Molecular Conformation of Patellamide A, a Cytotoxic Cyclic Peptide from the Ascidian *Lissoclinum patella*, by X-Ray Crystal Analysis

Yasuko IN,[a] Mitsunobu DOI,[a] Masatoshi INOUE,[a] Toshimasa ISHIDA,*[,a] Yasumasa HAMADA,[b] and Takayuki SHIOIRI[b]

Department of Physical Chemistry, Osaka University of Pharmaceutical Sciences,[a] 2–10–65 Kawai, Matsubara, Osaka 580, Japan and Faculty of Pharmaceutical Sciences, Nagoya City University,[b] Tanabe-dori, Mizuho-ku, Nagoya 467, Japan. Received January 22, 1993

As part of a series of investigations into the conformational stability of a C_2-symmetric or related cyclic peptide isolated from the ascidian *Lissoclinum patella*, the molecular conformation of patellamide A, the chemical structure of which deviates slightly for C_2-symmetry, was determined by X-ray crystal analysis. Patellamide A took on a saddle-shaped rectangular form and wrapped around the water and methanol solvents. This conformation which is very similar to that of C_2-symmetric ascidiacyclamide would be proposed as a possible candidate for biologically "active" conformation.

Keywords patellamide A; cytotoxic cyclic peptide; C_2-symmetric molecular conformation; X-ray crystal analysis

In the course of elucidating the stereostructure–activity relationship of cytotoxic cyclic peptides from the ascidian, the molecular conformation of ascidiacyclamide (**1**) has been determined by X-ray diffraction and ^{1}H-NMR methods.[1] All conformations of **1** analyzed so far showed a C_2- or pseudo C_2-symmetric square form of type II in Chart 2. Since this conformation was also shown by ^{1}H-NMR analysis[2] to be a major form of ulithiacyclamide (**2**) in solution, the correlation between the type II square form and biological activity has been considered important.

On the other hand, it was recently shown[3] that the crystal structure of patellamide D (**3**), the only example among the cyclic peptides having non-C_2-symmetric chemical structures, takes on a molecular conformation of type III. Since this form would be converted to type II *via* type I, it appears important, upon considering the "active" conformation of the cyclic peptides from the ascidian, to know the factors which cause such a drastic

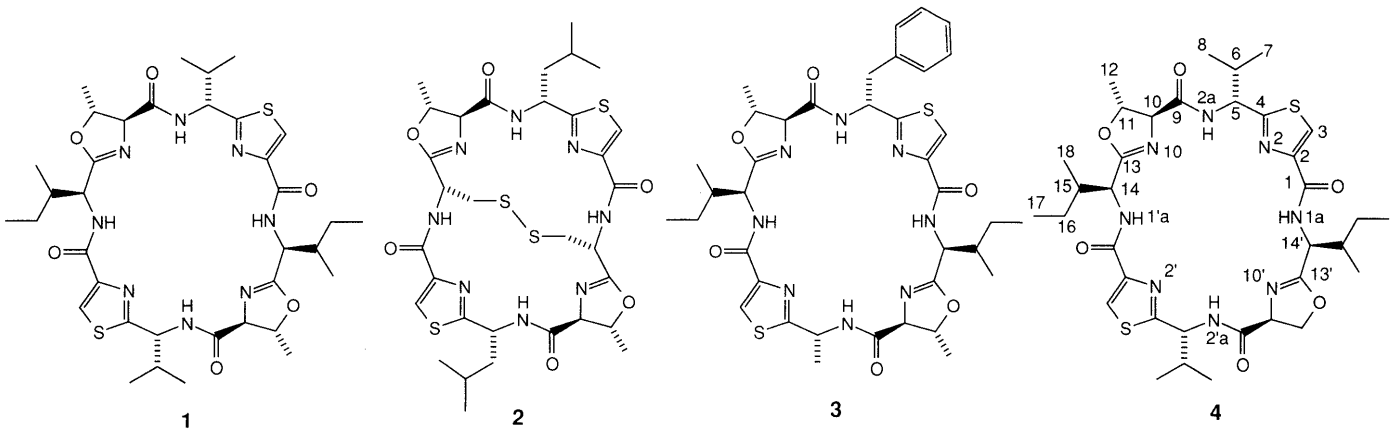

Chart 1

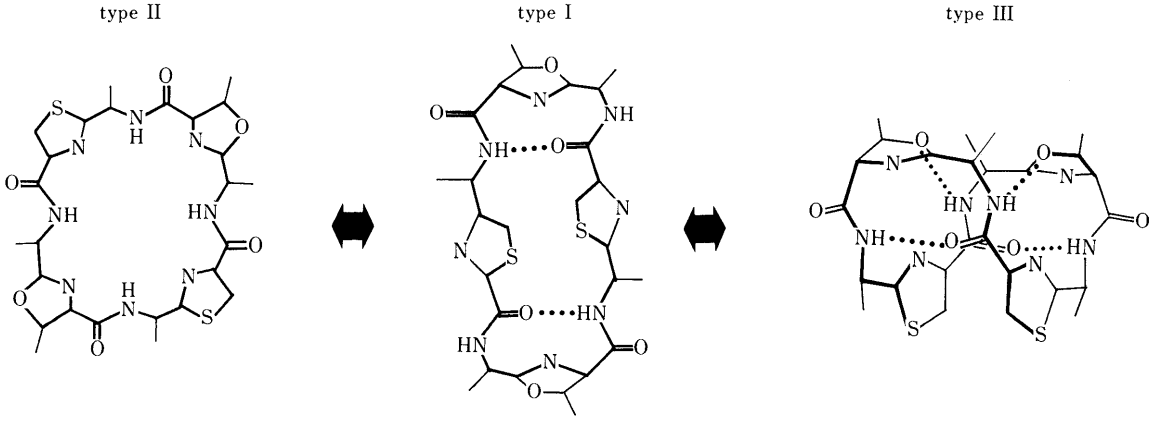

Chart 2

conformational change. A comparison of chemical structures **1** and **3** leads us to a hypothesis that the deviation from the C_2-symmetric chemical structure becomes a trigger to shift the molecular conformation from type II to type III. In this context, it would be interesting to know the molecular conformation of patellamide A (**4**), because its C_2-symmetry is least broken at the oxazole C(11) atom.

TABLE I. Atomic Coordinates and Isotropic Temperature Factors of Non-H Atoms with Their e.s.d.'s in Parentheses

Atom	x	y	z	U_{eq} (Å^2)
N(1a)	−0.0636 (7)	1.2377 (5)	0.4659 (6)	0.065 (3)
C(1)	−0.0294 (8)	1.1428 (6)	0.3951 (8)	0.068 (4)
O(1)	−0.0260 (9)	1.1321 (6)	0.2712 (7)	0.098 (5)
C(2)	−0.005 (1)	1.0520 (6)	0.4716 (9)	0.079 (5)
N(2)	0.0056 (6)	1.0593 (4)	0.6124 (7)	0.066 (4)
C(3)	0.016 (2)	0.9491 (8)	0.403 (1)	0.14 (1)
S(3)	0.0374	0.8634	0.5177	0.140 (3)
C(4)	0.0286 (8)	0.9665 (5)	0.6516 (9)	0.066 (4)
C(5)	0.0432 (8)	0.9494 (5)	0.7982 (9)	0.067 (4)
C(6)	0.1898 (8)	0.9690 (7)	0.888 (1)	0.086 (6)
C(7)	0.299 (1)	0.895 (1)	0.808 (3)	0.16 (1)
C(8)	0.193 (1)	0.964 (1)	1.041 (1)	0.117 (9)
N(2a)	−0.0667 (6)	1.0181 (4)	0.8556 (7)	0.066 (3)
C(9)	−0.1397 (8)	0.9882 (6)	0.9289 (9)	0.072 (4)
O(9)	−0.1260 (8)	0.8975 (4)	0.9627 (9)	0.112 (5)
C(10)	−0.2403 (7)	1.0734 (5)	0.9926 (8)	0.064 (4)
N(10)	−0.2698 (6)	1.1676 (4)	0.9239 (7)	0.061 (3)
C(11)	−0.3799 (9)	1.0365 (7)	0.976 (1)	0.092 (6)
O(11)	−0.4715 (5)	1.1023 (5)	0.8768 (8)	0.086 (4)
C(12)	−0.413 (3)	1.060 (2)	1.118 (3)	0.22 (2)
C(13)	−0.3969 (7)	1.1763 (5)	0.8624 (8)	0.061 (4)
C(14)	−0.4714 (7)	1.2564 (6)	0.7699 (9)	0.071 (4)
C(15)	−0.4920 (9)	1.2146 (9)	0.616 (1)	0.084 (5)
C(16)	−0.617 (1)	1.155 (2)	0.569 (1)	0.13 (1)
C(17)	−0.663 (2)	1.141 (3)	0.411 (2)	0.22 (2)
C(18)	−0.361 (1)	1.153 (1)	0.574 (1)	0.100 (7)
N(1'a)	−0.3984 (5)	1.3476 (4)	0.8033 (6)	0.061 (3)
C(1')	−0.4699 (8)	1.4415 (6)	0.8356 (9)	0.074 (5)
O(1')	−0.5939 (6)	1.4535 (5)	0.8401 (8)	0.110 (5)
C(2')	−0.394 (1)	1.5346 (5)	0.8634 (9)	0.082 (5)
N(2')	−0.2557 (6)	1.5251 (4)	0.8725 (6)	0.063 (3)
C(3')	−0.464 (1)	1.6341 (7)	0.878 (2)	0.16 (1)
S(3')	−0.3468 (3)	1.7221 (2)	0.9072 (5)	0.143 (2)
C(4')	−0.2150 (8)	1.6188 (4)	0.8941 (8)	0.070 (4)
C(5')	−0.0657 (8)	1.6352 (5)	0.9126 (7)	0.066 (4)
C(6')	0.021 (1)	1.6117 (6)	1.0587 (8)	0.088 (5)
C(7')	0.176 (1)	1.621 (1)	1.070 (1)	0.13 (1)
C(8')	−0.046 (2)	1.687 (1)	1.165 (1)	0.15 (1)
N(2'a)	−0.0092 (6)	1.5655 (4)	0.8009 (6)	0.066 (3)
C(9')	0.0638 (8)	1.5963 (5)	0.7281 (7)	0.070 (4)
O(9')	0.0925 (8)	1.6890 (4)	0.7420 (7)	0.113 (5)
C(10')	0.1248 (7)	1.5133 (5)	0.6260 (7)	0.067 (4)
N(10')	0.0570 (6)	1.4179 (4)	0.5957 (6)	0.059 (3)
C(11')	0.106 (1)	1.5482 (7)	0.4830 (8)	0.094 (5)
O(11')	0.0090 (7)	1.4829 (4)	0.3943 (6)	0.096 (4)
C(13')	−0.0045 (7)	1.4100 (5)	0.4701 (7)	0.060 (4)
C(14')	−0.0961 (8)	1.3302 (5)	0.3951 (7)	0.068 (4)
C(15')	−0.2498 (8)	1.3744 (7)	0.3740 (9)	0.082 (5)
C(16')	−0.296 (1)	1.426 (1)	0.248 (1)	0.13 (1)
C(17')	−0.455 (1)	1.453 (2)	0.203 (2)	0.19 (2)
C(18')	−0.292 (1)	1.4305 (9)	0.504 (1)	0.105 (7)
Solvents				
O(1)W	−0.0858 (6)	1.2925 (4)	0.7803 (6)	0.083 (4)
O(1a)Me	0.194 (2)	1.279 (1)	0.869 (2)	0.09 (1)
O(1b)Me	0.010 (2)	1.305 (1)	1.060 (1)	0.10 (1)
O(1c)Me	0.158 (2)	1.287 (2)	1.116 (2)	0.12 (2)
O(1d)Me	0.246 (3)	1.295 (2)	1.017 (2)	0.14 (2)
C(1)Me	0.0997 (5)	1.2904 (5)	0.9639 (6)	0.089 (4)

$U_{eq} = 1/3\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \boldsymbol{a}_i \cdot \boldsymbol{a}_j$.

Experimental

Materials Patellamide A was chemically synthesized according to Hamada *et al.*[4] Transparent platelet single crystals were grown from an aqueous methanol solution by slow evaporation at room temperature (20°C). The thermogravimetry (TG)/differential thermal analyses (DTA) and the qualitative chemical titrations suggested that the crystals contain equimolar H_2O and CH_3OH solvents.

X-Ray Crystal Analysis A single crystal of the dimensions $0.3 \times 0.3 \times 0.1$ mm^3 was sealed in a glass capillary containing some mother liquor to prevent the release of solvent molecules from the crystal, and was used for the subsequent X-ray work. Crystal data are as follows: $C_{35}H_{50}N_8O_6S_2 \cdot CH_3OH \cdot H_2O$, $M_r = 793.02$, triclinic, space group $P1$, $a = 10.035(4)$ Å, $b = 12.985(3)$ Å, $c = 10.022(2)$ Å, $\alpha = 99.91(3)°$, $\beta = 103.61(3)°$, $\gamma = 79.97(2)°$, $V = 1238.0(7)$ Å^3, $D_{calcd} = 1.064$ g·cm^{-3}, $Z = 1$, $\mu(CuK_\alpha) = 13.60$ cm^{-1}, $F(000) = 424$. Unit-cell dimensions were determined by a least-squares fit of 2θ angles of 25 reflections ranging from $20° \leq 2\theta \leq 46°$. Intensity data were measured by graphite-monochromated CuK_α radiation ($\lambda = 1.5418$ Å) on a Rigaku AFC-5 diffractometer with an $\omega - 2\theta$ scanning mode. Four standard reflections monitored for every 100 reflection intervals showed no significant deterioration ($< \pm 5.5\%$). The observed intensities were corrected for Lorentz and polarization effects, but not for absorption. A total of 4229 independent reflections were measured for $2° \leq 2\theta \leq 130°$, of which 3619 were considered to be observed [$I \geq 2\sigma(I)$].

The crystal structure was solved by a combination of the Patterson vector search and direct methods using the PATSEE[5] and SHELXS-86[6] programs. Several cycles of successive Fourier syntheses showed the atomic positions of patellamide A and solvet molecules. The refinement was carried out using full-matrix least-squares calculations with anisotropic thermal parameters. Hydrogen atoms were included in the structure factor calculations at their stereochemically expected positions with an isotropic temperature factor ($U = 0.05$ Å^2). The function of $\Sigma w(|F_O| - |F_C|)^2$ was minimized using the SHELX76 program,[7] where $w = 1/\sigma(F_O)^2$ was used. The final discrepancy indices were $R = 0.067$ and $R_w = 0.078$, and S (goodness of fit) was 1.211. None of the positional parameters for non-H atoms shifted more than their estimated standard deviations. The residual electron density in the difference Fourier map ranged from $-0.48e$ Å^{-3} to $0.52e$ Å^{-3}. Final positional and isotropic thermal parameters for non-H

TABLE II. Bond Length (Å) with Their e.s.d's in Parentheses

Bond	Distance	Bond	Distance
N(1a)–C(1)	1.34 (1)	N(1'a)–C(1')	1.33 (1)
N(1a)–C(14')	1.450 (9)	N(1'a)–C(14)	1.45 (1)
C(1)–O(1)	1.23 (1)	C(1')–O(1')	1.24 (1)
C(1)–C(2)	1.47 (1)	C(1')–C(2')	1.49 (1)
C(2)–N(2)	1.38 (1)	C(2')–N(2')	1.36 (1)
C(2)–C(3)	1.40 (2)	C(2')–C(3')	1.36 (2)
N(2)–C(4)	1.30 (1)	N(2')–C(4')	1.318 (9)
C(3)–S(3)	1.69 (1)	C(3')–S(3')	1.72 (1)
S(3)–C(4)	1.731 (8)	S(3')–C(4')	1.722 (8)
C(4)–C(5)	1.49 (1)	C(4')–C(5')	1.51 (1)
C(5)–C(6)	1.57 (1)	C(5')–C(6')	1.57 (1)
C(5)–N(2a)	1.46 (1)	C(5')–N(2'a)	1.471 (9)
C(6)–C(7)	1.59 (2)	C(6')–C(7')	1.56 (2)
C(6)–C(8)	1.55 (2)	C(6')–C(8')	1.52 (2)
N(2a)–C(9)	1.29 (1)	N(2'a)–C(9')	1.296 (9)
C(9)–O(9)	1.26 (1)	C(9')–O(9')	1.26 (1)
C(9)–C(10)	1.52 (1)	C(9')–C(10')	1.51 (1)
C(10)–N(10)	1.46 (1)	C(10')–N(10')	1.469 (9)
C(10)–C(11)	1.52 (1)	C(10')–C(11')	1.54 (1)
N(10)–C(13)	1.274 (9)	N(10')–C(13')	1.260 (9)
C(11)–O(11)	1.47 (1)	C(11')–O(11')	1.44 (1)
O(11)–C(13)	1.36 (1)	O(11')–C(13')	1.353 (9)
C(13)–C(14)	1.50 (1)	C(13')–C(14')	1.49 (1)
C(14)–C(15)	1.52 (1)	C(14')–C(15')	1.53 (1)
C(15)–C(16)	1.53 (2)	C(15')–C(16')	1.48 (2)
C(15)–C(18)	1.52 (2)	C(15')–C(18')	1.50 (1)
C(16)–C(17)	1.53 (3)	C(16')–C(17')	1.54 (2)
C(11)–C(12)	1.51 (3)		
Solvent			
C(1)Me–O(1a)Me	1.46 (2)	C(1)Me–O(1b)Me	1.44 (2)
C(1)Me–O(1c)Me	1.50 (2)	C(1)Me–O(1d)Me	1.45 (3)

atoms are listed in Table I, together with their e.s.d.'s in parentheses.[8] For all crystallographic computation, the UNICS program[9] was used, and the atomic scattering factors and terms of anomalous dispersion corrections were taken from ref. 10.

Results and Discussion

Molecular Structure Bond lengths and angles are listed in Tables II and III. The molecular conformation of patellamide A, viewed from the C_2-symmetry axis and perpendicular to it, is shown in Fig. 1. The conformational torsion angles are listed in Table IV.

Because of the relatively large thermal motion of side-chain atoms, the bond lengths and angles have large e.s.d.'s, and thus are not as accurate as the generally published values.[11] However, no notable abnormality was observed, the these values are all in the acceptable region. The largest difference between the bonding parameters related by the C_2-symmetry is 0.05 Å for the C(15)–C(16) bond length and 7.4° for the C(7)–C(6)–C(8) bond angle.

Patellamide A assumes a saddle-shaped rectangular conformation of type II, where the isoleucine and valine side chains protrude up and down the ring chain with four heterocyclic rings at the corners. Because of the attachment of a methyl group to one of the two oxazoline rings, the chemical structure is not exactly C_2-symmetric. However, the differences of torsion angles between respective halves of a C_2-related structure unit are all within 5° of each other. The peptide groups are all *trans* within a $\Delta\omega$ of 6.0° around the N(2a)–C(9) amide bond. The molecular conformation is cylindrically curved, with a depth of 2.398 Å.[12] The other conformational parameters of patellamide A are as follows: N(1a)···N(1′a)=5.174(8) Å, N(2a)···N(2′a)=7.354(8) Å, N(2)···N(2′)=6.520(8) Å, N(10)···N(10′)=6.678(8) Å, N(1a)···N(2)=2.851(9) Å, N(2)···N(2a)=2.859(9) Å, N(2a)···N(10)=2.685(9) Å, N(10)···N(1′a)=2.789(8) Å, N(1′a)···N(2′)=2.824(8) Å, N(2′)···N(2′a)=2.886(8) Å, N(2′a)···N(10′)=2.680(8) Å, N(10′)···N(1a)=2.798(8) Å and the angle intersecting the N(1a)···N(1′a) and N(2a)···N(2′a) lines=86.1°. When these values are compared with those of C_2-symmetric ascidiacyclamide (**1**) crystallized from various solvents,[1] it could be said that the molecular conformation of patellamide A belongs to a typical square form of type II. On the other hand, it appears interesting to note that the non-C_2-symmetric methyl group [C(12)] exhibits high thermal motion in the crystal, irrespective of the covalent bonding directly to the conformationally rigid oxazoline ring, and this may be a sign of deviation from the type II conformation.

The water and methanol solvents are located on a pseudo axis of C_2-symmetry of patellamide A and are wrapped up in the molecule, where they are stabilized by hydrogen bonds and van der Waals short contacts. The water molecule is relatively loosely hydrogen-bonded to the N(1a) [=3.160(9) Å], N(2) [=3.293(9) Å], N(10) [=3.348(8) Å], N(1′a) [=3.148(8) Å], N(2′) [=3.297(8) Å] and N(10′) [=3.350(8) Å] atoms. On the other hand, the exact positioning of the methanol solvent was impossible because of the appearance of five electron density peaks. However, the oxygen atom, though not definitive, was tentatively assigned at four disordered positions [O(1a)Me—O(1d)Me], and they were independently refined with an occupancy of 0.25.

Crystal Packing A stereoscopic view of the crystal structure is shown in Fig. 2, where the solvent molecules

TABLE III. Bond Angles (°) with Their e.s.d's in Parentheses

Bond	Angle	Bond	Angle
C(1)–N(1a)–C(14′)	119.1 (5)	C(1′)–N(1′a)–C(14)	117.7 (5)
N(1a)–C(1)–O(1)	121.9 (5)	N(1′a)–C(1′)–O(1′)	123.0 (4)
N(1a)–C(1)–C(2)	116.0 (5)	N(1′a)–C(1′)–C(2′)	116.8 (5)
O(1)–C(1)–C(2)	122.0 (5)	O(1′)–C(1′)–C(2′)	120.2 (5)
C(1)–C(2)–N(2)	124.6 (5)	C(1′)–C(2′)–N(2′)	122.5 (4)
C(1)–C(2)–C(3)	120.2 (7)	C(1′)–C(2′)–C(3′)	120.2 (6)
N(2)–C(2)–C(3)	115.1 (7)	N(2′)–C(2′)–C(3′)	117.2 (6)
C(2)–N(2)–C(4)	111.2 (5)	C(2′)–N(2′)–C(4′)	110.6 (5)
C(2)–C(3)–S(3)	108.6 (4)	C(2′)–C(3′)–S(3′)	108.2 (4)
C(3)–S(3)–C(4)	91.1 (5)	C(3′)–S(3′)–C(4′)	90.3 (5)
N(2)–C(4)–S(3)	113.9 (3)	N(2′)–C(4′)–S(3′)	113.7 (3)
N(2)–C(4)–C(5)	123.4 (4)	N(2′)–C(4′)–C(5′)	123.5 (4)
S(3)–C(4)–C(5)	122.7 (3)	S(3′)–C(4′)–C(5′)	122.7 (3)
C(4)–C(5)–C(6)	111.4 (5)	C(4′)–C(5′)–C(6′)	111.2 (5)
C(4)–C(5)–N(2a)	109.0 (4)	C(4′)–C(5′)–N(2′a)	107.7 (4)
C(6)–C(5)–N(2a)	111.3 (5)	C(6′)–C(5′)–N(2′a)	111.3 (4)
C(5)–C(6)–C(7)	106.1 (7)	C(5′)–C(6′)–C(7′)	109.9 (6)
C(5)–C(6)–C(8)	109.3 (6)	C(5′)–C(6′)–C(8′)	106.9 (6)
C(7)–C(6)–C(8)	121.4 (8)	C(7′)–C(6′)–C(8′)	114.0 (8)
C(5)–N(2a)–C(9)	124.2 (5)	C(5′)–N(2′a)–C(9′)	123.3 (4)
N(2a)–C(9)–O(9)	125.9 (5)	N(2′a)–C(9′)–O(9′)	124.6 (4)
N(2a)–C(9)–C(10)	116.9 (4)	N(2′a)–C(9′)–C(10′)	117.0 (4)
O(9)–C(9)–C(10)	116.9 (5)	O(9′)–C(9′)–C(10′)	118.3 (4)
C(9)–C(10)–N(10)	111.6 (4)	C(9′)–C(10′)–N(10′)	112.0 (4)
C(9)–C(10)–C(11)	111.5 (5)	C(9′)–C(10′)–C(11′)	113.4 (5)
N(10)–C(10)–C(11)	105.5 (5)	N(10′)–C(10′)–C(11′)	103.7 (4)
C(10)–N(10)–C(13)	107.4 (5)	C(10′)–N(10′)–C(13′)	107.4 (4)
C(10)–C(11)–O(11)	102.6 (5)	C(10′)–C(11′)–O(11′)	103.6 (4)
C(11)–O(11)–C(13)	106.4 (5)	C(11′)–O(11′)–C(13′)	106.4 (5)
N(10)–C(13)–O(11)	117.0 (4)	N(10′)–C(13′)–O(11′)	117.7 (4)
N(10)–C(13)–C(14)	126.7 (5)	N(10′)–C(13′)–C(14′)	126.9 (4)
O(11)–C(13)–C(14)	116.3 (5)	O(11′)–C(13′)–C(14′)	115.3 (4)
C(13)–C(14)–C(15)	114.0 (5)	C(13′)–C(14′)–C(15′)	113.0 (4)
C(13)–C(14)–N(1′a)	108.9 (4)	C(13′)–C(14′)–N(1a)	109.7 (4)
C(15)–C(14)–N(1′a)	111.1 (5)	C(15′)–C(14′)–N(1a)	111.9 (4)
C(14)–C(15)–C(16)	110.7 (7)	C(14′)–C(15′)–C(16′)	111.1 (6)
C(14)–C(15)–C(18)	113.3 (6)	C(14′)–C(15′)–C(18′)	113.4 (5)
C(16)–C(15)–C(18)	113.4 (8)	C(16′)–C(15′)–C(18′)	118.3 (7)
C(15)–C(16)–C(17)	111.0 (1)	C(15′)–C(16′)–C(17′)	114.0 (9)
C(10)–C(11)–C(12)	106.0 (1)		
O(11)–C(11)–C(12)	113.0 (1)		

TABLE IV. Conformational Torsion Angles (°) of Patellamide A[a]

	A part	B part
Thiazole		
N(1a)–C(1)–C(2)–N(2)	−10.2 (8)	−7.8 (7)
C(14′)–N(1a)–C(1)–C(2)	−176.9 (9)	−177.4 (9)
Valine		
C(9)–N(2a)–C(5)–C(4)	135.3 (8)	134.3 (7)
N(2a)–C(5)–C(4)–N(2)	45.6 (6)	47.8 (5)
N(2a)–C(5)–C(6)–C(7)	−176.3 (9)	−180.0 (8)
N(2a)–C(5)–C(6)–C(8)	51.2 (8)	55.8 (7)
Oxazoline		
N(10)–C(10)–C(9)–N(2a)	18.7 (6)	17.4 (5)
C(10)–C(9)–N(2a)–C(5)	174.0 (9)	174.8 (8)
Isoleucine		
C(1′)–N(1′a)–C(14)–C(13)	−124.9 (7)	−124.1 (7)
N(1′a)–C(14)–C(13)–N(10)	−23.3 (5)	−23.0 (5)
N(1′a)–C(14)–C(15)–C(16)	−155 (1)	−150.0 (9)
N(1′a)–C(14)–C(15)–C(18)	76.1 (8)	73.9 (8)
C(14)–C(15)–C(16)–C(17)	163 (2)	168 (1)

a) Respective halves of the C_2-related structure are designated as A and B parts.

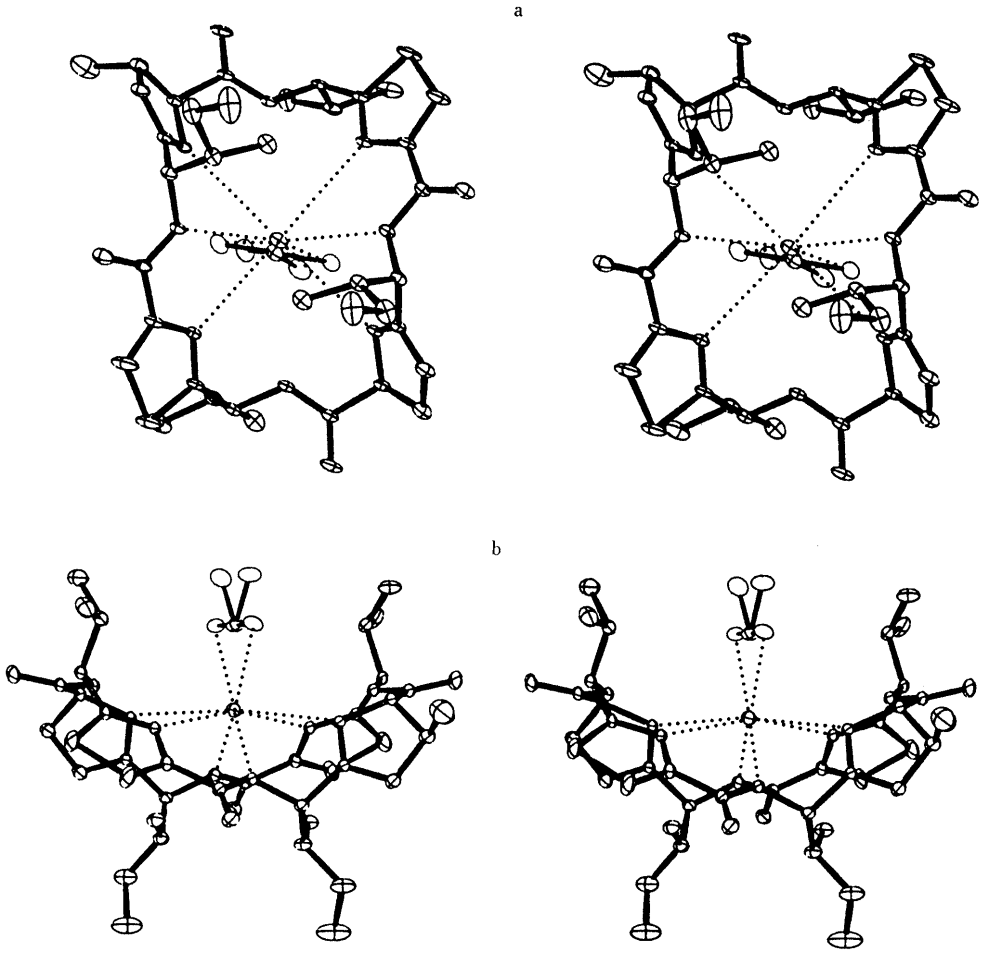

Fig. 1. Stereoscopic Drawing of Patellamide A, Viewed along the Pseudo C_2-Symmetry Axis (a) and Perpendicular to It (b)

Ellipsoids are scaled to enclose 30% of the electric density. The disordered oxygen atoms of methanol solvent are shown with open circles. The dotted lines indicate possible hydrogen bonds.

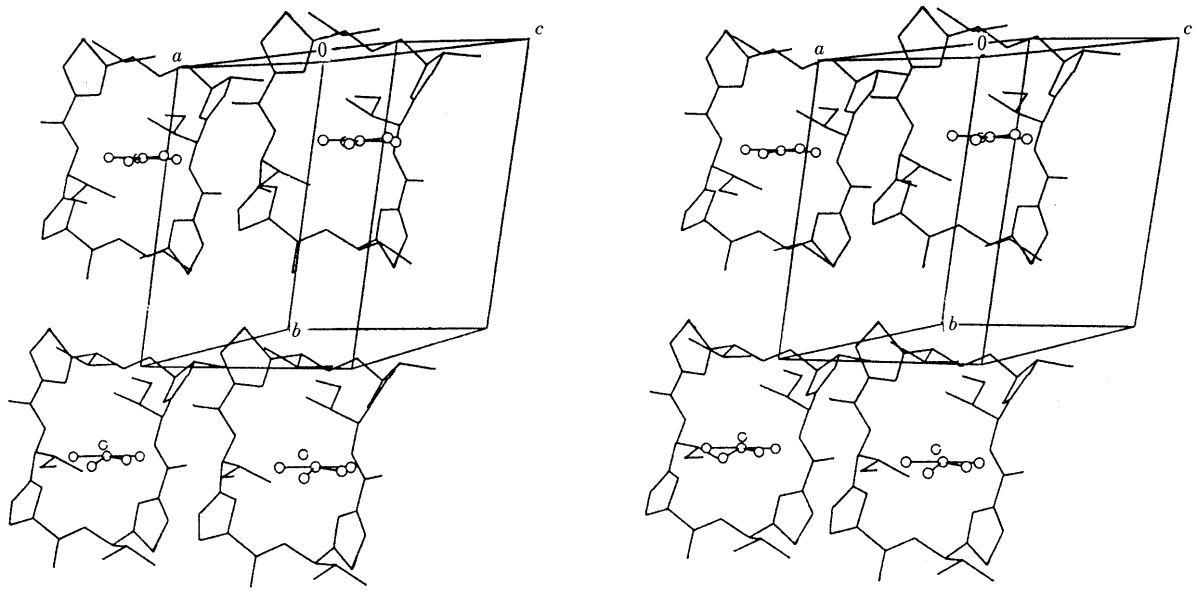

Fig. 2. Stereoscopic View of Crystal Structure, Viewed Perpendicular to the *b*-Direction

The water oxygen atom and the carbon atom of methanol are shown with filled circles and the disordered oxygen atoms of methanol with open circles.

are shown with circles. The molecular structures of patellamide A along the diagonal direction of the *ac* plane form the columns, in which solvent water and methanol molecules are located. The crystal structure is mainly stabilized by usual van der Waals contacts among these neighboring columns, and no hydrogen bonds are inter-

molecularly formed. This packing mode without intermolecular hydrogen bonds may be a reason why the side chain atoms of patellamide A show relatively high thermal motion.

The present X-ray analysis indicated that the molecular conformation of patellamide A agrees well with that of ascidiacyclamide,[1] and suggested that the conformation of type II has, to some extent, the ability to be held stable against structural deviation from C_2-symmetry. In this context, it would be reasonable to imagine that the non-C_2-symmetric patellamide D (**3**) could also take on a type II conformation under moderate conditions, although its crystal structure showed a type III conform-action.[3] On the other hand, it was shown by molecular mechanics calculations[3] that the conformation of type III, which is stabilized by four intramolecular hydrogen bonds, is roughly 10 kcal/mol more stable than that of type II. Therefore, the type III conformation may be a major form of the related cyclic peptides from the ascidian. When the "active" conformation of the cyclic peptide is considered, however, the present result leads us to propose a close relationship between biological function and type II conformation. This is also supported by the computer molecular modeling of ulithiacyclamide (**2**), the most potent cytotoxic molecule among the related peptides from the ascidian,[13] in which a type III conformation is unfavorable for constructing a reasonable three-dimensional structure because of a disulfide linkage.

References and Notes

1) *a*) T. Ishida, M. Tanaka, M. Nabae, M. Inoue, S. Kato, Y. Hamada, T. Shioiri, *J. Org. Chem.*, **53**, 107 (1988); *b*) T. Ishida, Y. In, M. Doi, M. Inoue, Y. Hamada, T. Shioiri, *Biopolymers*, **32**, 131 (1992).
2) T. Ishida, H. Ohishi, M. Inoue, M. Kamigauchi, M. Sugiura, N. Takao, S. Kato, Y. Hamada, T. Shioiri, *J. Org. Chem.*, **54**, 5337 (1989).
3) F. J. Schmitz, M. B. Ksebati, J. S. Chang, J. L. Wang, M. B. Hossain, D. van der Helm, M. H. Engel, A. Serban, J. A. Silfer, *J. Org. Chem.*, **54**, 3463 (1989).
4) Y. Hamada, M. Shibata, T. Shioiri, *Tetrahedron Lett.*, **26**, 6501 (1985).
5) E. Egert, G. M. Sheldrick, *Acta Cryst.*, **A41**, 262 (1985).
6) G. M. Sheldrick, "Crystallographic Computing 3," ed. by G. M. Sheldrick, C. Kruger, R. Goddard, Oxford University Press, Oxford, 1985, pp. 175—189.
7) G. M. Sheldrick, SHELX76, Programs for Crystal Structure Determination, University of Cambridge, England, 1975.
8) Tables of anisotropic thermal parameters of non-H atoms, atomic coordinates of H atoms, torsion angles between the non-H atoms, and list of observed and calculated structure factors have been deposited at the Cambridge Crystallographic Data Centre.
9) The Universal Crystallographic Computing System-Osaka, The Computation Center, Osaka University, Osaka, 1979.
10) International Tables for X-Ray Crystallography, Kynock Press, Birmingham, England, 1974, Vol. 4.
11) This also resulted because the ratio of the number of reflections used for the refinement (=3619) against the number of parameters refined (=505) is rather small.
12) This value corresponds to the length between the midpoints of the C_2-related N(1a)–N(1′a) and N(2a)–N(2′a). The primed atom is related to the nonprimed one by C_2-symmetry.
13) C. M. Ireland, A. R. Durso, Jr., R. A. Newman, M. Hacker, *J. Org. Chem.*, **47**, 1807 (1982).