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Solid-state transformations in the β-form of chlorpropamide on cooling to 100 K

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A single-crystal X-ray diffraction study of the effect of cooling down to 100 K on the β-form of chlorpropamide, 4-chloro-*N*-(propylaminocarbonyl)benzenesulfonamide, has revealed reversible phase transitions at $\sim$257 K and between 150 and 125 K: β (*Pbcn*, $Z' = 1$) $\Leftrightarrow$ β^{II} (*P*2/*c*, $Z' = 2$) $\Leftrightarrow$ β^{III} (*P*2/*n*, $a' = 2a$, $Z' = 4$); the sequence corresponds to cooling. Despite changes in the space group and number of symmetry-independent molecules, the volume per molecule changes continuously in the temperature range 100–300 K. The phase transition at $\sim$257 K is accompanied by non-merohedral twinning, which is preserved on further cooling and through the second phase transition, but the original single crystal does not crack. DSC (differential scanning calorimetry) and X-ray powder diffraction investigations confirm the phase transitions. Twinning disappears on heating as the reverse transformations take place. The second phase transition is related to a change in conformation of the alkyl tail from *trans* to *gauche* in 1/4 of the molecules, regularly distributed in the space. Possible reasons for the increase in Z' upon cooling are discussed in comparison to other reported examples of processes (crystallization, phase transitions) in which organic crystals with $Z' > 1$ have been formed. Implications for pharmaceutical applications are discussed.

1. Introduction

Studies of the crystal structures of small-molecule organic solids at variable temperatures are important in several respects. From a fundamental point of view they provide insight into the intermolecular interactions and intramolecular motions in crystals and biological systems (which can be mimicked by molecular crystals used as model systems). Detailed structural studies at multiple temperatures help to understand the factors determining crystal structures, solid-state reactivity and the nature of phase transitions, even if the data are collected in a range where no phase transitions or reactions take place (see Boldyreva, 2009; Boldyreva *et al.*, 1997*a*,*b*, 2004, as entry points, and references therein). From a practical point of view variable-temperature studies are important to pharmaceutical chemists who need to identify crystal forms of active pharmaceutical ingredients. Measuring powder diffraction patterns at ambient temperature and comparing them to those calculated from single-crystal diffraction data, which are often collected under cryogenic conditions, is common practice today (Stephenson, 2006; Sun, 2007). It is necessary to establish if the low-temperature phase is the same as the ambient-temperature one and, even if no phase transitions occur on cooling, to know how the structure

compresses on cooling, taking into account the anisotropy of strain.

Chlorpropamide, 4-chloro-*N*-(propylaminocarbonyl)benzenesulfonamide, is suitable for investigating polymorphism in molecular crystals. Five polymorphs of chlorpropamide can be obtained by varying the crystallization conditions. Once obtained they can be preserved for some time and co-exist under ambient conditions (Al-Saieq & Riley, 1982; Burger, 1975; Drebushchak, Drebushchak *et al.*, 2008; Chesalov *et al.*, 2008; Drebushchak *et al.*, 2006, 2007; Drebushchak, Chukanov & Boldyreva, 2008; Simmons *et al.*, 1973). The main structure-forming units (infinite hydrogen-bonded ribbons; Fig. 1*a*) are preserved in all forms. The polymorphs differ in molecular conformation (Fig. 1*b*) and the aromatic ring orientation of neighbouring molecules in a ribbon (Fig. 1*c*). The rings can either be on different sides of the hydrogen-bond plane forming a z-shaped motif (α-, γ-, δ- and ε-polymorphs) or on the same side forming a π-shaped motif (β-polymorph). The polymorphs can also differ in packing of the ribbons of the same motif in the crystal structure (Drebushchak, Chukanov & Boldyreva, 2008; Drebushchak *et al.*, 2009).

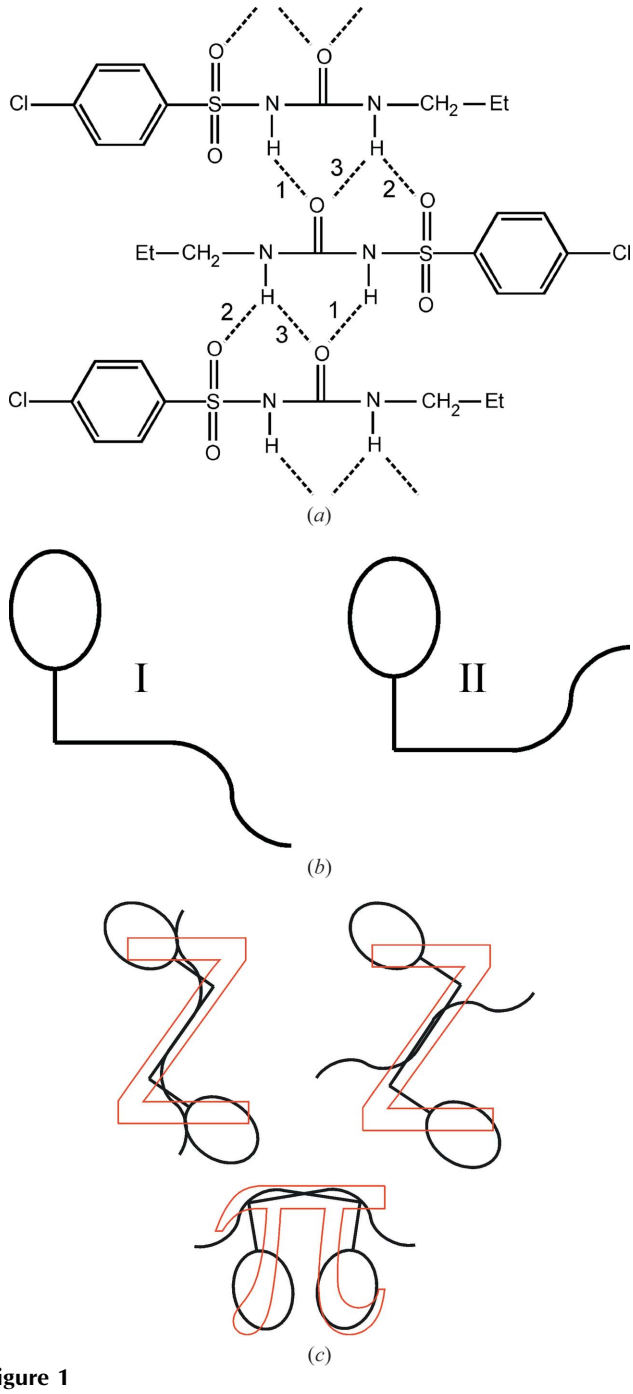

Figure 1
The main structural features of chlorpropamide polymorphs: (*a*) an infinite hydrogen-bonded ribbon (common for all the polymorphs), where hydrogen bonds are shown by dotted lines; (*b*) molecular conformations with the orientation of the alkyl tail in the molecule of type I (left) and of type II (right); (*c*) z-shaped (above) and π-shaped (below) motifs of a hydrogen-bonded ribbon. Adapted from Drebushchak *et al.* (2009).

Solid-state phase transitions on heating from ambient temperature up to the melting point and cooling back to ambient conditions have been studied in detail by DSC, IR spectroscopy and X-ray diffraction (Drebushchak, Drebushchak *et al.*, 2008; Chesalov *et al.*, 2008). Four polymorphs (α, β, γ and δ) transform into the low-density ε-form on heating to temperatures just below the melting point. The high-temperature transformations are mainly concerned with conformational changes, and the hydrogen bonds and crystal packing are only slightly affected. At cryogenic temperatures major changes in the intermolecular hydrogen-bond networks are even more difficult than at temperatures close to the melting point. Therefore, the possibility of changing molecular conformations while preserving the packing motif could be expected to be even higher on cooling than on heating: noticeably less energy is needed to rotate a molecular fragment (phenyl ring with an alkyl tail as a whole or part of it) than to rearrange the packing of molecules linked by intermolecular hydrogen bonds. We have thus started a systematic study of the polymorphic transformations in chlorpropamide below ambient temperature in order to see if the initial molecular conformation (ribbon type) and the packing of the ribbons can be correlated with the occurrence and type of polymorphic transformation (Drebushchak *et al.*, 2009). No phase transitions have been detected on cooling the stable α-polymorph. The high-temperature ε-polymorph can also exist as a metastable form at room temperature, and a reversible phase transition into a new polymorph (termed the ε'-form) has been observed at temperatures below 200 K (Drebushchak *et al.*, 2009). This polymorphic transition preserves the space group $Pna2_1$ and is accompanied by jump-wise changes in cell volume and parameters resulting from changes in molecular conformation (from type II to type I, Fig. 1). The packing of the z-shaped molecular ribbons linked by hydrogen bonds is inherited from the ε-form. On first cooling the reversible low-temperature $\varepsilon \Leftrightarrow \varepsilon'$ transition is of single-crystal-to-single-crystal type, but the sample eventually splits along its longest axis after three runs (cooling–heating–cooling) through the transition point.

The present paper continues the study of the effect of cooling on chlorpropamide polymorphs with a report on the structural changes in another low-density chlorpropamide

polymorph, the β-form, which has the same alkyl tail orientation (type II) as the ε-form, but with a π-type hydrogen-bonded ribbon. The β-polymorph of chlorpropamide is metastable under ambient conditions, but can be stored without any evidence of transformation into the stable α-polymorph much longer than any other metastable form (practially infinite at ambient conditions). Its transformation into the high-temperature ε-polymorph on heating is also kinetically hindered, so that, in contrast to the α-, γ- and δ-polymorphs, this form can melt without transforming into the ε-form if heated at 6 K min^{-1} or faster (Drebushchak, Drebushchak *et al.*, 2008; Chesalov *et al.*, 2008). The long shelf-life of the metastable β-polymorph[1] is due to the unique π-type hydrogen-bonded ribbon, differing from the z-type in all other polymorphs. We were interested to see if cooling the β-polymorph would result in conformational change of molecules from type II to type I (as for the ε-form) and if π-type packing would be preserved.

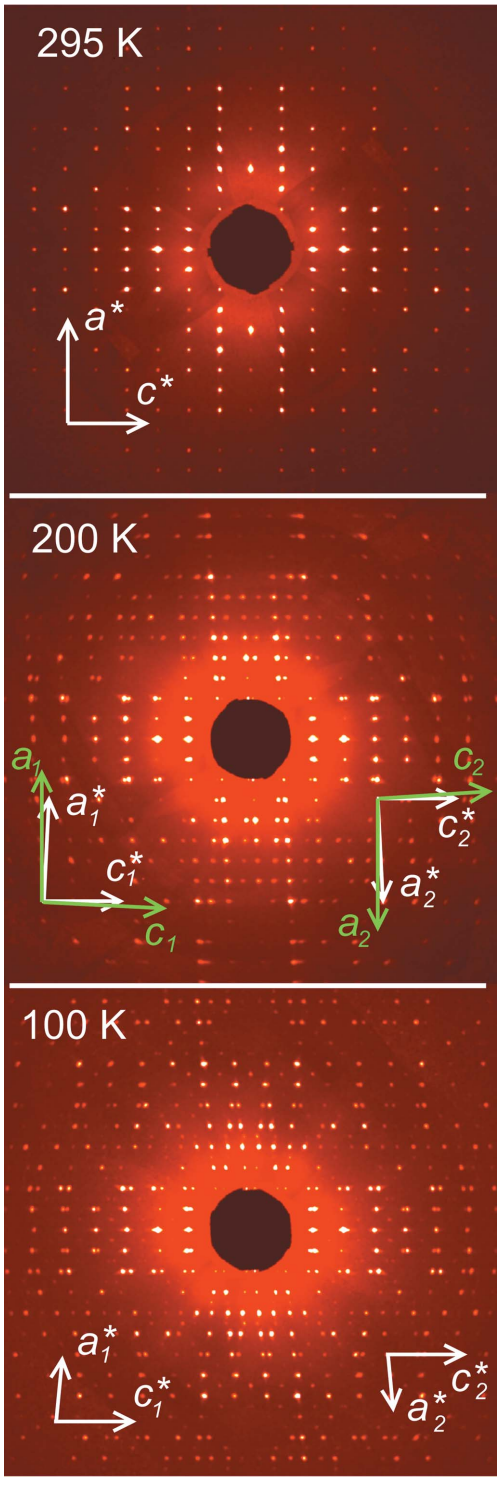

Figure 2
Reciprocal layers *h*0*l* of the crystal of chlorpropamide at three temperatures, corresponding to the β-, β^{II}- and β^{III}-forms.

2. Experimental

2.1. Samples

Crystals of the β-form of chlorpropamide suitable for single-crystal X-ray diffraction analysis were selected from the batch grown by Dr Chukanov, as described elsewhere (Drebushchak, Drebushchak *et al.*, 2008). Chlorpropamide 97% (Sigma Chemical Co) was used as the starting material. Experiments were performed several times with different crystals to test the reproducibility of the results. The crystal structures of the two new polymorphs reported in this paper are based on the data collected for two different crystals.[2] One more crystal was used to monitor the temperature dependence of the cell parameters. Data obtained with other crystals were the same within experimental error.

2.2. X-ray diffraction

A variable-temperature single-crystal X-ray diffraction study was carried out using an Oxford Diffraction KM-4 diffractometer with a two-dimensional Ruby CCD detector (graphite monochromator, Mo $K\alpha$ radiation) and a low-temperature Oxford Instruments Cryojet device. The crystals were cooled from ambient temperature down to 100 K in 25 or 50 K steps (depending on the experiment), and then heated again to 300 K following the reverse procedure. Data collection to estimate cell parameters was carried out at every step (about 2.5 h per temperature point), while data for structure solution and refinement were collected at 200 and 100 K (for 1–2 d). Data for structure refinement at ambient temperature were collected before and after the cooling cycle. The structural data were the same within error limits[3] and agreed with those reported by Drebushchak *et al.* (2006). Decreasing temperature from one point to another usually took approximately 20 min. In general, one cycle of experiments (cooling and heating back to ambient temperature with data collection at intermediate points) took from 3 d to 2 weeks.

[1] The long shelf-life of the β-polymorph makes it the most interesting of all the metastable chlorpropamide polymorphs in terms of pharmaceutical applications.
[2] The best datasets were selected.
[3] Supplementary data for this paper are available from the IUCr electronic archives (Reference: GP5041). Services for accessing these data are described at the back of the journal.

Table 1
Experimental details.

For all structures: $C_{10}H_{13}ClN_2O_3S$, M_r = 276.73. Experiments were carried out with Mo $K\alpha$ radiation using an Oxford Diffraction KM4 CCD diffractometer. Absorption was corrected for by multi-scan methods, *CrysAlis RED* (Oxford Diffraction, 2008*b*). Refinement was with 0 restraints. H-atom parameters were constrained.

	Form β^{II}	Form β^{III}
Crystal data		
Crystal system, space group	Monoclinic, *P*2/*c*	Monoclinic, *P*2/*n*
Temperature (K)	200	100
a, *b*, *c* (Å)	14.5882 (5), 9.2584 (2), 19.1532 (6)	28.4475 (12), 9.2322 (3), 19.2298 (7)
β (°)	93.260 (3)	95.562 (4)
V (Å^3)	2582.71 (13)	5026.6 (3)
Z	8	16
μ (mm^{-1})	0.46	0.47
Crystal size (mm)	0.32 × 0.20 × 0.08	0.22 × 0.15 × 0.06
Data collection		
T_{min}, T_{max}	0.899, 0.965	0.946, 0.973
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	53 248, 7720, 2794	42 040, 14 436, 6814
R_{int}	0.111	0.087
Refinement		
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.055, 0.147, 0.75	0.053, 0.139, 0.81
No. of reflections	7720	14 436
No. of parameters	310	618
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.40, −0.30	0.37, −0.45

Computer programs used: *CrysAlis CCD* (Oxford Diffraction, 2008*a*), *CrysAlis RED* (Oxford Diffraction, 2008*b*), *SHELXS*97, *SHELXL*97 (Sheldrick, 2008).

CrysAlis software (Oxford Diffraction, 2008*a*,*b*) was used for cell refinement, data collection and processing. The crystal structures of the two new polymorphs β^{II} and β^{III} were solved from diffraction data collected at 200 K (crystal 1) and 100 K (crystal 2).

The crystal was twinned by non-merohedry after the β into β^{II} transition. Initially orthorhombic, the structure became monoclinic with the orientation matrices of the two twin components rotated by 180° around the *c** axis with respect to one another (Fig. 2). Data for the twinned structure were processed using *CrysAlis RED* (Oxford Diffraction, 2008*b*). The twin ratio was first suggested by *CrysAlis RED* (Oxford Diffraction, 2008*b*) and then refined with *SHELXL* (Sheldrick, 2008). All crystal structures were solved by direct methods using *SHELXS* (Sheldrick, 2008) and refined on F^2 with all data using *SHELXL* (Sheldrick, 2008). For the twinned samples the solution was carried out using the set of non-overlapping reflections of one twin component (HKLF4), and then the structure was refined using the overlapping reflections (HKLF5). Final *hkl* files with merged reflections were obtained using *CrysAlis* software. Crystal data collection and refinement parameters for two new polymorphs of chlorpropamide are listed in Table 1. There were 8202 isolated (R_{int} = 0.051) and 53 248 overlapping reflections (R_{int} = 0.111) for component 1 of crystal 1 measured at T = 200 K (twin component ratio 0.73:0.27 and then 0.81:0.19), and 9590 isolated (R_{int} = 0.065) and 42 040 overlapping reflections (R_{int} = 0.087) for component 1 of crystal 2 measured at T = 100 K (twin component ratio 0.56:0.44 and then 0.60:0.40) in the 2θ range 3.05–29.31° before data merging. H atoms were located in difference maps or were positioned geometrically and refined with a riding model. Displacement ellipsoids are shown in Fig. 3. Crystallographic axes for the β^{III}-polymorph were chosen in such a way as to facilitate a comparison of its structure with those of β- and β^{II}-polymorphs. The structural study of other crystals confirmed twinning and the occurrence of $\beta \Leftrightarrow \beta^{II} \Leftrightarrow \beta^{III}$ transformations.

X-ray powder diffraction data have been collected using a Stoe Stadi MP diffractometer (linear PSD detector, Ge monochromator, Cu $K\alpha_1$ radiation). Data were collected in the transmission mode from a sample in the capillary (0.5 mm diameter) which was cooled by a dry N_2 stream from an Oxford Cryosystems, 700 Series device. Data collection and processing

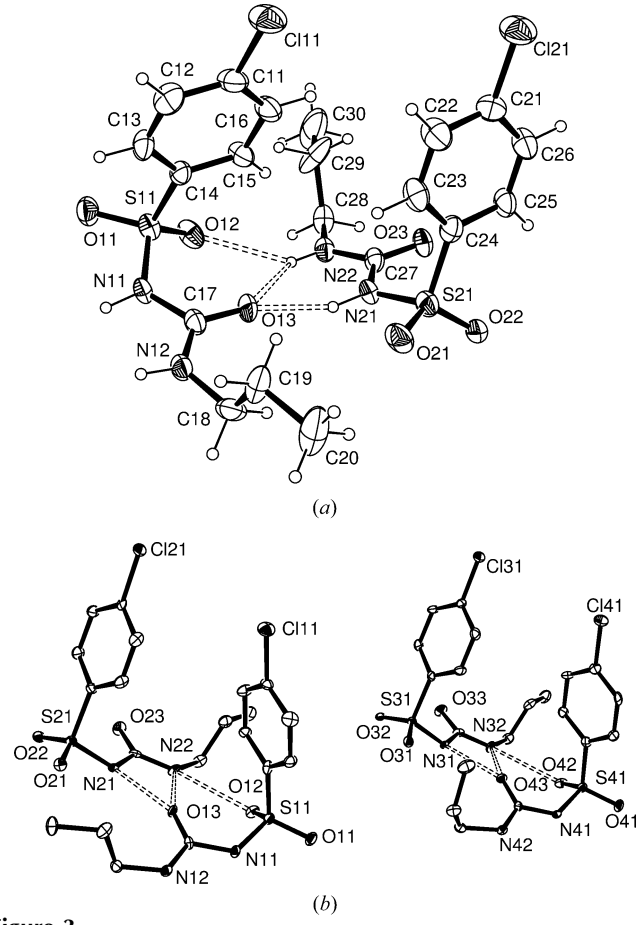

Figure 3
The asymmetric unit of (*a*) the β^{II}-form of chlorpropamide at 200 K and (*b*) the β^{III}-form at 100 K. H atoms have been omitted for clarity. Displacement ellipsoids are drawn at 30% probability. Hydrogen bonds are shown by double dashed lines.

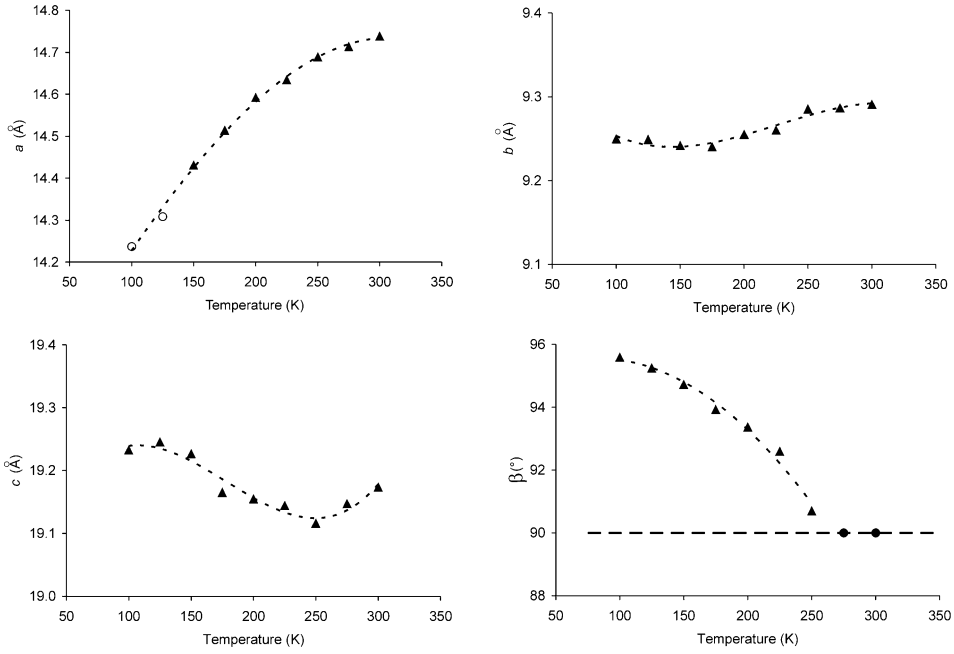

Figure 4
The cell parameters of the β-form of chlorpropamide *versus* temperature. To make a comparison easier, at 125 and 100 K the values of *a*/2 (open circles) are plotted, and not those of *a*.

were carried out using *WinXPOW* (Stoe & Cie, 2007).

The programs *WinGX* (Farrugia, 1999), *Mercury* (Macrae *et al.*, 2006), *PLATON* (Spek, 2009) and *ORTEP*3 for Windows (Farrugia, 1997) were used for visualization and analysis.

2.3. Differential scanning calorimetry

Heat effects in the temperature range 150–300 K have been measured using a DSC-204 (Netzsch; standard Al crucibles with an argon flow of 15 ml min^{-1}; heating rate 6 K min^{-1}). DSC-204 does not permit the measurement of heat effects below 150 K, *i.e.* in the range where the $\beta^{II} \Leftrightarrow \beta^{III}$ transformation takes place, therefore only the temperature range of the $\beta^{I} \Leftrightarrow \beta^{II}$ transition was studied by DSC. Several very small single crystals (total sample mass of 6.35 mg) were put into the crucible and distributed uniformly over its bottom. The crucible was not sealed, only covered by a lid, and was placed inside a DSC block and measured four times without touching the crucible between the runs. This procedure allowed us to collect data of high reproducibility ($\sim$ 0.1–0.2%), but not high accuracy ($\sim$ 2.5%).

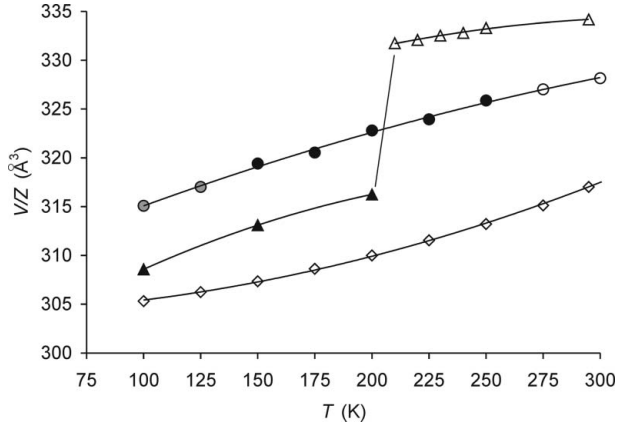

Figure 5
The volume per molecule (*V*/*Z*) of the β-form of chlorpropamide *versus* temperature (open circles – β, black circles – β^{II}, grey circles – β^{III}); for comparison, the data for the α- (rhombs), ε- (open triangles) and ε'-forms (black triangles) are also given in the same plot.

3. Results and discussion

3.1. Changes in cell parameters and volume, X-ray powder diffraction and DSC measurements: occurrence of phase transitions

The changes in cell parameters *versus* temperature were more intriguing than the change in volume per molecule. Parameters *b* and *c* changed non-monotonically *versus* temperature, while the value of the cell parameter *a* doubled at temperatures below 150 K. The value of the β angle changed from 90 to 90.69 (2)° at 250 K and then grew continuously on further cooling (Fig. 4). At the same time, the volume per molecule *versus* temperature changed continuously within the temperature range (Fig. 5). Crystal structure determination at several selected temperatures revealed the occurrence of two reversible phase transitions upon cooling: β (*Pbcn*) $\Leftrightarrow$ β^{II} (*P*2/*c*) $\Leftrightarrow$ β^{III} (*P*2/*n*, $a' = 2a$), see Table 1. DSC measurements confirmed the occurrence of the phase transition $\beta \Leftrightarrow \beta^{II}$ (Fig. 6). The DSC curve averaged over four runs was rather smooth except for the narrow temperature interval from 257.5 to 259.5 K in which a small anomaly (*ca* 2–3%) with the maximum near 257.5 K was observed. X-ray powder diffraction studies confirmed the occurrence of two phase transitions (Fig. 7). For the sake of clarity, only powder patterns measured at 295, 200 and 100 K are shown in Fig. 7, where they are compared with the corresponding patterns calculated from the models based on single-crystal diffraction data.[4]

The phase transition at $\sim$257 K was accompanied by twinning. During the second phase transition ($\beta^{II} \Leftrightarrow \beta^{III}$) a twinned crystal transformed into a similarly twinned crystal without additional twinning (Fig. 2). Still, the original single crystal did not crack and remained transparent without any

[4] The powder diffraction patterns were calculated using *WinXPOW* (Stoe & Cie, 2007).

visible changes. Twinning reversibly disappeared on heating, as confirmed by crystal structure refinement at ambient temperature before and after the cooling cycle.

3.2. Crystal structure of the β^{II}-form

The crystal structure of the β^{II}-form inherits the main features of the initial (room-temperature) β-polymorph of chlorpropamide, such as the π-type hydrogen-bonded ribbons (Figs. 8*a* and *b*). At the same time, the symmetry of the structure changes from orthorhombic to monoclinic. In particular, the two molecules which were related by the *b*-glide plane in the β-polymorph become symmetry-independent with the loss of the glide plane in the II form, and the number of molecules in the asymmetric unit increases from one in the β-form to two in the β^{II}-polymorph (Fig. 3*a*). The molecules, although symmetry-independent, do not differ within experimental error in the values of bond lengths and valence angles. The difference in their geometry is limited to the values of the torsion angles. The most significant difference (4–6°) is observed for the torsion angles characterizing rotation around the C7—N1 bond (τ_4 and τ_5 in Table 2). Other torsion angle differences do not exceed 3°. The shapes of the displacement ellipsoids suggest that the alkyl tails are disordered. However, attempts to refine the structure with partly populated 'split' positions did not improve the model. Apparently, the disorder is dynamic.

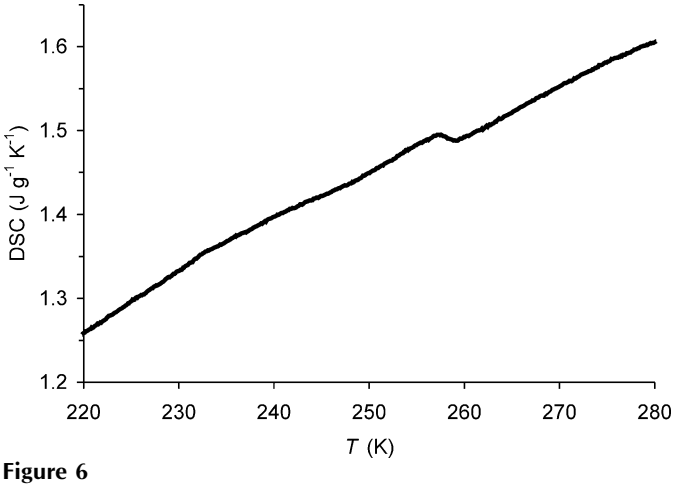

Figure 6
DSC results indicating a heat effect of the phase transition near 257 K.

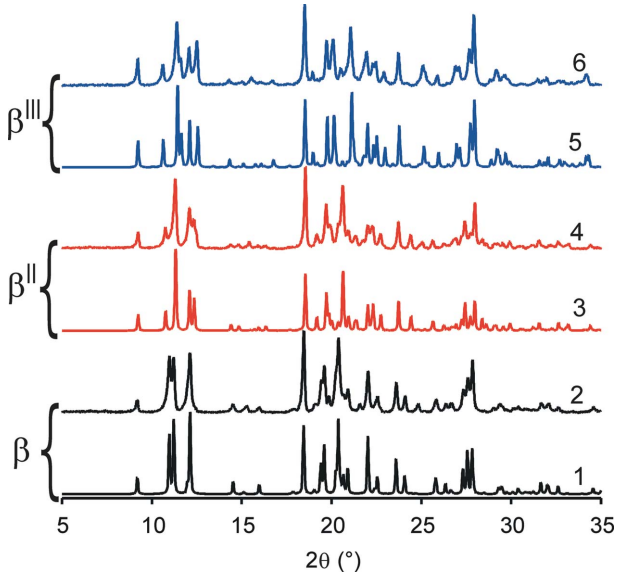

Figure 7
Powder diffraction patterns of the β-form at ambient temperature (1: calculated from the single-crystal diffraction data, 2: experimental), β^{II}-form at 200 K (3: calculated, 4: experimental), β^{III}-form at 100 K (5: calculated, 6: experimental).

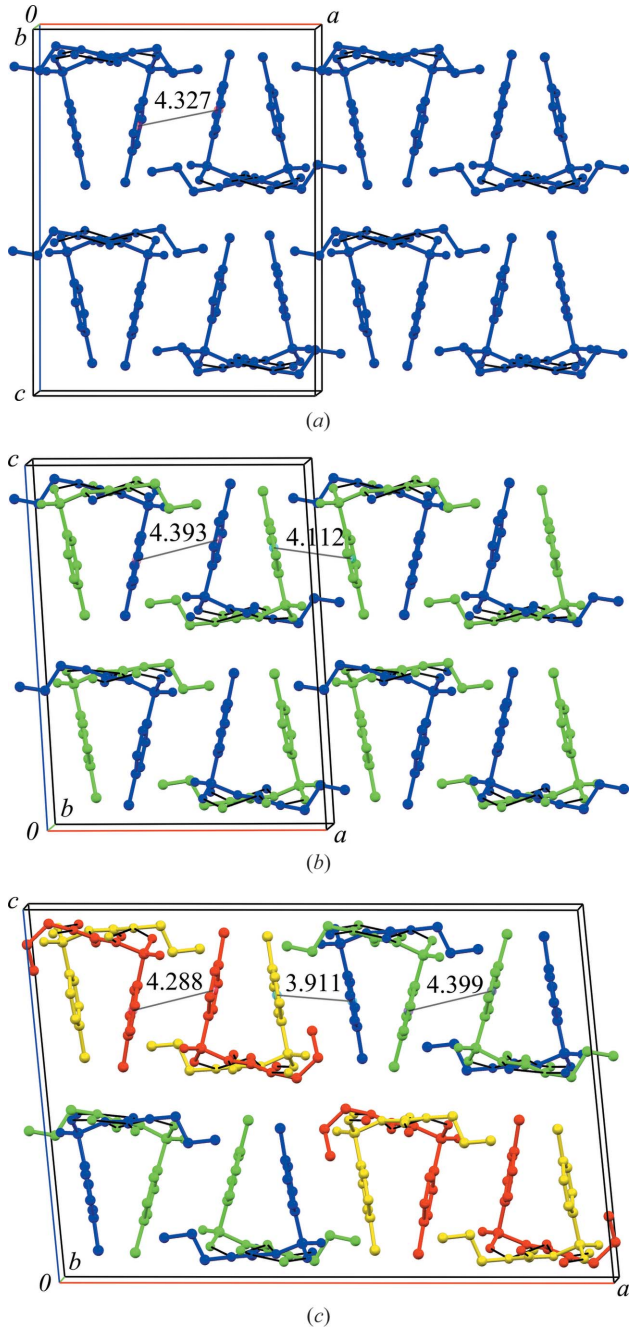

Figure 8
Fragments of the crystal structures of (*a*) the β-form of chlorpropamide at room temperature, (*b*) the β^{II}-polymorph at 200 K and (*c*) the β^{III}-form at 100 K viewed along the *b* axis. Symmetry-independent molecules are coloured differently.

Table 2
Selected torsion angles (°) in the β-, β^{II}- and β^{III}-polymorphs of chlorpropamide (°).

Polymorph, T		β,† 295 K	β^{II}-form, 200 K		β^{III}-form, 100 K			
Numeration of molecule in the asymmetric unit			1	2	1	2	3	4
τ_1	O2—S1—C4—C5‡	12.6 (6)	−11.5 (4)	12.1 (5)	11.6 (5)	−5.3 (5)	−9.9 (5)	14.9 (5)
τ_2	N1—S1—C4—C5‡	−105.2 (5)	106.0 (4)	−106.3 (4)	−106.1 (4)	112.0 (5)	106.4 (4)	−102.7 (4)
τ_3	S1—N1—C7—O3‡	10.1 (8)	−16.5 (7)	5.0 (6)	5.9 (7)	−18.1 (7)	−19.2 (7)	0.7 (7)
τ_4	S1—N1—C7—N2‡	−168.8 (4)	164.1 (3)	−172.6 (3)	−171.8 (4)	161.1 (4)	159.9 (4)	−176.3 (4)
τ_5	C7—N2—C8—C9‡	−94.5 (7)	91.5 (6)	−91.2 (6)	−84.2 (6)	86.6 (6)	84.7 (6)	−107.6 (5)
τ_6	N2—C8—C9—C10‡	−179.7 (7)	−179.2 (4)	−179.0 (5)	179.7 (4)	−179.0 (4)	−177.7 (4)	66.3 (6)

† These values are given for comparison (Drebushchak *et al.*, 2006). ‡ The atom numbering corresponds to that in the initial β-form (Drebushchak *et al.*, 2006).

Table 3
Parameters (Å, °) for hydrogen bonds at several temperatures.

N†	D—H···A	D—H	H···A	D···A	D—H···A
β-form,‡ 295 K					
1	N1—H1N···O3	0.86	1.95	2.740 (5)	152
2	N2—H2N···O2^{i}	0.86	2.41	3.130 (6)	142
3	N2—H2N···O3^{i}	0.86	2.58	3.280 (6)	140
β^{II}-form, 200 K					
1	N11—H11N···O23^{ii}	0.88	2.00	2.737 (4)	141
2	N12—H12N···O22^{ii}	0.88	2.37	3.100 (5)	141
3	N12—H12N···O23^{ii}	0.88	2.55	3.271 (5)	139
1	N21—H21N···O13	0.88	1.89	2.728 (4)	159
2	N22—H22N···O12	0.88	2.36	3.086 (5)	140
3	N22—H22N···O13	0.88	2.52	3.244 (5)	140
β^{III}-form, 100 K					
1	N11—H11N···O23^{ii}	0.88	1.90	2.744 (5)	160
2	N12—H12N···O22^{ii}	0.88	2.28	3.008 (5)	140
3	N12—H12N···O23^{ii}	0.88	2.57	3.295 (5)	140
1	N21—H12N···O13	0.88	2.04	2.750 (5)	137
2	N22—H22N···O12	0.88	2.31	3.027 (5)	138
3	N22—H22N···O13	0.88	2.45	3.183 (5)	141
1	N31—H31N···O43	0.88	2.06	2.725 (5)	132
2	N32—H32N···O42	0.88	2.28	3.005 (5)	140
3	N32—H32N···O43	0.88	2.53	3.237 (5)	138
4	N31—H31N···Cl11^{iii}	0.88	2.83	3.542 (4)	139
1	N41—H41N···O33^{ii}	0.88	1.86	2.726 (5)	170
2	N42—H42N···O32^{ii}	0.88	2.22	2.994 (5)	146
3	N42—H42N···O33^{ii}	0.88	2.68	3.386 (5)	139

Changes in molecular conformations are interrelated with the distortion of hydrogen bonds, although the network itself is largely preserved. In the room-temperature orthorhombic β-polymorph there are three types of N—H···O bond which form infinite ribbons along the b axis. In the β^{II}-polymorph the number of sets of N—H···O bonds doubles compared with the β-polymorph, each set including three types of bond similar to those in the β-form (Table 3). Infinite hydrogen-bonded ribbons are very similar to those in the initial polymorph, but now the three bonds binding a molecule with one neighbour are not identical to those binding it with the other neighbour. Despite the difference in symmetry, the geometric parameters of hydrogen bonds in the β^{II}-polymorph are, in general, close to those of the β-polymorph at room temperature, except for the D—H···A angle of the shortest bond (1), which at 200 K differ by 18° (Table 3), with an intermediate value for the single molecule of the β-form at room temperature.

The aromatic rings of the chlorpropamide molecules in neighbouring ribbons are close to one another (Figs. 8*a* and *b*). On the $\beta \rightarrow \beta^{II}$ phase transition, the distance between the centroids of the aromatic rings becomes $\sim$ 5.1 (2)% shorter [4.112 (3) Å rather than 4.327 (3) Å] for one neighbouring pair, but $\sim$ 1.4 (2)% longer [4.393 (3) Å rather than 4.327 (3) Å] for the other compared with the distance between the centroids of the rings in the initial form. One can suppose that attractive interactions between the aromatic rings contribute to the stabilization of the new phase. It is worth noting that the β-form with its π-type packing is the only polymorph of chlorpropamide in which neighbouring phenyl rings are so close to each other. The symmetry of the initial phase does not allow all the phenyl rings to become simultaneously closer on structural compression. As a result two systems of 'chains' differing in symmetry and the distances between the ring centroids are formed (shown by different colours in Fig. 8). The decrease in distances between the aromatic rings at the same time provokes the monoclinic lattice distortion, twinning and distortion of hydrogen bonds

Structural changes during this phase transition are compatible with the small effect measured by DSC (*cf. e.g.* Coles *et al.*, 2010). From the experimental relation between the orientation matrices of the two twin components it can be concluded that layers of the components must alternate [twin reflection plane (001)]. The directions of the crystallographic axes a and b are not changed compared with those in the starting phase and are the same in the twin components. Twinning can be described by a twofold twin rotation around the a axis and the displacement by the vector $[\frac{1}{2}, 0, \frac{1}{2}]$ (Fig. 9). The c direction is characterized by a negative thermal expansion in the range 150–250 K (Fig. 4). This type of twinning cannot be expected to induce large mechanical stresses and the twin boundaries disappear as soon as the orthorhombic symmetry of the components is restored during the reverse transformation.

3.3. Crystal structure of the β^{III} form

The second polymorphic transition, β^{II} ($P2/c$) $\Leftrightarrow$ β^{III} ($P2/n$), retains a monoclinic crystal lattice, but one of the cell parameters (a) is doubled, and the number of molecules in the asymmetric unit further increases from two to four (Fig. 3*b*).[5] Bond distances and valence angles are similar for all four molecules, even though they are not symmetry related. The most significant difference is in the torsion angles (Table 2), particularly those characterizing rotation around the C7—N1 bond, similar to that observed in the β to β^{II} transition. Although all the molecules preserve the conformation of type II, three of them have the propyl tail in the *trans* conformation and one *gauche* (see torsion angles τ_6 in Table 2, and Fig. 10). The *gauche* conformation is rather rare for chlorpropamide. Of all the polymorphs it was observed only in δ-chlorpropamide (Drebushchak, Chukanov & Boldyreva, 2008). The *gauche* conformation of the propyl tail in δ-chlorpropamide is associated with a type I orientation, but with a type II orientation in the β^{III}-polymorph.

The rare π-shaped motif of the infinite hydrogen-bonded ribbons is also preserved in the β^{III}-form (Fig. 8*c*). However, whereas all the ribbons are symmetrically equivalent in the β- and β^{II}-forms, two symmetrically non-equivalent ribbons are present in the β^{III}-form. As in the β^{II}-form, each ribbon in the β^{III}-form consists of two different molecules. In the ribbons of the first type molecules 1 and 2 each have propyl tails in the *trans* conformation. In the ribbons of the second type, molecule 3 has the *trans* conformation and molecule 4 the *gauche* conformation.

The conformational changes are interrelated with the distortion of the hydrogen-bond network. Geometric parameters of all the hydrogen bonds are listed in Table 3. The general topology of the hydrogen-bond network is to a large extent preserved compared with the initial β- and β^{II}-forms. At the same time, some distances in the hydrogen bonds in the 'low-symmetry' ribbons formed by molecules 3 and 4 of β^{III}-form expand to such an extent that the interactions can no longer be qualified as conventional hydrogen bonds (*e.g.* N42—H42N$\cdots$O33^{ii}), whereas a few new bonds are formed (*e.g.* N31—H31N$\cdots$Cl11^{iii}). The two N—H groups in molecule 3 become bifurcated donors.

The neighbouring aromatic rings in the β^{III}-form at 100 K become even closer than they do in the β^{II}-form at 200 K (Fig. 8*c*): the separation between the centroids of the aromatic rings of molecules 2 and 3 (symmetry code: $\frac{1}{2}-x, y, \frac{1}{2}-z$) becomes 3.911 (3) Å [$\sim$ 4.9 (2)% shorter than at 200 K], and the two other short distances do not increase compared with the corresponding distances in the form at 200 K. We suppose that attractive interactions between aromatic rings constitute an important factor in stabilizing the low-temperature β^{III}-phase, just as for the first phase transition $\beta \rightarrow \beta^{II}$.

3.4. Comparison with phase transitions in other crystals with flexible molecules

The phase transitions discovered in the present work can be compared with recently reported transformations in other crystals of flexible molecules. For example, a low-temperature structural phase transition has been observed in form (II) of benzocaine. It was associated with a sequential displacement parallel to zigzag b-layers of ribbons perpendicular to b^*. The low-temperature phase was characterized by doubling of the b-axis repeat, and a change in space group from $P2_12_12_1$ to $P112_1$. After the phase transition the crystal became twinned (the twin rule corresponding to a 2_1 screw rotation parallel to

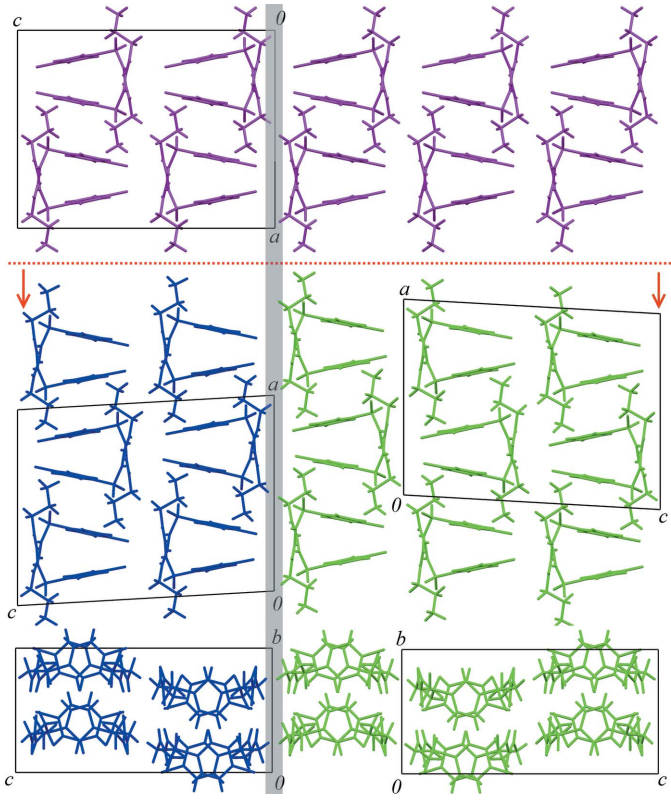

Figure 9
Representation of the twinning mechanism: the fragments of the crystal structures of the starting β-form (magenta) and of the two twin components of the β^{II}-form (first component: blue; second component: light green) viewed along the b and a axes. The twin interface is marked grey.

[5] First we tried to ignore the reflections attributed to the doubled parameter and to refine the structure of the β^{II}-polymorph at 100 K, with unit-cell parameters similar to those at 200 K, *i.e.* a = 14.224 Å. We obtained a model with two molecules in the asymmetric unit, where one of the molecules had the propyl tail in *trans* and *gauche* conformations simultaneously, as if the tail were disordered between the two positions. A feature inherent to X-ray diffraction techniques is that the results give the time- and space-averaged structure. They can, for example, depend on the volume of coherently scattering domains. In general, on the basis of X-ray analysis only it is not trivial to distinguish between a partly disordered structure and a structure consisting of completely ordered coherently conjugated domains of two types (see Herbstein, 1964; Zorky & Nesterova, 1986, 1990, 1993, as examples). In the case of the β^{III}-form of chlorpropamide, we consider a structure with a stochastic static disorder of the alkyl tails as unrealistic because the *gauche* conformation of the neighbouring molecules in the space group $P2/c$ would lead to an extremely short distance between their methyl fragments. A dynamic disordering of the tail between *gauche* and *trans* conformations at such low temperatures, at which the β^{III} polymorph structure is formed, is also unlikely. We therefore reached the conclusion that molecules with different orientations of the tail alternate regularly in the crystal structure, and this results in the doubling of the unit-cell parameter a. The structure at 100 K was solved with a = 28.447 Å and four molecules in the asymmetric unit in $P2/n$.

a; Chan *et al.*, 2009). It is not clear from the published results if all these changes occurred simultaneously or in a step-wise manner. In our example of the low-temperature transitions in β-chlorpropamide we could see two transitions distinctly separated from one another: first twinning with symmetry lowering from orthorhombic to monoclinic, and then doubling of a translational repeat along one of the crystallographic axes accompanied by a pronounced conformational transition.

A low-temperature single-crystal-to-single-crystal phase transition has been observed in one of the polymorphs of a structural analog of chlorpropamide, *i.e.* of tolbutamide, *N*-[(butylamino)carbonyl]-4-methylbenzenesulfonamide. Compared with chlorpropamide, in tolbutamide the Cl atom is substituted by a methyl group, and the propyl tail by a butyl tail. In form (III) of tolbutamide the butyl tail is disordered at ambient temperature and remains disordered on cooling below 150 K. Between 150 and 125 K the diffraction pattern significantly changes. The translation along the *b* axis triples and Z' becomes 3. Instead of all the molecules being symmetry equivalent with the alkyl tails disordered, one of the molecules in the asymmetric unit adopts a *gauche* conformation, and the other two *trans* conformations. The change in volume per molecule during this phase transition does not exceed 1% (Drebushchak *et al.*, 2011).

Another recent example of a sequence of two reversible single-crystal-to-single-crystal low-temperature phase transitions accompanied by a change in the symmetry and an increase in Z' on cooling has been reported for $[Ni(H_2O)_2(15\text{-crown-}5)](HSO_4)_2$ (Siegler & Stavitski, 2010). In the latter example, however, discontinuities in the volume per unit-cell ratios were found for the two transitions.

We can compare the transition in the β-polymorph of chlorpropamide with some other transformations related to the changes in the orientation and/or conformation of the alkyl tails (Coles *et al.*, 2009, 2010; Ferrarini *et al.*, 2003; Herbstein, 2006; Naik & Vasudevan, 2009; Sokolov *et al.*, 2008; Takahashi & Ito, 2010). The conformational changes involving the alkyl tails in chlorpropamide occur between 260 and 125 K. Dynamical transitions related to the orientation of the alkyl tails and changes in their conformations (*trans versus gauche*) in other crystalline and biological systems have been observed in a similar temperature range (180–260 K; Coles *et al.*, 2010; Surovtsev & Dzuba, 2009; Takahashi & Ito, 2010). This suggests that the information on the dynamics of selected molecular fragments is to some extent transferable from system to system. At the same time, the fine details (the exact temperature at which the conformation of the alkyl tail is changed, the preference of *gauche versus trans* conformations *etc.*) depend on the whole structural framework and on the interactions of the alkyl tails with the nearest environment. For example, the *gauche* $\Leftrightarrow$ *trans* isomerization of the end-segment of an alkyl tail has been observed in many systems (Naik & Vasudevan, 2009). Still, the cooling of β-chlorpropamide triggers the *trans* $\rightarrow$ *gauche* isomerization of part of the alkyl tails, whereas a reverse process has been observed in some model synthetic membranes with lipid bilayers (Surovtsev & Dzuba, 2009).

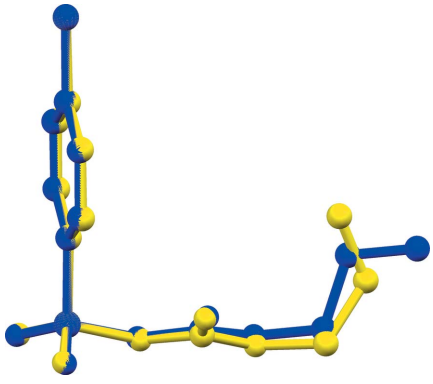

Figure 10
Overlay of the molecular structures of two of the different molecules of chlorpropamide. In the interest of clarity only two molecules for which the difference is the largest are shown. Molecule 2 of the β^{II}-form is darker and molecule 4 of the β^{III}-form is lighter.

One of the intriguing features of the phase transitions described in this paper is that they are not accompanied by any discontinuities in the changes of volume per molecule *versus* temperature, despite pronounced symmetry changes. From a fundamental point of view, the rare phase transitions without a jump-wise change in the volume are very interesting. A discontinuity in the volume decrease is not an absolute must to accompany the changes in symmetry, as in the case discussed in this paper. Moreover, not only can the volume change continuously throughout the phase transition, but also the space-group symmetry is preserved at the same time. As an example, consider the high-pressure phase transition from L-serine^{II} to L-serine^{III} (Boldyreva *et al.*, 2006; Moggach *et al.*, 2006), during which only the hydrogen-bond network changes. This illustrates that the bulk density is not the only parameter determining the lattice energy and stability if there are specific and directional interactions in a structure. Optimizing local packing is at least no less important than decreasing the density averaged over the whole structure.

3.5. Comparison with other molecular crystals with $Z' > 1$

An interesting feature of the series of conformational phase transitions on cooling of β-chlorpropamide is an increase in the number of molecules in the asymmetric unit (Z') from one to two, and then from two to four. In general, the problem of homomolecular organic crystals with $Z' > 1$ is widely discussed in the literature (see for example Anderson *et al.*, 2008; Belsky *et al.*, 1995; Bernstein *et al.*, 2008; Bishop & Scudder, 2009; Brock & Duncan, 1994; Desiraju, 1999, 2007; Gavezzotti, 2008; Görbitz, 2010; Görbitz *et al.*, 2009; Hao *et al.*, 2005; Kuleshova *et al.*, 2003; Nangia, 2008; Nichol & Clegg, 2007; Pidcock, 2006; Siegler & Stavitski, 2010; Steed, 2003; Steed & Atwood, 2009; Steiner, 2000; Zorky, 1994).[6]

[6] Zorky and co-workers have suggested a more detailed description of the structures with $Z' > 1$ than a mere indication of the Z' value. This description is based on the concepts of structural class and orbits (equivalent positions; see *e.g.* Belsky & Zorky, 1970, 1977; Belsky *et al.*, 1995; Chernikova *et al.*, 1990; Zorky, 1996). Zorky & Dashevskaya (1992) proposed to call the homomolecular crystals in which more than two orbits are occupied (*i.e.* $Z' > 1$) 'multisystem' crystals.

According to the statistical surveys published in 2000–2006, less than 8–12% of organic crystal structures reported in the Cambridge Structural Database (CSD) had $Z' > 1$ (Anderson *et al.*, 2006; Steiner, 2000).[7] However, these statistics may be misleading since the structures with high Z' values can be under-represented in the database compared with their actual occurrence simply because their crystals are of poorer quality, and the refinement of such structures may encounter problems arising, in particular, from an unfavourable ratio between the number of measured reflections and the number of parameters. Statistical data on crystal structures also reflect the development of X-ray diffraction methods, as well as (varying with time) trends in the choice of materials for study. Strictly speaking, any presented statistics characterize not the laws of formation of crystal structures, but the existing set of X-ray data (Belsky *et al.*, 1995). The growing increase in interest in the 'multisystem' structures, *i.e.* in the structures with peculiar $Z' >> 1$, has resulted in an increase in the number of such structures described in the literature.

Some structures refined as structures with low Z' and disorder can be not properly refined structures with higher Z' values and *vice versa* (Bernstein *et al.*, 2008). Structures with $Z' > 1$ may be artifacts of structure refinement for crystals of poor quality, *e.g.* because of unrecognized crystal twinning (Herbstein, 1964). Structures with $Z' > 1$ can indicate that the crystal is actually a domain intergrowth of two or more different polymorphs (Bernstein *et al.*, 2008; Bishop & Scudder, 2009; Bond, 2009; Bond *et al.*, 2007; Zorky & Nesterova, 1986, 1990, 1993). Structures with high Z' values are often characterized by pseudosymmetry or modulation (Kuleshova *et al.*, 2003; Schönleber *et al.*, 2003) and can be modified, distorted or modulated versions of the lower Z' structures (Bernstein *et al.*, 2008).

Structures with $Z' > 1$ are often formed from the non-equilibrium crystallization of solutions and are supposed to serve as 'snapshot pictures' and 'fossil relics' of the early stages of crystallization, indicating that there may be several low-lying interconverting conformers in solution, and more than one may crystallize simultaneously because of kinetic factors (Desiraju, 1999, 2007).

As in the case of β-chlorpropamide described in this work, many 'multisystem' structures are formed as a result of solid-state transformations (for recent examples see Coles *et al.*, 2009, 2010; Drebushchak *et al.*, 2011; Fernandes *et al.*, 2004; Siegler & Stavitski, 2010; Takahashi & Ito, 2010). In this case the high Z' values can be a consequence of a supramolecular synthon frustration (Anderson *et al.*, 2008). They usually show signs of structural complexity and arise when it is necessary to find a compromise between optimization of several types of intermolecular interactions and optimal packing requirements (Schönleber *et al.*, 2003). Such structures can be a result of packing frustration because of the awkward molecular shape (Siegler & Stavitski, 2010). Modulation can also be a compromise in optimizing several different types of intermolecular interactions in the structure.

Opposite conclusions on the relation between the packing density and the occurrence of $Z' > 1$ can be found in the literature. Bernstein *et al.* (2008) have noted that 'there is a slight tendency for the high Z' polymorph to have a lower density and therefore when phase transitions could be observed, to correspond in general to the high-temperature form'. A similar conclusion could be derived from a recent observation of a decrease in Z' from 8 to 2 during a pressure-induced phase transition in methyl 2-(carbazol-9-yl)benzoate giving a denser polymorph. The molecules in the $Z' = 2$ high-pressure phase have unfavourable conformations, but these are stabilized in the crystal by their efficient packing (Johnstone *et al.*, 2010). Nangia (2008), on the contrary, writes that 'polymorphs with a larger number of symmetry-independent molecules (high Z') generally have better interactions when compared with the polymorphs with lower Z' values, with the implication that these symmetry-independent molecules have different conformations.... The 'packing problem' of awkwardly shaped molecules is resolved through the presence of multiple molecules or conformers'.

The low-temperature phase transitions in β-chlorpropamide support the observations of Nangia (2008). An increase in Z' is observed as the structure shrinks on cooling and the low-temperature (not the high-temperature) polymorphs are formed. Increasing Z' makes it possible to optimize packing when other options (such as changing molecular conformation from type II to type I, which is more favourable for dense packing; Drebushchak *et al.*, 2009; or changing the molecular packing itself) are not possible because of restricted molecular mobility. In this respect it is relevant to mention a recent study of the structures of alkyl-substituted Trögers base derivatives with the methyl groups replaced by ethyl, iso-propyl and *tert*-butyl groups, which have $Z' > 1$ (Vande Velde *et al.*, 2010). The increasing size of the asymmetric unit is explained by the flexibility of the alkyl substituents and van der Waals stabilization. In addition these effects allow for an additional stabilization of the packing by small changes in the molecular conformations. A similar explanation can be suggested for increasing Z' in form (III) of tolbutamide (Drebushchak *et al.*, 2011) and in β-chlorpropamide (this work) on cooling.

If a 'multisystem' structure is formed during a solid-state transformation, this might, among other possibilities, indicate a continuous process when the motions of different molecular fragments are frozen and activated at different temperatures. Freezing of one or several degrees of freedom in conformational movement of a molecule can produce a polymorphic transition. On the other side, the formation of a 'multisystem structure' can be a consequence of the relaxation of mechanical stress induced in the crystal by transformation. A regular spatial alternation of conformers in a periodic structure may be advantageous to minimize strain (Andrievski, 2003; Boldyreva, 1990, 1992, 1994, 1997; Boldyreva & Boldyrev, 1999; Cahn, 1961, 1968; Cook & De Fontaine, 1969, 1971). In this respect it is interesting that such structures are often observed as the products of solid-state transformations,

[7] A statistical analysis of data deposited in the most recent version of the CSD gives an even smaller number, ~ 5%.

which preserve a single crystal as mechanically intact, independent of whether the transformation is induced by heating or cooling. Minimizing strain can also account for increasing Z' in the course of the phase transitions of β-chlorpropamide on cooling.

3.6. Low-temperature phase transitions in β-chlorpropamide and conformational polymorphism

An increase in Z' means that molecules become non-equivalent and thus, strictly speaking, change their conformation. However, in the case of β-chlorpropamide the significant conformational changes occur only during the phase transition in the range between 150 and 125 K, and not in all, but only in 1/4 of the molecules regularly distributed in the structure. Thus only the β^{III}-form represents a new conformational polymorph compared with β and β^{II}.

The phenomenon of the conformational polymorphism or contact conformery (the occurrence of different conformers of the same molecule in different crystal forms) has been attracting attention for a long time (see *e.g.* Anderson *et al.*, 2008; Bernal, 2007; Bernstein, 1987, 2002; Bishop & Scudder, 2009; Bond, 2010; Brock & Minton, 1989; Gavezzotti, 2008; Hao *et al.*, 2005; Lavut *et al.*, 1981; Leonidov *et al.*, 1993; Nangia, 2008; Nichol & Clegg, 2007; Pidcock, 2006; Vande Velde *et al.*, 2010; Zorky & Razumaeva, 1979). X-ray crystal structures of conformational polymorphs help to understand the interplay of intramolecular (conformer) and intermolecular (lattice) energy in the crystallization and stability of polymorphs. In organic crystals, molecular conformer and crystal lattice energy differences are usually of the same magnitude (typically < 21 kJ mol^{-1}; Nangia, 2008). Therefore, they often compensate one another, giving rise to new crystal structures in which strained conformers can be stabilized by crystal packing forces. On another side, different conformations can lead to different hydrogen-bonding patterns or different close-packing modes.

Usually, the conformational polymorphs are obtained by varying the crystallization conditions, sometimes concomitantly from the same batch. Reports on the transformations between the conformational polymorphs, which can take place in the solid state, are relatively less frequent compared with the number of papers describing the crystallization of a new form, or a solvent-mediated transformation. Still, these processes are very interesting and important. They help us to understand the dynamic properties of molecules when they are not isolated, but are incorporated into a supramolecular assembly, *e.g.* in a molecular crystal. The information on the process can be used to compare the efforts which are required to modify a molecular conformation, to distort the intermolecular hydrogen bonds, to rotate or to shift a molecule as a whole in its environment. Such transformations help us to understand the basics of solid-state reactivity, and the role of the generation and relaxation of the mechanical stress. They are important for designing solid-state devices and molecular machines based on reversible solid-state processes not destroying single crystals.[8]

Solid-state transformations between the conformational polymorphs of chlorpropamide, occurring on heating to almost melting temperatures/cooling back down to ambient temperature (Drebushchak, Drebushchak *et al.*, 2008; Chesalov *et al.*, 2008), as well as on cooling from ambient temperature down to 100 K and reheating to ambient conditions (Drebushchak *et al.*, 2009, and this work), allow the influence of molecular packing in a crystal structure on the relative mobility of selected molecular fragments to be studied. One can conclude from these studies that it is extremely difficult to change the z-type packing for π-type packing and *vice versa*. It is also more difficult to invert a chlorpropamide molecule in the crystal structure producing its enantiomer than to change the orientation of the alkyl tail from type II to type I. For the molecular packing of the π-type it also becomes difficult to change the orientation of the alkyl tail from type II to type I, and the conformational changes on temperature variation are limited in this case to the conformation of propyl tails themselves, and only in some molecules regularly distributed in the structure. The π-type packing seems to hinder the rotations/inclinations of the phenyl rings, but favours the enforcement of attractive interactions between the aromatic rings and the formation of additional N—H$\cdots$Cl hydrogen bonds when the neighbouring molecules approach each other on cooling.

The transitions in the chlorpropamide system studied thus far can serve as illustrations of Ostwald's Rule of Stages: 'When leaving a metastable state, a given chemical system does not seek out the most stable state, rather the nearest metastable one that can be reached with minimum loss of free energy' (Ostwald, 1897). The rule was originally devised to characterize the crystallization from solution but it holds even better for solid-state transformations, when molecular mobility is more restricted, than in the liquid state. This property is widely used to obtain solids as metastable polymorphs *via* topotactic reactions, selecting suitable precursors (for entry points see reviews by Boldyreva, 1999; Boldyreva & Boldyrev, 1999). In the case of chlorpropamide, the polymorphism can be fine-tuned on crystallization and on solid-state transformations, since there are many various options for changing the molecular conformation, which are very sensitive to the environment of the molecule in solution, in the melt, or in the solid state (either a glass or a crystal).

3.7. Possible consequences for pharmaceutical applications

As was mentioned in §1, variable-temperature studies are important for pharmaceutical chemists who need to identify

[8] A solid-state transformation always generates mechanical stress, which can relax either causing single crystals to fragment or, alternatively, preserving crystals intact but changing their size and shape. The topic of reversible single-crystal-to-single-crystal transformations has been very popular in the 1980s–1990s (see reviews: Desiraju, 1987; Boldyreva, 1990, 1992, 1994, 1997; Ohashi, 1993; Boldyreva & Boldyrev, 1999, and references therein), and now is revisited actively again, in particular, in relation to the design of 'molecular machines' and photomechanical devices (Garcia-Garibay, 2007; Halasz, 2010, and references therein).

the crystal forms of active pharmaceutical ingredients. The low-temperature phase transitions in β-chlorpropamide could be easily overlooked if the crystal structure determination were not carried out at multiple temperatures. The volume change per molecule is continuous, and the single crystals remain intact. It is common practice that a single-crystal diffraction experiment aimed at characterizing a new structure is carried out at a single temperature. Nowadays this single temperature is often selected as 150 or 100 K to improve the data quality. The example of polymorphism of chlorpropamide shows that even if the single crystal is preserved on cooling, the low-temperature phase(s) can be different from the ambient temperature one and hence a comparison of the two diffraction patterns, calculated from the single-crystal diffraction data and the experimental one measured at ambient temperature, will differ not because of the anisotropic distortion of the structure (which is very common, see Stephenson, 2006, or Sun, 2007, as recent examples of discussing this problem in relation to pharmaceuticals) but because they correspond to different phases.

4. Conclusions

The example of chlorpropamide shows that a system with a robust hydrogen-bond framework can exhibit rich polymorphism, on crystallization and as a result of solid-state transformations. Even if the hydrogen-bond network is preserved to a large extent over a wide range of temperatures, starting from the cryogenic ones and ending with the melting point, conformational polymorphism can arise because the mobility of different molecular fragments is not the same.

In contrast to the low-temperature phase transition in the ε-form with z-type molecular packing, the cooling of the β-polymorph with π-type packing does not change molecular conformations from type II to type I. The rare π-type packing is also preserved. Thus, the relative energies required to rotate the alkyl tail seem to depend on the packing type in the crystal structure and on the density of the initial polymorph.

The two phase transitions observed in the β-polymorph on cooling are interesting in several respects. First, they provide new examples of polymorphic transformations, with changes in molecular conformations that are so small that the related changes in the energy of the forms are hardly detectable by DSC measurements but nevertheless provoke changes in the crystal symmetry, in Z', in intermolecular contacts and in hydrogen bonding. Second, the phase transitions are observed in a polymorph that is metastable at ambient conditions. Still two other metastable forms, which are structurally related to the β-form, are formed upon cooling and not the stable α-polymorph. Third, the phase transitions are not accompanied by any discontinuities in changes of volume per molecule *versus* temperature, despite pronounced symmetry changes. Last but not least, the single crystals are not destroyed during the phase transitions,[9] despite transformational twinning on cooling and detwinning on heating back to ambient conditions.

The structures of all three phases preserve many similar elements. When the structures are as similar as the β-, β^{II}- and β^{III}-forms of chlorpropamide are, it becomes arguable whether they should be regarded as distinct polymorphs or as modulated and demodulated versions of the same basic molecular arrangement (Bernstein *et al.*, 2008). Whatever terminology is accepted, we cannot deny, however, that the symmetry changes (the crystal system during the first transformation and the translational symmetry during the second one), Z' changes, and the transitions manifest themselves in the X-ray powder diffraction patterns and DSC curves. The relatively small changes in molecular conformations are accompanied by the weakening of the existing intermolecular hydrogen bonds and the formation of some new ones (in particular, a new N—H$\cdots$Cl bond appears in the β^{III}-form). Thus, chlorpropamide can be added to the list of examples appearing in the literature in recent years for which crystallization and solid-state processes can produce phases that are borderline between distinctly different polymorphs and transient states between other forms. These structures often have peculiar properties and therefore attract much attention (see *e.g.* a discussion on the 'new phases' of aspirin by Bond *et al.*, 2007).

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[9] At least under the experimental conditions described in this paper. In general, the ability of a crystal to remain intact during a transformation despite mechanical strain is known to be strongly dependent, among other factors, on the crystal size and shape, the presence of defects and on the cooling rate. We do not know to which extent this holds for chlorpropamide crystals. Under all the conditions tried in our experiments the single crystals twinned, but otherwise were not damaged. The twin ratio differed from crystal to crystal. In this work we did not aim to study the effect of cooling/heating rate, of the crystal size/shape/defect structure on twinning or on preserving crystal integrity.

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