Low-temperature polymorphic transitions in chlorpropamide and tolbutamide
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Structure solution of molecular crystals at low temperatures does not necessarily mean, that it is the same as at ambient temperature, even if there are no visible changes in the crystal colour, shape, transparency and temperature variation. This can be illustrated at the examples of two recently discovered low-temperature polymorphic transitions in the antidiabetic drugs with related molecular structures, chlorpropamide, $\text{C}_8\text{H}_9\text{Cl}\text{N}_2\text{O}_3\text{S}$, [1], and tolbutamide, $\text{C}_9\text{H}_{14}\text{N}_2\text{O}_3\text{S}$, [2]. These transitions are reversible and leave the crystals intact. Solving crystal structure at low temperature only, one cannot make a correct conclusion on the crystal structure under the crystallization conditions.

The polymorphic transitions are very interesting, since they are accompanied by a peculiar conformational ordering on cooling, resulting in an increase in $\beta$. In other words, several conformers not related by any symmetry operations are distributed regularly in the crystal structures of the low-temperature forms, in contrast to high-temperature phases, which have only one conformer per unit cell. An increase in $\beta$ is accompanied by changes in either the elementary translations, or the crystal system. Thus, at temperatures below 260 K β-chlorpropamide transforms from the orthorhombic into the monoclinic polymorph, and this transition is accompanied by non-merohedral twinning; below 150 K one of the cell parameters doubles. In tolbutamide III below 150 K one of the cell parameters triples. All the transitions were studied by single-crystal and powder variable-temperature X-ray diffraction. The crystal structures of the high-temperature and low-temperature polymorphs were solved and refined at multiple temperatures. The changes in the translational symmetry was shown to be related to the regular changes in the conformations of the alkyl tails in some of the molecules, regularly distributed in the structure. All the low-temperature transitions were observed on cooling the polymorphs, which are metastable already at ambient conditions. At the same time, the stable forms of these compounds, which correspond to the commercially available samples, do not undergo any phase transitions on cooling.

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Keywords: phase transitions in solids, drug polymorphism, low-temperature structure

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