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Turn-over of an oxazoline ring induced by chiral change of a folded ascidiacyclamide analogue: cyclo(Ile-D–aThr–D-Val–Thz–Ile–D-Oxz–D-Val–Thz) *N,N*-dimethylformamide disolvate

Akiko Asano and Mitsunobu Doi*

Osaka University of Pharmaceutical Sciences, 4-20-1 Nasahara, Takatsuki, Osaka 569-1094, Japan

Correspondence e-mail: doit@gly.oups.ac.jp

Key indicators

Single-crystal X-ray study
T = 120 K
Mean σ(C–C) = 0.004 Å
R factor = 0.052
wR factor = 0.148
Data-to-parameter ratio = 17.4

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

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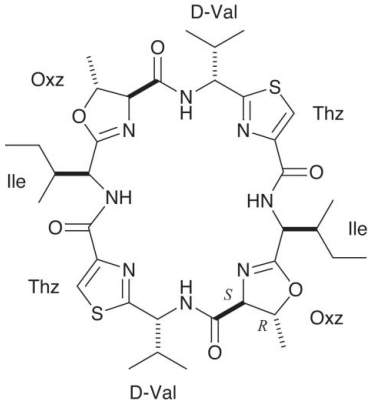
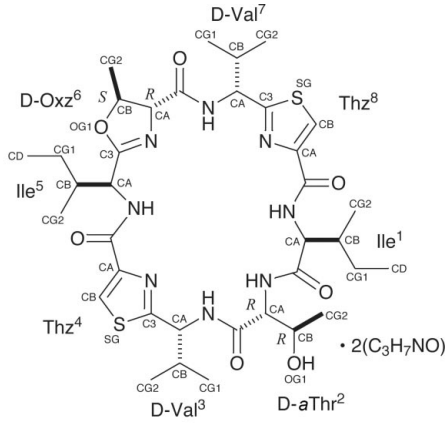
Ascidiacyclamide (ASC) has two oxazoline (Oxz) residues with 2*S*,3*R* configurations. In the title compound, $C_{36}H_{54}N_8O_7S_2\cdot 2C_3H_7NO$, these Oxz residues were replaced with D-aThr and (2*R*,3*S*)–Oxz (D-Oxz). The overall structure is similar to the folded from of ASC analogues previously reported, but a difference was found at the D-Oxz residue. The D-Oxz ring was turned over in relation to the disposition of the Oxz rings in natural ASC. This result suggested that the modification of Oxz could induce a new type of molecular folding in ASC.

Comment

Ascidiacyclamide (ASC) is a cytotoxic peptide containing unusual amino acids, such as oxazoline (Oxz) and thiazole (Thz) (Hamamoto *et al.*, 1983). Folded and square forms have been observed for ASC (Ishida *et al.*, 1992; In *et al.*, 1993; In, Doi, Inoue *et al.*, 1994; In, Doi & Ishida, 1994) and its analogues (Doi *et al.*, 1999; Asano, Minoura *et al.*, 2002; Asano *et al.*, 2003). In our series of studies, we have attempted to control the structures of ASCs by modifications of the Oxz residues. The removal of Oxz rings resulted in molecular folding (Asano, Doi *et al.*, 2001; Doi *et al.*, 2001). The chiral changes of Oxz residues resulted in a flat structure (Asano, Yamada *et al.*, 2002) with the additional modifications induced forming a β-sheet (Asano, Taniguchi *et al.*, 2001). In this paper, a new type of ASC folding is reported for cyclo(Ile–D-aThr–D-Val–Thz–Ile–D-Oxz–D-Val–Thz), (I), where Oxz residues are replaced with D-aThr (allothreonine) and D-Oxz.



Ascidiacyclamide (ASC)



(I)

Compound (I) crystallized as an *N,N*-dimethylformamide (DMF) solvated form, and the peptide is folded as shown in Fig. 1. The molecular folding is stabilized by intramolecular hydrogen bonds (Table 1): (D-Val^3)—NH···O=(Thz^8),

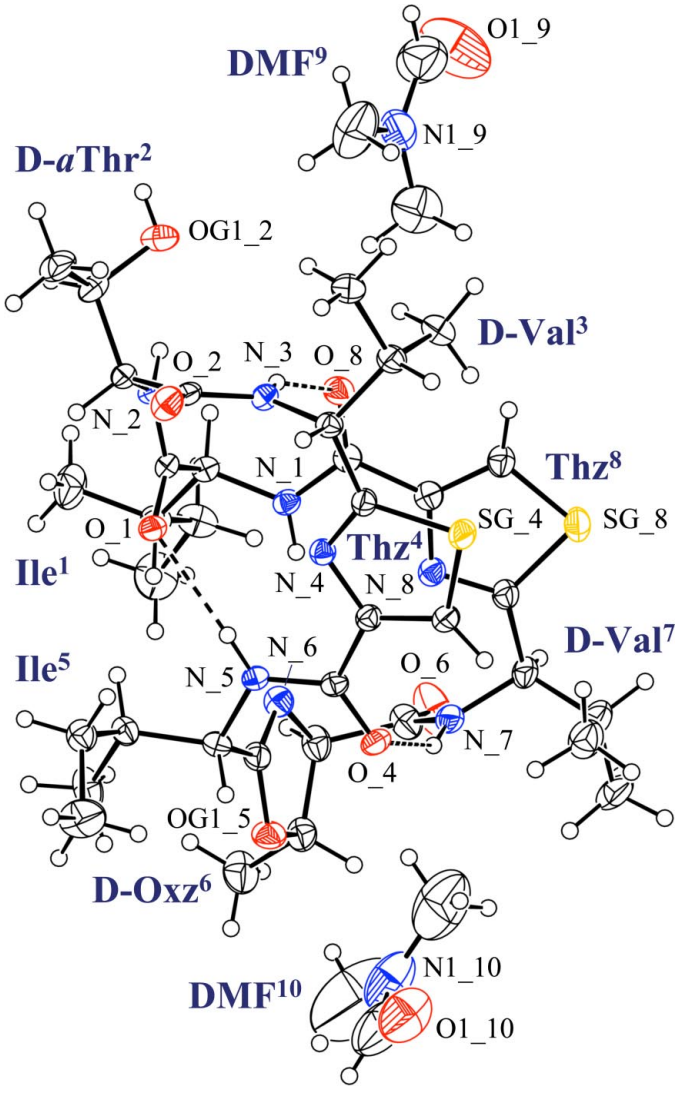


Figure 1
A view of compound (I), with displacement ellipsoids drawn at the 40% probability level. Dotted lines represent hydrogen bonds. Only heteroatoms are labeled for clarity.

(Ile^5)—NH···O═(Ile^1) and (D-Val^7)—NH···O═(Thz^4). The Thz rings face one another, with an SG(Thz^4)···SG(Thz^8) distance of 4.69 Å; the average SG···SG distances are 4.5 (1) and 4.4 (3) Å for the ASC and desoxazoline analogues, respectively. These features indicated that the structure of (I) is similar to the folded forms of ASC analogues. When molecular fittings are carried out, the peptide backbone of (I) is similarly folded to those of the ASC and desoxazoline analogues (Fig. 2). However, differences are found in the D-Oxz^6 residue. In the folded forms of ASC, the OG1 atoms of Oxz are directed to the inside of the peptide (Fig. 2*a*), with an average OG1···OG1 distance of 3.94 (4) Å and an average N(Ile)—CA(Ile)—C3(Oxz)—OG1(Oxz) angle of 65 (2)°. In compound (I), the D-Oxz^6 ring is turned over, with an O(D-aThr^2)···N(D-Oxz^6) distance of 4.62 Å and an N(Ile^5)—CA(Ile^5)—C3(D-Oxz^6)—OG1(D-Oxz^6) angle of 138.6 (2)° (Fig. 2*b*). This disposition of the Oxz ring is the first example in

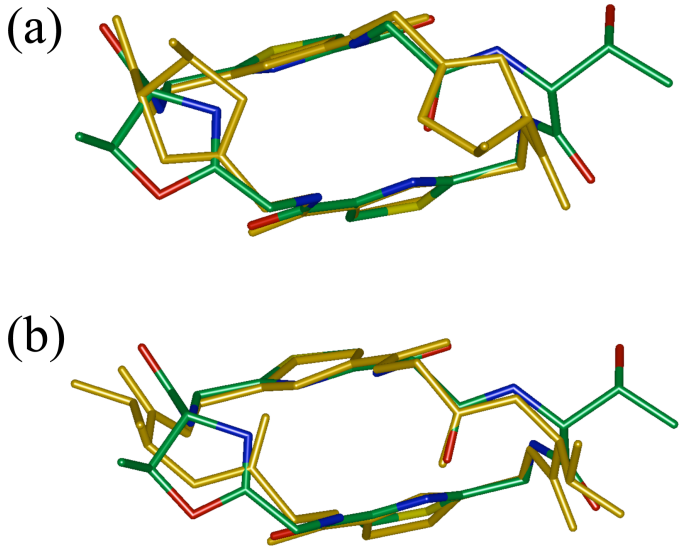


Figure 2
Superimpositions. (*a*) [Ala]ASC and (*b*) desoxazoline ASC were fitted for (I). The fitted molecule is coloured gold. C, N, O and S atoms are coloured green, red, blue and yellow, respectively. Side chains of Ile and D-Val are omitted for clarity. Fitting and drawings were made using *iMol* (Rotkiewicz, 2004).

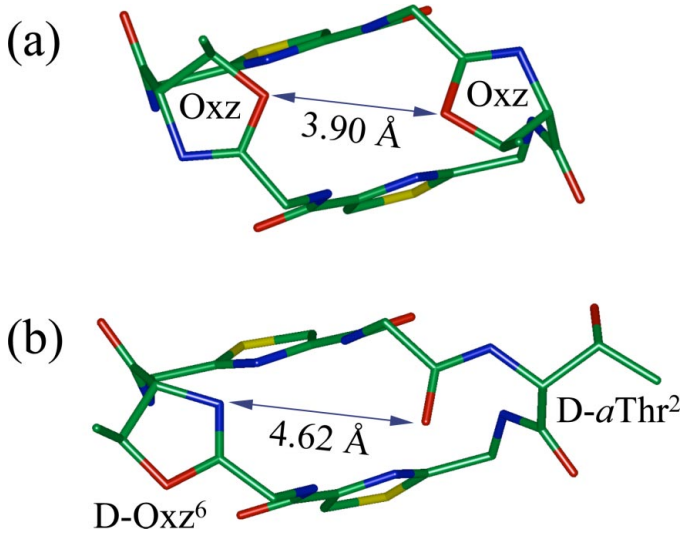


Figure 3
Views of folded forms projected on Oxz rings. (*a*) [Ala]ASC and (*b*) compound (I). C, N, O and S atoms are coloured green, red, blue and yellow, respectively. Side chains of Ile and D-Val are omitted for clarity.

an ASC analogue. These results imply that structural variation of ASC could be induced by modification of the Oxz residues.

Experimental

The synthesis of (I) was carried out as previously described (Hamada *et al.*, 1987). In the cyclization of threonine step using thionyl chloride, the main product was isolated by column chromatography giving compound (I). Crystals of (I) were grown from *N,N*-dimethylformamide solution over a period of three months at room temperature.

Crystal data

$C_{36}H_{54}N_8O_7S_2\cdot 2C_3H_7NO$	D_x = 1.265 Mg m^{-3}
M_r = 921.18	Mo $K\alpha$ radiation
Monoclinic, $P2_1$	Cell parameters from 8060 reflections
a = 13.031 (1) Å	θ = 2.5–28.1°
b = 11.0503 (9) Å	μ = 0.17 mm^{-1}
c = 17.358 (1) Å	T = 120.0 (2) K
β = 104.654 (1)°	Plate, colourless
V = 2418.2 (3) Å^3	0.40 × 0.30 × 0.02 mm
Z = 2	

Data collection

Bruker SMART APEX CCD area-detector diffractometer	10109 independent reflections
ω scans	8732 reflections with $I > 2\sigma(I)$
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)	R_{int} = 0.026
T_{min} = 0.887, T_{max} = 0.997	θ_{max} = 27.1°
20955 measured reflections	$h = -16 \rightarrow 16$
	$k = -14 \rightarrow 14$
	$l = -22 \rightarrow 22$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0967P)^2 + 0.6439P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.052	$(\Delta/\sigma)_{max}$ = 0.013
$wR(F^2)$ = 0.148	$\Delta\rho_{max}$ = 0.80 e Å^{-3}
S = 1.03	$\Delta\rho_{min}$ = −0.52 e Å^{-3}
10109 reflections	Absolute structure: Flack (1983), 4576 Friedel pairs
582 parameters	Flack parameter = 0.04 (7)
H-atom parameters constrained	

Table 1
Hydrogen-bonding geometry (Å,°)..

D—H	A	D—H	H···A	D···A	D—H···A
(D-aThr^2)—NH	O = (D-aThr^2)^{i}	0.88	2.08	2.921 (3)	159
(D-aThr^2)—OH	O = (Ile^1)^{i}	0.84	2.29	3.053 (3)	152
(D-Val^3)—NH	O = (Thz^8)	0.88	2.19	3.012 (3)	156
(Ile^5)—NH	O = (Ile^1)	0.88	2.17	3.014 (3)	162
(D-Val^7)—NH	O = (Thz^4)	0.88	2.47	3.255 (3)	149

Symmetry code: (i) $-x, y-\frac{1}{2}, -z$.

H atoms were placed at ideal positions (C—H = 0.95–1.00 Å and N—H = 0.88 Å) and refined as riding, with U_{iso}(H) = 1.2 or 1.5 times U_{eq}(parent atom). The H atom of the hydroxyl group (D-aThr^2) was located in a difference Fourier map and fixed during refinement. The absolute configuration was confirmed by the Flack (1983) parameter to be the same as that of the starting material.

Data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT-Plus* (Bruker, 1998); data reduction: *SAINT-Plus*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003) and *iMol* (Rotkiewicz, 2004); software used to prepare material for publication: *SHELXL*97.

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