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cis,*cis*-Ceratospongamide *N*,*N*-dimethylacetamide hemisolvate in the presence of twinning

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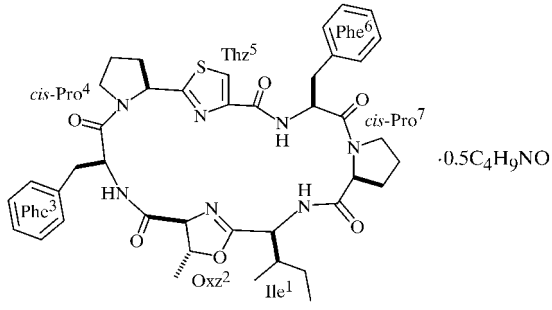
Ceratospongamide (CS) is a potent inhibitor of secreted phospholipase A_2, and *cis*,*cis* and *trans*,*trans* isomers, related with respect to the two proline amide bonds, are known. Crystals of *cis*,*cis*-CS were grown from *N*,*N*-dimethylacetamide solution, giving the title compound, the cyclic ester of isoleucyloxazolinylphenylalanylprolylthiazolylphenylalanylproline [cyclo(-Ile–Oxz–Phe–Pro–Thz–Phe–Pro-)] *N*,*N*-dimethylacetamide hemisolvate, $C_{41}H_{49}N_7O_6S\cdot0.5C_4H_9NO$. The structure is the third example of *cis*,*cis*-CS to be investigated and comprises twinned crystals, in which the *a* and *b* axes are interchanged. The ratio of co-existing twin crystals is approximately 50%. The peptide has a 'saddle-like' structure and is very similar to previously reported structures of *cis*,*cis*-CS, which implies that the structure of *cis*,*cis*-CS is very stable in spite of differences in crystallization conditions.

Comment

Ceratospongamide (CS) is a cyclic heptapeptide containing oxazoline (Oxz) and thiazole (Thz) that has two isomers, namely *cis*,*cis*-CS and *trans*,*trans*-CS, which show different bioactivities (Tan *et al.*, 2000). The isomerization is caused by



(I)

the *cis* and *trans* rotamers of the proline residues (see the closed bonds in Fig. 1), and the peptide conformation is directly related to the activity. Recent work has suggested that the conversion from the *cis*,*cis* to the *trans*,*trans* isomer is accompanied by the chiral inversion of Ile (Yokokawa *et al.*, 2002) or Oxz (Kutsumura *et al.*, 2002). Therefore, CS is of interest in the investigation of relationships between structure

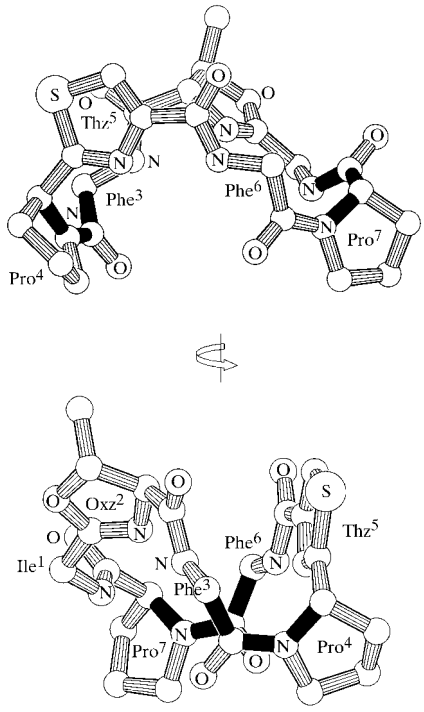


Figure 1
View of the peptide backbone, with side chains omitted for clarity. The closed bonds around the Pro residues indicate the *cis*-amide bonds.

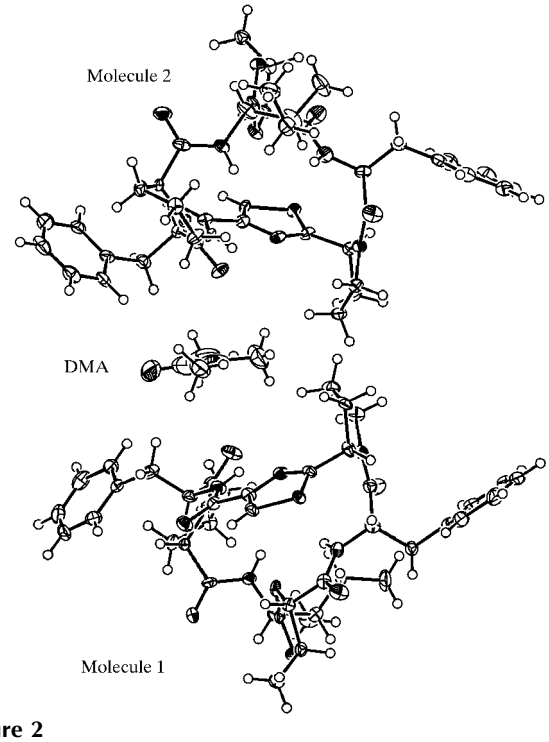


Figure 2
View of the structure of *cis*,*cis*-CS. The components of the asymmetric unit of (I) are drawn with displacement ellipsoids at the 50% probability level.

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Figure 3
A superposition of the four molecules of *cis*,*cis*-CS in the three crystal forms.

and activity (Yokokawa *et al.*, 2001; Deng & Taunton, 2002). Two crystal forms of *cis*,*cis*-CS were known previously (Doi *et al.*, 2002; Doi & Asano, 2002). Crystals of the title compound, (I), were grown from *N*,*N*-dimethylacetamide (DMA) in the presence of twinning, and the structure of (I) is reported here.

In (I), two peptide molecules are located in the asymmetric unit together with a solvent DMA molecule (Fig. 2). A *cis* rotamer is observed for the Pro[4] and Pro[7] residues of both molecules (Table 1). The structures of the two molecules of *cis*,*cis*-CS are very similar, and no significant difference is observed in the conformations of the peptide backbones (Table 1). The shape of the peptide ring is 'saddle-like', and the *cis*-Pro residues are located at turns of the ring (Fig. 2). The Ile[1]–Oxz[2]–Phe[3] moiety faces the Thz[5]–Phe[6] moiety, but no intramolecular hydrogen bond is formed. The amide plane of Oxz[2]–Phe[3] is stacked parallel to the plane of the Thz ring. These features are similar to those of two previously known structures of *cis*,*cis*-CS (Doi & Asano, 2002; Doi *et al.*, 2002); a superposition of the four molecules is shown in Fig. 3. Molecular fitting for the Cα atoms resulted in r.m.s. deviations of 0.019–0.041 Å. The peptide backbones are very similar to each other, and relatively large shifts are only observed for the side chains of Ile[1] and Phe[3]. It is surprising that similar structures are found in crystals grown under three different conditions. This result suggests that the structures of *cis*,*cis*-CS are very stable.

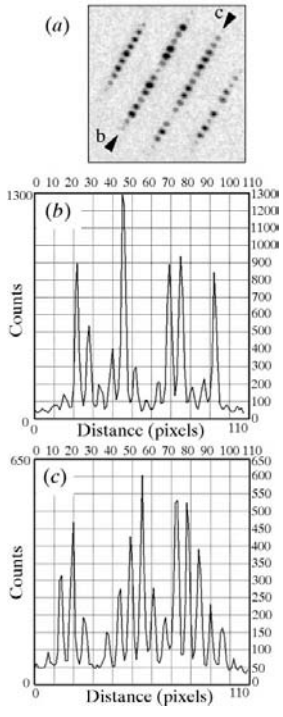

Figure 4
A CCD image and peak profiles along the longest *c* axis, with, in (*a*), layered spots showing the longest *c* axis. The peak profiles (*b*) and (*c*) were produced along the layers indicated in (*a*) by arrows b and c, respectively.

Experimental

CS was synthesized as described by Yokokawa *et al.* (2001). The peptide was dissolved in DMA (7–10 mg per 0.10–0.15 ml of DMA), and crystals of (I) were grown over a period of 2–3 weeks. The single crystal selected for investigation was passed briefly through glycerol and was mounted on a nylon loop under a nitrogen stream at 90 K.

Crystal data

$C_{41}H_{49}N_7O_6S\cdot0.5C_4H_9NO$
M_r = 811.51
Orthorhombic, $P2_12_12_1$
a = 12.6034 (7) Å
b = 12.6075 (7) Å
c = 53.536 (3) Å
V = 8506.7 (8) Å^3
Z = 8
D_x = 1.267 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 8337 reflections
θ = 2.3–27.7°
μ = 0.13 mm^{-1}
T = 90.0 (2) K
Plate, colorless
0.45 × 0.30 × 0.10 mm

Data collection

Bruker SMART APEX area-detector diffractometer
ω scans
Absorption correction: empirical (*SADABS*; Sheldrick, 1996)
T_{min} = 0.883, T_{max} = 0.987
102 830 measured reflections
20 493 independent reflections
20 401 reflections with $I > 2\sigma(I)$
R_{int} = 0.038
θ_{max} = 28.3°
$h = -16 \rightarrow 16$
$k = -16 \rightarrow 16$
$l = -71 \rightarrow 70$
1242 standard reflections
every 102 830 reflections
frequency: 330 min
intensity decay: 0.4%

Refinement

Refinement on F^2
$R(F)$ = 0.050
$wR(F^2)$ = 0.127
S = 1.16
20 493 reflections
1046 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0783P)^2 + 1.9396P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.012
$\Delta\rho_{max}$ = 0.86 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}
Absolute structure: (Flack, 1983), 8904 Friedel pairs
Flack parameter = 0.09 (6)

Reflections were measured for the full sphere of data. The camera distance of 60 mm was expected to cause problems, with the peak separation along the longest *c* axis when Mo $K\alpha$ radiation was used. However, a capillary collimator (causing total external reflection) gave a clear peak separation even for relatively strong reflections

Table 1
Selected torsion angles (°).

The φ, ψ and ω angles of the peptide backbone represent the torsion angles C—N—Cα—C, N—Cα—C—N and Cα—C—N—Cα, respectively.

Angle	Molecule 1	Molecule 2
Ile[1]		
φ1	−97.1 (3)	−83.0 (4)
ψ1	−19.4 (4)	−32.8 (5)
ω1	−174.9 (2)	−174.3 (3)
Oxz[2]		
φ2	120.6 (3)	121.7 (3)
ψ2	0.9 (3)	−4.8 (4)
ω2	−175.9 (2)	−178.3 (3)
Phe[3]		
φ3	−162.8 (3)	−154.0 (3)
ψ3	109.6 (3)	104.2 (3)
ω3	−7.2 (5)	0.5 (4)
Pro[4]		
φ4	−62.5 (4)	−71.1 (3)
ψ4	−34.5 (4)	−31.2 (4)
ω4	−179.3 (3)	−178.9 (2)
Thz[5]		
φ5	−175.1 (3)	−176.2 (2)
ψ5	−0.1 (4)	−1.1 (4)
ω5	172.9 (3)	171.7 (2)
Phe[6]		
φ6	−164.0 (3)	−165.8 (2)
ψ6	139.8 (3)	141.4 (2)
ω6	0.6 (4)	−4.2 (4)
Pro[7]		
φ7	−92.4 (3)	−89.2 (3)
ψ7	−7.8 (3)	−11.8 (4)
ω7	177.0 (2)	177.0 (3)

(Fig. 4), and the peak intensities were properly integrated. The data were processed with *XPREP* (Bruker, 2001), and the merging processes resulted in $R_{\rm int}$ values of 0.039 and 0.041 for orthorhombic and tetragonal systems, respectively. The mean value of $|E^2 - 1|$ was 0.548, where theoretical values of 0.938 and 0.736 were expected for centrosymmetric and non-centrosymmetric space groups, respectively (Iwasaki & Ito, 1977).

The crystal system could not be determined in the early stages of analysis, but the solution was finally obtained with space group $P2_12_12_1$ using the dual-spacing recycling method (Sheldrick & Gould, 1996). An orthorhombic lattice with *a* and *b* axes equal in length was emulating a tetragonal lattice. A test for twinning using *XPREP* showed signs of 'partial merohedral twinning'. Moreover, straightforward refinements did not converge for the solved structure. Therefore, twinning with the *a* and *b* axes interchanged was accounted for in the refinement. The twinning ratio was 0.492 (1). H atoms were placed in ideal positions and refined as riding atoms (C—H = 0.95–1.00 Å and N—H = 0.88 Å).

Data collection: *SMART* (Bruker, 1998); cell refinement: *SMART*; data reduction: *SAINT-Plus* (Bruker, 1998); program(s) used to solve structure: *SHELXD* (Sheldrick & Gould, 1996); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *PARST* (Nardelli, 1983).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: OB1101). Services for accessing these data are described at the back of the journal.

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