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L-Methionyl-L-alanine: a dipeptide with hexagonal symmetry and $Z' = 7$

Carl Henrik Görbitz

Department of Chemistry, University of Oslo, PO Box 1033, Blindern, N-0315 Oslo, Norway
Correspondence e-mail: c.h.gorbitz@kjemi.uio.no

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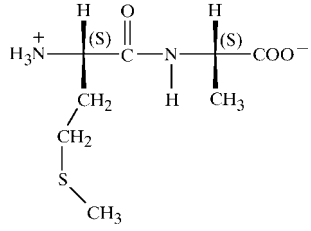
The crystal structure of L-methionyl-L-alanine, $C_8H_{16}N_2O_3S$, is very similar to that of L-valyl-L-alanine [Görbitz & Gundersen (1996). *Acta Cryst.* C**52**, 1764–1767] and other related dipeptides in space group $P6_1$, but there are seven molecules in the asymmetric unit. The Z value of 42 is the highest ever observed for a chiral molecule.

Comment

The crystal structure of L-Val-L-Ala (VA; Görbitz & Gundersen, 1996) comprised the first example of nanotube formation by such a small molecule. Subsequently, the retro-analogue L-Ala-L-Val (Görbitz, 2002*a*), as well as a series of other dipeptides with L-Ala, L-Val and L-Ile residues (Görbitz, 2003), have been found to form structures very similar to VA, differing only in the way the side chains partly fill the channels along the hexagonal axes, which translates directly to pore size.



MA

To investigate whether crystallization in the VA class is compatible with dipeptides incorporating unbranched side chains (apart from the methyl group of L-Ala), crystallization and structure determination have been carried out for the title compound, L-Met-L-Ala, hereinafter MA.

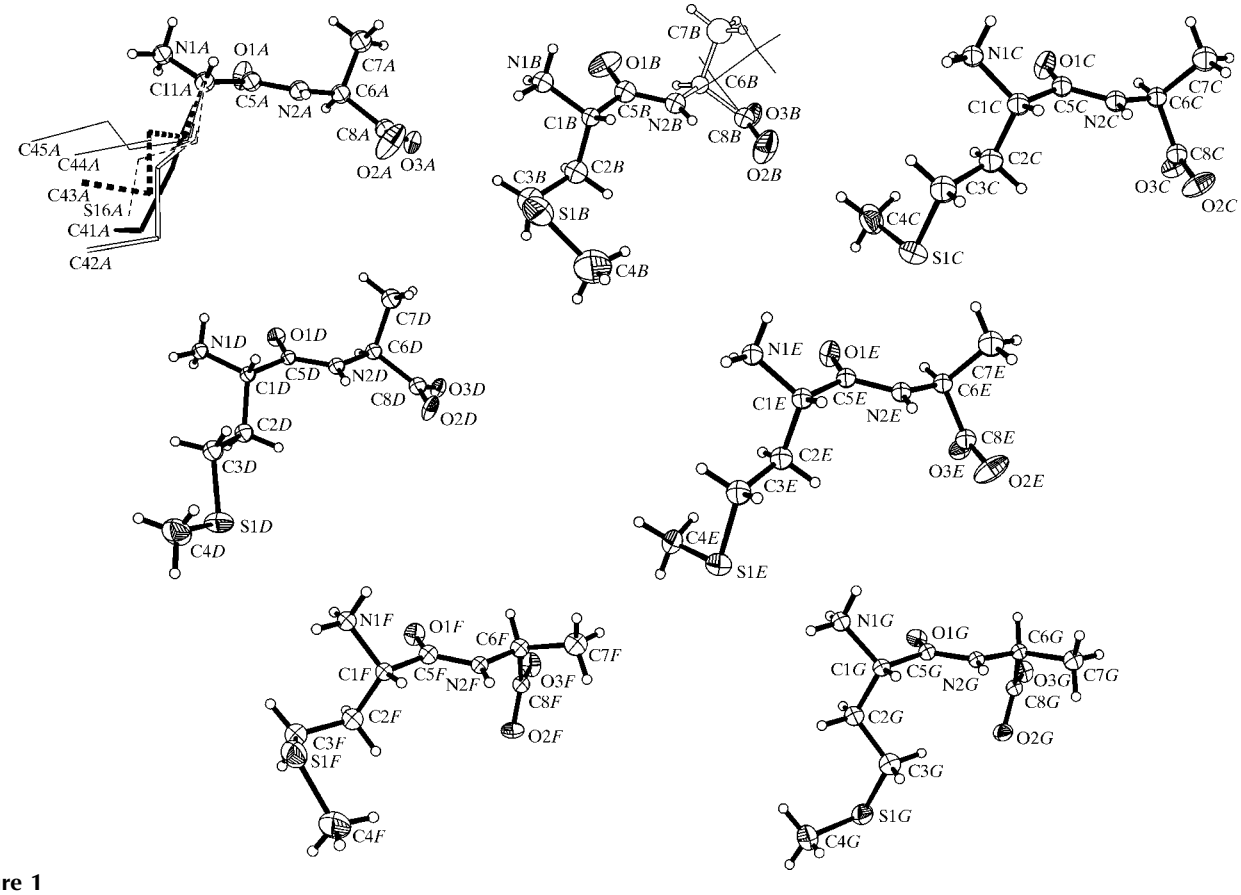


Figure 1
The seven molecules in the asymmetric unit of MA, with the atomic numbering schemes. Displacement ellipsoids and spheres are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. For molecule *A*, six alternative side-chain orientations are shown; a thick black line (to atom C41*A*) is used for the most populated orientation (*A*1; see Table 1). For molecule *B*, there is disorder at C6*B*—C7*B*; the major component [occupancy 0.609 (18)] is shown with open bonds and the minor component as a stick drawing.

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Compound MA was crystallized for the first time in our laboratory in 1996 using 2-propanol as the precipitating agent. High initial solute concentrations led to the formation of ultrathin plates that were, after several attempts, found to be the 1:2 2-propanol solvate (Görbitz, 2000), while bundles of very thin needles appeared when low concentrations were used (0.16–0.32 mg of peptide in 30 µl of water). At the time, we had a traditional diffractometer with a scintillation counter that was able to detect only a few hundred reflections for one of these crystals. It was not possible to solve the structure from this experimental material, but the apparent cell dimensions [$P6_1$, a = 14.261 (7) and c = 9.715 (5) Å] indicated that the MA structure was very similar to that of VA [a = 14.424 (4) and c = 9.996 (6) Å; Görbitz & Gundersen, 1996]. Later, it was found that larger needles could be grown with acetonitrile rather than 2-propanol as the precipitating agent, and when data were collected using a CCD detector it became evident that the MA unit cell was in fact much larger, with Z' = 7, and that the first data collection had provided a subcell of the true crystal lattice.

Structures with Z' = 7 are extremely uncommon; the C-terminal dipeptide fragment (Boc-L-Phe-L-Leu-OBzl) of enkephalin, in space group $P2_1$ (Antolić *et al.*, 1999), is the only example in the Cambridge Structural Database (CSD, Version 5.24; Allen, 2002). There is also just a single observation of Z = 42 (acoradiene in space group $R\overline{3}$, Z' = 2.33; Chen & Lin, 1993), while about 25 organic molecules, all achiral, have $Z > 42$ (Z' = 0.5–16). Statistical data for Z' values have been provided by Kumar *et al.* (2000).

The seven independent peptide molecules in the crystal structure of MA are shown in Fig. 1. Bond lengths and angles are normal. Torsion angles are listed in Table 1. The peptide main chain is observed in three different conformations: extended (molecules *A*, *B* and *D*), semi-extended (molecules *C* and *E*) and S-shaped (molecules *F* and *G*). Structures in the VA class all have extended conformations, with ψ_1 in the range 151–171° and φ_2 ranging from −129 to −154° (Görbitz, 2003).

An understanding of the side-chain conformations in MA can be gained by considering the crystal-packing arrangement shown in Fig. 2. Compared with the VA class, the lengths of the *a* and *b* axes are more than doubled [from approximately 14.2 to 37.6488 (15) Å], which makes room for the increase in Z' from 1 to 7. In the process, two different types of hydrophobic columns are created, Column 1 and Column 2.

Column 1 and its surroundings on the hexagonal axis closely mimic the structures of the VA class. The side chains in these structures are unable to fill the central cavity, leaving a conspicuous empty (or solvent-filled) channel or nanotube of varying diameter (Görbitz & Gundersen, 1996; Görbitz, 2002*a*, 2003). The long L-Met side chains of molecule *A*, however, can fill these channels more or less completely, but not in a very straightforward manner, since selection of any one L-Met conformation leads to serious intermolecular steric conflict between adjacent molecules related by the 6_1 screw axis. Accordingly, the side chain is heavily disordered. The refinement of the structure applied six different orientations, *A*1–*A*6 (Table 1), which can conveniently be divided into two

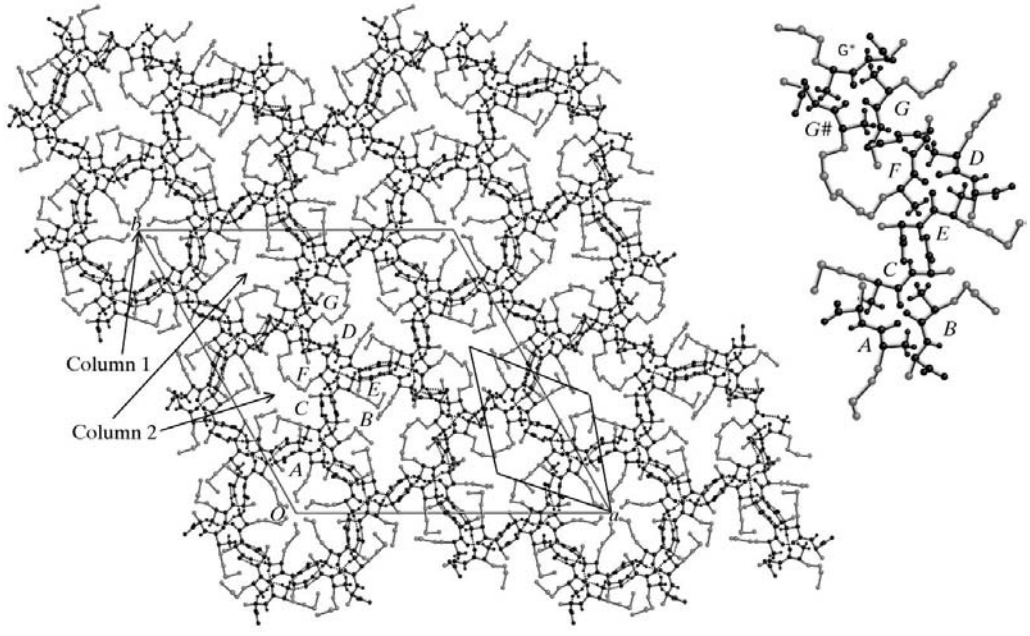

Figure 2
The crystal packing of MA viewed along the *c* axis. Side chains are shown in light grey. The letters *A*–*G* identify the seven independent peptide molecules in the asymmetric unit, which are shown in more detail in the right-hand diagram, along with two additional *G* molecules, *viz.* *G** [at symmetry position $(1-x, 1+x-y, z-\frac{2}{3})$] and *G*# [at symmetry position $(y-x, 1-x, z-\frac{1}{3})$]. Two unit cells are shown; the larger is the true unit cell, while the smaller is the subcell found in the earlier investigation of an MA crystal. The latter also corresponds to the true unit cell in the VA class. Note that the illustration does not tell the full story about column 1, since the extended *A*3 conformation (see Table 1) for L-Met is shown for all *A* molecules. This side chain is, in fact, disordered over six positions.

groups, namely *A*1 and *A*2 with χ_1^1 = *gauche*+, and *A*3–*A*6 with χ_1^1 = *gauche*−.

The rare *gauche*+/*trans*/*trans* *A*1 conformation, observed only once before in peptides (for DL-Ala-LD-Met; Guillot *et al.*, 2001), is exceptional in that it does not create side-chain–side-chain conflict when introduced in adjacent molecule-*A* positions. Instead, atom C41*A* comes close to the C7*B* methyl group of one (but not both) of the two neighbouring *B* molecules. This forces a disorder for molecule *B*, with two alternative L-Ala methyl positions (Fig. 1). Each *A* molecule in conformation *A*1 must be flanked by one *B* molecule in the major orientation and one in the minor orientation. It follows that adjacent *A*1 conformations are prohibited.

Conformation *A*2 is essentially the same as *A*1, but the torsion angles are shifted to more awkward values (Table 1), which serves to eliminate the conflict with atom C7*B*, at the expense of reintroducing side-chain conflict with neighbouring molecules in conformations *A*1 and *A*2. The result of this analysis is that two neighbouring *A* molecules must always have side-chain orientations from different groups (*A*1/*A*2 or *A*3–*A*6) in order to avoid steric conflict. The sum of the occupancies for *A*1 and *A*2 should thus ideally be 0.50, the same as for *A*3–*A*6. This is in close agreement with the refinement results (Table 1; sum of all occupancies constrained to 1.00).

Column 2 has no crystallographic symmetry, but the peptide backbones are related by pseudo-sixfold screw symmetry. The column is generated from an intricate close-packing of L-Met side chains from molecules *B*, *C*, *D*, *E*, *F* and *G*, together with minor contributions from the L-Ala side chains of molecules *A*, *C*, *D*, *E*, *F* and *G* (the L-Ala side chain of molecule *B* is part of column 1).

It is noteworthy that, in three previous structures of peptides with N-terminal L-Met residues [L-Met-L-Met (Stenkamp & Jensen, 1975), L-Met-L-Glu-L-His-L-Phe hydrate (Admiraal & Vos, 1983) and L-Met-L-Ala 2-propanol solvate (Z' = 2; Görbitz, 2000)], both χ_1^1 and χ_1^2 torsion angles were *trans*. The MA conformations represent a clear departure from this pattern. Overall, molecules *C* and *E* are very similar, while the other molecules differ in either their side-chain or their main-chain conformations.

The hydrogen-bond geometry for MA is listed in Table 2. The hydrogen bonding in the MA crystal structure closely follows the pattern of the VA class, including the left-handed dipeptide double helix described previously (Görbitz & Gundersen, 1996; Görbitz, 2002*b*, 2003). In the VA class, this motif involves molecules related by threefold screw symmetry, as seen for *G* molecules in the MA structure (*G*, *G** and *G*# in Fig. 2). Pseudo-threefold screw symmetry, which is very accurate if the side chains are disregarded, relates molecules *A* + *B* + *C* and *D* + *E* + *F* in exactly the same manner.

Experimental

The title compound was obtained from Bachem and used as received. Crystals of MA were grown by slow diffusion of acetonitrile into an aqueous solution of the peptide.

Crystal data

$C_8H_{16}N_2O_3S$
M_r = 220.29
Hexagonal, $P6_1$
a = 37.6488 (15) Å
c = 9.6613 (8) Å
V = 11859.6 (12) Å^3
Z = 42
D_x = 1.295 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 14 292 reflections
θ = 1.1–25.1°
μ = 0.27 mm^{-1}
T = 105 (2) K
Needle, colourless
0.80 × 0.18 × 0.15 mm

Data collection

Siemens SMART CCD area-detector diffractometer
Sets of exposures each taken over 0.3° ω rotation scans
Absorption correction: empirical (*SADABS*; Sheldrick, 1996)
T_{min} = 0.789, T_{max} = 0.960
79 465 measured reflections
7460 independent reflections
4308 reflections with $I > 2\sigma(I)$
R_{int} = 0.195
θ_{max} = 25.1°
$h = -44 \rightarrow 44$
$k = -40 \rightarrow 44$
$l = -11 \rightarrow 8$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.058
$wR(F^2)$ = 0.145
S = 1.03
7460 reflections
633 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0446P)^2 + 18.1456P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.48 e Å^{-3}
$\Delta\rho_{min}$ = −0.35 e Å^{-3}

Table 1
Torsion angles (°) for molecules *A*–*G* of MA.

Molecule	N1—C1—C5—N2 (ψ_1)	C1—C5—N2—C6 (ω_1)	C5—N2—C6—C8 (φ_2)	N2—C6—C8—O2 (ψ_T)†	N1—C1—C2—C3 (χ_1^1)	C1—C2—C3—S1 (χ_1^2)	C2—C3—S1—C4 (χ_1^3)	Occupancy
*A*1	161.7 (5)	175.5 (5)	−151.7 (6)	−16.8 (10)	65.8 (16)	−175.6 (16)	154 (2)	0.285 (9)
*A*2	161.7 (5)	175.5 (5)	−151.7 (6)	−16.8 (10)	35 (6)	162 (3)	121 (5)	0.190 (8)
*A*3	161.7 (5)	175.5 (5)	−151.7 (6)	−16.8 (10)	−83 (3)	−147 (3)	−162 (4)	0.229 (7)
*A*4	161.7 (5)	175.5 (5)	−151.7 (6)	−16.8 (10)	−78 (4)	−50 (6)	165 (4)	0.142 (6)
*A*5	161.7 (5)	175.5 (5)	−151.7 (6)	−16.8 (10)	−49 (5)	−60 (6)	154 (2)	0.101 (5)
*A*6	161.7 (5)	175.5 (5)	−151.7 (6)	−16.8 (10)	−50 (14)	−135 (8)	‡	0.051 (5)
B (major)	158.0 (7)	169.2 (8)	−154.9 (9)	−15.3 (16)	−52.0 (9)	−54.3 (9)	−72.8 (7)	0.609 (18)
B (minor)	158.0 (7)	−167.8 (11)	−133.1 (11)	−59.0 (17)	−52.0 (9)	−54.3 (9)	−72.8 (7)	0.391 (18)
C	143.7 (7)	168.5 (6)	−117.2 (8)	−54.5 (9)	−63.5 (9)	178.4 (5)	−76.0 (7)	1.0
D	168.5 (6)	−179.8 (6)	−148.4 (6)	−29.5 (9)	−77.0 (8)	−169.0 (5)	177.5 (6)	1.0
E	148.5 (6)	172.0 (6)	−118.4 (4)	−59.7 (9)	−67.8 (8)	−175.9 (5)	−74.7 (7)	1.0
F	130.1 (7)	−177.8 (6)	−79.7 (8)	−32.5 (9)	−48.5 (9)	−55.6 (8)	−69.8 (6)	1.0
G	131.0 (7)	173.7 (6)	−63.6 (8)	−41.9 (8)	−177.8 (6)	−173.6 (6)	−65.5 (7)	1.0

† Measured to the O atom giving the smallest positive or negative value. ‡ C atom not located.

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

D—H···A	D—H	H···A	D···A	D—H···A
N1A—H1A···O3B^{i}	0.91	1.82	2.661 (8)	153
N1A—H2A···O2A^{ii}	0.91	1.90	2.761 (8)	158
N1A—H3A···O1C	0.91	1.87	2.728 (8)	156
N2A—H4A···O3B^{iii}	0.88	2.20	3.034 (7)	159
N1B—H1B···O3C	0.91	1.90	2.729 (8)	150
N1B—H2B···O2E^{iv}	0.91	1.91	2.765 (8)	156
N1B—H3B···O1A	0.91	1.88	2.685 (8)	146
N2B—H4B···O3A^{ii}	0.88	2.08	2.932 (8)	162
N1C—H1C···O3A^{i}	0.91	1.89	2.742 (8)	155
N1C—H2C···O2B^{iii}	0.91	1.83	2.675 (8)	153
N1C—H3C···O1B^{i}	0.91	1.80	2.702 (8)	169
N2C—H4C···O3E	0.88	1.98	2.853 (8)	172
N1D—H1D···O3F^{i}	0.91	1.81	2.702 (8)	166
N1D—H2D···O2G^{i}	0.91	2.14	2.994 (8)	155
N1D—H3D···O1E	0.91	1.91	2.729 (7)	148
N2D—H4D···O3D^{v}	0.88	2.07	2.943 (8)	170
N1E—H1E···O3D^{i}	0.91	1.86	2.739 (8)	161
N1E—H2E···O2D^{v}	0.91	1.95	2.718 (8)	141
N1E—H3E···O1F^{i}	0.91	1.88	2.775 (8)	166
N2E—H4E···O3C^{i}	0.88	2.02	2.887 (8)	168
N1F—H1F···O3E	0.91	1.84	2.676 (8)	152
N1F—H2F···O2C	0.91	1.87	2.750 (8)	161
N1F—H3F···O1D	0.91	1.94	2.747 (7)	146
N2F—H4F···O2G^{i}	0.88	2.00	2.794 (8)	150
N1G—H1G···O3G^{vi}	0.91	1.80	2.693 (8)	165
N1G—H2G···O2F^{vii}	0.91	1.96	2.846 (8)	165
N1G—H3G···O1G^{viii}	0.91	1.88	2.741 (7)	156
N2G—H4G···O2F	0.88	1.92	2.761 (8)	161

Symmetry codes: (i) $x, y, z-1$; (ii) $y, -x+y, z-\frac{1}{6}$; (iii) $x-y, x, z-\frac{5}{6}$; (iv) $x, y, 1+z$; (v) $1-x, 1-y, z-\frac{1}{2}$; (vi) $1-y, 1+x-y, z-\frac{2}{3}$; (vii) $1-y, 1+x-y, \frac{1}{3}+z$; (viii) $-x+y, 1-x, z-\frac{1}{3}$.

Due to the low reflection-to-parameter ratio, only fully ordered S and O atoms and the terminal C atoms of the L-Met side chains were refined anisotropically. A full anisotropic refinement (908 parameters) was found to give only a very moderate decrease in the R value (to 0.0556) and a small increase in the s.u. values of the geometric parameters. Refinement of the complex disorder for the L-Met side chain of peptide molecule A was handled by mild *SHELXTL* (Sheldrick, 1997) SAME 0.02 0.03 constraints for six different orientations. H atoms were placed geometrically and refined with constraints. Free rotation of the amino and methyl groups (without disorder) was permitted. U_{iso}(H) values were set at $1.2U_{eq}$ of the carrier atom, or $1.5U_{eq}$ for methyl and amino groups. Friedel pairs were merged in the final refinements.

Data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT* (Bruker, 1998); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Bruker, 2000); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1702). Services for accessing these data are described at the back of the journal.

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