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Crystal forms of Barbital: News about a classic polymorphic system

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Four of six known crystal polymorphs and four new solvates, as well as one known solvate [1] with dimethylformamide of the hypnotic agent barbital (5,5-Diethyl-2,4,6(1H,3H,5H)-pyrimidinetrione) were characterized by numerous analytical techniques including hot stage microscopy, differential scanning calorimetry and single crystal diffractometry. The stable modification (mod.) at 20°C (mod. I, m.p. 189 °C) is obtained by annealing the commercial form (mod. III) at 160°C, from the slowly cooled melt and by solvent crystallization from acetone. Mod. III (m.p. 183°C) in mostly obtained when the compound is crystallized from organic solvents or water whereas the unstable mod. IV (m.p. 181°C) crystallizes exclusivly from the super-cooled melt. By rapid cooling a hot saturated solution in water, propanol or acetone/water we can obtain the metastable mod. V (m.p. 176°C). Barbital sublimes strongly which allows to produce mod. I and III by sublimation on a hot bench above 100°C and mod. IV and V by sublimation below 100°C [2]. Furthermore the solvates, which are only stable in solution, can be crystallized from acetonitrile, chloroform, methylenchloride, DMSO and DMF. The single crystal structure of the solvates with DMF and DMSO have been solved by us so far.

Based on the results of thermal analysis and solvent mediated transformation studies, the thermodynamic relationships among the polymorphic phases of barbital were evaluated and a semi-schematic energy/temperature-diagram was constructed the first time. The data clearly indicate that the modifications I, III and V are enantiotropically related to each other, whereas mod. IV is enantiotropically related to mod. V and monotropically related to the other two forms. In total there are four transition points. The transition point of the pairs I/III, I/V and IV lie below 20°C, that of the pair IV/V above 20°C. At room temperature the order of thermodynamic stability is I > III > V > IV. The metastable mod. III shows a high kinetic stability and is present in commercial samples [3, 4]. Mod. V is also kinetically stable at room temperature under dry atmospheric conditions.

Our main motivation to reinvestigate this classic polymorphic system, which is frequently used as a standard example for the demonstration of solid-solid transformations in hot stage microscopy courses, was to elaborate a clearer and comprehensive picture of the system as well as to confirm and summarize the data of the numerous, mostly incomprehensive studies reported in the literature. It is surprising, that this study revealed the existence of four solvates which have not been recognized in any of the previous studies.

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