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Charge density studies on 1:1 co-crystals of ethenzamide and saccharin

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The study of multi-component crystals, as well as the phenomenon of polymorphism, both have relevance to crystal engineering. Obtaining a specific polymorph is crucial as different polymorphs usually exhibit different physical and chemical properties and often the origin of this behaviour is unknown. This is especially important in the pharmaceutical industry. Herein, we present results of comparative studies of an analgesic drug, ethenzamide and its co-crystals with saccharin. The co-crystalisation of ethenzamide (2-ethoxybenzamide, EA) with saccharin (1,1-dioxo-,1,2-benzothiazol-3-one, SAC) with a 1:1 stoichiometric ratio resulted in two polymorphic forms of the co-crystal. Form I crystallises in the triclinic P-1 space group, whereas form II crystallises in monoclinic space group P21/n. Previous crystal structure analyses on forms I and II revealed that in both polymorphs the primary carboxy-amide-imide heterosynthon is the same, however the secondary level of interactions which extends the hydrogen bond network is different. Form I consists of extended linear tapes via N-H···O hydrogen bonds, whereas form II is composed of stacks of tetrameric motifs including N-H···O hydrogen bonds and C-H···O interactions. These two forms of EA-SAC can be classified as synthon polymorphs at a secondary level of hydrogen bonding [1]. In our approach an accurate, high resolution charge density distribution analysis has been carried out to obtain greater insight into the electronic structures of both types of the EA-SAC co-crystals and relate differences in electronic distribution with their polymorphic behaviour. To describe the nature and role of inter and intra-molecular interactions in a quantitative manner, the Hansen-Coppens formalism [2] and Bader's AIM theory [3] approach have been applied.

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