

6-(2-Chloroacetamido)hexanoic acid

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Crystals of the title compound, C₈H₁₄ClNO₃, belong to the space group *Cc* and are characterized by an asymmetric unit containing two molecules, both with a twisted conformation. The molecular packing is stabilized by N—H···O=C hydrogen bonds between the amide groups of molecules with the same conformation. In addition, hydrogen-bonded cyclic carboxylic acid dimers are established between molecules with a different conformation. The ClCH₂—CONH bond has a *cis* conformation in order to favour an intramolecular Cl···HN electrostatic interaction. Weak intra- and intermolecular CH₂···O=C interactions are also present.

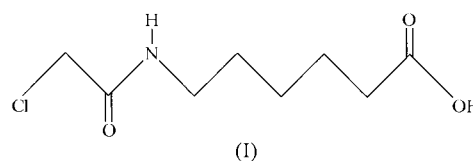
Comment

The development of materials for biomedical applications, such as orthopedic devices, scaffolds for tissue engineering, bioabsorbable surgical sutures and drug delivery systems, is nowadays a subject of considerable interest. Polyesters constitute the main family of biodegradable polymers that has until now been commercialized for the indicated uses (Huang, 1985). Natural hydroxy acid derivatives, such as the polymers constituted by glycolic acid units, are the most widely applied since these materials may be safe for *in vivo* use.

Efforts are also focused on providing new materials that can cover a wider range of properties. Poly(ester amide)s can be mentioned as a promising family because of the occurrence of strong intermolecular interactions between amide groups and the presence of degradable ester groups (Montané *et al.*, 2002). Recently, we have found that alternating poly(ester amide)s constituted by glycolic acid and ω -amino acid units can be prepared easily by a solid- or a melt-state thermal polycondensation that involves a metal salt of the appropriate chlorinated derivative [ClCH₂CONH(CH₂)_{*n*-1}COO⁻·M⁺] (Vera, Rodríguez-Galán & Puiggalí, 2004; Vera, Franco & Puiggalí, 2004). The high yield and molecular weight that can be attained by this method have aroused interest in these polymers. Solid-state polycondensation of halogenated carboxylates had previously been assayed to obtain polyglycolide (Herzberg & Epple, 2001) and other polyesters

(Epple & Kirschnick, 1997). Unfortunately, the occurrence of secondary reactions limited the molecular weight of the polymer and the applicability of the method.

A molecular solid-state reaction relies on a suitable arrangement of the reactants in the crystal structure, and consequently structural studies become interesting. The title compound, (I), has been chosen for being the precursor of metal salts that can be polymerized to obtain the alternating poly(ester amide) constituted by glycolic acid and 6-aminohexanoic residues. Structural data of related compounds are only available for *N*-chloroacetyl- β -alanine (Urpi *et al.*, 2003). In this case, the polymerization of the corresponding salt led to a low molecular weight sample since a stable seven-membered cyclic compound was favoured (Rodríguez-Galán *et al.*, 2003).



The asymmetric unit of (I), with two crystallographically independent molecules, *A* and *B*, is shown in Fig. 1, while selected torsion angles and hydrogen-bond geometry are reported in Tables 1 and 2, respectively. Both molecules show a twisted conformation caused by the deviation of the CONH—CH₂CH₂ and NHCH₂—CH₂CH₂ torsion angles of the 6-aminohexanoic residue from 180°. This twisting constitutes the main crystallographic difference between the two molecules [torsion angle values of 113.4 (4) and -66.4 (4)° for molecule *A*, and 81.8 (4) and 67.7 (4)° for molecule *B*] and demonstrates the absence of an additional symmetry element. The experimental values found for the CONH—CH₂CH₂ torsion angle agree with that determined by quantum mechanical calculations on small molecules. A stabilization near 90° was found and was attributed to the overlap between the nitrogen lone pair and the CH₂—CH₂ bond (Dasgupta *et al.*, 1996). The value of 113.4° found in molecule *A* for the CONH—CH₂CH₂ torsion angle also allows a weak intramolecular hydrogen bond to be established between atom H31A of a methylene group and atom O1A of the amide group (Table 2 and Fig. 1). This hydrogen bond is of the *S*(5) type according to graph-set theory (Etter, 1990). Note that this interaction cannot be found in molecule *B*.

Inspection of the Cambridge Structural Database (CSD, Version 5.27 of January 2006; *ConQuest* Version 1.8; Allen, 2002; Bruno *et al.*, 2002) shows that only three compounds with ε -aminohexanoic acid units have been solved. The conjugate of indole-3-acetic acid with this ω -amino acid has a similar conformation to molecule *B*, with values of 99.8 and 54.4° for the two indicated torsion angles, which cause a folding of the aliphatic side chain over the indole ring (Nigović *et al.*, 1992). However, it should be pointed out that an all-*trans* conformation was found for the ε -aminohexanoic acid units in the other two studied derivatives [6,6'-ureylenedihexanoic acid and 6,6'-(oxalyldiimino)dihexanoic acid (Coe *et al.*, 1997)], and also that this zigzag conformation is usually

postulated for aliphatic polyamides derived from ω -amino acids (Kohan, 1995).

The $\text{ClCH}_2\text{—CONH}$ torsion angle has a *cis* conformation, which is in agreement with the results obtained with other related structures, such as chloroacetylglucylglycine (Rao & Mallikarjunan, 1973), 2-chloroacetamide (Kalyanaraman *et al.*, 1978) and *N*-chloroacetyl- β -alanine (Urpí *et al.*, 2003). This conformation appears stabilized by the $\text{Cl}\cdots\text{HN}$ intramolecular electrostatic interaction (Table 2), which is of the $S(5)$ type (Etter, 1990).

The molecular conformation is finally characterized by the planarity within experimental accuracy of both the amide and the carboxylic acid groups. The r.m.s. deviation is 0.0073 Å for atoms C1A/C2A/O1A/N1A/C3A, 0.0051 Å for atoms C1B/C2B/O1B/N1B/C3B, 0.0005 Å for atoms C7A/C8A/O2A/O3A, and 0.0017 Å for atoms C7B/C8B/O2B/O3B from the mean planes passing through these atoms.

The packing is characterized by the establishment of a network of intermolecular hydrogen bonds that involve amide–amide and acid–acid interactions. Hydrogen bonds between amide groups [$C(4)$ type; Etter, 1990] are established between equivalent molecules along a direction parallel to the crystallographic b axis (Fig. 2). Note that the hydrogen-bonding geometry is slightly different for molecules *A* and *B* (Table 2) owing to their distinct molecular conformation. The carboxamide groups of the two molecules of the asymmetric unit appear shifted along the a axis and point in approximately the same sense. However, the crystal structure becomes non-polar owing to the c -glide plane symmetry. These carboxylic acid groups are also involved in weak intermolecular hydrogen bonds with the C1 methylene groups. This interaction is established between inequivalent molecules (Table 2 and Fig. 2) and gives rise to a ring of the $R_2^2(8)$ type (Etter, 1990).

Hydrogen bonding of the carboxylic acid groups is of cyclic dimer type $R_2^2(8)$ (Etter, 1990). It involves two crystallographically inequivalent molecules and does not occur about a centre of inversion. There are, therefore, two inequivalent hydrogen bonds involving atoms O2A and O2B as acceptors

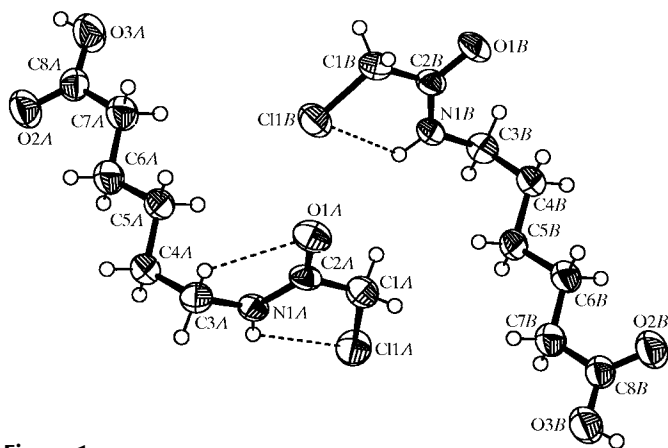


Figure 1

The asymmetric unit of (I), showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and dashed lines indicate intramolecular hydrogen bonds or short contacts.

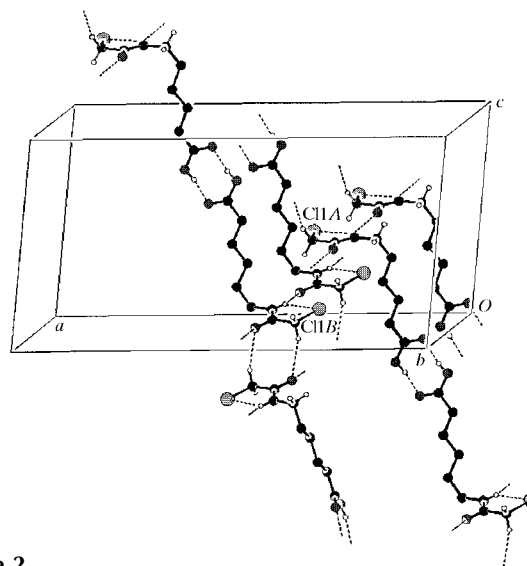


Figure 2

The molecular packing of (I). Only the two molecules (*A* and *B*) of the asymmetric unit and the neighbouring molecules that interact by hydrogen bonds (dashed lines) are represented. H atoms not involved in hydrogen bonding have been omitted in order to clarify the interactions.

and atoms O3A and O3B as donors. Note, however, that a pseudo-centre of symmetry exists at the ‘mid-point’ of the cyclic dimer portion since the torsion angles of the $\text{—(CH}_2\text{)}_4\text{COOH}$ groups are very close to 180° for both molecules of the asymmetric unit. The disubstituted eight-membered ring is almost planar, with an r.m.s. deviation of 0.0323 Å for atoms C7A/C8A/O2A/O3A/C7B/C8B/O2B/O3B from the mean plane passing through them, as expected from the interaction of the hydrogen-bonding protons and the lone pairs of the carbonyl O atoms that have sp^2 -hybridization (Robertson, 1964). The observed hydrogen-bond geometry (Table 2) is fully consistent with the average geometry deduced from the data corresponding to 2228 fragments deposited in the CSD; the O—O distance and O—H—O angle are 2.647 Å and 170.45° , respectively. Furthermore, the experimental C=O—H angles (119.77 and 118.80°) are also close to the mean value of 122.01° . A stacking of cyclic dimers where carboxyl groups are offset along their shorter C=O bonds is observed, as commonly found in the packing of carboxylic acids (Leiserowitz, 1976).

There are great differences between the packing of the title compound and of the related compound *N*-chloroacetyl- β -alanine (Urpí *et al.*, 2003), where a ribbon structure is generated owing to the establishment of a network of hydrogen bonds between amide and acid groups. This feature suggests that the length of the amino acid unit has a strong influence on the packing preferences.

Experimental

The title compound was synthesized by dropwise addition of a diethyl ether solution of chloroacetyl chloride (0.11 mol in 23 ml) and aqueous 1 M sodium hydroxide (0.1 mol) to a water solution of 6-amino-hexanoic acid (0.1 mol in 25 ml) and NaOH (0.1 mol). The reaction mixture was maintained at a temperature of 273 K for 2 h. The pH

was kept close to 11–12 by gradual addition of aqueous 1 M sodium hydroxide to neutralize the hydrochloric acid produced during the condensation. After 16 h of stirring at room temperature, the solution was acidified with 1 M HCl to pH 1.5. A white solid was filtered off and recrystallized from water to give colourless prismatic crystals (yield 85%, m.p. 359 K). ¹H NMR (TFA/CDCl₃, TMS, internal reference): δ 8.40 (*b*, 1H, COOH), 6.66 (*b*, 1H, NH), 4.06 (*s*, 2H, ClCH₂CO), 3.32 (*q*, 2H, NHCH₂), 2.36 (*t*, 2H, CH₂COOH), 1.65 (*m*, 4H, NHCH₂CH₂ + CH₂CH₂COOH), 1.41 (*m*, 2H, NHCH₂CH₂-CH₂). IR (KBr, cm⁻¹): 3331 (amide A), 2946 and 2864 (CH₂), 1697 (C=O), 1647 (amide I), 1543 (amide II), 1262 (C–O).

Crystal data

C₈H₁₄ClNO₃ Z = 8
M_r = 207.65 D_x = 1.360 Mg m⁻³
Monoclinic, Cc Mo Kα radiation
a = 29.149 (4) Å μ = 0.35 mm⁻¹
b = 5.139 (4) Å T = 293 (2) K
c = 14.498 (4) Å Prism, colourless
β = 110.90 (2)° 0.42 × 0.18 × 0.10 mm
V = 2028.9 (17) Å³

Data collection

Enraf–Nonius CAD-4 2118 reflections with I > 2σ(I)
diffractometer θ_{max} = 30.0°
ω/2θ scans 1 standard reflection
3057 measured reflections frequency: 120 min
3057 independent reflections intensity decay: 1%

Refinement

Refinement on F² w = 1/[σ²(F_o²) + (0.072P)²
R[F² > 2σ(F²)] = 0.048 + 0.2711P]
wR(F²) = 0.132 where P = (F_o² + 2F_c²)/3
S = 1.06 (Δ/σ)_{max} < 0.001
3057 reflections Δρ_{max} = 0.36 e Å⁻³
237 parameters Δρ_{min} = -0.25 e Å⁻³
H-atom parameters constrained Absolute structure: Flack (1983),
97 Friedel pairs
Flack parameter: 0.05 (9)

Table 1

Selected torsion angles (°).

C1A–C1A–C2A–N1A	1.2 (5)	C1B–C1B–C2B–N1B	5.9 (5)
C1A–C2A–N1A–C3A	178.7 (4)	C1B–C2B–N1B–C3B	179.0 (4)
C2A–N1A–C3A–C4A	113.4 (4)	C2B–N1B–C3B–C4B	81.8 (4)
N1A–C3A–C4A–C5A	-66.4 (4)	N1B–C3B–C4B–C5B	67.7 (4)
C3A–C4A–C5A–C6A	-179.6 (4)	C3B–C4B–C5B–C6B	179.1 (4)
C4A–C5A–C6A–C7A	179.2 (4)	C4B–C5B–C6B–C7B	-178.9 (4)
C5A–C6A–C7A–C8A	-179.8 (4)	C5B–C6B–C7B–C8B	-177.4 (4)
C6A–C7A–C8A–O3A	-173.6 (4)	C6B–C7B–C8B–O3B	174.2 (4)

Table 2

Hydrogen-bond and short-contact geometry (Å, °).

D–H...A	D–H	H...A	D...A	D–H...A
N1A–H1A...O1A ⁱ	0.86	2.24	2.897 (5)	133
N1A–H1A...C11A	0.86	2.52	2.990 (3)	115
N1B–H1B...O1B ⁱ	0.86	2.19	2.907 (4)	141
N1B–H1B...C11B	0.86	2.53	2.989 (4)	114
O3A–H3A...O2B ⁱⁱ	0.82	1.84	2.646 (5)	166
O3B–H3B...O2A ⁱⁱⁱ	0.82	1.87	2.669 (5)	166
C1A–H11A...O1B ^{iv}	0.97	2.52	3.435 (6)	157
C1B–H11B...O1A ^v	0.97	2.50	3.413 (6)	157
C3A–H31A...O1A	0.97	2.45	2.836 (5)	104

Symmetry codes: (i) x, y – 1, z; (ii) x – ½, y – ½, z – 1; (iii) x + ½, y + ½, z + 1; (iv) x, –y + 2, z + ½; (v) x, –y + 2, z – ½.

All H atoms were placed in calculated positions. H atoms bonded to C atoms and amide H atoms were treated as riding, with C–H distances of 0.97 Å, H–N distances of 0.86 Å and U_{iso}(H) values of 1.2U_{eq}(C,N). Acid H atoms were refined as rotating atoms, with H–O distances of 0.82 Å and U_{iso}(H) values of 1.5U_{eq}(O).

Data collection: CAD-4 Software (Kiers, 1994); cell refinement: CAD-4 Software; data reduction: WinGX-PC (Version 1.64.05; Farrugia, 1999); program(s) used to solve structure: SHELXS97 (Sheldrick, 1997); program(s) used to refine structure: SHELXL97 (Sheldrick, 1997); molecular graphics: ORTEPII (Johnson, 1976) and PLATON (Spek, 2003); software used to prepare material for publication: SHELXL97 and WinGX-PC.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: DN3018). Services for accessing these data are described at the back of the journal.

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