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The *cis,cis*-proline isomer of ceratospongamide

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.020 Å
R factor = 0.098
wR factor = 0.155
Data-to-parameter ratio = 8.2

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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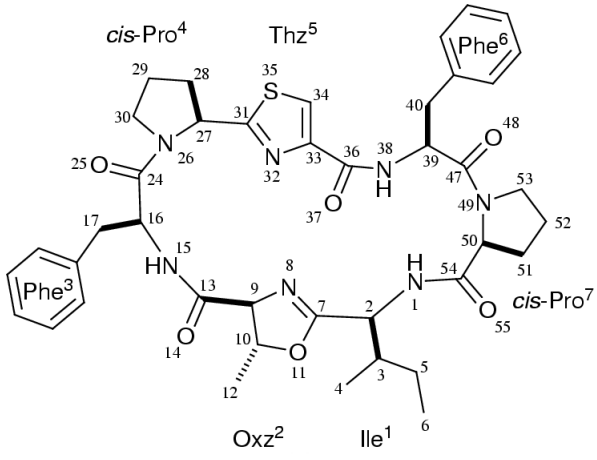
Ceratospongamide, *cyclo*(-Ile-Oxz-Phe-Pro-Thz-Phe-Pro-) (Oxz = oxazoline and Thz = thiazole), $C_{41}H_{49}N_7O_6S$, is a thiazole-containing cyclic peptide isolated from marine sources. Two stable isomers are known and the structure of the *cis,cis*-isomer has been determined. The peptide ring is folded in a new manner for thiazole-containing peptides. The thiazole ring faces the amide bond plane between the Oxz and Phe residues, with π–π interactions. This interaction stabilizes the peptide conformation with no hydrogen bonding.

Comment

Ceratospongamide (CS), *cyclo*(-Ile-Oxz-Phe-Pro-Thz-Phe-Pro-), was isolated from the marine red alga (Rhodophyta) Ceratodictyon spongiosum (Tan *et al.*, 2000). This cyclic heptapeptide contains oxazoline (Oxz) and thiazole (Thz), and is a potent inhibitor of secreted phospholipase A_2 ($sPLA_2$). It is known that two stable isomers, related with respect to the two proline amide bonds, exist in nature and show different activities for $sPLA_2$: the ED_{50} of [*trans,trans*]-CS is 32 nM in inhibition for $sPLA_2$, but [*cis,cis*]-CS is inactive. Such a conformation-dependant activity is strikingly interesting in studying the relationship between its activity and structure.



(I)

Synthesized CS, (I), was crystallized from methanol solution and its structure is shown in Fig. 1. The torsion angles C16—C24—N26—C27 and C39—C47—N49—C50 are −1.4 (15) and 0.4 (14)° (Table 1), respectively, and show a *cis*-form for both proline residues. The peptide backbone is folded, but in a manner different from those of other Thz-containing peptides such as ascidiacyclamides (Ishida *et al.*, 1988). The backbone is

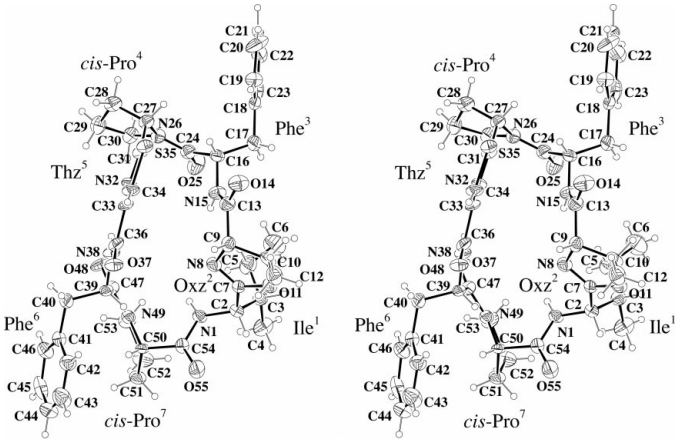


Figure 1
Stereoview of ceratospongamide with displacement ellipsoids drawn at the 30% probability level.

turned at two Pro residues (Fig. 2), and their *cis*-forms are important in this folded ring. The Thz ring and amide bond plane (composed of atoms C13, O14, N15 and C16) face each other with a plane–plane angle of 13.5°. Furthermore, a short contact is observed between atoms N15 and N32 (3.39 Å). This indicates a π–π electron interaction between the Thz ring and the amide bond. This interaction stabilizes the folded structure with no hydrogen bonding.

Experimental

Ceratospongamide was synthesized by a reported method (Yokokawa *et al.*, 2001) following the synthetic methods for thiazole-containing peptides (Hamamoto *et al.*, 1983; Hamada *et al.*, 1987).

Crystal data

$C_{41}H_{49}N_7O_6S$
M_r = 767.93
Tetragonal, $P4_12_12$
a = 12.805 (2) Å
c = 54.013 (11) Å
V = 8857 (3) Å^3
Z = 8
D_x = 1.152 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 24 reflections
θ = 9.8–21.2°
μ = 1.06 mm^{-1}
T = 293 (2) K
Plate, colorless
0.26 × 0.17 × 0.06 mm

Data collection

Rigaku AFC-5*R* diffractometer
θ–ω scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.78, T_{max} = 0.97
4364 measured reflections
4062 independent reflections
2203 reflections with $I > 2\sigma(I)$
R_{int} = 0.194
θ_{max} = 56.0°
$h = 0 \rightarrow 13$
$k = 0 \rightarrow 9$
$l = -16 \rightarrow 58$
3 standard reflections
every 150 reflections
intensity decay: 1.8%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.098
$wR(F^2)$ = 0.155
S = 1.69
4062 reflections
496 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.002P)^2 + 5.2P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.007
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.22 e Å^{-3}
Absolute structure: Flack (1983)
Flack parameter = 0.04 (6)

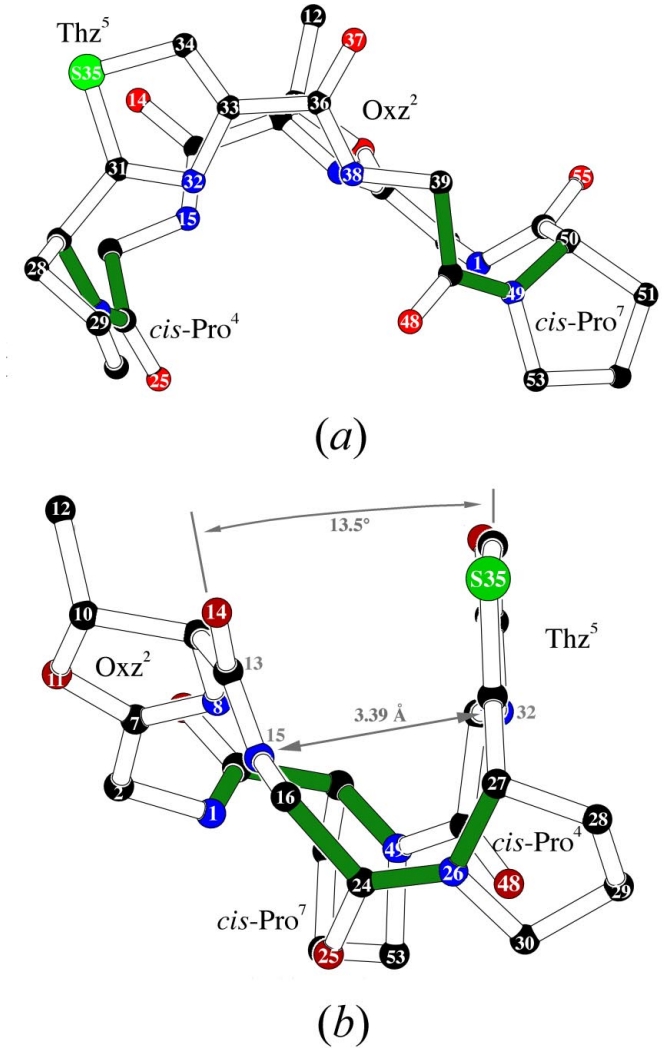


Figure 2
Conformation of the peptide ring: (*a*) projection on Thz ring, and (*b*) orthogonal projection. Side chains and H atoms have been omitted for clarity. Colored balls of black, red, blue and green represent C, O, N and S atoms, respectively. *cis*-Amide bonds are represented by green rods.

Table 1
Selected torsion angles (°).

C54—N1—C2—C7	−97.9 (10)	C27—C31—N32—C33	−179.7 (8)
N1—C2—C7—N8	−18.5 (15)	C31—N32—C33—C36	−175.1 (9)
C2—C7—N8—C9	−176.3 (10)	N32—C33—C36—N38	−0.3 (13)
C7—N8—C9—C10	0.1 (11)	C33—C36—N38—C39	172.3 (8)
N8—C9—C13—N15	−5.5 (15)	C36—N38—C39—C47	−167.3 (9)
C9—C13—N15—C16	−178.1 (10)	N38—C39—C47—N49	142.5 (8)
C13—N15—C16—C24	−156.2 (11)	C39—C47—N49—C50	0.4 (14)
N15—C16—C24—N26	109.0 (11)	C47—N49—C50—C54	−97.2 (11)
C16—C24—N26—C27	−1.4 (15)	N49—C50—C54—N1	−2.2 (12)
C24—N26—C27—C31	−67.7 (13)	C2—N1—C54—C50	170.9 (8)
N26—C27—C31—N32	−31.5 (12)		

H atoms of the peptide were placed in calculated positions and constrained during the refinement. The absolute configuration indicated by the Flack x parameter (Flack, 1983) of 0.04 (6) agrees with the L-configuration of natural amino acids.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1991); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *MSC/AFC Diffractometer Control Software*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*III (Burnett & Johnson, 1996); software used to prepare material for publication: *PARST* (Nardelli, 1983).

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