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A folded conformation of an ascidiacyclamide derivative: 3-methoxysulfoxide-(2*R*,3*R*)-threoninyl desoxazoline-ascidiacyclamide

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Key indicators

Single-crystal synchrotron study
T = 100 K
Mean σ(C–C) = 0.009 Å
R factor = 0.075
wR factor = 0.201
Data-to-parameter ratio = 8.9

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

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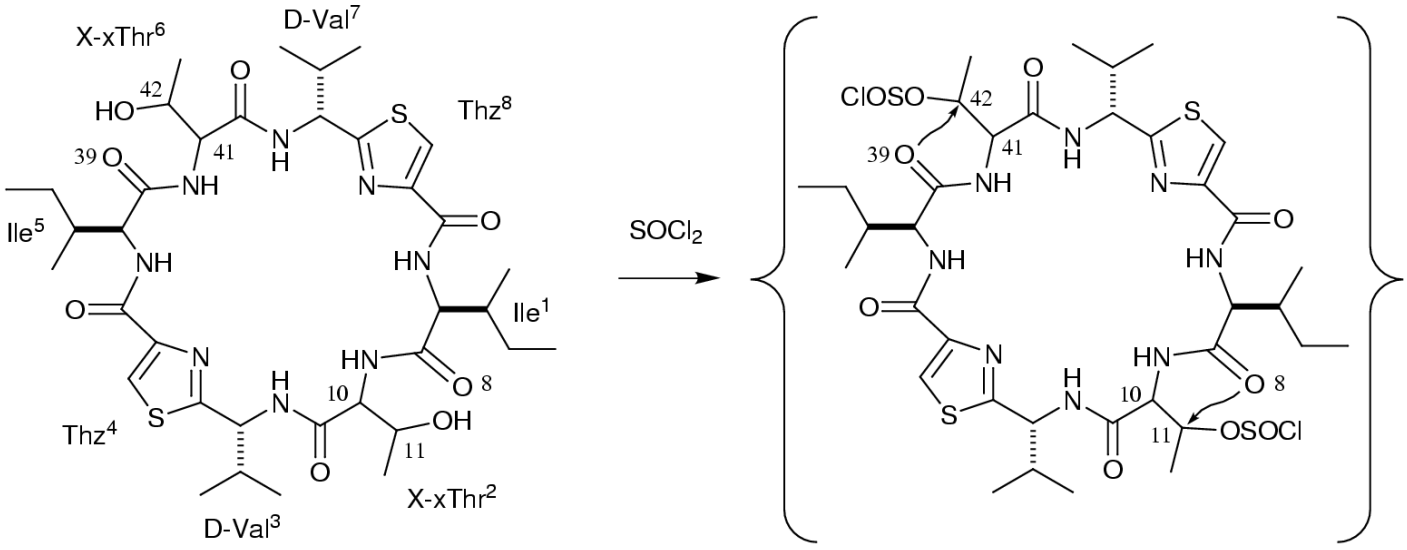
Ascidiacyclamide, *cyclo*(–Ile–Oxz–D-Val–Thz–)$_2$, has two methyl-oxazoline (Oxz) residues, and each Oxz residue has two chiral C atoms. In the present work, $C_{38}H_{60}N_8O_{12}S_4$, a chiral modification of these atoms was attempted. A total of ten diastereomers were considered, of which seven were synthesized. For the three remaining diastereomers, the reaction was incomplete or very much slowed down. These diastereomers had the D configuration for both Oxz residues. This result appeared to be related to the conformation of the reaction intermediates. Therefore, the intermediates were converted into stable forms and then isolated to confirm their structures. Crystals were obtained from one derivative and its structure was found to be of the folded form. In this form, the activated atoms were separated from the target atoms. It is suggested that this folded conformation hinders the completion of the reaction.

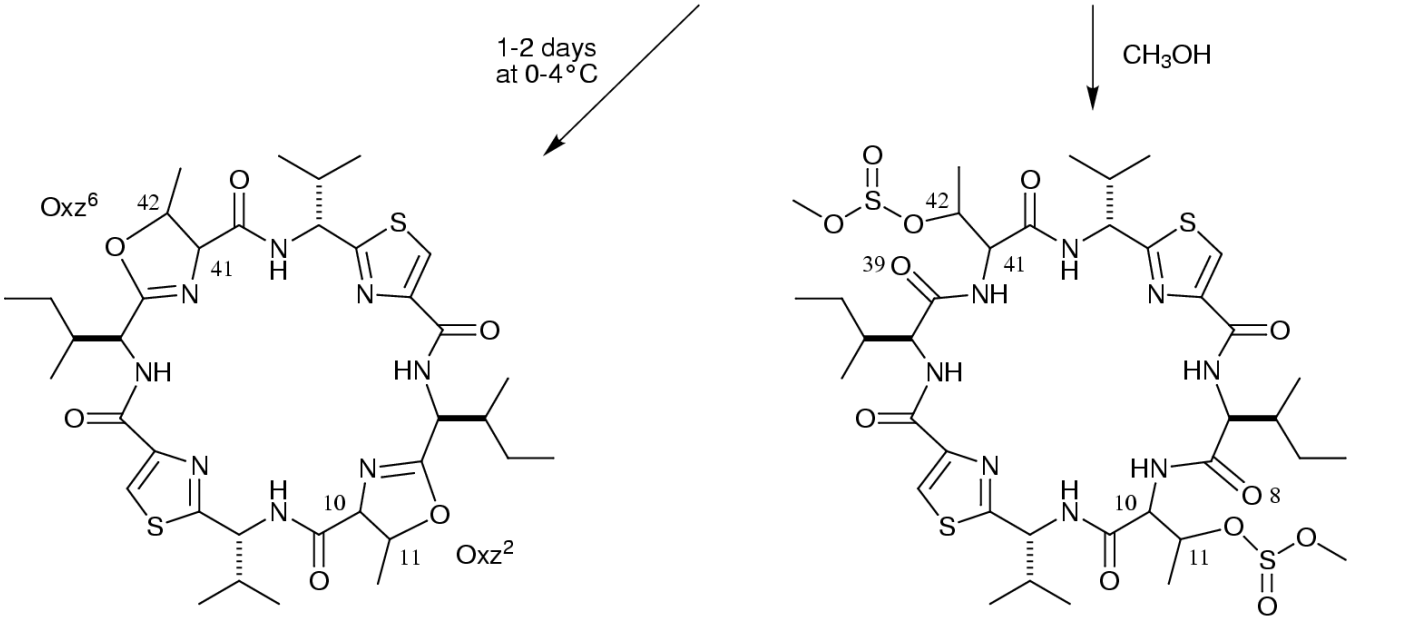
Comment

Ascidiacyclamide (ASC), (3), is a symmetric cyclic peptide containing unusual amino acids, such as oxazoline (Oxz) and thiazole (Thz) (Hamamoto *et al.*, 1983). Two major conformations and their conformational equilibrium have been suggested for ASC (Ishida *et al.*, 1988; In *et al.*, 1993). In our series of studies, the relationships between ASC conformation and symmetry of the chemical structure have been examined; additionally, we have studied the asymmetric modifications which disturb the C_2 symmetry of ASC and how this affects the ASC structures in both the solid state and in solution (Doi *et al.*, 1999; Asano *et al.*, 2001). Here, we extend the asymmetric modifications by substituting the Oxz residues with their diastereomers.

ASC is synthesized from a cyclic hexapeptide, (1), using thionyl chloride (Hamada *et al.*, 1987). Oxz rings are formed from the threonine residues *via* the chlorosulfoxide intermediate (2) after reacting for 1–2 d at 273–277 K. For the synthesis of the ASC diastereomers, the threonine residues of (1) are replaced by the following threonine diastereomers: Thr, *allo*-threonine (aThr), D-Thr and D-aThr (in the Scheme, X-xThr refers to the four epimers of threonine, *i.e.* L-Thr, L-aThr, D-Thr and D-aThr). A total of ten diastereomers of (1) were synthesized and their configurations at positions (10,11,41,42) are (*S*,*S*,*S*,*S*), (*S*,*S*,*S*,*R*), (*S*,*S*,*R*,*R*), (*S*,*S*,*R*,*S*), (*S*,*R*,*S*,*R*), (*S*,*R*,*R*,*R*), (*S*,*R*,*R*,*S*), (*R*,*R*,*R*,*R*), (*R*,*R*,*R*,*S*) and (*R*,*S*,*R*,*S*). Natural ASC is synthesized from (*S*,*S*,*S*,*S*)-(1). For seven of the ten diastereomers, the reaction of Oxz formation was completed under the reported conditions. However, this reaction did not complete or was very much slowed down for the three diastereomers having (*R*,*R*,*R*,*R*), (*R*,*R*,*R*,*S*) and (*R*,*S*,*R*,*S*) configurations. These configurations imply that



(1) (2)



(3) (4)

residues 2 and 6 are D-amino acids (Cα at positions 10 and 41). We presume that a particular conformation, which hinders the completion of the reaction, is present in the intermediates (2) derived from these three diastereomers. Such a conformation is interesting because it is stable, even in thionyl chloride solution. To clarify this conformation, three methyl sulfoxide derivatives of 4 were isolated, by the addition of methanol to intermediates (2), and the structure of (*R,R,R,R*)-(4) was analyzed.

The structure of (*R,R,R,R*)-(4) is shown in Fig. 1. The configuration (*R,R,R,R*) is confirmed for atoms C10, C11, C41 and C42 in the structure. The molecule is folded and four intramolecular hydrogen bonds are formed to stabilize the folded conformation: N1···O39 2.983 (6), N20···O62 3.017 (6), N32···O8 2.950 (6) and N51···O31 3.112 (6) Å. This structure is very similar to the folded forms of ASC and its derivatives (Doi *et al.*, 1999). The Thz rings (C25—N26—C27—C28—S29 and C56—N57—C58—C59—S60) face each other with an angle of 15.3° between the ring planes. The distance between the thiazole rings indicates π–π electron stacking [*e.g.* C27···C58 3.414 (8) Å]. This feature is an important characteristic of the folded ascidiacyclamide.

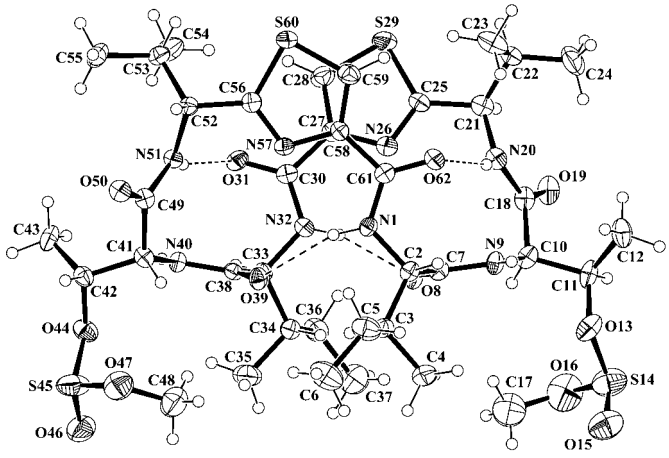


Figure 1
The structure of (*R,R,R,R*)-(4). Dashed lines indicate intramolecular hydrogen bonds.

In the reaction for Oxz ring formation, the activated Cβ atoms of D-Thr residues (C11 and C42) are necessary for contact with the carbonyl O atoms of Ile (O8 and O39). However, the C11 (or C42) atom is well separated from the O8 (or O39) atom in this folded structure (Fig 1). It seems that such spatial arrangements cause incompletion or slow down of the reaction.

Experimental

The compound (*R,R,R,R*)-(4) was crystallized from chloroform solution as clusters of blocks. These crystals were crushed in 100% glycerol and a single crystal was mounted on a nylon loop under a nitrogen stream at 100 K. Data were measured on a Rigaku R-AXIS-IV using synchrotron radiation. A total of 42 images were collected for each 4° oscillation angle and these were integrated to 35 905 reflections by *MOSFLM* (Leslie, 1999). They were successively processed yielding 17501 reflections with R_{sym} = 0.054 and R_{merg} = 0.076, using *SCALA* (Evans, 1997) of the *CCP*4 Suite (Collaborative Computational Project, Number 4, 1994). In the refinement the *R* value increased in the high-resolution shell greater than 0.82 Å. Therefore, reflections from this shell were omitted from the refinement. The absolute configuration agreed with the L- and D-configurations of the materials (amino acids), and the Flack *x* parameter was 0.38 (15). In the final refinement, a peak with 1.31 e Å^{-3} was observed at a distance of 0.92 Å from atom S45.

Crystal data

$C_{38}H_{60}N_8O_{12}S_4$	Synchrotron radiation
M_r = 949.18	λ = 0.8360 Å
Orthorhombic, $P2_12_12_1$	Cell parameters from 6840 reflections
a = 10.7820 (3) Å	θ = 1.2–31.0°
b = 19.6026 (4) Å	μ = 0.27 mm^{-1}
c = 22.5181 (7) Å	T = 100 (2) K
V = 4759.3 (2) Å^3	Block, colorless
Z = 4	0.08 × 0.08 × 0.08 mm
D_x = 1.325 Mg m^{-3}	

Data collection

Rigaku R-AXIS-IV diffractometer	R_{int} = 0.055
Oscillation (φ) scans	θ_{max} = 30.6°
16 269 measured reflections	$h = -13 \rightarrow 13$
4973 independent reflections	$k = -23 \rightarrow 23$
4759 reflections with $I > 2\sigma(I)$	$l = 0 \rightarrow 27$

Refinement

Refinement on F^2	$(\Delta/\sigma)_{max}$ = 0.042
$R[F^2 > 2\sigma(F^2)]$ = 0.075	$\Delta\rho_{max}$ = 1.31 e Å^{-3}
$wR(F^2)$ = 0.201	$\Delta\rho_{min}$ = −0.67 e Å^{-3}
S = 1.05	Extinction correction: *SHELXL*97
4973 reflections	Extinction coefficient: 0.0085 (10)
560 parameters	Absolute structure: Flack (1983)
H-atom parameters constrained	Flack parameter = 0.38 (15)
$w = 1/[\sigma^2(F_o^2) + (0.1152P)^2 + 7.3374P]$ where $P = (F_o^2 + 2F_c^2)/3$	

Data collection: *PROCESS* (Higashi, 1996); cell refinement: *MOSFLM* (Leslie, 1999); data reduction: *MOSFLM*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 1998); software used to prepare material for publication: *PLATON*.

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