

(S)-3-(Ammoniomethyl)-5-methylhexanoate (pregabalin)¹

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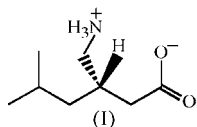
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The title compound, C₈H₁₇NO₂, exists as a zwitterion, adopting a propeller conformation. Molecules self-assemble to form a hydrogen-bonded layer parallel to the *ab* crystallographic plane connected by N⁺—H···O⁻ and C—H···O⁻ hydrogen bonds. These layers are stacked along the *c* axis and are stabilized by van der Waals interactions.

Comment

The title compound, (*S*)-3-(aminomethyl)-5-methylhexanoic acid, (I), is also known as pregabalin. It is used for the treatment of neuropathic pain and in generalized anxiety disorder (Huckle, 2004), and is marketed by Pfizer as Lyrica. The asymmetric unit consists of one molecule, as shown in Fig. 1. The N atom is protonated by proton transfer from the acid group, and thus the molecule exists in a zwitterionic state and adopts a propeller conformation. There are no intramolecular hydrogen bonds. The C—O bond lengths of the carboxylate group are comparable (Table 1), and this behavior is indicative of a partial double-bond character of the C—O bonds as a



result of the delocalization of the negative charge. The molecular geometry of (I), however, is significantly distorted in the solid state. The torsion angles around the C—C bonds bearing the carboxylate and ammonium groups deviate significantly from the ideal values, while those of the isobutyl group are close to the expected values. For instance, the C1—C2—C3—C4 and N1—C4—C3—C5 torsion angles deviate from the ideal value (180°) by about 18 and 11°, respectively (Table 1). In one related 1-(aminomethyl)- structure, *viz.*

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gabapentin monohydrate (Ibers, 2001), the corresponding torsion angles are 171.1 and 45.8°, respectively.

In the crystal structure (Table 2), each molecule is connected to four other molecules *via* three distinct N⁺—H···O⁻ hydrogen bonds and a weak C—H···O⁻ hydrogen bond (Desiraju & Steiner, 1999). Asymmetric dimers are formed between molecules related by 2₁ along [100], and these are connected by N⁺—H···O⁻ hydrogen bonds into a one-dimensional chain running parallel to [100] (entries 1 and 3 in Table 2; Fig. 2). The one-dimensional chain is further stabilized by a C—H···O⁻ hydrogen bond (entry 4 in Table 2). These translation-related chains are interlinked along [010] by N⁺—H···O⁻ hydrogen bonds (entry 3 in Table 2), generating

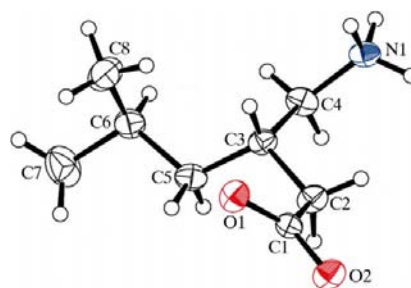


Figure 1 An ORTEP III drawing (Burnett & Johnson, 1996) of the title compound, showing the atomic numbering. Displacement ellipsoids of non-H atoms are drawn at the 30% probability level. H atoms are shown as small spheres of arbitrary radii.

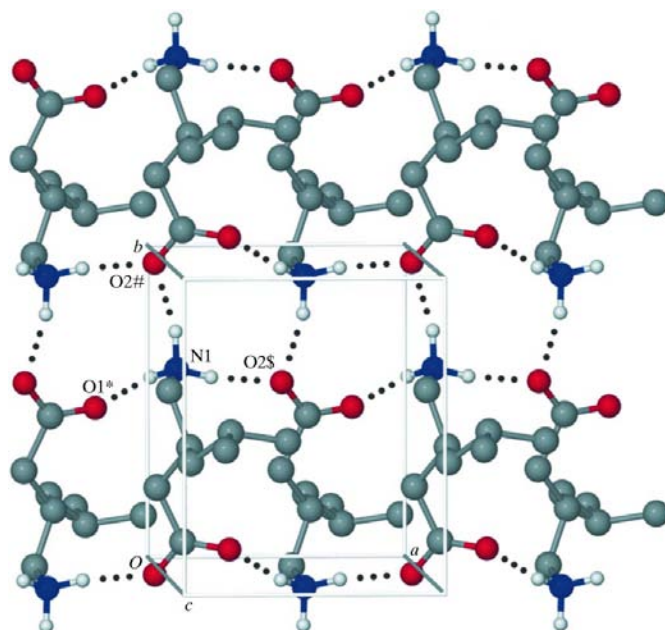


Figure 2 A packing diagram of compound (I), showing one N⁺—H···O⁻ hydrogen-bonded (dashed lines) layer parallel to the (001) plane (see *Comment*). Atoms marked with an asterisk (*), hash (#) or dollar sign (\$) are at the symmetry positions (x - 1/2, -y + 1/2, -z), (x, y + 1, z) and (x + 1/2, -y + 1/2, -z), respectively.

a layer parallel to the *ab* crystallographic plane in such a way that the isobutyl groups point away perpendicularly on either side of the layer. The packing of hydrogen-bonded layers creates an interdigitated arrangement of isobutyl groups in the interlayer region, and the layers are close packed through van der Waals interactions. Thus, the hydrophilic layers (containing ionic groups) alternate with the hydrophobic layers (containing isobutyl groups) in the crystal along [001] with layer thicknesses of about $c/3.3$ and $c/5$ Å (*c* refers to the unit-cell spacing along [001]), respectively. While the hydrophilic layers are centered on $z = \frac{1}{2}$ and 1, the hydrophobic layers are at $z = \frac{1}{4}$ and $\frac{3}{4}$. Because there are a greater number of hydrogen-bond donors than acceptors in the system, carboxylate atoms O1 and O2 are involved in bifurcated hydrogen bonds (Table 2).

Hydrogen bonds between ammonium and carboxylate groups are considered to be stronger than those between the corresponding neutral groups because of reinforcement by charge assistance in the presence of anion–cation interactions (Jeffrey, 1997). The occurrence of such strong intermolecular interactions in the crystal structure of (I) explains the significant torsion-angle distortion around the C–C bonds bearing the carboxylate and ammonium groups (Tables 1 and 2). Distortion of molecular shape in response to the requirements of the strong hydrogen-bonding interactions is a well understood phenomenon both in small molecules and in proteins (Steiner *et al.*, 2000; Russell *et al.*, 2006; Thaimattam *et al.*, 2002). This possibility further complicates prediction of organic crystal structures, which remains a major challenge in crystal engineering (Dey *et al.*, 2005). The simulated X-ray diffraction pattern of compound (I) duplicates the experimental one, which confirms the single-phase nature of the bulk sample. The crystal structure of (I) provides a good model for study of the packing of the leucine side chain in protein structures.

Experimental

The title compound was synthesized and purified in our laboratory according to reported procedures (Silverman & Andruszkiewicz, 2001). Diffraction quality single crystals of (I) were obtained by dissolving the compound in a minimum quantity of 2-propanol at 338 K and keeping the solution undisturbed for crystallization at ambient temperature (m.p. 467–468 K). See the supplementary CIF for differential scanning calorimetry and powder X-ray diffraction data.

Crystal data

$C_8H_{17}NO_2$	$V = 941.12$ (11) Å ³
$M_r = 159.23$	$Z = 4$
Orthorhombic, $P2_12_12_1$	Mo $K\alpha$ radiation
$a = 6.4641$ (4) Å	$\mu = 0.08$ mm ⁻¹
$b = 7.8224$ (5) Å	$T = 298$ K
$c = 18.6122$ (13) Å	$0.40 \times 0.22 \times 0.20$ mm

Data collection

Rigaku Mercury diffractometer	7834 measured reflections
Absorption correction: multi-scan (Jacobson, 1998)	1284 independent reflections
$T_{\min} = 0.981$, $T_{\max} = 0.985$	870 reflections with $F^2 > 2\sigma(F^2)$
	$R_{\text{int}} = 0.034$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.051$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.056$	
$S = 1.10$	$\Delta\rho_{\max} = 0.20$ e Å ⁻³
1284 reflections	$\Delta\rho_{\min} = -0.22$ e Å ⁻³
127 parameters	

Table 1

Selected geometric parameters (Å, °).

O1–C1	1.244 (3)	C3–C5	1.529 (3)
O2–C1	1.254 (3)	C3–C4	1.520 (3)
N1–C4	1.491 (3)	C5–C6	1.526 (3)
C1–C2	1.530 (3)	C6–C7	1.532 (3)
C2–C3	1.523 (3)	C6–C8	1.514 (4)
O1–C1–C2–C3	–5.0 (3)	C5–C3–C4–N1	169.3 (2)
O2–C1–C2–C3	177.8 (2)	C2–C3–C5–C6	168.3 (2)
C1–C2–C3–C4	161.71 (19)	C4–C3–C5–C6	–66.8 (3)
C1–C2–C3–C5	–74.2 (3)	C3–C5–C6–C7	177.2 (2)
C2–C3–C4–N1	–66.2 (3)	C3–C5–C6–C8	–60.3 (3)

Table 2

Hydrogen-bond geometry (Å, °).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
N1–H11 \cdots O2 ⁱ	0.94 (3)	1.83 (3)	2.764 (3)	169 (2)
N1–H12 \cdots O2 ⁱⁱ	0.949 (16)	1.811 (17)	2.736 (3)	164 (2)
N1–H13 \cdots O1 ⁱⁱⁱ	0.94 (2)	1.85 (3)	2.768 (3)	164 (3)
C2–H22 \cdots O1 ⁱⁱⁱ	0.95	2.57	3.439 (3)	152

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

Friedel pairs were merged in the absence of significant anomalous scattering effects. H atoms bound to carbon were positioned geometrically, with C–H distances of 0.95 Å, and refined using a riding model. H atoms bound to the nitrogen of the ammonium group were refined isotropically.

Data collection: *CrystalClear* (Rigaku, 1999); cell refinement: *CrystalClear*; data reduction: *CrystalStructure* (Rigaku/MSK, 2004); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Watkin *et al.*, 1996); molecular graphics: *X-SEED* (Version 2.0; Barbour, 2001); software used to prepare material for publication: *CrystalStructure*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GA3046). Services for accessing these data are described at the back of the journal.

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