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# Two polymorphs of chlorpropamide: the δ-form and the high-temperature ε-form

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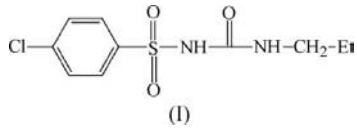
The ε-form of chlorpropamide [systematic name: 4-chloro-*N*-(propylaminocarbonyl)benzenesulfonamide], $C_{10}H_{13}ClN_2O_3S$, has been obtained as single crystals from solution (and not as a polycrystalline sample by heating the α-, γ- or δ-forms). The results of anisotropic structure refinements for the ε- and δ-forms are reported. The density of the δ-polymorph is the highest, and that of the ε-polymorph the lowest, among the five known chlorpropamide polymorphs. The main intermolecular hydrogen-bonding pattern in polymorphs δ and ε is the same as in polymorphs α, β and γ, but the conformations differ. The densities of the polymorphs were found to depend on the molecular conformations.

## Comment

Chlorpropamide, or 4-chloro-*N*-(propylaminocarbonyl)benzenesulfonamide, (I), is an antidiabetic drug and the crystal structures have been reported for three polymorphs, namely α (Koo *et al.*, 1980), β (Drebushchak *et al.*, 2006) and γ (Drebushchak *et al.*, 2007). This work reports the crystal structures of two additional polymorphs, namely δ and ε. The latter has previously only been obtained by heating of the α-, γ- or δ-forms as a polycrystalline sample. Although the structure of this form was claimed to be solved from powder diffraction data, the atomic coordinates were not published (Wildfong *et al.*, 2007). Our work reports the results of a single-crystal structure determination of ε-chlorpropamide, which became possible after this polymorph was obtained for the first time as single crystals from solution. The δ-form is a new polymorph first described by Drebushchak *et al.* (2008), where the structure was refined isotropically to $R[F^2 > 2\sigma(F^2)] = 0.187$ because of the poor quality of the crystals available. The quality of the data was, however, sufficiently good to establish reliably the *gauche* conformation of the alkyl tail. All polymorphs were characterized by differential scanning calorimetry (Drebushchak *et al.*, 2008) and FT–IR spectroscopy (Chesalov *et al.*, 2008).




(I)

The asymmetric unit of each of the δ- and ε-forms contains only one molecule, like the other polymorphs (Fig. 1). The bond lengths and angles in all the polymorphs are similar, and agree with statistical data from *Mogul* [Bruno *et al.*, 2004; Cambridge Structural Database, Version 5.29 (Allen, 2002)]. However, the conformations are different (Table 1 and Fig. 1). In the δ-polymorph, the ethyl tail and the benzene ring are on opposite sides of the N1/C7/O3/N2/C8 plane, as in the α-polymorph (orientation I), whereas in the ε-form they are on the same side, as in the β- and γ-forms (orientation II). The δ-form differs from all other polymorphs in the *gauche* conformation of the propyl tail (compare the N2—C8—C9—C10 torsion angle in Table 1 with the values close to 180° observed for this angle in all the other forms). The ε-form differs significantly from the other polymorphs in the angle between the planes of the benzene ring and atoms N1/C7/O3/N2/C8.

In all the chlorpropamide polymorphs reported to date, the molecules are linked *via* N—H···O hydrogen bonds (Table 2) to form infinite ribbons. The N1—H1N···O3$^{i}$ hydrogen bond [symmetry code: (i) $x-\frac{1}{2}, -y+\frac{3}{2}, -z+1$] in the ε-polymorph (Table 2) is the shortest of all the hydrogen bonds observed in the chlorpropamide polymorphs, although the ε-form is the least dense. The structural motif in the δ- and ε-polymorphs is the same as in the α- and γ-forms (Z-shaped), in contrast with the π-shaped motif observed in the β-form (Fig. 2). Despite having the same Z-shaped motif, the ribbons in the α-, γ-, δ- and ε-polymorphs pack in different ways. Orientation II of the

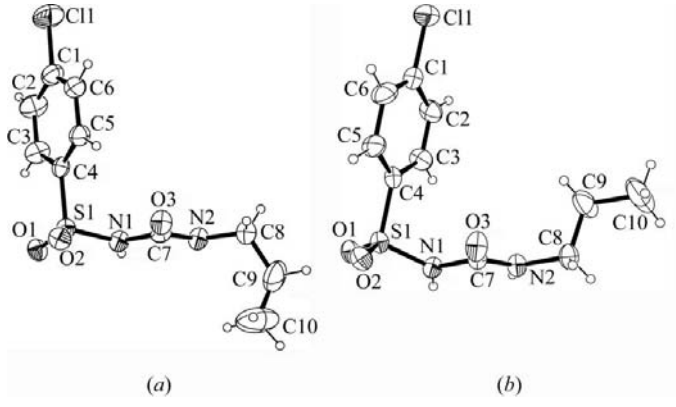



**Figure 1**
The molecular structure of (*a*) δ-chlorpropamide and (*b*) ε-chlorpropamide, viewed along the O3—C7 bond, showing the atom-labelling schemes. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

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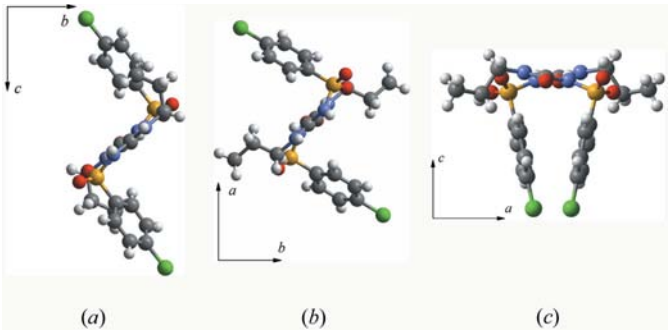


**Figure 2**
The hydrogen-bonded ribbons in (*a*) the δ-form of chlorpropamide, viewed along the *a* axis (Z-shaped motif), (*b*) the ε-form, viewed along the *c* axis (Z-shaped motif), and (*c*) the β-form, viewed along the *b* axis (π-shaped motif) (Drebushchak *et al.*, 2006).

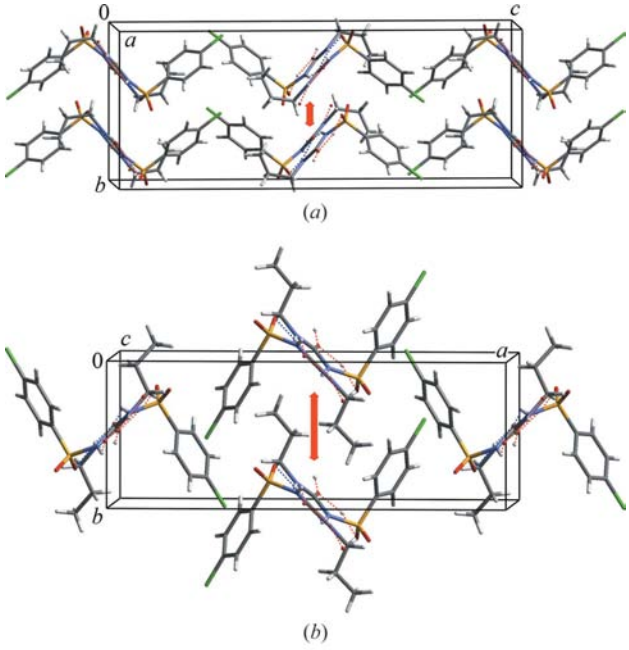


**Figure 3**
Comparative views of the crystal packing of the polymorphs of chlorpropamide, showing (*a*) the δ-form, viewed along the *a* axis, and (*b*) the ε-form, viewed along the *c* axis. Hydrogen bonds are shown as dashed lines. Broad arrows mark the distances between neighbouring hydrogen-bonded ribbons.

alkyl tails does not allow the Z-shaped ribbons to pack in dense piles (Fig. 3), which is why structures with tail orientation I are denser. The difference between the highest (δ-form, tail orientation I) and lowest (ε-form, tail orientation II) density values is 5.6%.

The structural data obtained for the ε-form explain the peculiar behaviour of the β-form with increasing temperature, compared with that of the α-, γ- and δ-polymorphs. In contrast with the other forms, which are converted into the ε-form on heating, samples of the β-form often melt prior to transformation into the ε-form (Drebushchak *et al.*, 2008). The preservation of the packing motif is more important for these structural transformations than the similarity or difference in the molecular conformations. The Z-shaped motif is inherited after $\alpha \rightarrow \varepsilon$, $\gamma \rightarrow \varepsilon$ and $\delta \rightarrow \varepsilon$ polymorphic transitions, while the conformation of the molecules changes significantly. The flexible alkyl tail rotates during the transitions $\alpha \rightarrow \varepsilon$ and $\delta \rightarrow \varepsilon$, changing its orientation from type I to type II. The propyl tail changes its conformation from *gauche* to *trans* in the transition $\delta \rightarrow \varepsilon$. However, these transitions do not require the breaking of intermolecular hydrogen bonds or rotation of the molecules to a noticeable extent with respect to each other. In contrast, the $\beta \rightarrow \varepsilon$ transformation is related to a change from the π-shaped motif to the Z-shaped motif, requiring a change in the orientation of every second molecule in the ribbon (Fig. 2). Therefore, this process seems kinetically hindered in the solid state.

The chlorpropamide polymorphs can be obtained by crystallization from the same solvents under different conditions, and are often present as mixtures in the same batch. The different conformations and packing motifs of nearest neighbours in the different polymorphs might reflect the different conformations and molecular aggregates co-existing in solution, giving rise to different crystal structures depending on the crystallization conditions (Gavezzotti, 2007).

## Experimental

Single crystals of the δ-form were obtained by recrystallization of a commercial sample of chlorpropamide from a heptane–ethyl acetate (2:1 *v*/*v*) solution on rapid cooling, as described by Drebushchak *et al.* (2008). Powder diffraction did not reveal the presence of any other polymorphs in this sample. Single crystals of the ε-polymorph were obtained by dissolving a commercial sample of chlorpropamide (30 mg) in chloroform (0.5 ml) and keeping it at 373 K until complete evaporation of the solvent. According to X-ray powder diffraction, the batch contained a mixture of the ε-form as the dominant phase and the α- and β-forms as minor admixtures. Single crystals of the ε-form for X-ray diffraction study could be selected from the batch.

### Polymorph δ of compound (I)

*Crystal data*

$C_{10}H_{13}ClN_2O_3S$
$M_r$ = 276.73
Orthorhombic, *Pbca*
*a* = 9.3198 (4) Å
*b* = 10.3218 (3) Å
*c* = 26.2663 (10) Å
*V* = 2526.74 (16) Å$^3$
*Z* = 8
Cu *Kα* radiation
μ = 4.24 mm$^{-1}$
*T* = 295 (2) K
0.22 × 0.14 × 0.03 mm

*Data collection*

Oxford Diffraction KM-4-CCD diffractometer
Absorption correction: multi-scan (*CrysAlis RED*; Oxford Diffraction, 2008)
$T_{min}$ = 0.432, $T_{max}$ = 0.883
6522 measured reflections
2159 independent reflections
1318 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.074

*Refinement*

$R[F^2 > 2\sigma(F^2)]$ = 0.062
$wR(F^2)$ = 0.169
*S* = 0.93
2159 reflections
156 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.35 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.38 e Å$^{-3}$

**Table 1**
Selected torsion angles (°) for the δ- and ε-forms of (I).

| | δ-form | ε-form |
|---|---|---|
| N2—C8—C9—C10 | −50.9 (8) | −179.4 (4) |
| O3—C7—N1—S1 | 11.8 (5) | 25.3 (4) |
| N2—C7—N1—S1 | −167.8 (3) | −155.7 (2) |
| O3—C7—N2—C8 | 0.7 (6) | −3.0 (5) |
| N1—C7—N2—C8 | −179.6 (4) | 178.0 (3) |
| C9—C8—N2—C7 | 115.4 (6) | −88.9 (5) |
| C7—N1—S1—O1 | −169.5 (3) | 168.1 (2) |
| C7—N1—S1—O2 | −39.1 (4) | −62.6 (3) |
| C7—N1—S1—C4 | 76.9 (3) | 54.1 (3) |
| C5—C4—S1—O1 | 169.9 (3) | 114.0 (3) |
| C3—C4—S1—O1 | −7.9 (4) | −65.8 (3) |
| C5—C4—S1—O2 | 38.6 (4) | −17.4 (3) |
| C3—C4—S1—O2 | −139.2 (3) | 162.8 (3) |
| C5—C4—S1—N1 | −78.5 (4) | −135.7 (3) |
| C3—C4—S1—N1 | 103.7 (4) | 44.6 (3) |

**Table 2**
Hydrogen-bond geometry for the δ- and ε-forms of (I) (Å, °).

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| δ-form | | | | |
| N1—H1N···O3$^{i}$ | 0.86 | 1.96 | 2.788 (4) | 160 |
| N2—H2N···O2$^{i}$ | 0.86 | 2.34 | 3.058 (4) | 141 |
| N2—H2N···O3$^{i}$ | 0.86 | 2.38 | 3.135 (4) | 146 |
| ε-form | | | | |
| N1—H1N···O3$^{ii}$ | 0.86 | 2.02 | 2.727 (3) | 138 |
| N2—H2N···O2$^{ii}$ | 0.86 | 2.36 | 3.026 (3) | 134 |
| N2—H2N···O3$^{ii}$ | 0.86 | 2.31 | 3.054 (3) | 145 |

Symmetry codes: (i) $x-\frac{1}{2}, -y+\frac{3}{2}, -z+1$; (ii) $-x+1, -y, z-\frac{1}{2}$.

## Polymorph ε of compound (I)

*Crystal data*

$C_{10}H_{13}ClN_2O_3S$
$M_r$ = 276.73
Orthorhombic, $Pna2_1$
$a$ = 19.9121 (10) Å
$b$ = 7.3459 (4) Å
$c$ = 9.1384 (4) Å
$V$ = 1336.69 (12) Å$^3$
$Z$ = 4
Mo $K\alpha$ radiation
$\mu$ = 0.44 mm$^{-1}$
$T$ = 295 (2) K
0.40 × 0.15 × 0.03 mm

*Data collection*

Oxford Diffraction KM-4-CCD diffractometer
Absorption correction: multi-scan (*CrysAlis RED*; Oxford Diffraction, 2008)
$T_{min}$ = 0.893, $T_{max}$ = 0.987
6456 measured reflections
2447 independent reflections
1556 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.034

*Refinement*

$R[F^2 > 2\sigma(F^2)]$ = 0.035
$wR(F^2)$ = 0.080
$S$ = 0.87
2447 reflections
155 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.33 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.26 e Å$^{-3}$
Absolute structure: Flack (1983), with 1102 Friedel pairs
Flack parameter: 0.07 (8)

All H atoms were positioned geometrically and refined using a riding model, with C—H = 0.93 (aromatic), 0.96 ($CH_3$) or 0.97 Å ($CH_2$) and N—H = 0.86 Å, and with $U_{iso}$(H) = 1.2$U_{eq}$(C,N). A bond-length restraint (DFIX in *SHELXL97*; Sheldrick, 2008) was applied to the C9—C10 bond during the refinement of the δ-polymorph. The δ- and ε-polymorphs show poor diffraction properties, which may be a result of the high mobility of the alkyl chains, manifested by the large values of the atomic displacement parameters for C9 and C10 (Fig. 1). The same was observed previously for the β-polymorph (Drebushchak *et al.*, 2006).

For both compounds, data collection: *CrysAlis CCD* (Oxford Diffraction, 2008); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2008); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997) and *Mercury* (Macrae *et al.*, 2006); software used to prepare material for publication: *SHELXL97*, *WinGX* (Farrugia, 1999) and *publCIF* (Westrip, 2008).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: TR3050). Services for accessing these data are described at the back of the journal.

## References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.
Bruno, I. J., Cole, J. C., Kessler, M., Luo, J., Motherwell, W. D. S., Purkis, L. H., Smith, B. R., Taylor, R., Cooper, R. I., Harris, S. E. & Orpen, A. G. J. (2004). *J. Chem. Inf. Comput. Sci.* **44**, 2133–2144.
Chesalov, Yu. A., Baltakhinov, V. P., Drebushchak, T. N., Boldyreva, E. V., Chukanov, N. V. & Drebushchak, V. A. (2008). *J. Mol. Struct.* doi:10.1016/j.molstruc.2008.03.006.
Drebushchak, T. N., Chukanov, N. V. & Boldyreva, E. V. (2006). *Acta Cryst.* E**62**, o4393–o4395.
Drebushchak, T. N., Chukanov, N. V. & Boldyreva, E. V. (2007). *Acta Cryst.* C**63**, o355–o357.
Drebushchak, V. A., Drebushchak, T. N., Chukanov, N. V. & Boldyreva, E. V. (2008). *J. Therm. Anal. Calorim.* **93**, 343–351.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Farrugia, L. J. (1999). *J. Appl. Cryst.* **32**, 837–838.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Gavezzotti, A. (2007). *Molecular Aggregation*. IUCr Monographs on Crystallography, No. 19. Oxford Science Publications.
Koo, C. H., Cho, S. I. & Yeon, Y. H. (1980). *Arch. Pharmacol. Res.* **3**, 37–49.
Macrae, C. F., Edgington, P. R., McCabe, P., Pidcock, E., Shields, G. P., Taylor, R., Towler, M. & van de Streek, J. (2006). *J. Appl. Cryst.* **39**, 453–457.
Oxford Diffraction (2008). *CrysAlis CCD* and *CrysAlis RED*. Oxford Diffraction Ltd, Abingdon, England.
Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.
Westrip, S. P. (2008). *publCIF*. In preparation.
Wildfong, P. L. D., Morris, K. R., Anderson, C. A. & Short, S. M. (2007). *J. Pharm. Sci.* **96**, 1100–1113.