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Polymorphs of gabapentin

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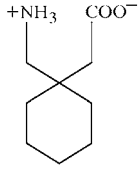
Gabapentin [or 1-(aminomethyl)cyclohexaneacetic acid], $C_9H_{17}NO_2$, exists as a zwitterion [1-(ammoniomethyl)cyclohexaneacetate] in the solid state. The crystal structures and bonding networks of two new monoclinic polymorphs (β-gabapentin and γ-gabapentin) are studied and compared with a previously reported gabapentin polymorph [α-gabapentin: Ibers (2001). *Acta Cryst.* C**57**, 641–643]. All three polymorphs have extensive networks of hydrogen bonds between the NH_3^+ and COO^- groups of neighbouring molecules. In β-gabapentin, there is an additional weak intramolecular hydrogen bond.

Comment

Gabapentin is structurally related to the neurotransmitter γ-aminobutyric acid (GABA), which has been widely studied for its significant inhibitory action in the central nervous system (Bowery, 1993). There have also been studies on the cocrystallization of GABA with various carboxylic acids as a means of possibly improving the effectiveness of GABA (Wenger & Bernstein, 2006).



(I)

In recent years, there has been intense interest in the polymorphs of gabapentin and in the synthesis of gabapentin analogues. Gabapentin was originally used as an antiepileptic drug, but its applications have been extended to the treatment of neuropathic pain (Magnus, 1999). One form of gabapentin (α-gabapentin) crystallizes as a zwitterion in the space group $P2_1/c$ [a = 5.8759 (6) Å, b = 6.9189 (7) Å, c = 22.262 (2) Å, β = 90.080 (2)° and V = 905.173 Å^3; Ibers, 2001]. Note that α-gabapentin corresponds to form II of Lladó *et al.* (2003) and to the form of gabapentin found in the commercially available Pfizer pharmaceutical Neurontin®.

The structures of a gabapentin monohydrate (Ibers, 2001), several gabapentin derivatives (Ananda *et al.*, 2003), peptides incorporating gabapentin (Vasudev *et al.*, 2007) and a related 1-(aminomethyl) structure called pregabalin (Venu *et al.*, 2007) have also been reported. The crystal structures of two previously unreported gabapentin polymorphs, *viz*. β-gabapentin, (I) (Fig. 1), and γ-gabapentin, (II) (Fig. 2), are presented here. X-ray powder diffraction (XRPD) studies show that β-gabapentin corresponds to form III of Pesachovich *et al.* (2001) and γ-gabapentin corresponds to form IV of Satyanarayana *et al.* (2004).

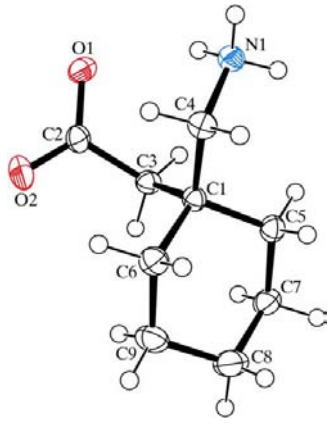


Figure 1
The atomic numbering scheme of β-gabapentin. Displacement ellipsoids are drawn at the 50% probability level.

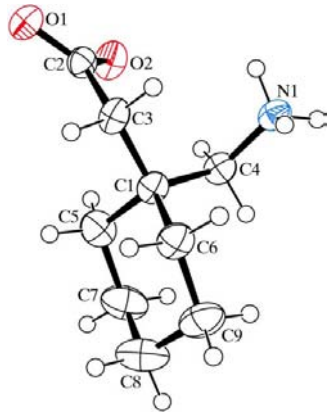


Figure 2
The atomic numbering scheme of γ-gabapentin. Displacement ellipsoids are drawn at the 50% probability level.

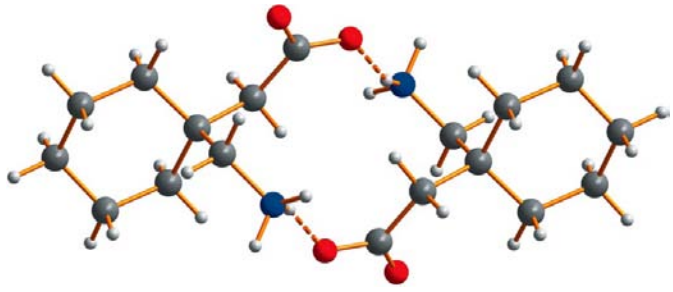


Figure 3
A view of the $R_2^2(14)$ centrosymmetric hydrogen-bonded dimer in α-gabapentin.

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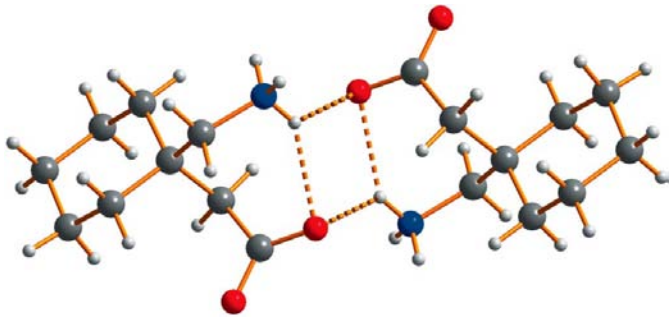

Figure 4
A view of the $R_2^2(14)$ centrosymmetric hydrogen-bonded dimer in β-gabapentin.

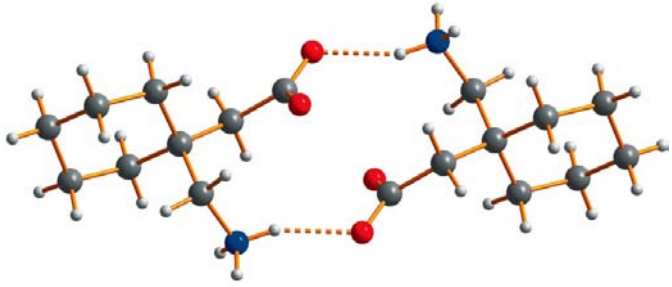

Figure 5
A view of the $R_2^2(14)$ centrosymmetric hydrogen-bonded dimer in γ-gabapentin.

As in the case of α-gabapentin, β- and γ-gabapentin also exist as zwitterions. In all three forms, the cyclohexane ring has a chair conformation. However, as shown in Figs. 3–5, the three polymorphs have different orientations of the NH_3^+ and COO^- groups. Significantly, in β-gabapentin, the NH_3^+ group is in an equatorial position and the COO^- group in an axial position, while in the α- and γ-gabapentin polymorphs, these groups are in the opposite positions. This difference is further indicated by the torsion angle C3—C1—C5—C7 (Table 1). There is an interesting difference in the rotation of the amine group, which is in an unusual eclipsed conformation for the α form and in a normal staggered conformation for the β and γ forms. These differences are quantified by the torsion angles O1—C2—C3—C1, C2—C3—C1—C4 and C3—C1—C4—N1 (Table 1), showing the different angles and directions in which the NH_3^+ and COO^- groups are twisted (see Figs. 3–5). The torsion angles in Table 1 indicate that the largest conformational difference is due to the twisting of the COO^- group.

In β- and γ-gabapentin, there is extensive hydrogen bonding between the NH_3^+ and COO^- groups of neighbouring molecules. The NH_3^+ group hydrogen bonds to three COO^- groups, each from a different neighbouring molecule. The geometries of the hydrogen-bonding interactions for the three polymorphs of gabapentin are compared in Table 2. There is a significant difference in the hydrogen-bonding networks of α- and β-gabapentin, and this is primarily due to the presence of an intramolecular hydrogen bond in β-gabapentin [N1(H15)$\cdots$O1 = 2.940 (2) Å]. Atom O1 acts as a

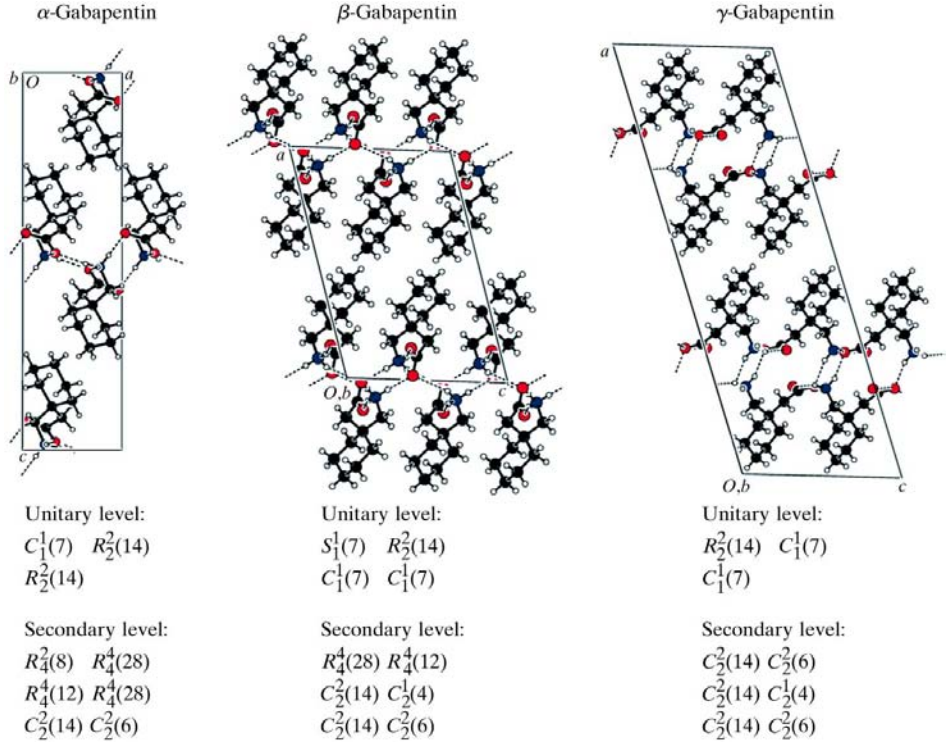

Figure 6
The hydrogen-bonding networks and associated unitary and secondary level graph sets for α-, β- and γ-gabapentin. The α-form (left) is viewed down the a axis. The β (centre) and γ (right) forms are viewed down the b axis.

trifurcated hydrogen-bond acceptor in β-gabapentin as opposed to the bifurcated acceptor seen in α-gabapentin. There is a corresponding lengthening of the N1—H15···O1^{i} hydrogen bond between two neighbouring molecules [*i.e.* N1(H15)···O1^{i} = 2.783 (2) and 3.024 (2) Å for α- and β-gabapentin, respectively; symmetry codes: (i) $-x+1, -y+1, -z+1$; $-x, -y, -z+1$].

As with α-gabapentin, there is no intramolecular hydrogen bond in γ-gabapentin. The N···O hydrogen-bond distances are very similar in α- and γ-gabapentin (average N1···O = 2.763 and 2.771 Å for α- and γ-gabapentin, respectively). In both the α and γ polymorphs, atom O1 acts as a bifurcated hydrogen-bond acceptor. The differences in the packing of gabapentin in the three polymorphs are evident from Fig. 6, which shows their hydrogen-bonding networks and the graph sets (Bernstein *et al.*, 1995) of these networks. In Fig. 6, the hydrogen-bonded chains and rings are shown along the *b* axis of the α polymorph (left) and along the *c* axes of the β and γ polymorphs (centre and right). There are four graph sets common to each polymorph, *i.e.* two unitary-level graph sets, $C_1^1(7)$ and $R_2^2(14)$, and two secondary-level graph sets, $C_2^2(14)$ and $C_2^2(6)$. The centrosymmetric hydrogen-bonded dimers shown in Figs. 3–5 all have the $R_2^2(14)$ graph set. Only the γ polymorph has the unitary-level $S(7)$ graph set for the intramolecular interaction.

A comparison of the densities (1.257, 1.247 and 1.216 Mg m^{-3}) and packing efficiencies (71.3, 70.5 and 68.7%) for the three gabapentin polymorphs shows that the molecules are most efficiently packed in α-gabapentin and suggests, as shown by preliminary differential scanning calorimetry (DSC) studies, that it is the thermodynamically most stable form. Hot stage microscopy and DSC (see supplementary material, Figs. 7 and 8) were used to measure the melting points of the three polymorphs, which occur over a broad temperature range. The melting points (peak positions and range) are 434.0 (428–439), 439.28 (428–441) and 436.80 K (423–441 K) for the α-, β- and γ-gabapentin forms, respectively. However, DSC studies also show that possible phase transitions occur at temperatures between 358 and 368 K in both the β (small endotherm) and γ polymorphs (small exotherm), implying that the final melting points refer to only one thermodynamically stable polymorph. Further investigations of these phase transformations are currently being undertaken (Levendis & Reece, 2007). A fourth polymorph has been reported in the patent literature, referred to as form I by Lladó *et al.* (2003). However, single crystals of this polymorph have not yet been isolated.

Experimental

Gabapentin purchased from Sigma–Aldrich was found by XRPD to correspond to the α polymorph. β-Gabapentin was prepared by dissolving the commercially available gabapentin (Sigma–Aldrich) in 96% ethanol until the solution was saturated. The solution was then heated at 333 K for 48 h. Needle-like crystals of β-gabapentin were grown from the solution at 333 K. In the preparation of γ-gabapentin, α-gabapentin was dissolved in 96% ethanol at 333 K. The solution was then cooled to room temperature. Plate-like crystals of γ-gabapentin formed after 3 d of slow evaporation (see supplementary material for photographs of the β and γ crystals; Fig. 7). In each case, crystals suitable for single-crystal X-ray diffraction were selected directly from the samples. A comparison of the experimental and calculated XRPD of each of the bulk samples confirmed that the bulk solid was, in fact, a pure form of the polymorph studied by single-crystal X-ray diffraction.

Compound (I)

Crystal data

$C_9H_{17}NO_2$
M_r = 171.24
Monoclinic, $P2_1/c$
a = 14.5376 (16) Å
b = 6.6329 (6) Å
c = 9.8343 (9) Å
β = 105.922 (5)°
V = 911.91 (15) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 173 (2) K
0.58 × 0.10 × 0.02 mm

Data collection

Bruker APEXII CCD detector diffractometer
5118 measured reflections
2195 independent reflections
1168 reflections with $I > 2\sigma(I)$
R_{int} = 0.084

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.046
$wR(F^2)$ = 0.101
S = 0.87
2195 reflections
109 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.28 e Å^{-3}

Compound (II)

Crystal data

$C_9H_{17}NO_2$
M_r = 171.24
Monoclinic, $C2/c$
a = 30.5452 (11) Å
b = 5.9268 (2) Å
c = 10.8841 (4) Å
β = 108.316 (2)°
V = 1870.58 (12) Å^3
Z = 8
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 173 (2) K
0.58 × 0.49 × 0.11 mm

Data collection

Bruker APEXII CCD detector diffractometer
7746 measured reflections
2042 independent reflections
1608 reflections with $I > 2\sigma(I)$
R_{int} = 0.031

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.046
$wR(F^2)$ = 0.125
S = 1.06
2042 reflections
110 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.17 e Å^{-3}

Table 1
Selected torsion angles (°) for α-, β- and γ-gabapentin.

	α	β	γ
C3—C1—C5—C7	−166.22	−65.44 (18)	−168.79 (15)
O1—C2—C3—C1	−161.36	95.97 (18)	151.56 (14)
C2—C3—C1—C4	51.21	−46.4 (2)	63.47 (18)
C3—C1—C4—N1	60.07	−52.5 (2)	47.74 (17)
C2—C3—C1—C5	−68.63	−168.37 (14)	−56.38 (18)
C2—C3—C1—C6	172.52	71.87 (18)	−174.14 (14)
N1—C4—C1—C6	−58.28	−173.57 (14)	−72.56 (17)
N1—C4—C1—C5	−178.71	69.42 (18)	168.72 (13)

Note: α-gabapentin parameters obtained from Ibers (2001).

Table 2
Hydrogen-bonding parameters (Å) for the α-, β- and γ-gabapentin.

D—H···A	D—H	H···A	D···A	D—H···A
α-Gabapentin				
N1—H15—O1^{i}	0.92	1.91	2.7827 (16)	158.2
N1—H16—O2^{ii}	0.92	1.85	2.7525 (16)	165.3
N1—H17—O1^{iii}	0.96	1.81	2.7547 (18)	165.8
β-Gabapentin				
N1—H15—O1	0.91	2.19	2.9398 (19)	138.7
N1—H15—O1^{i}	0.91	2.42	3.0242 (18)	123.8
N1—H16—O2^{ii}	0.91	1.86	2.723 (2)	157.0
N1—H17—O1^{iii}	0.91	1.81	2.7174 (19)	175.8
γ-Gabapentin				
N1—H15—O1^{i}	0.91	1.93	2.7980 (16)	159.2
N1—H16—O2^{ii}	0.91	1.85	2.7324 (17)	161.5
N1—H17—O1^{iii}	0.91	1.91	2.7851 (18)	161.3

Symmetry codes for α-gabapentin: (i) $-x+1, -y+1, -z+1$; (ii) $-x, -y+1, -z+1$; (iii) $x, y+1, z$; for β-gabapentin: (i) $-x, -y, -z+1$; (ii) $x, y-1, z$; (iii) $-x, y-\frac{1}{2}, -z+\frac{1}{2}$; for γ-gabapentin: (i) $-x+\frac{1}{2}, -y+\frac{1}{2}, -z+1$; (ii) $x, -y+1, z+\frac{1}{2}$; (iii) $x, -y, z+\frac{1}{2}$. Note: α-gabapentin parameters obtained from Ibers (2001).

H atoms were positioned geometrically and allowed to ride on their respective parent atoms.

For both polymorphs, data collection: *APEX2* (Bruker, 2005); cell refinement: *SAINT-NT* (Bruker, 2005); data reduction: *SAINT-NT*; program(s) used to solve structure: *SHELXTL* (Bruker, 1999); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL* and *DIAMOND* (Brandenburg, 2004); software used to prepare material for publication: *SHELXTL*, *ORTEP-3* (Farrugia, 1997) and *PLATON* (Spek, 2003).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: TR3031). Services for accessing these data are described at the back of the journal.

References

Ananda, K., Aravinda, S., Vasudev, P. G., Raja, K. M. P., Sivaramakrishnan, H., Nagarajan, K., Shamala, N. & Balaram, P. (2003). *Curr. Sci.* **85**, 1002–1011.
Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
Bowery, N. G. (1993). *Annu. Rev. Pharmacol. Toxicol.* **33**, 109–147.
Brandenburg, K. (2004). *DIAMOND*. Version 3.1d. Crystal Impact GbR, Bonn, Germany.
Bruker (1999). *SHELXTL*. Version 5.1. Bruker AXS Inc., Madison, Wisconsin, USA.
Bruker (2005). *APEX2* (Version 2.0-1) and *SAINT-NT* (Version 6.0). Bruker AXS Inc., Madison, Wisconsin, USA.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Ibers, J. A. (2001). *Acta Cryst.* C**57**, 641–643.
Levendis, D. C. & Reece, H. A. (2007). Unpublished results.
Lladó, J. B., Cruz, R. G., Grau, E. M., del Carmen, M. & Miguel, O. (2003). US Patent No. 6 521 787.
Magnus, L. (1999). *Epilepsia*, **40**, s66–s72.
Pesachovich, M., Singer, C. & Pilarski, G. (2001). US Patent No. 6 255 526 B1.
Satyanarayana, C., Ramanjaneyulu, G. S. & Kumar, I. V. S. (2004). World Intellectual Property Organization, Publication No. WO 2004/110342.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
Vasudev, P. G., Ananda, K., Chatterjee, S., Aravinda, S., Shamala, N. & Balaram, P. (2007). *J. Am. Chem. Soc.* **129**, 4039–4048.
Venu, N., Vishweshwar, P., Ram, T., Surya, D. & Apurba, B. (2007). *Acta Cryst.* C**63**, o306–o308.
Wenger, M. & Bernstein, J. (2006). *Angew. Chem. Int. Ed.* **45**, 7966–7969.