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A comparative study of the effect of pressure on the polymorphs of paracetamol and on phenacetine

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Effect of pressure on solid drugs is of great interest, and there are two main reasons of this. First, when processed many solid drugs are subjected to mechanical action and, in particular, to high pressure, for example when pellets are produced. It is important to know what can happen to a given polymorph during such a treatment, for example, if any phase transition is possible, in order to control the properties and bioavailability of drugs. Second, the studies of the anisotropy of the response of a crystal structure to hydrostatic pressure provide important knowledge on the intermolecular interactions in the crystals, in particular, of the hydrogen bonds. These interactions, in turn, are known to account for many properties of solid drugs important for their processing, storage, delivery.

In the present study we have applied high-pressure powder and single-crystal X-ray diffraction in the diamond anvil cell (DAC), in order to follow the effect of hydrostatic pressure on the two polymorphs (orthorhombic and monoclinic) of paracetamol and on the phenacetine. The crystals of these compounds are built from molecules with similar structure, but their differ in the way how these molecules are linked together by networks of hydrogen bonds. In phenacetine there is only one type of hydrogen bonds, NH---O, linking molecules in chains. In both polymorps of paracetamol there are hydrogen bonds NH---0 and OH---0 which link molecules in folded sheets. Two polymorps of paracetamol differe in the way how similar chains of molecules are linked further with each other.

The anisotropy of structural distortion of the crystal structures of phenacetine and the monoclinic polymorph of paracetamol was shown to be qualitatively different. In paracetamol, despite the overall decrease in the molar volume with pressure, the structure *expanded* in particular crystallographic directions. One of the linear lattice parameters and the monoclinic angle p passed through extrema as the pressure increased. In phenacetine, however, such effects were not observed. The anisotropy of structural distortion of both compounds was interpreted taking into account the differences in the hydrogen-bonds networks in the two crystal structures. The measurements of changes of lattice parameters at pressures up to 4.0 GPa were completed by full structure refinements at 1.0, 2.0, 3.0 GPa giving direct data on the effect of pressure on the interatomic distances and angles in the structures.

Pressure was also shown to induce (under particular conditions determined by the rates and the sequence of cyclic loading-unloading) polymorph transitions between monoclinic and orthorhombic polymorphs of paracetamol, as well as amorphization of the orthorhombic polymorph with the subsequent crystallization of the amorphous phase into a mixture of the monoclinic and orthorhombic phases. The conditions of these transformations between the polymorphs are compared with those required for thermally induced polymorph transitions. A possible structural model of the polymorph transformations is discussed.

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