Stoe & Cie (1992*a*). *EMPIR. Empirical Absorption Correction Program*. Version 1.03. Stoe & Cie, Darmstadt, Germany.
Stoe & Cie (1992*b*). *DIF*4. *Diffractometer Control Program*. Version 7.09. Stoe & Cie, Darmstadt, Germany.
Stoe & Cie (1992*c*). *REDU*4. *Data Reduction Program*. Version 7.03. Stoe & Cie, Darmstadt, Germany.

Acta Cryst. (1999). C**55**, 796–798

The highly solvated structure of theonellapeptolide Id, a tridecapeptide lactone from the Okinawa marine sponge *Theonella swinhoei*

Mitsunobu Doi,[a] Toshimasa Ishida,[a] Motomasa Kobayashi,[b] Jeffrey R. Deschamps[c] and Judith L. Flippen-Anderson[c]

[a]*Osaka University of Pharmaceutical Sciences, 4-20-1 Nasahara, Takatsuki, Osaka 569-11, Japan,* [b]*Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565, Japan, and* [c]*Laboratory for the Structure of Matter, Code 6030, Naval Research Laboratory, Washington, DC 20375, USA. E-mail: doit@oysun01.oups.ac.jp*

(*Received 9 September 1997; accepted 4 November 1998*)

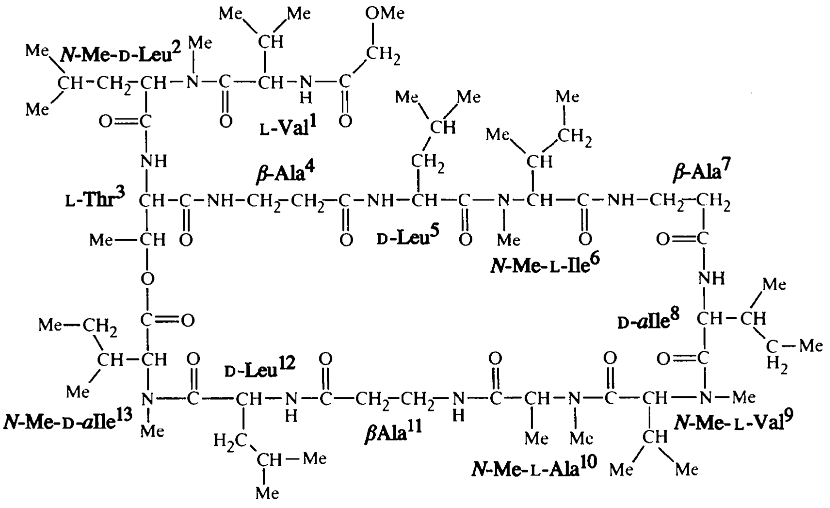
Abstract

Theonellapeptolide Id (TNLP-Id), $C_{70}H_{125}N_{13}O_{16}\cdot 12H_2O$, was crystallized from an aqueous methanol solution. This crystalline cyclic tridecapeptide is solvated by 12 water molecules, which interact with the backbone. All the solvent molecules are located on one face of the hydrophobic peptide. This suggests that the molecule also has unanticipated amphipathic properties. The uniquely folded cyclic backbone is composed of short and long turn units.

Comment

Theonellapeptolide Id (TNLP-Id) is the tridecapeptide lactone isolated from the Okinawa marine sponge *Theonella swinhoei*, and it shows potent cytotoxicity (Kobayashi *et al.*, 1991). The TNLP family has high hydrophobicity and is extracted by ethyl acetate with related peptides and macrolides (Kobayashi, Kanzaki *et al.*, 1994; Kobayashi, Kawazoe *et al.*, 1994). Their chemical structures contain unusual amino acids and most of the amide bonds are methylated. In TNLP-Id, the terminal N atom is capped by the methoxyacetate, and the terminal C atom bonds through an ester linkage to the hydroxyl group of the threonine^3 residue.

The highly hydrophobic title polypeptide was crystallized from aqueous methanol solution in a solvated form (Bernardinelli *et al.*, 1992). The 12 independent water molecules are associated with one face of TNLP-Id. The alkyl groups of the hydrophobic residues (Val, Leu and Ile) are assembled on the opposing face, as shown in Fig. 1. Previously, only hydrophobic properties were presumed to be associated with this molecule; selective hydration of a single surface, however, suggests that TNLP-Id also has amphipathic characteristics. Solvation occurs through hydrogen bonding with the amide bonds (Table 1) and networks are observed among the solvent molecules (not indicated). No direct interaction is observed between neighboring peptides, except for van der Waals contacts and water-mediated indirect connections that stabilize the molecular packing in the crystal. The intermolecular hydrogen bonds contribute to the formation of turn segments, which have



TNLP-Id

© 1999 International Union of Crystallography
Printed in Great Britain – all rights reserved

Acta Crystallographica Section C
ISSN 0108-2701 © 1999

different characteristics from some β-turns. A 1 → 3 turn is formed between N-3(L-Thr^3) → O-5(D-Leu^5). This type of turn leads to unfavorable steric interactions. However, in this case, the turn does not appear to be tight because it includes a β-alanine residue. The conformation of the peptide is also stabilized by two 1 → 5 turn units formed between N-5(D-Leu^5) → O-1(L-Val^1) and N-12(D-Leu^{12}) → O-8(D-*a*Ile^8). A *cis*-amide bond is observed between *N*-Me-L-Val^9 and *N*-Me-L-Ala^{10} (Table 2). Finally, a long loop is formed between *N*-Me-L-Ile^6 and *N*-Me-D-*a*Ile^{13}.

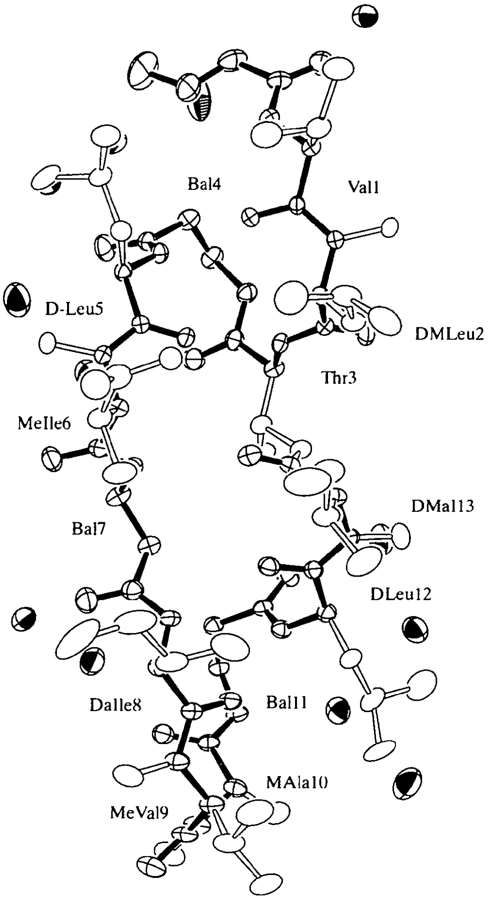


Fig. 1. A view of TNLP-Id with the residue names. The displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity.

Experimental

The title compound, TNLP-Id, was crystallized from an aqueous methanol solution.

Crystal data

$C_{70}H_{125}N_{13}O_{16}\cdot 12H_2O$
M_r = 1621.0
Orthorhombic
$P2_12_12_1$
a = 21.205 (4) Å
b = 37.941 (8) Å
c = 12.227 (2) Å
V = 9837 (3) Å^3
Z = 4
D_x = 1.095 Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
λ = 1.54180 Å
Cell parameters from 20 reflections
θ = 9.92–10.09°
μ = 0.697 mm^{-1}
T = 293 (2) K
Block
0.8 × 0.3 × 0.2 mm
Colorless

Data collection

Rigaku AFC-5*R*/RU-200 diffractometer
$2\theta/\omega$ scans
Absorption correction: none
8571 measured reflections
8571 independent reflections
7490 reflections with $I > 2\sigma(I)$

θ_{max} = 62.89°
$h = 0 \rightarrow 24$
$k = 0 \rightarrow 43$
$l = 0 \rightarrow 13$
4 standard reflections every 100 reflections intensity decay: 3.64%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.113
$wR(F^2)$ = 0.287
S = 1.020
8571 reflections
1001 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.14P)^2 + 18.50P]$ where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max}$ = 0.074
$\Delta\rho_{max}$ = 0.615 e Å^{-3}
$\Delta\rho_{min}$ = −0.594 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute structure: determined by chemical methods (see Kobayashi, Kanzaki *et al.*, 1994)

Table 1. *Selected hydrogen bonds (Å, °)*

D—H···*A*	*D*···*A*	*D*—H	H···*A*	*D*—H···*A*
N(L-Thr^3)—H···O(D-Leu^5)	2.832 (8)	0.860	1.978	171.4
N(D-Leu^5)—H···O(L-Val^1)	2.861 (8)	0.860	2.073	151.8
N(D-*a*Ile^8)—H···O(D-Leu^{12})	2.900 (7)	0.860	2.058	166.2
N(D-Leu^{12})—H···O(D-*a*Ile^8)	2.921 (8)	0.860	2.110	157.1
Peptide···water				
O(methoxy)···O(*W*1)	2.74 (1)			
O(methoxy)···O(*W*10)^i	2.95 (2)			
O(*N*-Me-D-Leu^2)···O(*W*3)^i	2.84 (1)			
O(*N*-Me-D-Leu^2)···O(*W*11)^{ii}	2.87 (1)			
O(L-Thr^3)···O(*W*8)	2.86 (1)			
O(βAla^4)···O(*W*2)	2.90 (1)			
O(βAla^4)···O(*W*10)	2.69 (2)			
O(βAla^7)···O(*W*3)	2.65 (1)			
O(*N*-Me-L-Ala^{10})···O(*W*6)	2.81 (1)			
N(βAla^{11})···O(*W*4)	2.97 (1)	0.860	2.189	150.7
O(βAla^{11})···O(*W*5)	2.78 (1)			
O(βAla^{11})···O(*W*1)^{iii}	2.86 (1)			

Symmetry codes: (i) $x, y, z+1$; (ii) $x+\frac{1}{2}, \frac{3}{2}-y, 2-z$; (iii) $x-\frac{1}{2}, \frac{3}{2}-y, 2-z$.

Table 2. *Selected torsion angles (°)*

L-Val^1					
φ	C1	N-1	Cα-1	C-1	−135.1 (8)
ψ	N-1	Cα-1	C-1	N-2	161.1 (7)
ω	Cα-1	C-1	N-2	Cα-2	166.6 (7)
N-Me-D-Leu^2					
φ	C-1	N-2	Cα-2	C-2	98.9 (6)
ψ	N-2	Cα-2	C-2	N-3	−112.8 (7)
ω	Cα-2	C-2	N-3	Cα-3	175.5 (8)

L-Thr[3]					
φ	C-2	N-3	Cα-3	C-3	−125.7 (8)
ψ	N-3	Cα-3	C-3	N-4	64.6 (7)
ω	N-3	Cα-3	Cβ-3	Cγ-3	−171.7 (7)
βAla[4]					
φ	C-3	N-4	Cα-4	Cβ-4	98.6 (9)
ψ	N-4	Cα-4	Cβ-4	C-4	−74.1 (7)
ψ†	Cα-4	Cβ-4	C-4	N-5	99.6 (8)
ω	Cβ-4	C-4	N-5	Cα-5	174.9 (8)
D-Leu[5]					
φ	C-4	N-5	Cα-5	C-5	122.7 (8)
ψ	N-5	Cα-5	C-5	N-6	−158.5 (7)
ω	Cα-5	C-5	N-6	Cα-6	−179.0 (7)
N-Me-L-Ile[6]					
φ	C-5	N-6	Cα-6	C-6	−106.3 (7)
ψ	N-6	Cα-6	C-6	N-7	100.2 (8)
ω	Cα-6	C-6	N-7	Cα-7	−165.9 (9)
βAla[7]					
φ	C-6	N-7	Cα-7	Cβ-7	−131.5 (9)
ψ	N-7	Cα-7	Cβ-7	C-7	78.0 (8)
ψ†	Cα-7	Cβ-7	C-7	N-8	−137.3 (9)
ω	Cβ-7	C-7	N-8	Cα-8	−173.7 (9)
D-*a*Ile[8]					
φ	C-7	N-8	Cα-8	C-8	126.0 (9)
ψ	N-8	Cα-8	C-8	N-9	−161.6 (8)
ω	Cα-8	C-8	N-9	Cα-9	−171.3 (8)
N-Me-L-Val[9]					
φ	C-8	N-9	Cα-9	C-9	−112.7 (8)
ψ	N-9	Cα-9	C-9	N-10	100.2 (9)
ω	Cα-9	C-9	N-10	Cα-10	0.7 (9)
N-Me-L-Ala[10]					
φ	C-9	N-10	Cα-10	C-10	−109.4 (9)
ψ	N-10	Cα-10	C-10	N-11	−164.6 (8)
ω	Cα-10	C-10	N-11	Cα-11	−171.2 (8)
βAla[11]					
φ	C-10	N-11	Cα-11	Cβ-11	72.3 (7)
ψ	N-11	Cα-11	Cβ-11	C-11	68.5 (6)
ψ†	N-12	C-11	Cβ-11	Cα-11	−93.3 (7)
ω	Cβ-11	C-11	N-12	Cα-12	−173.3 (8)
D-Leu[12]					
φ	C-11	N-12	Cα-12	C-12	87.0 (7)
ψ	N-12	Cα-12	C-12	N-13	−158.1 (8)
ω	Cα-12	C-12	N-13	Cα-13	−177.2 (8)
N-Me-D-*a*Ile[13]					
φ	C-12	N-13	Cα-13	C-13	−56.3 (7)
ψ‡	N-13	Cα-13	C-13	Oγ-3	−50.1 (6)
ω‡	Cβ-3	Oγ-3	C-13	Cα-13	172.2 (8)

† The β-alanine has two torsion angles corresponding to ψ. ‡ The angle is for the ester linkage between C-13(*N*-Me-D-*a*Ile[13]) and the hydroxy Oγ-3(L-Thr[3]) atom.

Intensities were measured to a maximum 2θ value of 120°, because reflections are only detected poorly beyond this limit. Direct-methods trials were extensively carried out using *SHELXS*86 (Sheldrick, 1985), but no clear solution was obtained. The structure was solved by the Shake-and-Bake method using the program *SnB* (Miller *et al.*, 1994; Chang *et al.*, 1996); a single running of the program gave a solution with a default setting and 700 trial structures. The absolute stereochemistry was assigned from chemical methods (Kobayashi, Kanzaki *et al.*, 1994). Successful refinement of the Flack (1983) parameter was not possible because intensities from Friedel pairs were not measured. The difference Fourier map showed 12 peaks, which were interpreted as solvent molecules. At the *N*-Me-Ile[6] residue, the Cδ1 atom was disordered into two parts, with probabilities of 0.78 and 0.22.

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: *SnB*. Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP*III (Burnett & Johnson, 1996).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1064). Services for accessing these data are described at the back of the journal.

References

Bernardinelli, G., Jefford, C. W., Sakai, R. & Higa, T. (1992). *Seventh International Symposium on Marine Natural Products*, Abstracts of Papers, pp. 29–30. Capri, Italy.

Burnett, M. N. & Johnson, C. K. (1996). *ORTEP*III. Report ORNL-6895. Oak Ridge National Laboratory, Tennessee, USA.

Chang, C.-S., DeTitta, G. T., Gallo, S. M., Hauptman, H. A., Jones, R., Khalak, A., Khalak, H., Langs, D. A., Miller, R., Potte, S., Thuman, P. & Weeks, C. M. (1996). *SnB. A Program for Crystal Structure Determination by Shake-and-Bake*. Version 1.5.0. Hauptman-Woodward Medical Research Institute, Buffalo, New York, USA.

Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.

Kobayashi, M., Kanzaki, K., Katayama, S., Ohashi, K., Okada, H., Ikegami, S. & Kitagawa, I. (1994). *Chem. Pharm. Bull.* **42**, 1410–1415.

Kobayashi, M., Kawazoe, K., Okamoto, T., Sasaki, T. & Kitagawa, I. (1994). *Chem. Pharm. Bull.* **42**, 19–26.

Kobayashi, M., Lee, N. K., Shibuya, H., Momose, T. & Kitagawa, I. (1991). *Chem. Pharm. Bull.* **39**, 1177–1184.

Miller, R., Gallo, S. M., Khalak, H. G. & Weeks, C. M. (1994). *J. Appl. Cryst.* **27**, 613–621.

Molecular Structure Corporation (1991). *MSC/AFC Diffractometer Control Software*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

Sheldrick, G. M. (1985). *SHELXS*86. *Program for the Solution of Crystal Structures*. University of Göttingen, Germany.

Sheldrick, G. M. (1993). *SHELXL*93. *Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.

Acta Cryst. (1999). C**55**, 798–801

3-[2-(1,3-Dioxolan-2-yl)ethyl]-2-methylbenzoic acid

Roger E. Gerkin

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210, USA. E-mail: gerkin@chemistry.ohio-state.edu

(*Received 3 November 1998; accepted 4 January 1999*)

Abstract

The title acid, $C_{13}H_{16}O_4$, crystallized in the centrosymmetric space group *Pbca* with one molecule in the asymmetric unit. In the single type of hydrogen bond, which forms cyclic dimers about centers of symme-

© 1999 International Union of Crystallography
Printed in Great Britain – all rights reserved