The structure of a mechanochemically synthesised cocrystal containing theophylline (TP) and benzoic acid (BA) has been determined from powder X-ray diffraction data.

Cocrystals are molecular complexes of two or more uncharged solid organic compounds.[1–4] In the context of pharmaceutical research, cocrystallization is typically used with the intent to enhance physicochemical properties of drugs. The resulting compounds exhibit considerable advantages compared to salts and solvates/hydrates.[1,5] Cocrystallization can improve properties of active pharmaceutical ingredients (APIs), *i.e.* their stability, solubility, dissolution rate and bioavailability.

Theophylline (TP) is an API which is used in asthma-therapy[6] and the fight against chronic obstructive pulmonary disease.[7] The bioavailability of the amphoteric TP is limited by its low solubility. Hence, the synthesis of its cocrystals with acids and bases can increase its solubility. The structure of TP has great potential to form stable cocrystals, assuming that the carbonyl groups and aromatic nitrogen atoms participate in hydrogen bonds with the cocrystal former (Fig. 1). Examples for cocrystals containing TP are discussed in the literature.[8–10] In this work, benzoic acid (BA) is used to form a cocrystal. The ΔpK_a value serves as an indicator for the possibility of cocrystallization. Formation of a cocrystal is favoured whenever the difference of the pK_a values is lower than 0. For a combination with $\Delta pK_a > 0$ the formation of salts is also possible.[11,12] Since the measured pK_a value of BA is 4.19 and that of the conjugated acid of TP is 0.5, the ΔpK_a value of TP:BA is −3.69.[12,13] This indicates a strong tendency of the two compounds to form a cocrystal. This assumption was verified by Childs *et al.* who identified the respective cocrystal based on IR measurements.[12] However, the crystal structure has not been reported yet.

This communication focuses on the structural determination of the cocrystal TP:BA, which was synthesized mechanochemically. Different crystallization methods are applied for cocrystallisation, for example sonochemical[14] approaches, as well as cocrystallization from solution[15] and mechanochemical[16,17] synthesis. In mechanochemical experiments both neat grinding and liquid assisted grinding are promising techniques for screening of new cocrystals.[16,18] The title compound was synthesised by neat grinding at 30 Hz in a ball mill (MM400, Retsch, Germany) for 25 min. A 10 mL steel vessel was used with three steel balls (10 mm) for a total load of 1 g. Theophylline (99%, Sigma Aldrich, Germany) and benzoic acid (99,5%, Acros Organics, USA) were purchased commercially and were used without further purification. The completeness of the reaction was confirmed by X-ray diffraction (XRD), no residues of the reagents were present in the final powder (Fig. 2). Further experiments showed that reaction was completed within 10 min. The XRD measurements were performed on a D8 diffractometer (Bruker AXS, Karlsruhe, Germany) in transmission geometry (Cu-Kα_1 radiation, λ = 1.54056 Å). Structure determination was carried out based on the powder XRD pattern. Indexing and structure calculation were performed using the open source program FOX.[19].‡ The unit cell and space group were confirmed using CHEKCELL.[20] FOX uses global-optimization algorithms to solve the structure by performing trials in direct space. This search algorithm uses random sampling coupled with simulated temperature annealing to locate the global minimum of the figure-of-merit factor. To reduce the total number of degrees of freedom, parts of the molecule were refined as a rigid group. The whole theophylline molecule was set rigid, while benzoic acid was set rigid with the exception of the carboxyl oxygen and hydrogen atoms. The crystal structure of the cocrystal was solved by the simulated annealing procedure on a standard personal computer within 6 h, finding the deepest minimum of the cost function several times during the procedure. To complete the structure determination, the structural solution obtained from MC/SA was subsequently subjected to a Rietveld refinement employing the TOPAS software.[21] Fig. 3 shows the result of the Rietveld refinement illustrating the agreement of the

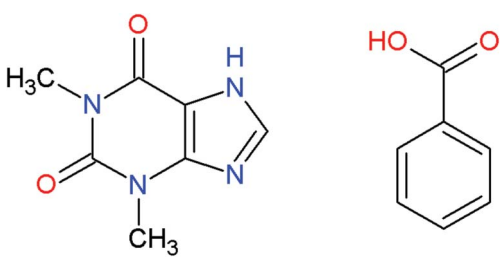

Fig. 1 Molecular diagram of theophylline (left) and benzoic acid (right).

BAM Federal Institute for Materials Research and Testing, Richard-Willstaetter-Strasse 11, 12489, Berlin, Germany.
E-mail: franziska.emmerling@bam.de; Fax: +49 30/8104-1137;
Tel: +49 30/8104-1133

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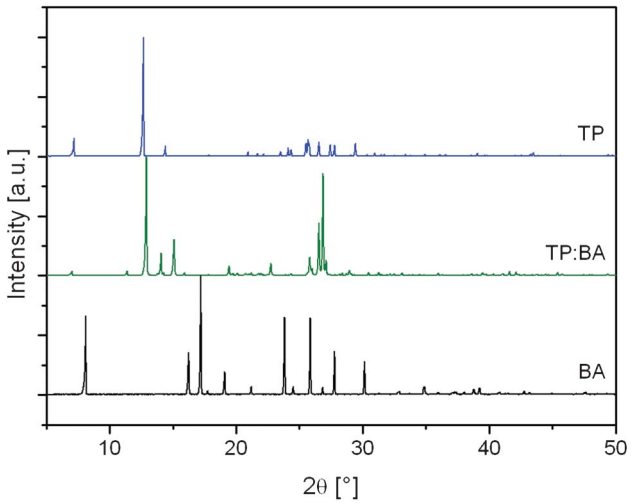

Fig. 2 Powder XRD patterns of the synthesised cocrystal TP:BA (green) and educts TP (blue) and BA (black). Background contributions of the sample holder were corrected.

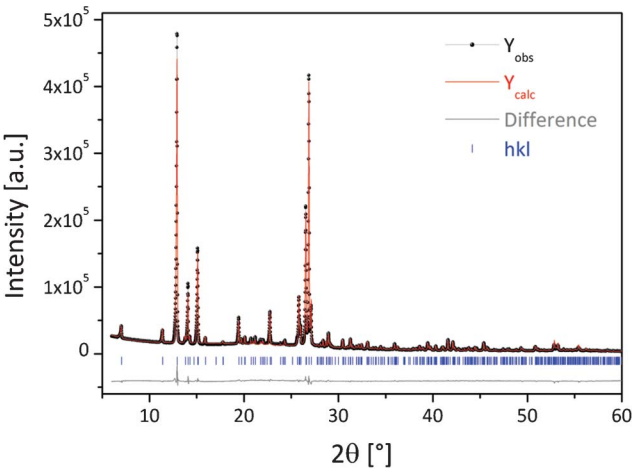

Fig. 3 Rietveld refinement of the cocrystal TP:BA.

simulated powder pattern with the measured one. The refinement converged at an R_{wp} = 8.34% (R_p = 6.28%).

TP:BA crystallizes in the monoclinic space group $P2_1/n$. TP and BA molecules form pairs connected *via* two strong hydrogen bonds. One hydrogen bond is formed between the carbonyl group of TP and the carboxyl group of BA (O–H···O, 2.6149 Å, 168°), the other one between the acidic imidazolic nitrogen atom of TP and the carboxyl oxygen atom of BA (N–H···O, 2.7680 Å, 169°). The dimers are arranged parallel to the *b*–*c* plane and form stacks along the *a*-axis (Fig. 4). The π–stacking of the phenyl ring of BA and of the six membered ring of TP is collinear to *a*, with a distance of 3.551 Å between the ring centers. Based on the presented results it is clear why attempts to synthesise the similar caffeine derivative were not successful. The alkylated caffeine derivative cannot be stabilized in a similar manner because of the inability to form stable hydrogen bonds in that dimension.

In summary, the mechanochemical synthesis proved to be a fast and successful approach towards the synthesis of cocrystals. It was used to successfully synthesise the cocrystal TP:BA by neat grinding for a few minutes. The crystal structure of the new cocrystal was determined from the powder XRD pattern.

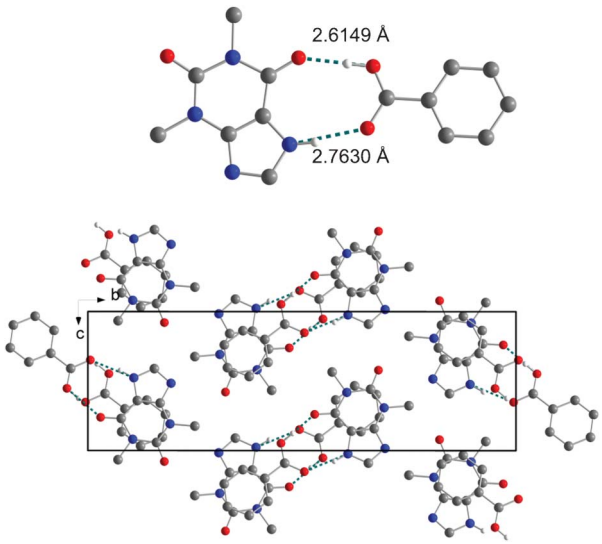

Fig. 4 Dimer of TP and BA (top) and layered cocrystal structure of TP:BA seen from the *b*–*c* plane (bottom). The hydrogen atoms not involved in the hydrogen bonding were omitted for clarity. Dashed green lines indicate hydrogen bonds.

References

‡ Powder pattern were collected using a Bruker D8 Discover (Bruker AXS GmbH, Germany) operated in transmission geometry and equipped with a Lynxeye detector. The samples were measured over a range of 5–60° 2θ (2 kW; Cu-Kα, 1.54056 Å, step width 0.009°, count time 20 s step^{-1}). Unit cell parameter for TP:BA: monoclinic, $P2_1/n$, a = 6.98690(17) Å, b = 25.10944(84) Å, c = 8.60685(30) Å, β = 108.5597(18), V = 1431.431(78) Å^3.

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