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Gabapentin and gabapentin monohydrate

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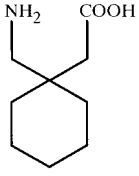
Gabapentin [1-(aminomethyl)cyclohexaneacetic acid, $C_9H_{17}NO_2$] is a zwitterion in the solid state. Its crystal structure involves extensive hydrogen bonding between the NH_3^+ and COO^- groups of neighboring molecules. The structure of gabapentin monohydrate [1-(aminomethyl)cyclohexaneacetic acid monohydrate, $C_9H_{17}NO_2{\cdot}H_2O$] also involves such hydrogen bonding and, in addition, has a hydrogen-bonding network comprising the water molecules and both the NH_3^+ and COO^- groups.

Comment

Gabapentin is a new-generation antiepileptic drug that is used as add-on therapy (Placidi *et al.*, 2000), as well as monotherapy (Chadwick *et al.*, 1998) in patients with partial seizures (Lima, 2000; Morton & Pellock, 2000). With the introduction of gabapentin and other promising new antiepileptic drugs, safe and effective seizure control may become a reality for an increasing number of adults with epilepsy (Mattson, 1998). The mechanism of action of gabapentin remains unclear, although it is apparently dissimilar to that of other antiepileptic agents (Gee *et al.*, 1996). Earlier data suggest that an effect of gabapentin on the formation of γ-aminobutyric acid



(I)
(II) = (I)·H_2O

(gaba), a non-protein amino acid that functions as a neurotransmitter, might be involved in its mechanism of action (Loescher *et al.*, 1991). A later study in which a [3H]-gabapentin-binding protein was isolated and characterized indicates that [3H]gabapentin interacts with the $\alpha 2\delta$ subunit of a voltage-dependent Ca^{2+} channel (Gee *et al.*, 1996).

Despite intense interest in gabapentin and its polymorphs (Pesachovich *et al.*, 1998), its crystal structure is unknown, as is that of its monohydrate. The structures of these two compounds, (I) and (II), respectively, are presented here.

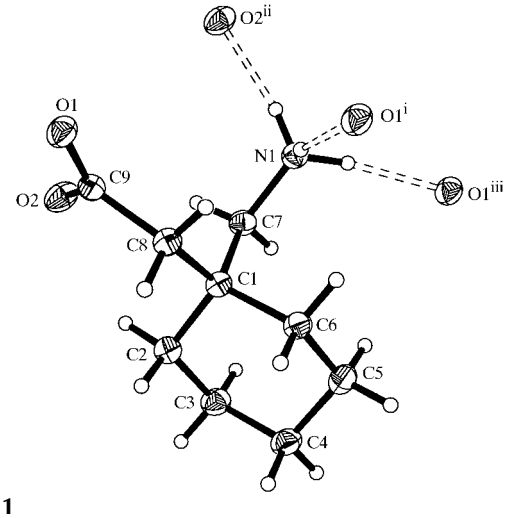


Figure 1
The structure of gabapentin shown with 50% probability displacement ellipsoids, except for the H atoms, which are shown as small circles. The symmetry codes are as in Table 2.

Gabapentin, (I), is a zwitterion in the solid state, as shown in Fig. 1. Metrical data for the non-H atoms are given in Table 1. These data are in good agreement with those found in the low-temperature determination of the structure of γ-aminobutyric acid (gaba: Craven & Weber, 1983; Weber *et al.*, 1983). Gaba is also a zwitterion.

The structure of gabapentin monohydrate, (II), is shown in Fig. 2. It too is a zwitterion. Metrical data for the non-H atoms are given in Table 3 and again agree well with those in gaba as well as with those in anhydrous gabapentin.

In gabapentin, as in gaba, there is extensive hydrogen bonding between the NH_3^+ and COO^- groups of neighboring molecules. These hydrogen-bonding interactions are detailed in Table 2. In the monohydrate, in addition to the direct hydrogen bonding between the NH_3^+ and COO^- groups of neighboring molecules, the O atom (O*W*) of the water mol-

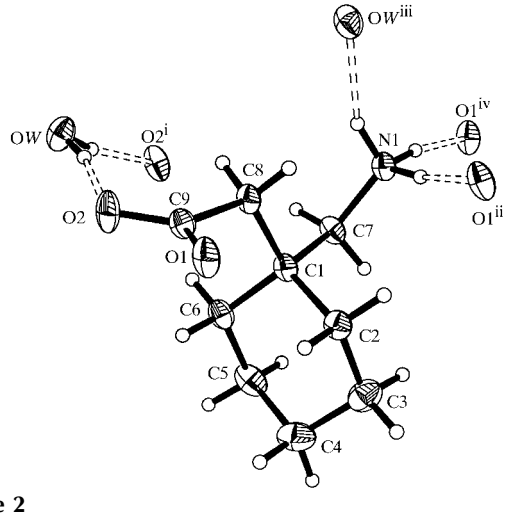


Figure 2
The structure of gabapentin monohydrate shown with 50% probability displacement ellipsoids, except for the H atoms, which are shown as small circles. The O atom of the water molecule is O*W*. The symmetry codes are as in Table 4.

ecule is hydrogen bonded to both groups. The hydrogen-bonding interactions are detailed in Table 4.

In gaba, the difference [0.019 (6) Å] in carboxylate C—O bond lengths was ascribed to hydrogen bonding, with the long bond involving an O atom that forms two N—H···O bonds and the short bond involving the other O atom that forms only one N—H···O bond. In gabapentin, the carboxylate C—O bonds differ by 0.020 (2) Å and again the long bond involves an O atom that forms two N—H···O bonds and the short bond involves an O atom that forms only one N—H···O bond. In the monohydrate, the C—O bond lengths differ by 0.017 (3) Å, with the long bond involving an O atom that forms two N—H···O bonds and the short bond involving an O atom that forms two O*W*—H···O bonds. In all three compounds, the hydrogen bonds are strong.

Experimental

The sample of gabapentin provided by Purepac Pharmaceutical Company contained crystals suitable for diffraction studies. For the preparation of the monohydrate, 160 mg of gabapentin was dissolved in 1 ml of water and 3 ml of 2-propanol was added. The resultant solution was placed in a freezer. Four days later, crystals of gabapentin monohydrate were harvested from the precipitate, which also contained gabapentin. The two materials differ in their crystal habits and are readily distinguished from one another.

Compound (I)

Crystal data

$C_9H_{17}NO_2$
M_r = 171.24
Monoclinic, $P2_1/c$
a = 5.8759 (6) Å
b = 6.9198 (7) Å
c = 22.262 (2) Å
β = 90.080 (2)°
V = 905.18 (16) Å^3
Z = 4
D_x = 1.257 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2674 reflections
θ = 6.2–28.1°
μ = 0.09 mm^{-1}
T = 153 (2) K
Needle, colorless
0.30 × 0.09 × 0.09 mm

Data collection

Bruker SMART 1000 CCD diffractometer
ω scans
7951 measured reflections
2147 independent reflections
1572 reflections with $I > 2\sigma(I)$
R_{int} = 0.042
θ_{max} = 28.3°
$h = -7 \rightarrow 7$
$k = -8 \rightarrow 8$
$l = -29 \rightarrow 29$
Intensity decay: <2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.046
$wR(F^2)$ = 0.118
S = 0.98
2147 reflections
177 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0752F_o^2)^2]$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.39 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

Table 1
Selected geometric parameters (Å, °) for (I).

O1—C9	1.2717 (17)	C1—C6	1.5524 (18)
O2—C9	1.2519 (17)	C2—C3	1.533 (2)
N1—C7	1.4998 (19)	C3—C4	1.528 (2)
C1—C7	1.5353 (19)	C4—C5	1.524 (2)
C1—C2	1.544 (2)	C5—C6	1.525 (2)
C1—C8	1.5446 (18)	C8—C9	1.5277 (18)
C7—C1—C2	108.23 (11)	C5—C4—C3	110.54 (12)
C7—C1—C8	110.60 (11)	C4—C5—C6	111.07 (12)
C2—C1—C8	110.56 (11)	C5—C6—C1	113.95 (11)
C7—C1—C6	111.47 (11)	N1—C7—C1	114.03 (11)
C2—C1—C6	109.45 (11)	C9—C8—C1	119.68 (11)
C8—C1—C6	106.54 (10)	O2—C9—O1	123.48 (12)
C3—C2—C1	114.37 (12)	O2—C9—C8	120.88 (12)
C4—C3—C2	111.42 (12)	O1—C9—C8	115.62 (12)

Table 2
Hydrogen-bonding geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
N1—HN1···O1^{i}	0.918 (18)	1.910 (18)	2.7827 (16)	158.2 (15)
N1—HN2···O2^{ii}	0.92 (2)	1.85 (2)	2.7525 (16)	165.3 (16)
N1—HN3···O1^{iii}	0.96 (2)	1.81 (2)	2.7547 (16)	165.8 (16)

Symmetry codes: (i) $1-x, 1-y, 1-z$; (ii) $-x, 1-y, 1-z$; (iii) $x, 1+y, z$.

Compound (II)

Crystal data

$C_9H_{17}NO_2{\cdot}H_2O$
M_r = 189.25
Monoclinic, $P2_1/c$
a = 14.567 (3) Å
b = 9.2153 (18) Å
c = 7.6503 (15) Å
β = 93.375 (3)°
V = 1025.2 (3) Å^3
Z = 4
D_x = 1.226 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 1958 reflections
θ = 2.6–28.2°
μ = 0.09 mm^{-1}
T = 153 (2) K
Flat plate, colorless
0.35 × 0.26 × 0.03 mm

Data collection

Bruker SMART 1000 CCD diffractometer
ω scans
Absorption correction: numerical face indexed
T_{min} = 0.972, T_{max} = 0.998
9122 measured reflections
2461 independent reflections
1550 reflections with $I > 2\sigma(I)$
R_{int} = 0.058
θ_{max} = 28.3°
$h = -19 \rightarrow 18$
$k = -12 \rightarrow 12$
$l = -10 \rightarrow 10$
Intensity decay: <2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.057
$wR(F^2)$ = 0.133
S = 0.97
2461 reflections
194 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.07F_o^2)^2]$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.42 e Å^{-3}
$\Delta\rho_{min}$ = −0.22 e Å^{-3}

Table 3
Selected geometric parameters (Å, °) for (II).

O1—C9	1.268 (2)	C1—C8	1.549 (3)
O2—C9	1.251 (2)	C2—C3	1.526 (3)
N1—C7	1.493 (2)	C3—C4	1.524 (3)
C1—C7	1.542 (2)	C4—C5	1.525 (3)
C1—C2	1.544 (2)	C5—C6	1.521 (3)
C1—C6	1.546 (2)	C8—C9	1.525 (2)
C7—C1—C2	111.23 (15)	C3—C4—C5	110.60 (18)
C7—C1—C6	107.67 (15)	C6—C5—C4	111.17 (17)
C2—C1—C6	109.01 (15)	C5—C6—C1	113.28 (16)
C7—C1—C8	107.22 (15)	N1—C7—C1	114.11 (15)
C2—C1—C8	111.88 (15)	C9—C8—C1	115.38 (15)
C6—C1—C8	109.73 (15)	O2—C9—O1	124.28 (17)
C3—C2—C1	113.95 (16)	O2—C9—C8	118.50 (16)
C4—C3—C2	111.62 (18)	O1—C9—C8	117.22 (16)

Table 4
Hydrogen-bonding geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
O*W*—H*WA*···O2	0.88 (3)	1.89 (3)	2.748 (2)	165 (2)
O*W*—H*WB*···O2^{i}	0.91 (3)	1.85 (3)	2.7503 (19)	170 (3)
N1—HN1···O1^{ii}	0.96 (2)	1.91 (2)	2.846 (2)	165.1 (18)
N1—HN2···O*W*^{iii}	0.91 (2)	1.97 (2)	2.796 (2)	151.0 (18)
N1—HN3···O1^{iv}	1.02 (2)	1.74 (2)	2.755 (2)	171.7 (19)

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

The positional and isotropic displacement parameters of all H atoms were refined. The refined C—H distances are in the range 0.95 (2)–1.02 (2) Å for gabapentin and 0.96 (2)–1.05 (2) Å for gabapentin monohydrate.

For both compounds, data collection: *SMART* (Bruker, 2000); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 2000); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997*a*); molecular graphics: *SHELXTL*/*PC* (Sheldrick, 1997*b*); software used to prepare material for publication: *SHELXL*97.

I thank Purepac Pharmaceutical Company for the gift of gabapentin.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: DA1172). Services for accessing these data are described at the back of the journal.

References

Bruker (2000). *SMART* (Version 5.054) and *SAINT* (Version 6.02A). Bruker AXS Inc., Madison, Wisconsin, USA.
Chadwick, D. W., Anhut, H., Greiner, M. J., Alexander, J., Murray, G. H., Garofalo, E. A. & Pierce, M. W. (1998). *Neurology*, **51**, 1282–1288.
Craven, B. M. & Weber, H. P. (1983). *Acta Cryst.* B**39**, 743–748.
Gee, N. S., Brown, J. P., Dissanayake, V. U. K., Offord, J., Thurlow, R. & Woodruff, G. N. (1996). *J. Biol. Chem.* **271**, 5768–5776.
Lima, J. M. L. (2000). *Curr. Pharm. Des*. **6**, 873–878.
Loescher, W., Hoenack, D. & Taylor, C. P. (1991). *Neurosci. Lett.* **128**, 150–154.
Mattson, R. H. (1998). *Neurology*, **51**, S15–20.
Morton, L. D. & Pellock, J. M. (2000). *Curr. Pharm. Des*. **6**, 879–900.
Pesachovich, M., Singer, C. & Pilarski, G. (1998). PCT Int. Appl. WO 9828255.
Placidi, F., Mattia, D., Romigi, A., Bassetti, M. A., Spanedda, F. & Marciani, M. G. (2000). *Clin. Neurophysiol*. **111**, 1637–1642.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1997*a*). *SHELXL*97. University of Göttingen, Germany.
Sheldrick, G. M. (1997*b*). *SHELXTL*/*PC*. Version 5.101. Bruker AXS Inc., Madison, Wisconsin, USA.
Weber, H. P., Craven, B. M. & McMullan, R. K. (1983). *Acta Cryst.* B**39**, 360–366.